The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

Evidence Report

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

Version 1.0, September 2021

Authors: Dressler, C1; Nast, A1; Gaskins M1

1 Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Department of Dermatology, Venereology and Allergology; euroguiderm@debm.de

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

Introduction

The last revision of the *international guideline for urticaria* was published in 2018. Three years later, we have now updated the evidence, conducting a systematic review, meta-analysis and GRADE evaluation according to the same criteria used in the previous version of the guideline. These criteria were published in the Methods & Evidence Report for that version of the guideline (https://onlinelibrary.wiley.com/action/downloadSupplement?doi=10.1111%2Fall.13414&file=all134">https://onlinelibrary.wiley.com/action/downloadSupplement?doi=10.1111%2Fall.13414&file=all134">https://onlinelibrary.wiley.com/action/downloadSupplement?doi=10.1111%2Fall.13414&file=all134">https://onlinelibrary.wiley.com/action/downloadSupplement?doi=10.1111%2Fall.13414&file=all134">https://onlinelibrary.wiley.com/action/downloadSupplement?doi=10.1111%2Fall.13414&file=all134">https://onlinelibrary.wiley.com/action/downloadSupplement?doi=10.1111%2Fall.13414&file=all134">https://onlinelibrary.wiley.com/action/downloadSupplement?doi=10.1111%2Fall.13414&file=all134">https://onlinelibrary.wiley.com/action/downloadSupplement?doi=10.1111%2Fall.13414&file=all134">https://onlinelibrary.wiley.com/action/downloadSupplement?doi=10.1111%2Fall.13414&file=all134">https://onlinelibrary.wiley.com/action/downloadSupplement?doi=10.1111%2Fall.13414&file=all134">https://onlinelibrary.wiley.com/action/downloadSupplement?doi=10.1111%2Fall.13414&file=all134">https://onlinelibrary.wiley.com/action/downloadSupplement?doi=10.1111%2Fall.13414&file=all134">https://onlinelibrary.wiley.com/action/downloadSupplement?doi=10.1111%2Fall.13414&file=all134">https://onlinelibrary.wiley.com/action/downloadSupplement?doi=10.1111%2Fall.13414&file=all134">https://onlinelibrary.wiley.com/action/downloadSupplement?doi=10.1111%2Fall.13414&file=all134">https://onlinelibrary.wiley.com/action/downloadSupplement?doi=10.11111%2Fall.13414&file=all134">https://onlinelibrary.wiley.com/actio

- 1. The present Evidence Report contains all the evidence we identified for chronic spontaneous urticaria (CSU) and for chronic inducible urticaria (CINDU).
- 2. Part 1 includes the evidence-to-decision frameworks for all comparisons pertaining to the treatment of chronic spontaneous urticaria.
- 3. Part 2 includes the evidence-to-decision frameworks for all comparisons pertaining to the treatment of chronic inducible urticaria.
- 4. For your convenience, we have also listed the guideline questions in the same order and in the same format as they appear in the old guideline. These are for reference only and may change during the process of guideline development.

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

Classification + diagnosis (consensus-based questions):

- How should urticaria be classified?
- Should we maintain the current classification of chronic urticaria?
- Should routine diagnostic measures be performed in acute urticaria?
- Should differential diagnoses be considered in patients with chronic spontaneous urticaria?
- What routine diagnostic measures should be performed in chronic spontaneous urticaria?
- Should routine diagnostic measures be performed in inducible urticaria?
- Should patients with chronic urticaria be assessed for disease activity, impact, and control?
- Which instruments should be used to assess and monitor disease activity in chronic spontaneous urticaria patients?
- Which instruments should be used to assess and monitor quality of life impairment in chronic spontaneous urticaria patients?
- Which instruments should be used to assess and monitor disease control in chronic spontaneous urticaria patients?

Management questions (evidence-based questions in bold):

- Should treatment aim at complete symptom control in urticaria?
- Should patients with chronic spontaneous urticaria be advised to discontinue medication that is suspected to worsen the disease?
- Are 2nd generation H1-antihistamines to be preferred over 1st generation H1-antihistamines for the treatment of urticaria? No new evidence identified
- Should modern 2nd generation H1-antihistamines be used as first-line treatment of urticaria? New evidence found, EtD framework updated
- Should modern 2nd generation H1-antihistamines be taken regularly or as needed by patients with chronic urticaria? No new evidence identified
- Should different 2nd generation H1-antihistamines be used at the same time? New evidence identified, EtD framework created
- Is an increase in the dose to fourfold of modern 2nd generation H1-antihistamines useful and to be preferred over other treatments in urticaria (second-line treatment)? New evidence found, EtD framework updated
- If there is no improvement, should higher than fourfold doses of 2nd generation H1-antihistamines be used? No evidence identified
- Is omalizumab useful as add-on treatment in patients unresponsive to high doses of H1-antihistamines (third-line treatment)? New evidence found, EtD framework updated
- Is cyclosporine A useful as add-on treatment in patients unresponsive to high doses of H1antihistamines? No new evidence identified
- Are leukotriene antagonists useful as add-on treatment in patients unresponsive to high doses of H1-antihistamines? New evidence found, EtD framework updated
- Should oral corticosteroids be used as add-on treatment in the treatment of urticaria? No evidence identified
- Are H2-antihistamines useful as add-on treatment in patients unresponsive to low or high doses of H1-antihistamines?
- Could any other treatment options be recommended as third line treatment for treatment in urticaria? New evidence found, EtD frameworks updated
- Should the same treatment algorithm be used in children?
- Should the same treatment algorithm be used in pregnant women and during lactation?

Box 1: Key questions

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

Results of the systematic review, meta-analysis and GRADE evaluation 2020:

We included a total of 21 new records and produced a total of 13 new or updated evidence-to-decision frameworks in 2020. Please note that the present Evidence Report contains *all* of the evidence-to-decision frameworks for the guideline – whether new or unchanged since 2016 – in order to provide the reader with a clearer overview of the entirety of the available evidence.

List of included comparisons for CSU (Part I) and CINDU (Part II):

| PART I: CSU | 5 |
|--|-----|
| 2nd generation H1-AH versus 1st generation H1-AH for CSU | 5 |
| 2nd gen H1-AH 1-fold versus placebo | 12 |
| 2nd generation H1-AH taken regularly versus 2nd generation H1-AH taken as needed | 21 |
| 2nd gen H1-AH + 2nd gen H1-AH (different H1AH) versus 2nd gen H1-AH alone | 24 |
| 2nd gen H1-AH x-fold versus 2nd gen H1-AH x-fold | 27 |
| Higher than fourfold doses of 2nd gen H1-AH | 36 |
| Omalizumab versus placebo | 37 |
| Cyclosporine versus placebo | 47 |
| Montelukast + 2nd gen H1-AH versus 2nd gen H1-AH 1-fold or 2-fold or placebo | 50 |
| Should oral corticosteroids be used as add-on treatment in the treatment of urticaria? | 57 |
| NB-UVB versus PUVA | 58 |
| NB-UVB versus 2nd gen H1-AH | 62 |
| Autologeous whole blood injections versus placebo | 67 |
| Hydroxychloroquine versus placebo | 70 |
| Methotrexate versus placebo | 73 |
| Dapsone | 76 |
| Motelukast versus montelukast + desloratadine | 80 |
| PART II: CINDU | 82 |
| Symptomatic dermographism (3 comparisons in total) | 82 |
| Cold urticaria (8 comparisons in total) | 91 |
| Cholinergic urticaria (1 comparison) | 113 |
| Solar urticaria/vihratory AF/aguagenic urticaria/contact urticaria | 116 |

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

PART I: CSU

2nd generation H1-AH versus 1st generation H1-AH for CSU

| Should 2nd gen | Should 2nd gen H1-AH vs. 1st gen H1-AH be used for urticaria - KQ09? | | | | |
|----------------|---|--|--|--|--|
| POPULATION: | patients with CSU | | | | |
| INTERVENTION: | 2nd gen H1-AH | | | | |
| COMPARISON: | 1st gen H1-AH | | | | |
| BIBLIOGRAPHY | Monroe 1992, Monroe 1992a, Ishibashi 1990, Kukita 194, Mensing 1991, Breneman 1996, Kalivas 1990 | | | | |

Assessment

| JUDGEMENT | RESEARCH EVIDENCE | RESEARCH EVIDENCE | | | | | |
|----------------------------|--|------------------------------------|-----------------------------------|---|--------------------------------|--|--|
| Trivial Small | Evidence week 1-2: | | | | | | |
| O Small O Moderate O Large | Outcomes | Nº of participants (studies) | Certainty of the evidence (GRADE) | Relative effect (95% CI) | Anticipated a | absolute effects* (95% | |
| O Varies O Don't | | Follow up | | | Risk with 1st gen H1- AH | Risk difference with 2nd gen H1-AH | |
| | good or excellent response (by investigator and patient) - w1 good or excellent response (by investigtor) - w1-2 | 147 (2 RCTs) 766 (4 RCTs) | ⊕⊕⊖⊖ LOWª,b ⊕⊕⊕⊕ HIGH | RR 1.04 (0.80 to 1.35) RR 1.04 (0.93 to | Study population | | |
| | | | | | 595 per 1.000 | 24 more per 1.000 (119 fewer to 208 more) | |
| | | | | | Study population | | |
| | | | ine. | 1.17) | 599 per 1.000 | 24 more per 1.000 (42 fewer to 102 more) | |
| | a. unclear randomization method and allocation concealment, selective reporting b. CI crossed line of no effect and MID threshold(s): uncertain whether there is any difference c. wide CI d. statistical heterogeneity (I² = 86%) maybe due to methodological differences e. statistical heterogeneity (I² = 82%) maybe due to methodological differences | | | | | | |

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

| | Outcomes | № of participants (studies) Follow up | Certainty of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects* (95% CI) | |
|--------|--|--|-----------------------------------|---|--|---|
| | | | | | Risk with 1st gen H1- AH | Risk difference with 2nd gen H1-AH |
| | good or excellent response (by investigator and patient) - w4 | 135 (1 RCT) | ⊕⊕⊜⊝ LOW ^{a,b} | RR 1.01 (0.79 to | Study popula | tion |
| | | | 100 | 1.30) | 647 per 1.000 | 6 more per 1.000 (136 fewer to 194 more) |
| | good or excellent response (by investigator) - w4 | 197 (2 RCTs) | ⊕⊕⊖⊖ LOW ^{a,b} | RR 1.09 (0.87 to | Study population | |
| | 1.37) | 1.37) | 571 per 1.000 | 51 more per 1.000 (74 fewer to 211 more) | | |
| | patients with relapse after 1w of stopping treatment | 68 (1 RCT) | ⊕⊕⊕○ MODERATE ^b | RR 0.66 (0.41 to 1.06) | Study population | |
| | | | | | 625 per 1.000 | 212 fewer per 1.000 (369 fewer to 38 more) |
| | a. unclear randomization r b. CI crossed line of no effe c. wide CI d. unclear/high risk of bias e. CI crosses MID threshol f. unclear risk of bias asses g. statistical heterogeneity | ect and MID thresho assessment d: statistically signif ssment | old(s): uncertain whether | er there is any o | | |
| | able Effects ial are the undesirable anticipated | l effects? | | | | |
| GEMENT | RESEARCH EVIDENCE | | | | | |

(95% CI)

Risk with 1st

Study population

gen H1-AH

Risk difference with

2nd gen H1-AH

(GRADE)

(studies)

Follow up

O Varies

O Don't know

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

| withdrawal due to AE - w2 | 637 (2 RCTs) | ⊕⊕⊜⊝ LOW ^{b,c} | RR 0.14 (0.01 to 2.76) | 12 per 1.000 | 10 fewer per 1.000 (12 fewer to 21 more) |
|-------------------------------------|-----------------|---------------------------------|------------------------------|------------------|---|
| patients with at least 1 AE (w2) | 637 (2 RCTs) | ⊕○○○ VERY LOW ^{b,d} | RR 0.55 (0.23 to | Study population | 1 |
| | | | 1.33) | 298 per 1.000 | 134 fewer per 1.000 (229 fewer to 98 more) |
| AE: somnolence - w2 | 637 (2 RCTs) | ⊕○○○ VERY LOW ^{b,e} | RR 0.49 (0.20 to | Study population | |
| | | | 1.19) | 259 per 1.000 | 132 fewer per 1.000 (207 fewer to 49 more) |
| AE: tiredness (w2) | 636 (2 RCTs) | ⊕⊕⊜⊝ LOW ^{c,f} | RR 0.29 (0.08 to | Study population | |
| | | | 0.97) | 39 per 1.000 | 28 fewer per 1.000 (36 fewer to 1 fewer) |

- unclear randomization method and allocation concealment, selective reporting CI crossed line of no effect and MID threshold(s): uncertain whether there is any difference b.
- wide CI
- c. d.
- statistical heterogeneity (I² = 86%) maybe due to methodological differences statistical heterogeneity (I² = 82%) maybe due to methodological differences CI crosses MID threshold: statistically significant difference of uncertain clinical importance

Evidence week 4:

| Outcomes | Nº of participants (studies) Follow up Certainty of the evidence effect (GRADE) (95% CI) | | effect CI) | | |
|---------------------------|---|----------------------------|----------------------------|------------------------------------|---|
| | | | Risk with 1st gen H1-AH | Risk difference with 2nd gen H1-AH | |
| withdrawal due to AE - w2 | 637 (2 RCTs) | ⊕⊕⊜⊝ LOW ^{b,c} | RR 0.14 (0.01 to | Study population | |
| | | | 2.76) | 12 per 1.000 | 10 fewer per 1.000 (12 fewer to 21 more) |
| withdrawal due to AE - w4 | 399 (3 RCTs) | ⊕⊕⊖⊖ LOW ^{d,e} | RR 0.22 (0.06 to | Study populati | on |
| | | | 0.87) | 64 per 1.000 | 50 fewer per 1.000 (60 fewer to 8 fewer) |
| AE: sedation (w4) | | | | Study populati | on |

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

| | 258 (2 RCTs) | ⊕⊖⊖⊖ VERY LOW ^{b,c,f,g} | RR 0.34 (0.07 to 1.64) | 397 per 1.000 | 262 fewer per 1.000 (369 fewer to 254 more) |
|--|-----------------|-------------------------------------|------------------------------|------------------|--|
| AE: somnolence - w4 | 264 (2 RCTs) | RR 0.60 LOWe,f (0.38 to | | Study populat | ion |
| | | | 0.94) | 296 per 1.000 | 119 fewer per 1.000 (184 fewer to 18 fewer) |
| AE: fatigue (w4) | 141 (1 RCT) | ⊕⊕⊜⊝ LOW ^{b,d} | RR 1.04 (0.27 to | Study population | |
| | | | 4.01) | 56 per 1.000 | 2 more per 1.000 (41 fewer to 167 more) |
| patients with relapse after 1w of stopping treatment | 68 (1 RCT) | ⊕⊕⊕○ MODERATE ^b | RR 0.66 (0.41 to | Study population | |
| | | | 1.06) | 625 per 1.000 | 212 fewer per 1.000 (369 fewer to 38 more) |

- unclear randomization method and allocation concealment, selective reporting
- CI crossed line of no effect and MID threshold(s): uncertain whether there is any difference
- unclear/high risk of bias assessment
- ${\it CI\ crosses\ MID\ threshold: statistically\ significant\ difference\ of\ uncertain\ clinical\ importance}$
- unclear risk of bias assessment
- statistical heterogeneity (I² = 88%) maybe due to methodological differences

Values and overall certainty of evidence What is the overall certainty of the evidence of effects?

| JUDGEMENT | RESEARCH EVIDENCE | | |
|---------------------|---|---------------------|-----------------------------------|
| O Very low | The relative importance or values of the main outcome | s of interest: | |
| Low Moderate | Outcome | Relative importance | Certainty of the evidence (GRADE) |
| O High | good or excellent response (by investigator and patient) - w1 | critical | ⊕⊕⊜⊝ LOW |
| O No | good or excellent response (by investigator and patient) - w4 | critical | ФФ○○ LOW |
| included studies | good or excellent response (by investiagtor) - w1-2 | critical | ⊕⊕⊕⊕ ні с н |
| | good or excellent response (by investiagtor) - w4 | critical | Ф⊕○○ LOW |
| | withdrawal due to AE - w2 | critical | ФФ○○ LOW |
| | withdrawal due to AE - w4 | critical | Ф⊕○○ LOW |
| | patients with at least 1 AE (w2) | important | ⊕○○○ VERY LOW |
| | AE: sedation (w4) | critical | ⊕○○○ VERY LOW |
| | AE: somnolence - w2 | critical | ⊕○○○ VERY LOW |
| | AE: somnolence - w4 | critical | ⊕⊕⊖⊝ LOW |

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

| AE: tiredness (w2) | critical | ⊕⊕○○ LOW |
|--|-----------|---------------|
| AE: fatigue (w4) | critical | Ф⊕○○ LOW |
| patients with relapse after 1w of stopping treatment | important | ⊕⊕⊕⊜ MODERATE |

| JUDGEMENT | RESEARCH EVIDENCE | | | | | | | |
|--|---|--------------------|-----------------------------------|--|-------------------------------|--|--|--|
| O Favors the comparison | Summary of findings: | | | | | | | |
| O Probably favors the comparison O Does not | Outcomes | With 1st gen H1-AH | With 2nd gen H1-AH | Difference | Relative effect (95% CI) | | | |
| favor either the intervention or the comparison • Probably favors the intervention O Favors the intervention O Varies O Don't know | good or excellent response (by investigator and patient) - w1 | 595 per 1.000 | 618 per 1.000 (476 to 803) | 24 more per 1.000 (119 fewer to 208 more) | RR 1.04 (0.80 to 1.35) | | | |
| | good or excellent response (by investigator and patient) - w4 | 647 per 1.000 | 654 per 1.000 (511 to 841) | 6 more per 1.000 (136 fewer to 194 more) | RR 1.01 (0.79 to 1.30) | | | |
| | good or excellent response (by investiagtor) - w1-2 | 599 per 1.000 | 623 per 1.000 (557 to 701) | 24 more per 1.000 (42 fewer to 102 more) | RR 1.04 (0.93 to 1.17) | | | |
| | good or excellent response (by investiagtor) - w4 | 571 per 1.000 | 623 per 1.000 (497 to 783) | 51 more per 1.000 (74 fewer to 211 more) | RR 1.09 (0.87 to 1.37) | | | |
| | withdrawal due to AE - w2 | 12 per 1.000 | 2 per 1.000 (0 to 32) | 10 fewer per 1.000 (12 fewer to 21 more) | RR 0.14 (0.01 to 2.76) | | | |
| | withdrawal due to AE - w4 | 64 per 1.000 | 14 per 1.000 (4 to 56) | 50 fewer per 1.000 (60 fewer to 8 fewer) | RR 0.22 (0.06 to 0.87) | | | |
| | patients with at least 1 AE (w2) | 298 per 1.000 | 164 per 1.000 (69 to 396) | 134 fewer per 1.000 (229 fewer to 98 more) | RR 0.55 (0.23 to 1.33) | | | |
| | AE: sedation (w4) | 397 per 1.000 | 135 per 1.000 (28 to 651) | 262 fewer per 1.000 (369 fewer to 254 more) | RR 0.34 (0.07 to 1.64) | | | |
| | AE: somnolence - w2 | 259 per 1.000 | 127 per 1.000 (52 to 308) | 132 fewer per 1.000 (207 fewer to 49 more) | RR 0.49 (0.20 to 1.19) | | | |

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

| AE: somnolence - w4 | 296 per 1.000 | 178 per 1.000 | 119 fewer per 1.000 | RR 0.60 |
|-----------------------------|---------------|---------------|-------------------------|--------------|
| | | (113 to 279) | (184 fewer to 18 fewer) | (0.38 to 0.9 |
| AE: tiredness (w2) | 39 per 1.000 | 11 per 1.000 | 28 fewer per 1.000 | RR 0.29 |
| | | (3 to 38) | (36 fewer to 1 fewer) | (0.08 to 0.9 |
| AE: fatigue (w4) | 56 per 1.000 | 58 per 1.000 | 2 more per 1.000 | RR 1.04 |
| | | (15 to 223) | (41 fewer to 167 more) | (0.27 to 4.0 |
| patients with relapse after | 625 per 1.000 | 413 per 1.000 | 212 fewer per 1.000 | RR 0.66 |
| 1w of stopping treatment | | (256 to 663) | (369 fewer to 38 more) | (0.41 to 1.0 |

| Feasibilit | ty Ition feasible to implement? |
|--------------------------|---|
| JUDGEMENT | RESEARCH EVIDENCE |
| O No | Feasibility, costs, equity and acceptability of the intervention need to be considered in |
| O Probably | the context of the local health care systems. |
| no | |
| O Probably | |
| yes | |
| O Yes | |
| Varies | |
| O Don't | |
| know | |
| | |

Summary

No difference was found for 2nd gen H1-AH compared to 1st gen H1-AH based on 'good or excellent response' (low to high quality), 'withdrawal due to AE - w2' (low quality), 'patients with at least 1 AE' (very low), 'somnolence- w2' (very low quality), 'fatigue' (low quality) and 'relapse after one week of stopping treatment' (moderate quality).

2nd gen H1-AH were superior compared to 1st gen H1-AH based on 'withdrawal due to AE - w4' (low quality), 'somnolence- w4' (low quality) and 'tiredness' (low quality).

Expert opinion with supporting references:

In addition to the trials identified in the systematic search comparing first and second generation antihistamines in urticaria patients, the following selection of studies provide indirect evidence from from healthy volunteers or from study designs not matching the inclusion criteria to support the use of second generation H1:

The use of first generation antihistamines at night-time (hydroxyzine 50 mg) plus second generation antihistamines (levocetirizine 15 mg daily) versus second generation antihistamines alone (20 mg

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

levocetirizin daily) was shown to increase daytime somnolence without differences in night time sleep disturbances or quality of life parameters. [1]

Second generation antihistamines were found to have no or less impact on central nervous system functions in healthy volunteers than first generation antihistamines (demonstrated e.g. with psychomotor function tests, self-reported alertness, driving performance. [2-6]

1. Staevska M, Gugutkova M, Lazarova C, Kralimarkova T, Dimitrov V, Zuberbier T, Church MK, Popov TA. Night-time sedating H1 -antihistamine increases daytime somnolence but not treatment efficacy in chronic spontaneous urticaria: a randomized controlled trial. British Journal of Dermatology. 2014; 171: 148-54. 2. Gengo FM, Dabronzo J, Yurchak A, Love S, Miller JK. The relative antihistaminic and psychomotor effects of hydroxyzine and cetirizine. Clinical pharmacology and therapeutics. 1987; 42: 265-72. 3. Gengo FM, Gabos C. Antihistamines, drowsiness, and psychomotor impairment: central nervous system effect of cetirizine. Annals of allergy. 1987; 59: 53-7. 4. Conen S, Theunissen E, Ramaekers J. The effects of bilastine and hydroxyzine on actual driving performance. Allergy: European Journal of Allergy and Clinical Immunology. 2010; 65: 281-82. 5. Gandon JM, Allain H. Lack of effect of single and repeated doses of levocetirizine, a new antihistamine drug, on cognitive and psychomotor functions in healthy volunteers. British Journal of Clinical Pharmacology. 2002; 54: 51-8. 6. García-Gea C, Martínez-Colomer J, Antonijoan RM, Valiente R, Barbanoj MJ. Comparison of peripheral and central effects of single and repeated oral dose administrations of bilastine, a new H1 antihistamine: a dose-range study in healthy volunteers with hydroxyzine and placebo as control treatments. Journal of clinical psychopharmacology. 2008; 28: 675-85.

7. Finkle WD, Adams JL, Greenland S, Melmon KL. Ann Allergy Asthma Immunol. 2002 Sep;89(3):244-50

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

2nd gen H1-AH 1-fold versus placebo

| POPULATION: | patients with CSU |
|---------------|---|
| INTERVENTION: | 2nd gen H1-AH 1-fold |
| COMPARISON: | placebo |
| BIBLIOGRAPHY | Belaich 1990, Breneman 1995, Bristoff 1996, Camarasa 2001, Di Lorenzo 2004, Dubertret 2007, Gimenez-Arnau 2007, Grob 2008/Ortonne 2007, Guerra 1994, Hide 2017*, Hide 2019*, Hisada 2016*, Hoxha 2011, Juhlin 1988, Kaplan 2005/Spector 2007, Kapp 2006, Monroe 1992, Nettis 2004, Nettis 2006, Ollert 1999, Paul 1998, Potter 2016, Siergiejko 1994, Zuberbier 2010 *studies added in the 2020 update |

Assessment

| JUDGEMENT | RESEARCH EVIDENCE | | | | | | | |
|--|---|-----------------------------|-----------------------------------|---|--|--|--|--|
| o Trivial o Small | Evidence week 1-2: | | | | | | | |
| Moderate Large O Varies Don't know | Outcomes | № of participants (studies) | Certainty of the evidence (GRADE) | Relative effect (95% CI) | Anticipated CI) | l absolute effects* (95% | | |
| | | Follow up | | | Risk with placebo | Risk difference with 2nd gen H1-AH 1-fold | | |
| | complete suppression - w1 230 (2 RCTs) | | RR 4.33 (1.71 to | Study population | | | | |
| | | 10.92) | 41 per 1.000 | 136 more per 1.000 (29 more to 405 more) | | | | |
| | good or excellent response (by investigator) | 1092 (7 RCTs) | ⊕⊕⊖⊖ LOW ^{a,b} | RR 2.59 (1.96 to 3.43) | Study population | | | |
| | - w1-2* | | LOW * | | 218 per 1.000 | 347 more per 1.000 (209 more to 530 more) | | |
| | good or excellent response (by patient) - w1 | 135 (1 RCT) | ⊕⊕⊕○ MODERATE® | RR 2.84 (1.75 to | Study population | | | |
| | | WIODERATE | 4.61) | 221 per 1.000 | 406 more per 1.000 (165 more to 796 more) | | | |

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

| mean change in symptom score - w1-2 (SMD)* | 966 (6 RCTs) | ⊕⊕⊕⊖ MODERATE ^c | - | SMD 0.72 lower (0.99 lower to 0.45 lower) |
|---|-----------------|-------------------------------|---|---|
| mean change in SF-36 - w1 | 36 (1 RCT) | ⊕⊕○○ LOW ^{d,e} | - | MD 1.41 higher (1.07 lower to 3.89 higher) |
| mean change in DLQI - w2* | 356 (2 RCTs) | ⊕⊕⊕ нідн ^ғ | - | MD 1.91 lower (2.71 lower to 1.11 lower) |

- unclear method of randomization and allocation concealment; selective reporting
- statistical heterogeneity (l^2 =63%) may be due to methodological differences statistical heterogeneity (l^2 =71%) may be due to methodological differences
- unclear allocation concealment, blinding, selective reporting
- CI crossed line of no effect and MID threshold(s): uncertain whether there is any difference
- CI does not cross MID, statistically significant but not clinically
- unclear method of randomization and allocation concealment
- statistical heterogeneity (I²= 66%) may be due to methodological differences

Evidence week 3-4:

| Outcomes | № of participants (studies) | Certainty of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects* (95% CI) | | |
|---|---|-----------------------------------|--------------------------------|--|--|--|
| | Follow up | | | Risk with placebo | Risk difference with 2nd gen H1-AH 1-fold | |
| complete suppression - w3-w4 | \cdot | | Study popul | ation | | |
| | | | 4.84) | 86 per 1.000 | 177 more per 1.000 (80 more to 330 more) | |
| good or excellent response (by investigator) | $\phi = \phi = \phi$ | Study population | | | | |
| - w3-4 | | MODERATE | 2.44) | 260 per 1.000 | 271 more per 1.000 (182 more to 375 more) | |
| good or excellent response (by patient) - w4 | 301 (2 RCTs) | ⊕⊕⊕○ MODERATE® | RR 1.98 (1.49 to | | | |
| | | MODERATE | 2.61) | 294 per 1.000 | 288 more per 1.000 (144 more to 474 more) | |
| mean change in symptom score - w3-4 | 606 (3 RCTs) | ⊕⊕⊕⊜ MODERATE ^b | - | | MD 1.35 lower (1.92 lower to 0.77 lower) | |

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

| mean change in SF-36 - w3 | 35 (1 RCT) | LOW _{c,d} | - | MD 1.95 higher (0.88 lower to 4.78 higher) |
|---|-----------------|-------------------------------|---|---|
| mean change in DLQI - w4 | 696 (2 RCTs) | ⊕⊕⊕○ MODERATE ^b | - | MD 3.82 lower (4.94 lower to 2.71 lower) |
| mean difference (mean change in DLQI) - w4 | 258 (1 RCT) | ⊕⊕⊕⊖ MODERATEª | - | 1.5 higher (0.2 higher to 2.9 higher) |

- a. unclear method of randomization and allocation concealment; selective reporting
- b. CI crosses MID threshold: statistically significant difference of uncertain clinical importance
- c. unclear allocation concealment, blinding, selective reporting
- d. CI crossed line of no effect and MID threshold(s): uncertain whether there is any difference

Evidence week 5-6:

| Outcomes | № of participants (studies) | Certainty of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects* (95% CI) | | |
|--|-----------------------------|-----------------------------------|--------------------------------|--|---|--|
| | Follow up | | | Risk with placebo | Risk difference with 2nd gen H1-AH 1-fold | |
| complete suppression - w6 | 100 (1 RCT) | ⊕⊕⊖⊖ LOW ^{a,b} | RR 52.88 (3.31 to | Study popula | ation | |
| | | | 843.81) | 0 per 1.000 | 0 fewer per 1.000 (0 fewer to 0 fewer) | |
| good or excellent response (by investigator) | 367 (2 RCTs) | ⊕○○○ VERY LOW ^{c,d,e} | RR 1.54 (0.97 to | Study popula | ation | |
| - w6 | VERY LOW-555 (2.43) | 2.43) | 442 per 1.000 | 239 more per 1.000 (13 fewer to 632 more) | | |
| good or excellent response (by patient) - | 93 (1 RCT) | ⊕⊕⊖⊖ LOW ^{c,f} | RR 1.55 (1.03 to | Study population | | |
| w6 | | 100 | 2.32) | 413 per 1.000 | 227 more per 1.000 (12 more to 545 more) | |
| mean difference (mean change in TSS) - w6 | 80 (1 RCT) | ⊕⊕⊕⊖ MODERATE® | - | | 1.77 higher (1.89 lower to 1.66 higher) | |
| mean change in DLQI - w6 | 137 (1 RCT) | ⊕⊕⊖⊖ LOW ^{c,f} | - | | MD 3.8 lower (5.71 lower to 1.89 lower) | |

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

- b. unclear method of randomization and allocation concealment; selective reporting
- c. unclear allocation concealment, blinding, selective reporting
- d. statistical heterogeneity (I² = 79%) maybe due to methodological differences
- e. CI crossed line of no effect and MID threshold(s): uncertain whether there is any difference f. CI crosses MID threshold: statistically significant difference of uncertain clinical importance
- g. unclear method of randomization and allocation concealment

Undesirable Effects

How substantial are the undesirable anticipated effects?

patients with at

least 1 AE - w2*

| JUDGEMENT | RESEARCH EVIDENCE | | | | | | |
|--------------------------|-------------------------------------|------------------------|---------------------------|--------------------------------|-------------------|--|--|
| o Large o Moderate | Evidence week 1-2: | | | | | | |
| o Small ● Trivial | Outcomes | Nº of participants | Certainty of the evidence | Relative effect (95% CI) | Anticipated a | absolute effects* (95% CI) | |
| o Varies o Don't know | Vulles | (studies) Follow up | ` ' ` ` ' ' ' | | Risk with placebo | Risk difference with 2nd gen H1-AH 1-fold | |
| | withdrawal due to AE - w2 (RD) * | 449 (3 RCTs) | ⊕⊖⊖⊖ LOW ^g | not estimable | Study popula | tion | |
| | | | | (2/222;0/227) | 0 per 1.000 | 0 fewer per 1.000 (0 fewer to 0 fewer) | |

RR 1.26

(0.52 to

3.04)

Study population

37 more per 1.000 (69 fewer to 291 more)

143 per

1.000

- a. unclear method of randomization and allocation concealment; selective reporting
- b. statistical heterogeneity (I²=70%) may may be due to methodological differences
- c. statistical heterogeneity (I²=71%) may be due to methodological differences
- d. unclear allocation concealment, blinding, selective reporting

430

(3 RCTs)

e. CI crossed line of no effect and MID threshold(s): uncertain whether there is any difference

 $\Theta\Theta$

LOW^{e,h}

- f. CI does not cross MID, statistically significant but not clinically
- g. unclear method of randomization and allocation concealment
- h. statistical heterogeneity (I²= 66%) may be due to methodological differences

Evidence week 3-4:

| | participants e | Certainty of the evidence | Relative effect | Anticipated absolute effects* (95% CI) | | |
|---|----------------|---------------------------|--------------------|--|--|--|
| | | (GRADE) | (95% CI) | Risk with placebo | Risk difference with 2nd gen H1-AH 1-fold | |
| withdrawal due to AE - w3-4* 1223 (10 RCTs) DWa,d | | RR 0.86 (0.33 to | Study population | | | |
| | | | 2.26) | 16 per 1.000 | 2 fewer per 1.000 (10 fewer to 20 more) | |

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

| patients with at least 1 AE - w4* | 852 (6 RCTs) | ' MODERATE" ' | (1.02 to | Study population | | |
|--------------------------------------|-----------------|---------------|----------|------------------|---|--|
| | MODERATE | | 1.60) | 246 per 1.000 | 69 more per 1.000 (5 more to 148 more) | |

- unclear method of randomization and allocation concealment; selective reporting
- b. CI crosses MID threshold: statistically significant difference of uncertain clinical importance
- c. unclear allocation concealment, blinding, selective reporting
- d. CI crossed line of no effect and MID threshold(s): uncertain whether there is any difference

Evidence week 5-6:

| Outcomes No of participants (studies) Follow up Certainty of the evidence (GRADE) (GRADE) (95% CI) | | _ | | Anticipated absolute effects* (95% CI) | | |
|--|-------------------|--|--|---|---|--|
| | Risk with placebo | Risk difference with 2nd gen H1-AH 1-fold | | | | |
| withdrawal due to AE - w6 | 362 (2 RCTs) | Ts) RR 1.06 (0.11 to | | Study population | tion | |
| | | | 10.08) | 5 per 1.000 | 0 fewer per 1.000 (5 fewer to 49 more) | |
| patients with at least 1 AE - w6 | 127 (2 RCTs) | ⊕⊕⊕⊖ MODERATE ^b | not pooled (zero in both groups) | Study population: Zero events in both RCTs | | |

- a. wide CI
- b. unclear method of randomization and allocation concealment; selective reporting
- c. unclear allocation concealment, blinding, selective reporting
- d. statistical heterogeneity ($I^2 = 79\%$) maybe due to methodological differences
- e. CI crossed line of no effect and MID threshold(s): uncertain whether there is any difference
- f. CI crosses MID threshold: statistically significant difference of uncertain clinical importance
- g. unclear method of randomization and allocation concealment

Values and overall certainty of the evidence

| JUDGEMENT | RESEARCH EVIDENCE | | | | | | | |
|-----------|---|---------------------|-----------------------------------|--|--|--|--|--|
| • low | The relative importance or values of the main outcomes of interest: | | | | | | | |
| | Outcome | Relative importance | Certainty of the evidence (GRADE) | | | | | |
| | complete suppression - w1 | critical | ⊕⊕⊕⊜ MODERATE | | | | | |
| | complete suppression - w3-4 | critical | ⊕⊕⊕○ MODERATE | | | | | |
| | complete suppression - w6 | critical | ⊕⊕○○ LOW | | | | | |
| | good or excellent response (by investigator) - w1-2 | critical | ⊕⊕⊜⊜ LOW | | | | | |
| | good or excellent response (by investigator) - w3-4 | critical | ⊕⊕⊕○ MODERATE | | | | | |
| | good or excellent response (by investigator) - w6 | critical | ⊕○○○ VERY LOW | | | | | |

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

| good or excellent response (by patient) - w1 | critical | ⊕⊕⊕○ MODERATE |
|--|-----------|---------------|
| good or excellent response (by patient) - w4 | critical | ⊕⊕⊕⊜ MODERATE |
| good or excellent response (by patient) - w6 | critical | ⊕⊕○○ rom |
| mean change in symptom score - w1 | critical | ⊕⊕⊕⊜ MODERATE |
| mean change in symptom score - w3-4 | critical | ⊕⊕⊕○ MODERATE |
| mean difference (mean change in TSS) - w6 | critical | ⊕⊕⊕⊜ MODERATE |
| mean change in SF-36 - w1 | critical | Ф⊕○○ LOW |
| mean change in SF-36 - w3 | critical | Ф⊕○○ LOW |
| mean change in DLQI - w4 | critical | ⊕⊕⊕○ MODERATE |
| mean change in DLQI - w6 | critical | ⊕⊕○○ rom |
| mean difference (mean change in DLQI) - w4 | critical | ⊕⊕⊕○ MODERATE |
| withdrawal due to AE - w2 | critical | ⊕⊕⊕○ MODERATE |
| withdrawal due to AE - w3-4 | critical | Ф⊕○○ LOW |
| withdrawal due to AE - w6 | critical | ⊕○○○ VERY LOW |
| patients with at least 1 AE - w2 | important | ⊕⊕○○ rom |
| patients with at least 1 AE - w4 | important | ⊕⊕⊕○ MODERATE |
| patients with at least 1 AE - w6 | important | ⊕⊕⊕○ MODERATE |

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

| JUDGEMENT | RESEARCH EVIDENCE | | | | | | |
|--|--|------------------|-----------------------------------|--|---------------------------------|--|--|
| o Favors the comparison | Summary of findings: | | | | | | |
| o Probably favors the comparison o Does not favor either the intervention or | Outcomes | With placebo | With 2nd gen H1- AH 1-fold | Difference | Relative effect (95% CI) | | |
| the comparison O Probably favors the intervention • Favors the | complete suppression - w1 | 41 per 1.000 | 177 per 1.000 (70 to 446) | 136 more per 1.000 (29 more to 405 more) | RR 4.33 (1.71 to 10.92) | | |
| intervention o Varies o Don't know | complete suppression - w3-w4 | 86 per 1.000 | 263 per 1.000 (166 to 416) | 177 more per 1.000 (80 more to 330 more) | RR 3.06 (1.93 to 4.84) | | |
| | complete suppression - w6 | 0 per 1.000 | 0 per 1.000 (0 to 0) | 0 fewer per 1.000 (0 fewer to 0 fewer) | RR 52.88 (3.31 to 843.81) | | |
| | good or excellent response (by investigator) - w1-2* | 218 per 1.000 | 615 per 1.000 (439 to 864) | 397 more per 1.000 (220 more to 646 more) | RR 2.82 (2.01 to 3.96) | | |

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

| good or excellent response (by investigator) - w3-4 | 260 per 1.000 | 531 per 1.000 (443 to 635) | 271 more per 1.000 (182 more to 375 more) | RR 2.04 (1.70 to 2.44) |
|---|------------------|--|--|-------------------------------|
| good or excellent response (by investigator) - w6 | 442 per 1.000 | 681 per 1.000 (429 to 1.000) | 239 more per 1.000 (13 fewer to 632 more) | RR 1.54 (0.97 to 2.43) |
| good or excellent response (by patient) - w1 | 221 per 1.000 | 626 per 1.000 (386 to 1.000) | 406 more per 1.000 (165 more to 796 more) | RR 2.84 (1.75 to 4.61) |
| good or excellent response (by patient) - w4 | 294 per 1.000 | 582 per 1.000 (438 to 768) | 288 more per 1.000 (144 more to 474 more) | RR 1.98 (1.49 to 2.61) |
| good or excellent response (by patient) - w6 | 413 per 1.000 | 640 per 1.000 (425 to 958) | 227 more per 1.000 (12 more to 545 more) | RR 1.55 (1.03 to 2.32) |
| mean change in symptom score - w1-2 (SMD)* | | The meanchange in symptom score in the intervention group was 0,72 standard deviations points lower (0,99 lower to 0,45 lower) | SMD 0.72 lower (0.99 lower to 0.45 lower) | - |
| mean change in symptom score - w3-4 | | The mean change in symptom score - w3-4 in the intervention group was 1,35 points lower (1,92 lower to 0,77 lower) | MD 1.35 lower (1.92 lower to 0.77 lower) | - |
| mean difference (mean change in TSS) - w6 | | The mean difference in TSS in the intervention group was 1,77 points higher (1,89 lower to 1,66 higher) | 1.77 higher (1.89 lower to 1.66 higher) | - |
| mean change in SF-36 - w1 | | The mean change in SF-36 in the intervention group was 1,41 points higher | MD 1.41 higher (1.07 lower to 3.89 higher) | - |

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

| | | (1,07 lower to 3,89 higher) | | |
|---|--------------|--|--|---------------------------|
| mean change in SF-36 - w3 | | The mean change in SF-36 - in the intervention group was 1,95 points higher (0,88 lower to 4,78 higher) | MD 1.95 higher (0.88 lower to 4.78 higher) | - |
| mean change in DLQI - w2* | | The mean change in DLQI * in the intervention group was 1,91 points lower (2,71 lower to 1,11 lower) | MD 1.91 lower (2.71 lower to 1.11 lower) | - |
| mean change in DLQI - w4 | | The mean change in DLQI in the intervention group was 3,82 points lower (4,94 lower to 2,71 lower) | MD 3.82 lower (4.94 lower to 2.71 lower) | - |
| mean change in DLQI - w6 | | The mean change in DLQI in the intervention group was 3,8 points lower (5,71 lower to 1,89 lower) | MD 3.8 lower (5.71 lower to 1.89 lower) | - |
| mean difference (mean change in DLQI) - w4 | | The mean change in DLQI in the intervention group was 1,5 points higher (0,2 higher to 2,9 higher) | 1.5 higher (0.2 higher to 2.9 higher) | - |
| withdrawal due to AE - w2 (RD) * | 0 per 1.000 | 0 per 1.000 (0 to 0) | 0 fewer per 1.000 (0 fewer to 0 fewer) | not estimable |
| withdrawal due to AE - w3-4* | 16 per 1.000 | 13 per 1.000 (5 to 35) | 2 fewer per 1.000 (10 fewer to 20 more) | RR 0.86 (0.33 to 2.26) |

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

| withdrawal due to AE - w6 | 5 per 1.000 | 6 per 1.000 | 0 fewer per 1.000 | RR 1.06 |
|-----------------------------|-------------|---------------|------------------------|-----------------|
| | | (1 to 54) | (5 fewer to 49 more) | (0.11 to 10.08) |
| patients with at least 1 AE | 143 per | 180 per 1.000 | 37 more per 1.000 | RR 1.26 |
| - w2* | 1.000 | (74 to 434) | (69 fewer to 291 more) | (0.52 to 3.04) |
| patients with at least 1 AE | 246 per | 315 per 1.000 | 69 more per 1.000 | RR 1.28 |
| - w4* | 1.000 | (251 to 394) | (5 more to 148 more) | (1.02 to 1.60) |
| patients with at least 1 AE | not pooled | not pooled | not pooled | not pooled |

Summary:

2ND GENERATION H1-AH 1-FOLD vs. PLACEBO

Data added in 2020 update from 3 new studies (differences to 2016 marked in purple)

Efficacy

2nd generation H1-AH 1-fold was superior to placebo based on the outcomes: 'complete suppression' (low/moderate quality), 'good or excellent response' at weeks 1-2 and weeks 3-4 (low/moderate quality), 'change in symptom score [standardized mean difference]' (moderate quality), 'mean change in DLQI' at weeks 1-2 (high quality), 'mean change in DLQI' at week 4 (low) and 'mean change in DLQI' at week 6 (moderate quality).

No difference was found for the outcomes: 'good or excellent response' at week 6 (very low quality), 'mean difference in symptom score' (moderate quality) and 'mean change in SF-36' (low quality).

Safety

No difference was found for the outcomes: 'withdrawal due to adverse event' (very low/moderate quality) and 'patients with at least one adverse event' (low/moderate quality).

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

2nd generation H1-AH taken regularly versus 2nd generation H1-AH taken as needed

| POPULATION: | patients with chronic spontanious urticaria |
|---------------|---|
| INTERVENTION: | 2nd gen AH taken regularly |
| COMPARISON: | 2nd gen AH taken as needed |
| BIBLIOGRAPHY | Grob 2008 |

Assessment

| GEMENT | RESEARCH EVIDENCE | | | | | |
|---|--|---|--|--|---|---|
| o Trivial Small Moderate Large Varies Don't know | Outcomes | № of participants (studies) | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute Risk with 2nd gen AH as needed | effects Risk difference with 2nd gen AH regular |
| | complete suppression - w8 | 106 (1 RCT) | ⊕○○○ VERY LOW ^{a,b,c} | RR 1.71 (1.01 to 2.89) | 267 per 1.000 | 189 more per 1.000 (3 more to 504 more) |
| | c. CI crosses N | ts responding to pr MID threshold: stati | evious treatment with stically significant diff d MID threshold(s): un | erence of uncerta | · | |
| w substantia DGEMENT arge | b. only patien c. CI crosses N d. CI crossed I ble Effects II are the undesirable an RESEARCH EVIDENCE | ts responding to pr MID threshold: stati ine of no effect and nticipated effects | istically significant diffd MID threshold(s): un | erence of uncerta certain whether t | n clinical importance nere is any difference | |
| v substantia DGEMENT arge Inderate simall rivial | b. only patien c. CI crosses N d. CI crossed I ble Effects II are the undesirable ar | ts responding to pr MID threshold: stati ine of no effect and nticipated effects | istically significant diffd MID threshold(s): un | erence of uncerta | n clinical importance | ute effects |
| v substantia OGEMENT arge Ioderate | b. only patien c. CI crosses N d. CI crossed I ble Effects II are the undesirable an RESEARCH EVIDENCE | ts responding to provide the provided state of the office of the office of the office of the office | istically significant diffd MID threshold(s): un | Relative effect | Anticipated absolu Risk with 2nd gen AH as needed | ute effects Risk difference with |

o Don't know

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

| . | | | | | | | | |
|--|---|--------------------------|---------|-----------------------------------|---|----------------------------------|--|--|
| | d. CI crossed line of no effect and MID threshold(s): uncertain whether there is any difference | | | | | | | |
| Values an | d overall certaint | y of the ev | ideı | nce | | | | |
| JUDGEMENT | RESEARCH EVIDENCE | | | | | | | |
| • Very low o Low | The relative importance or values of the main outcomes of interest: | | | | | | | |
| o Moderate o High | Outcome | | Re | lative importance | Certainty of the | evidence (GRADE) | | |
| O No included | complete suppression - w | 8 | critic | al | ⊕○○○ VERY LOW | | | |
| studies | withdrawal due to AE - w8 | 3 | critic | al | ⊕⊕○○ LOW | | | |
| | patients with at least 1 AE | - w8 | impo | rtant | ⊕○○○ VERY LOW | | | |
| Balance o | f effects e between desirable and und | desirable effects fa | avor tl | he intervention or th | e comparison? | | | |
| JUDGEMENT | RESEARCH EVIDENCE | | | | | | | |
| o Favors the comparison | Summary of findings: | | | | | | | |
| o Probably favors the comparison | Outcome | With 2nd gen A needed | H as | With 2nd gen AH regular | Difference (95% CI) | Relative effect (RR) (95% CI) | | |
| o Does not favor either the | complete suppression - w8 | 267 per 1.00 | 0 | 456 per 1.000 (269 to 771) | 189 more per 1.000 (from 3 more to 504 more) | RR 1.71 (1.01 to 2.89) | | |
| intervention or the comparison | withdrawal due to AE - w8 | 0 per 1.000 | | 0 per 1.000 (0 to 0) | | not estimable | | |
| o Probably favors the intervention | patients with at least 1 AE - w8 | 267 per 1.00 | 0 | 413 per 1.000 (240 to 712) | 147 more per 1.000 (from 27 fewer to 445 more) | RR 1.55 (0.90 to 2.67) | | |
| ● Favors the intervention o Varies o Don't know | | | | | | | | |
| Feasibility Is the intervention | / on feasible to implement? | | | | | | | |
| JUDGEMENT | RESEARCH EVIDENCE | | | | | | | |
| o No o Probably no o Probably yes o Yes | Feasibility, costs, eq the context of the lo | • | • | • | ervention need to | be considered in | | |

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

Summary

Taking 2nd generation H1-AH regularly is marginally superior to taking 2nd generation H1-AH as needed based on 'complete suppression', however the quality of evidence is very low.

No difference was found for 'withdrawal due to AE' (low quality) and 'patients with at least one AE' (very low quality).

Expert opinion: Weller et al. 2013 found no difference in the reduction of wheal area size between taking H1-AH on-demand and no H1-AH.

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

2nd gen H1-AH + 2nd gen H1-AH (different H1AH) versus 2nd gen H1-AH alone

| POPULATION: | patients with chronic spontaneous urticaria |
|---------------|--|
| INTERVENTION: | 2nd gen H1-AH + 2nd gen H1-AH (different H1AH) |
| COMPARISON: | 2nd gen H1-AH alone |
| BIBLIOGRAPHY | Wang 2019* |
| | *- studies added in the 2020 update |
| | |

Assessment

| JUDGEMENT | RESEARCH EVID | ENCE | | | | |
|--|---|--|---|--------------------------------|--|--|
| • Trivial o Small o Moderate o Large o Varies o Don't know | Outcomes | Nº of participants | Certainty of the evidence | Relative effect (95% CI) | Anticipated absolute effects* (95% CI) | |
| | | (studies) Follow up | (GRADE) | | Risk with 2nd gen H1-Ah alone | Risk difference with 2nd gen H1-AH +2nd gen H1-AH (different H1AH) |
| | good or excellent | 234 (1 RCT) | ⊕○○○ VERY LOW ^{a,b} | RR 1.14 (1.03 to | Study populatio | n |
| | response | | VERY LOW- | 1.26) | 812 per 1.000 | 114 more per 1.000 (24 more to 211 more) |
| | l . | | | | | |
| | b. Ci cros c. Ci cros | ssed line of no effect | y significant of uncertain and MID threshold: und ffects? | | | nce |
| How substanti | b. Ci cros c. Ci cros | ssed MID, statisticall ssed line of no effect able anticipated e | and MID threshold: und | | | nce |
| How substanti JUDGEMENT O Large O Moderate | b. Ci cros c. Ci cros able Effects al are the undesir | ssed MID, statisticall ssed line of no effect able anticipated e | and MID threshold: und | | r there is any differe | osolute effects* (95% CI) |
| | b. Ci cros c. Cl cros able Effects al are the undesir RESEARCH EVID | ssed MID, statistically ssed line of no effect able anticipated e | ffects? Certainty of the | Relative | r there is any differe | |

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

| patients with at least 1 AE | 234 (1 RCT) | ⊕⊖⊖⊖ VERY LOW ^{a,c} | RR 0.70 (0.28 to 1.78) | 85 per 1.000 | 26 fewer per 1.000 (62 fewer to 67 more) |
|-----------------------------|----------------|---------------------------------|------------------------------|-----------------|---|
| withdrawal due to AE | 234 (1 RCT) | LOM _a ⊕⊕○○ | not estimable | Study populatio | n |
| | | | (zero in both groups) | 0 per 1.000 | 0 fewer per 1.000 (0 fewer to 0 fewer) |

- a. open-label trial
- b. Cl crossed MID, statistically significant of uncertain clinical importance
- c. CI crossed line of no effect and MID threshold: uncertain whether there is any difference

Values and overall certainty of evidence

JUDGEMENT RESEARCH EVIDENCE • Very low Outcome Relative importance Certainty of the evidence (GRADE) good or excellent response critical ⊕○○○ VERY LOW withdrawal due to AE critical ⊕○○○ VERY LOW patients with at least 1 AE important ⊕○○○ VERY LOW

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

| JUDGEMENT | RESEARCH EVIDENCE | | | | | | | | |
|---|-----------------------------|------------------------------|--|---|--------------------------------|--|--|--|--|
| o Favors the comparison | Summary of finding: | | | | | | | | |
| o Probably favors the comparison • Does not favor either | Outcomes | With 2nd gen H1- Ah alone | With 2nd gen H1-AH +2nd gen H1- AH (different H1AH) | Difference | Relative effect (95% CI) | | | | |
| the intervention or the comparison o Probably favors the | good or excellent response | 812 per 1.000 | 926 per 1.000 (836 to 1.000) | 114 more per 1.000 (24 more to 211 more) | RR 1.14 (1.03 to 1.26) | | | | |
| ntervention o Favors the ntervention o Varies o Don't | patients with at least 1 AE | 85 per 1.000 | 60 per 1.000 (24 to 152) | 26 fewer per 1.000 (62 fewer to 67 more) | RR 0.70 (0.28 to 1.78) | | | | |
| know | withdrawal due to AE | 0 per 1.000 | 0 per 1.000 (0 to 0) | 0 fewer per 1.000 (0 fewer to 0 fewer) | not estimable | | | | |

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

| Feasibilit | ty tion feasible to implement? |
|---|---|
| JUDGEMENT | RESEARCH EVIDENCE |
| o No o Probably no o Probably yes o Yes • Varies o Don't know | Feasibility, costs, equity and acceptability of the intervention need to be considered in the context of the local health care systems. |

Summary

2ND GENERATION H1-AH + DIFFERENT 2ND GENERATION H1-AH vs. 2ND GENERATION H1-AH ALONE

Data added in 2020 update from 1 new study (differences to 2016 marked in purple)

Efficacy

No difference was found for the outcome: 'good or excellent response' (very low quality).

Safety

No difference was found for the outcomes: 'withdrawal due to adverse event' (very low quality) or 'patients with at least one adverse event' (very low/low).

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

2nd gen H1-AH x-fold versus 2nd gen H1-AH x-fold

| POPULATION: | patients with CSU unresponsive to H1-AH |
|---------------|---|
| | <u>'</u> |
| INTERVENTION: | 2 nd gen H1-AH 2-fold versus 2 nd gen H1-AH 1-fold |
| COMPARISON: | 2 nd gen H1-AH 4-fold versus 2 nd gen H1-AH 1-fold |
| | 2 nd gen H1-AH 4-fold versus 2 nd gen H1-AH 2-fold |
| BIBLIOGRAPHY | Gimenez-Arnau 2007, Hide 2019*, Hisada 2019*, Ishibashi 1989, Ishibashi 1990, Kukita 1994, Niimura 1990, NCT00536389, NCT00536389 NCT00536389 |
| | *studies added in the 2020 update |

Assessment

| | Desirable Effects How substantial are the desirable anticipated effects? | | | | | | |
|--|---|-------------------|----------------------------|-----------------------------------|--|--|--|
| JUDGEME NT | RESEARCH EVIDENCE | | | | | | |
| • Trivial o Small o Moderat e | 1) 2 nd gen H1-AH 2-fold versus 2 nd gen H1-AH 1-fold Evidence week 1-2: | | | | | | |
| o Large o Varies | Outcomes | № of participants | Certainty of the evidence | Relative effect | Anticipated absolut | e effects* (95% CI) | |
| o Don't know | (studies) (GRADE) Follow up | (GRADE) | (95% CI) | Risk with 2nd gen H1-AH 1-fold | Risk difference with 2nd gen H1-AH 2-fold | | |
| | good or excellent response - w1-2* | 1042 (7 RCTs) | ⊕⊕⊜⊝ LOW ^{a,b} | RR 1.01 (0.93 to | Study population | | |
| | | | 2011 | 1.10) | 658 per 1,000 | 7 more per 1,000 (46 fewer to 66 more) | |
| | sum, itch+rash - w2* | 159 (1 RCT) | LOM _p 'c | - | | MD 0.03 higher (0.48 lower to 0.54 higher) | |
| | DLQI w2* | 156 (1 RCT) | LOM _p 'c | - | | MD 0.09 higher (0.93 lower to 1.11 higher) | |
| | | | | | Study population | | |

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

| patients with relapse after 1w of stopping treatment | 44 (1 RCT) | ⊕⊕⊜⊖ Low ^{b,d} | RR 0.76 (0.36 to 1.60) | 458 per 1,000 | 110 fewer per 1,000 (293 fewer to 275 more) |
|---|---------------|----------------------------|------------------------------|---------------|---|
|---|---------------|----------------------------|------------------------------|---------------|---|

- a. two open label studies included; unclear allocation +randomization method
- b. unclear if patients were nonresponders
- c. unclear randomization, allocation
- d. CI crossed line of no effect and MID threshold(s): uncertain whether there is any difference

Evidence week 4-6:

| Outcomes | № of participants (studies) Follow up | Certainty of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects* (95% CI) | | |
|------------------------------------|--|---|--------------------------------|--|--|--|
| | | | | Risk with 2nd gen H1- AH 1-fold | Risk difference with 2nd gen H1-AH 2-fold | |
| good or excellent response - w6 | 221 (1 RCT) | ⊕⊕⊖⊖ RR 1.19 (0.99 to | | Study population | | |
| | | | 1.42) | 625 per 1,000 | 119 more per 1,000 (6 fewer to 262 more) | |
| mean change in UAS - w4 | 208 (1 RCT) | ⊕⊕⊕⊖ MODERATE ^c | - | | MD 0.1 lower (0.43 lower to 0.23 higher) | |

- a. CI crossed line of no effect and MID threshold(s): uncertain whether there is any difference
- b. unclear if patients were nonresponders
- c. unclear risk of bias assessment
- d. unclear randomization, allocation, and blinding
- e. only one of the two studies included nonresponders
- f. CU crossed 0.02 and the line of no effect

2) 2nd gen H1-AH 4-fold versus 2nd gen H1-AH 1-fold

| Outcomes | Nº of participants | Quality of the evidence | Relative effect | Anticipated absolute effects | | |
|----------------------------|--------------------|-------------------------|-----------------------------------|--|--|--|
| (studies) | (GRADE) | (95% CI) | Risk with 2nd gen H1-AH 1 fold | Risk difference with 2nd gen H1-AH 4 fold | | |
| mean change in UAS - w4 | 204 (1 RCT) | ⊕⊕⊕⊜ MODERATE ª | - | | MD 0 (0.33 lower to 0.33 higher) | |

a. unclear method of randomization and allocation concealment, selective reporting

3) 2nd gen H1-AH 4-fold versus 2nd gen H1-AH 2-fold

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

| Outcomes | Nº of participants (studies) Follow-up Quality of the evidence (GRADE) | | Relative effect | Anticipated absolute effects | |
|----------------------------|--|-------------------------------|-----------------------------------|--|--|
| | | (95% CI) | Risk with 2nd gen H1-AH 2 fold | Risk difference with 2nd gen H1-AH 4 fold | |
| mean change in UAS - w4 | 204 (1 RCT) | ⊕⊕⊕○ MODERATE ^a | - | | MD 0.1 higher (0.23 lower to 0.43 higher) |

a. unclear method of randomization and allocation concealment, selective reporting

Undesirable Effects

| OGEME | RESEARCH EVIDENCE | | | | | | |
|------------------|---|---------------------------------------|---|-------------------------|------------------|--|--|
| arge Moderat | 1) 2 nd gene H1-AH 2-fold versus 2 nd gen H1-AH 1-fold Evidence week 1-2: | | | | | | |
| rivial /aries | Outcomes Nº of Certainty of the participants evidence effect | | Anticipated abso | olute effects* (95% CI) | | | |
| on't ow | | Risk with 2nd gen H1-AH 1- fold | Risk difference with 2nd gen H1-AH 2-fold | | | | |
| | patients with at least 1 AE - 696 | RR 1.00 (0.75 to | Study population | | | | |
| | | | | 1.34) | 207 per 1,000 | 0 fewer per 1,000 (52 fewer to 70 more) | |
| | withdrawal due to AE - w1- 2* | 700 (5 RCTs) | ⊕⊕⊕○ MODERATE ^b | not estimable | Study population | | |
| | (RD -0.00(- 0.01,0.01)) | 6 per 1,000 | 6 fewer per 1,000 (6 fewer to 6 fewer) | | | | |
| ' | patients with relapse after 1w of stopping treatment | · | ⊕⊕⊜⊝ LOW ^{b,d} | RR 0.76 (0.36 to | Study population | | |
| | 1.60) | 458 per 1,000 | 110 fewer per 1,000 (293 fewer to 275 more) | | | | |

- a. two open label studies included; unclear allocation +randomization method
- b. unclear if patients were nonresponders
- c. unclear randomization, allocation, and blinding
- d. CI crossed line of no effect and MID threshold(s): uncertain whether there is any difference

Evidence week 4-6:

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

| Outcomes | Nº of participants | Certainty of the evidence | Relative effect | Anticipated absolute effects* (95% CI) | | |
|--|------------------------|------------------------------|-------------------------------|--|--|--|
| | (studies) Follow up | (GRADE) (95% CI | | Risk with 2nd gen H1-AH 1-fold | Risk difference with 2nd gen H1-AH 2-fold | |
| patients with at least 1 AE - w3-4* | | | Study population | | | |
| | 1.3 | 1.29) | 300 per 1,000 | 72 fewer per 1,000 (165 fewer to 87 more) | | |
| withdrawal due to AE - w4* | 370 (2 RCTs) | ⊕⊕⊜⊝ LOW ^{d,e,f} | not estimable | Study population | | |
| | | | (RD 0.01(- 0.01,0.03)) | 0 per 1,000 | 0 fewer per 1,000 (0 fewer to 0 fewer) | |
| withdrawal due to AE 221 | | _ | not estimable | Study population | | |
| | | | (zero in both groups) | 0 per 1,000 | 0 fewer per 1,000 (0 fewer to 0 fewer) | |

- a. CI crossed line of no effect and MID threshold(s): uncertain whether there is any differenceb. unclear if patients were nonresponders
- c. unclear risk of bias assessment
- d. unclear randomization, allocation, and blinding
- e. f. only one of the two studies included nonresponders
- CU crossed 0.02 and the line of no effect

2) 2nd gen H1-AH 4-fold versus 2nd gen H1-AH 1-fold

| Nº of Quality of the Relative Outcomes evidence effect | | Anticipated absolute effects | | | |
|--|------------------------|------------------------------|--------------------------------|-----------------------------------|--|
| | (studies) Follow-up | | (95% CI) | Risk with 2nd gen H1-AH 1 fold | Risk difference with 2nd gen H1-AH 4 fold |
| withdrawal due to AE - w4 | 210 (1 RCT) | ⊕○○○ VERY LOW a,b,c | RR 5.10 (0.25 to 104.87) | 0 per 1.000 | O fewer per 1.000 (0 fewer to 0 fewer) |

- unclear method of randomization and allocation concealment, selective reporting
- b. wide CI
- CI crossed line of no effect and MID threshold(s): uncertain whether there is any difference

3) 2nd gen H1-AH 4-fold versus 2nd gen H1-AH 2-fold

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

| | Nº of participants (studies) Follow-up Quality of the evidence (GRADE) Relative effect (95% CI) | | Anticipated absolute effects | | |
|-----------------------------|---|--------------------|-----------------------------------|--|---|
| Outcomes | | | Risk with 2nd gen H1-AH 2 fold | Risk difference with 2nd gen H1-AH 4 fold | |
| withdrawal due to AE- w4 | 208 (1 RCT) | ⊕⊕⊕⊖ MODERATE ³ | RR 1.00 (0.14 to 6.97) | 19 per 1.000 | 0 fewer per 1.000 (17 fewer to 115 more) |

a. unclear method of randomization and allocation concealment, selective reporting

Values and overall Certainty of evidence

| JUDGEME | RESEARCH EVIDENCE |
|---------|-------------------|
| NT | |

• Low The r

The relative importance or values of the main outcomes of interest:

1) 2nd gene H1-AH 2-fold versus 2nd gen H1-AH 1-fold

| Outcome | Relative importance | Certainty of the evidence (GRADE) |
|--|---------------------|-----------------------------------|
| good or excellent response - w1-2 | critical | ⊕⊕⊕○ MODERATE |
| good or excellent response - w6 | critical | ⊕⊕○○ LOW |
| sum, itch+rash - w2* | critical | ⊕⊕○○ LOW |
| mean change in UAS - w4 | critical | ⊕⊕⊕○ MODERATE |
| DLQI w2* | critical | Ф⊕○○ LOW |
| withdrawal due to AE - w1-2 | critical | ⊕⊕⊕○ MODERATE |
| withdrawal due to AE - w4 | critical | ⊕○○○ VERY LOW |
| withdrawal due to AE - w6 | critical | ⊕⊕⊕○ MODERATE |
| patients with at least 1 AE -w1 - w2 | important | ⊕⊕○○ LOW |
| patients with relapse after 1w of stopping treatment | important | ⊕⊕○○ LOW |

2) 2^{nd} gen H1-AH 4-fold versus 2^{nd} gen H1-AH 1-fold

The relative importance or values of the main outcomes of interest:

| Outcome | Relative importance Certainty of the evidence | |
|---------------------------|---|---------------|
| mean change in UAS - w4 | critical | ⊕⊕⊕○ MODERATE |
| withdrawal due to AE - w4 | critical | ⊕○○○ VERY LOW |

3) 2nd gen H1-AH 4-fold versus 2nd gen H1-AH 2-fold

| Outcome | Relative importance Certainty of the evidence | |
|--------------------------|---|---------------|
| mean change in UAS - w4 | critical | ⊕⊕⊕○ MODERATE |
| withdrawal due to AE- w4 | critical | ⊕⊕⊕⊜ MODERATE |

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

| IDGEME T | RESEARCH EVIDENCE | | | | | | | |
|--|--|-----------------------------------|---|--|--------------------------------|--|--|--|
| Favors | 1) 2 nd gene H1-AH 2-fold | d versus 2 nd gen H1-A | H 1-fold | | | | | |
| e ompariso | Summary of findings: | Summary of findings: | | | | | | |
| Probably vors the empariso | Outcomes | With 2nd gen H1-AH 1-fold | With 2nd gen H1-AH 2-fold | Difference | Relative effect (95% CI) | | | |
| vor ther the terventio or the ompariso | good or excellent response - w1-2* | 658 per 1,000 | 664 per 1,000 (612 to 723) | 7 more per 1,000 (46 fewer to 66 more) | RR 1.01 (0.93 to 1.10) | | | |
| Probably vors the terventio Favors | good or excellent response - w6 | 625 per 1,000 | 744 per 1,000 (619 to 888) | 119 more per 1,000 (6 fewer to 262 more) | RR 1.19 (0.99 to 1.42) | | | |
| ne Iterventio Varies Don't | sum, itch+rash - w2* | | The mean itch and rash score in the intervention group was 0.03 points higher (0.48 lower to 0.54 higher) | MD 0.03 higher (0.48 lower to 0.54 higher) | - | | | |
| | mean change in UAS - w4 | | The mean change in UAS in the intervention group was 0.1 lower (0.43 lower to 0.23 higher) | MD 0.1 lower (0.43 lower to 0.23 higher) | - | | | |
| | DLQI w2* | | The mean DLQI in the intervention group was 0.09 pointshigher (0.93 lower to 1.11 higher) | MD 0.09 higher (0.93 lower to 1.11 higher) | - | | | |
| | patients with at least 1 AE - w1-2* | 207 per 1,000 | 207 per 1,000 (155 to 277) | 0 fewer per 1,000 (52 fewer to 70 more) | RR 1.00 (0.75 to 1.34) | | | |
| | patients with at least 1 AE - w3-4* | 300 per 1,000 | 228 per 1,000 (135 to 387) | 72 fewer per 1,000 (165 fewer to 87 more) | RR 0.76 (0.45 to 1.29) | | | |

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

| withdrawal due to AE - w1-2* | 6 per 1,000 | 0 per 1,000 (0 to 0) | 6 fewer per 1,000 (6 fewer to 6 fewer) | not estimabl e |
|--|---------------|-------------------------------|---|------------------------------|
| withdrawal due to AE - w4* | 0 per 1,000 | 0 per 1,000 (0 to 0) | 0 fewer per 1,000 (0 fewer to 0 fewer) | not estimabl e |
| withdrawal due to AE - w6 | 0 per 1,000 | 0 per 1,000 (0 to 0) | 0 fewer per 1,000 (0 fewer to 0 fewer) | not estimabl e |
| patients with relapse after 1w of stopping treatment | 458 per 1,000 | 348 per 1,000 (165 to 733) | 110 fewer per 1,000 (293 fewer to 275 more) | RR 0.76 (0.36 to 1.60) |

2) 2nd gen H1-AH 4-fold versus 2nd gen H1-AH 1-fold

| Outcome | With 2nd gen H1- AH 1 fold | With 2nd gen H1-AH 4 fold | Difference (|
|------------------------------|-------------------------------|--|--|
| mean change in UAS - w4 | | The mean change in UAS in the intervention group was 0 points (0,33 lower to 0,33 higher) | MD ((0.33 lower highe |
| withdrawal due to AE - w4 | 0 per 1.000 | 0 per 1.000 (0 to 0) | 0 fewer pe (from 0 few fewe |

3) 2nd gen H1-AH 4-fold versus 2nd gen H1-AH 2-fold

| Outcome | With 2nd gen H1-AH 2 fold | With 2nd gen H1-AH 4 fold | Difference (95% CI) | Relative effect (RR) (95% CI) |
|----------------------------|------------------------------|--|--|-------------------------------------|
| mean change in UAS - w4 | | The mean change in UAS in the intervention group was 0,1 points higher (0,23 lower to 0,43 higher) | MD 0.1 higher (0.23 lower to 0.43 higher) | - |

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

| | withdrawal due to AE- w4 | 19 per 1.000 | 19 per 1.000 (3 to 134) | 0 fewer per 1.000 (from 17 fewer to 115 more) |
|---|---|---------------|--------------------------------|--|
| Feasibil | ity ention feasible to imp | lement? | | |
| JUDGEME NT | RESEARCH EVIDENCE | ADDITIONAL CO | NSIDERATIONS | |
| o No o Probably no o Probably yes o Yes • Varies o Don't know | Feasibility, costs, equity and acceptability of the intervention need to be considered in the context of the local health care systems. | | | |

Summary

1) COMPARISON: 2ND GENERATION H1-AH 2-FOLD vs. 2ND GENERATION H1-AH 1-FOLD Data added in 2020 update from 2 new studies (differences to 2016 marked in purple)

Efficacy

No difference was found for the outcomes: 'good or excellent response' (low quality), 'itch+rash score'/'UAS7'/'DLQI' (low/moderate quality) and 'relapse' (low quality).

Safety

No difference was found for the outcomes: 'withdrawal due to adverse event' (moderate quality) and 'patients with at least one adverse event' (very low/low quality).

2) COMPARISON: 2ND GENERATION H1-AH 4-FOLD vs. 2ND GENERATION H1-AH 1-FOLD No new data added in 2020

Efficacy

No difference was found for the outcome: 'mean change in UAS' (moderate quality).

Safety

No difference was found for the outcome: 'withdrawal due to adverse event' (very low quality).

3) COMPARISON: 2ND GENERATION H1-AH 4-FOLD VS. 2ND GENERATION H1-AH 2-FOLD *No new data added in 2020*

CC BY NC ©European Dermatology Forum

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

Efficacy

No difference was found for the outcome: 'mean change in UAS' (moderate quality).

Safety

No difference was found for the outcome: 'withdrawal due to adverse event' (moderate quality).

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

Higher than fourfold doses of 2nd gen H1-AH

No evidence identified

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

Omalizumab versus placebo

| POPULATION: | patients with chronic spontanious urticaria unresponsive to 2nd gen H1-AH |
|------------------|--|
| INTERVENTION(S): | 1) add-on omalizumab 300mg every 4w, 2) add-omalizumab 150mg every 4w |
| COMPARISON: | placebo |
| BIBLIOGRAPHY | 1) omalizumab 300mg: Hide 2017*, Jörg 2018*, Kaplan 2013/2016, Maurer 2013, Maurer 2018*, Metz 2017*, Saini 2011, Saini 2015/Kaplan 2016, Staubach 2016, Staubach 2018* |
| | 2) omalizumab 150mg: Hide 2017*, Maurer 2013, Saini 2015/Kaplan 2016 |
| | * studies added in the 2020 update/ outcome with new data added 2020 |

Assessment

| Effects are the desirable anticipate | ed effects? | | | | | |
|---|--|---|---|--|--|--|
| RESEARCH EVIDENCE | | | | | | |
| 1) omalizumab 300mg | every 4w comp | pared to place | bo | | | |
| Outcomes | Nº of participants | Certainty of the | Relative effect | Anticipated abs | olute effects* (95% CI) | |
| | (studies) evidence (GRADE) | (95% CI) | Risk with placebo | Risk difference with add-on omalizumab 300mg every 4w | | |
| complete suppression w4* | | | RR 17.32 (5.97 to | Study population | | |
| | | 50.24) | 6 per 1,000 | 97 more per 1,000 (29 more to 291 more) | | |
| complete suppression w8 | 655 (3 RCTs) | ⊕⊕⊕⊕ ніGн | RR 5.36 (3.13 to | Study population | | |
| | | | 9.18) | 58 per 1,000 | 251 more per 1,000 (123 more to 471 more) | |
| complete suppression w12* | 923 (6 RCTs) | ⊕⊕⊕⊕ нібн | RR 6.34 (4.13 to | Study population | | |
| | | | 9.74) | 56 per 1,000 | 300 more per 1,000 (176 more to 491 more) | |
| good or excellent response w1-2* | 30 (1 RCT) | ⊕○○○ VERY | RR 1.57 (0.07 to | Study population | | |
| | | LOW ^{a,b} | 35.46) | 0 per 1,000 | 0 fewer per 1,000 (0 fewer to 0 fewer) | |
| | Complete suppression was complete suppression was complete suppression was complete suppression was | 1) omalizumab 300mg every 4w comp Outcomes No of participants (studies) Follow up complete suppression w4* complete suppression w8 complete suppression w8 complete suppression w8 good or excellent 30 | The second state of the suppression was a suppr | Tomplete suppression w8 Complete suppression w12* Complete suppression | The second state of the suppression with the suppression with the with the with the suppression with the with | |

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

| | good or excellent response w4 | 701 (4 RCTs) | ⊕⊕⊕⊕ нібн | RR 6.10 (3.40 to | Study population | Study population | | |
|--------------------|--|---------------------------------------|-------------------------------|----------------------------------|---|---|--|--|
| | | | | 10.92) | 68 per 1,000 | 348 more per 1,000 (164 more to 676 more | | |
| | good or excellent response w8 | 655 (3 RCTs) | ⊕⊕⊕⊕ ніGн | RR 4.29 (2.65 to | Study population | ו | | |
| | | | | 6.94) | 115 per 1,000 | 379 more per 1,000 (190 more to 684 more | | |
| | good or excellent response w12* | 862 (6 RCTs) | ⊕⊕⊕⊕ ніGн | RR 3.70 (2.83 to | Study population | 1 | | |
| | | | | 4.82) | 151 per 1,000 | 409 more per 1,000 (277 more to 578 more | | |
| | UAS7 w4 | 46 (1 RCT) | ⊕⊕⊕○ MODERATE ^c | - | | MD 13 lower (19.42 lower to 6.58 lower) | | |
| | UAS7 w12* | 827 (5 RCTs) | ⊕⊕⊕⊖ MODERATE° | - | | MD 13 lower (19.42 lower to 6.58 lower) | | |
| | DLQI w12* | 745 (5 RCTs) | ⊕⊕⊕ HIGH | - | | MD 3.85 lower (4.79 lower to 2.9 lower) | | |
| | CU-Q2oL w4 | 91 (1 RCT) | ФФФФ нібн | - | | MD 20.7 lower (29 lower to 12.5 lower | | |
| | CU-Q₂oL w12 | 336 (1 RCT) | ⊕⊕⊕○ MODERATE ^c | - | | MD 13 lower (18.44 lower to 7.56 lower) | | |
| | relapse: DLQI 12w after last treatment* | 57 (1 RCT) | ⊕⊕⊕ нібн | - | | MD 3.4 lower (7.72 lower to 0.92 higher) | | |
| mab | relapse: percent w/clinical worsening | 134 (1 RCT) | ⊕⊕⊕⊜ MODERATEª | RR 0.50 (0.34 to | Study population | | | |
| every | (UAS7>6 for 2w) w24- 48* | | | 0.73) | 642 per 1,000 | 321 fewer per 1,000 (423 fewer to 173 fewer) | | |
| erate s know | b. CI crossed line of | no effect and MI eshold: statistic | ally significant differ | ertain whether ence of uncert | ent there is any difference ain clinical importance | | | |

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

| Outcomes | № of participants | Certainty of the evidence | of the Relative effect (95% CI) | Anticipated | absolute effects* (95% CI) | |
|---------------------------------|-----------------------------|---|---------------------------------|-------------------|--|--|
| | (studies) (GRADE) Follow up | (GRADE) | | Risk with placebo | Risk difference with add-on omalizumab 150mg every 4 | |
| complete suppression w4* | 467 (3 RCTs) | ⊕⊕⊕ нібн | RR 6.81 (1.82 to | Study popula | ation | |
| | | | 25.43) | 9 per 1,000 | 50 more per 1,000 (7 more to 210 more) | |
| complete suppression w8 | 322 (2 RCTs) | ⊕⊕⊕⊜ MODERATE ^a | RR 2.20 (1.15 to | Study popula | ation | |
| | | | 4.18) | 75 per 1,000 | 91 more per 1,000 (11 more to 240 more) | |
| complete suppression w12* | 467 (3 RCTs) | ФФФФ HIGH | RR 2.95 (1.53 to | Study popula | ation | |
| 5.69) | 60 per 1,000 | 117 more per 1,000 (32 more to 282 more) | | | | |
| good or excellent response w4 | 322 (2 RCTs) | ФФФФ HIGH | RR 2.70 (1.47 to | Study population | | |
| | | | 4.96) | 88 per 1,000 | 150 more per 1,000 (41 more to 349 more) | |
| good or excellent response w8 | 322 (2 RCTs) | ФФФФ HIGH | RR 2.48 (1.39 to | Study popula | ation | |
| | | | 4.44) | 145 per 1,000 | 214 more per 1,000 (56 more to 498 more) | |
| good or excellent response w12* | 467 (3 RCTs) | ФФФФ НІGH | RR 2.49 (1.79 to | Study population | | |
| | | | 3.46) | 163 per 1,000 | 243 more per 1,000 (129 more to 401 more) | |
| UAS7 w12* | 465 (3 RCTs) | ⊕⊕⊕⊕ HIGH | - | | MD 6.2 lower (8.35 lower to 4.05 lower) | |
| DLQI w12* | 429 (3 RCTs) | ⊕⊕⊕○ MODERATE ^a | - | | MD 1.97 lower (3.04 lower to 0.9 lower) | |

a. CI crosses MID threshold: statistically significant difference of uncertain clinical importance

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT RES

RESEARCH EVIDENCE

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

| 1) |
|-------------|
| omalizumab |
| 300mg every |
| 4w vs. |
| placebo |

- o Largeo Moderateo Small
- TrivialVariesDon't know

150mg every
4w vs.
placebo

o Large
o Moderate
o Small

Trivial
o Varies
o Don't know

1) omalizumab 300mg every 4w compared to placebo

| Outcomes | № of participants | Certainty of the evidence | ence (95% CI) | Anticipated absolute effects* (95% CI) | | |
|------------------------------------|--------------------------|-------------------------------|---|--|--|--|
| | (studies) (Follow up | (GRADE) | | Risk with placebo | Risk difference with add- on omalizumab 300mg every 4w | |
| withdrawal due to AE up to w12* | 223 (3 RCTs) | ⊕⊕⊕⊕ ніGн | not estimable | Study population | on | |
| | | | | 0 per 1,000 | 0 fewer per 1,000 (0 fewer to 0 fewer) | |
| patients with at least 1 AE w4 | 46 (1 RCT) | ⊕⊕⊕○ MODERATE ^a | RR 1.01 (0.55 to 1.85) | Study population | on | |
| least I AL W4 (I NCI) | | 476 per 1,000 | 5 more per 1,000 (214 fewer to 405 more) | | | |
| patients with at | | | | Study population | on | |
| least 1 AE w12 | (2 RCTs) | HIGH | (0.84 to 1.20) | 651 per 1,000 | 7 more per 1,000 (104 fewer to 130 more) | |

2) omalizumab 150mg every 4w compared to placebo omalizumab

| Outcomes | participants | Certainty of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects* (95% CI) | | |
|------------------------------------|-------------------|---|--------------------------------|---|---|--|
| | | | | Risk with placebo | Risk difference with add-on omalizumab 150mg every 4w | |
| withdrawal due to AE up to w12* | 306 (2 RCTs) | ⊕⊕⊕⊜ MODERATEª | RR 1.59 (0.20 to 12.80) | Study population | on | |
| | | | 7 per 1,000 | 4 more per 1,000 (5 fewer to 77 more) | | |
| patients with at | 167 | 000 | RR 1.10 | Study population | on | |
| least 1 AE w12 | (1 RCT) MODERATE® | (0.88 to 1.39) | 608 per 1,000 | 61 more per 1,000 (73 fewer to 237 more) | | |

a. CI crossed line of no effect and MID threshold(s): uncertain whether there is any difference

Values and overall certainty of the evidence

| JUDGEMENT | RESEARCH EVIDENCE |
|------------------|---|
| 1) omalizumab | The relative importance or values of the main outcomes of interest: |
| 300mg every | 1) omalizumab 300mg every 4w compared to placebo |

^{*} outcomes with new data added in 2020

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

placebo o Very low o Low

4w vs.

LowModerateHighNo includedstudies

| Outcomes | Importance | Certainty of the evidence (GRADE) |
|---|------------|-----------------------------------|
| complete suppression w4* | critical | ⊕⊕⊕ ніGн |
| complete suppression w8 | critical | ⊕⊕⊕ нідн |
| complete suppression w12* | critical | ⊕⊕⊕ нібн |
| good or excellent response w1-2* | critical | ⊕○○○ VERY LOW |
| good or excellent response w4 | critical | ⊕⊕⊕ нідн |
| good or excellent response w8 | critical | ⊕⊕⊕ нідн |
| good or excellent response w12* | critical | ⊕⊕⊕ нібн |
| UAS7 w4 | critical | Ф⊕⊕○ MODERATE |
| UAS7 w12* | critical | ⊕⊕⊕○ MODERATE |
| DLQI w12* | critical | ⊕⊕⊕⊕ ні с н |
| CU-Q2oL w4 | critical | ⊕⊕⊕⊕ ні с н |
| CU-Q ₂ oL w12 | critical | ⊕⊕⊕○ moderate |
| withdrawal due to AE up to w12* | critical | ⊕⊕⊕ нідн |
| patients with at least 1 AE w4 | important | Ф⊕⊕○ MODERATE |
| patients with at least 1 AE w12 | important | ⊕⊕⊕⊕ ні с н |
| relapse: DLQI 12w after last treatment* | important | ⊕⊕⊕⊕ ні с н |
| relapse: percent w/clinical worsening (UAS7>6 for 2w) w24-48* | important | ⊕⊕⊕○ moderate |

2) omalizumab 150mg every 4w vs. placebo

o Very low o Low

ModerateO HighO No includedstudies

2) omalizumab 150mg every 4w compared to placebo

| Outcomes | Importance | Certainty of the evidence (GRADE) |
|---------------------------------|------------|--------------------------------------|
| complete suppression w4* | critical | ⊕⊕⊕ ніGн |
| complete suppression w8 | critical | ⊕⊕⊕○ MODERATE |
| complete suppression w12* | critical | ⊕⊕⊕ ніGн |
| good or excellent response w4 | critical | ⊕⊕⊕ ніGн |
| good or excellent response w8 | critical | ⊕⊕⊕ ніGн |
| good or excellent response w12* | critical | ⊕⊕⊕ ні с н |

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

| mean change in UAS7 w12* | critical | Ф⊕⊕ нібн |
|---------------------------------|-----------|---------------|
| DLQI w12* | critical | ⊕⊕⊕○ moderate |
| withdrawal due to AE up to w12* | critical | ⊕⊕⊕○ moderate |
| patients with at least 1 AE w12 | important | ⊕⊕⊕○ moderate |

Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison? RESEARCH EVIDENCE JUDGEMENT 1) 1) omalizumab 300mg every 4w compared to placebo omalizumab 300mg every 4w vs. Relative With add-on omalizumab 300mg placebo Outcomes With placebo Difference effect every 4w (95% CI) o Favors the comparison o Probably complete suppression w4* 6 per 1,000 102 per 1,000 97 more per RR 17.32 favors the (35 to 297) 1,000 (5.97 to comparison (29 more to 50.24) o Does not 291 more) favor either the intervention complete suppression w8 58 per 1,000 309 per 1,000 251 more RR 5.36 or the (180 to 529) per 1,000 (3.13 to 9.18) comparison (123 more o Probably to 471 favors the more) intervention Favors the 356 per 1,000 RR 6.34 complete suppression 56 per 1,000 300 more intervention (4.13 to w12* (232 to 547) per 1,000 o Varies (176 more 9.74) o Don't know to 491 more) good or excellent response 0 per 1,000 0 per 1,000 0 fewer per RR 1.57 w1-2* (0 to 0) 1,000 (0.07 to (0 fewer to 35.46) 0 fewer) good or excellent response 68 per 1,000 416 per 1,000 348 more RR 6.10 (232 to 745) (3.40 to w4 per 1,000 (164 more 10.92) to 676 more) RR 4.29 good or excellent response 115 per 1,000 494 per 1,000 379 more (305 to 800) (2.65 to w8 per 1,000 (190 more 6.94) to 684 more)

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

| good or excellent response w12* | 151 per 1,000 | 560 per 1,000 (428 to 729) | 409 more per 1,000 (277 more to 578 more) | RR 3.70 (2.83 to 4.82) |
|------------------------------------|--------------------------------------|--|---|------------------------------|
| UAS7 w4 | The mean UAS7 w4 was 0 | The mean UAS7 w4 in the intervention group was 13 undefined lower (19.42 lower to 6.58 lower) | MD 13 lower (19.42 lower to 6.58 lower) | - |
| UAS7 w12* | The mean UAS7 w12* was 0 | The mean UAS7 w12* in the intervention group was 10.76 undefined lower (12.47 lower to 9.05 lower) | MD 10.76 lower (12.47 lower to 9.05 lower) | - |
| DLQI w12* | The mean DLQI w12* was 0 | The mean DLQI w12* in the intervention group was 3.85 undefined lower (4.79 lower to 2.9 lower) | MD 3.85 lower (4.79 lower to 2.9 lower) | - |
| CU-Q2oL w4 | The mean cU-Q2oL w4 was 0 | The mean cU-Q2oL w4 in the intervention group was 20.7 lower (29 lower to 12.5 lower) | MD 20.7 lower (29 lower to 12.5 lower) | - |
| CU-Q₂oL w12 | The mean cU-Q₂oL w12 was 0 | The mean cU-Q ₂ oL w12 in the intervention group was 13 undefined lower (18.44 lower to 7.56 lower) | MD 13 lower (18.44 lower to 7.56 lower) | - |
| withdrawal due to AE up to w12* | 0 per 1,000 | 0 per 1,000 (0 to 0) | 0 fewer per 1,000 (0 fewer to 0 fewer) | not estimable |
| patients with at least 1 AE w4 | 476 per 1,000 | 481 per 1,000 (262 to 881) | 5 more per 1,000 (214 fewer to 405 more) | RR 1.01 (0.55 to 1.85) |
| patients with at least 1 AE w12 | 651 per 1,000 | 657 per 1,000 (547 to 781) | 7 more per 1,000 (104 fewer to 130 more) | RR 1.01 (0.84 to 1.20) |

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

| 2) |
|-------------|
| omalizumab |
| 150mg every |
| 4w vs. |
| placebo |
| |

o Favors the comparison o Probably favors the comparison o Does not favor either the intervention or the comparison

• Probably

• Probably favors the intervention o Favors the intervention o Varies o Don't know

| relapse: DLQI 12w after last treatment* | The mean relapse: DLQI 12w after last treatment* was 0 | The mean relapse: DLQI 12w after last treatment* in the intervention group was 3.4 undefined lower (7.72 lower to 0.92 higher) | MD 3.4 lower (7.72 lower to 0.92 higher) | - |
|---|---|--|---|------------------------------|
| relapse: percent w/clinical worsening (UAS7>6 for 2w) w24-48* | 642 per 1,000 | 321 per 1,000 (218 to 468) | 321 fewer per 1,000 (423 fewer to 173 fewer) | RR 0.50 (0.34 to 0.73) |

2) omalizumab 150mg every 4w compared to placebo

| Outcomes | With placebo | With add-on omalizumab 150mg every 4w | Difference | Relative effect (95% CI) | |
|------------------------------------|--|---|--|--------------------------------|--|
| complete suppression w4* | 9 per 1,000 | 58 per 1,000 (16 to 218) | 50 more per 1,000 (7 more to 210 more) | RR 6.81 (1.82 to 25.43) | |
| complete suppression w8 | 75 per 1,000 | 166 per 1,000 (87 to 315) | 91 more per 1,000 (11 more to 240 more) | RR 2.20 (1.15 to 4.18) | |
| complete suppression w12* | 60 per 1,000 | 177 per 1,000 (92 to 342) | 117 more per 1,000 (32 more to 282 more) | RR 2.95 (1.53 to 5.69) | |
| good or excellent response w4 | 88 per 1,000 | 238 per 1,000 (129 to 437) | 150 more per 1,000 (41 more to 349 more) | RR 2.70 (1.47 to 4.96) | |
| good or excellent response w8 | 145 per 1,000 | 359 per 1,000 (201 to 642) | 214 more per 1,000 (56 more to 498 more) | RR 2.48 (1.39 to 4.44) | |
| good or excellent response w12* | 163 per 1,000 | 406 per 1,000 (292 to 564) | 243 more per 1,000 (129 more to 401 more) | RR 2.49 (1.79 to 3.46) | |
| mean change in UAS7 w12* | The mean mean change in UAS7 - w12* was 0 | The mean mean change in UAS7 - w12* in the intervention group was 6.2 | MD 6.2 lower (8.35 lower | - | |

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

| | | undefined lower (8.35 lower to 4.05 lower) | to 4.05 lower) | |
|------------------------------------|------------------------------------|---|---|-------------------------------|
| DLQI w12* | The mean DLQI w12* was 0 | The mean DLQI w12* in the intervention group was 1.97 undefined lower (3.04 lower to 0.9 lower) | MD 1.97 lower (3.04 lower to 0.9 lower) | - |
| withdrawal due to AE up to w12* | 7 per 1,000 | 10 per 1,000 (1 to 84) | 4 more per 1,000 (5 fewer to 77 more) | RR 1.59 (0.20 to 12.80) |
| patients with at least 1 AE w12 | 608 per 1,000 | 668 per 1,000 (535 to 845) | 61 more per 1,000 (73 fewer to 237 more) | RR 1.10 (0.88 to 1.39) |

Feasibility

Is the intervention feasible to implement?

| JUDGEMENT | RESEARCH EVIDENCE |
|--|---|
| omalizumab | omalizumab 300mg or 150mg every 4w vs. placebo |
| 300mg or 150mg every 4w vs. placebo | Feasibility, costs, equity and acceptability of the intervention need to be considered in the context of the local health care systems. |
| o No o Probably no o Probably yes o Yes | |
| VariesO Don't know | |

Summary

1) COMPARISON: OMALIZUMAB 300MG EVERY 4 WEEKS AS ADD-ON TREATMENT vs. PLACEBO

Data added in 2020 update from 5 new studies (differences to 2016 marked in purple

Efficacy

Omalizumab 300mg every 4 weeks as add-on treatment was superior to placebo for the outcomes: 'complete suppression' (high quality), 'good or excellent response' at weeks 4, 8 and 12 (high quality), 'UAS7' (moderate quality), 'DLQI' (high quality), 'CU-Q2oL' (moderate/high quality), 'relapse: DLQI 12 weeks after last treatment' (high quality) and 'relapse: percent of patients with clinical worsening (UAS7>6 for 2 weeks) from week 24-48' (moderate quality).

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

No difference was found for the outcome: 'good or excellent response' at weeks 1-2 (very low quality)

Safety

No difference was found for the outcomes: 'withdrawal due to adverse events up to week 12' (high quality) and 'patients with at least one adverse event' (moderate/high quality).

2) COMPARISON: OMALIZUMAB 150MG EVERY 4 WEEKS AS ADD-ON TREATMENT vs. PLACEBO

Data added in 2020 update from 1 new study

Efficacy

Omalizumab 150mg every 4 weeks as add-on treatment was superior to placebo for the outcomes: 'complete suppression' (moderate/high quality), 'good or excellent response' at weeks 4, 8 and 12 (high quality), 'UAS7' (high quality) and 'DLQI' (moderate quality).

Safety

No difference was found for the outcomes: 'withdrawal due to adverse event up to week 12' (moderate quality) and for 'patients with at least one adverse event' (moderate quality).

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

Cyclosporine versus placebo

POPULATION: patients with chronic spontanious urticaria

INTERVENTION: CSA

COMPARISON: placebo

BIBLIOGRAPHY Grattan 2000, Toubi 1997

Assessment

| DGEMENT | RESEARCH EVIDENCE | | | | | | | |
|--|--------------------------------------|--|---------------------------------|---|---|---|--|--|
| o Trivial o Small o Moderate o Large o Varies • Don't know | Evidence week 1-2: | | | | | | | |
| | Outcomes | Nº of | Quality of the | Relative | Anticipated absolute | effects | | |
| | | participants (studies) Follow-up | evidence (GRADE) | effect (95% CI) | Risk with no add-on intervention | Risk difference with add-on CSA | | |
| | complete suppression - w1 | 35 (1 RCT) | ⊕○○○ VERY LOW a,b,c | RR 11.42 (0.74 to 175.71) | 0 per 1.000 | 0 fewer per 1.000 (0 fewer to 0 fewer) | | |
| | good or excellent response - w1-2 | 65 (2 RCTs) | ⊕⊕⊜⊖ LOW a,c | RR 14.11 (2.05 to 97.04) | 0 per 1.000 | 0 fewer per 1.000 (0 fewer to 0 fewer | | |
| | Evidence week 4: | | | | | | | |
| | Evidence week 4: Outcomes | № of | Quality of the | Relative | Anticipated absolute | effects | | |
| | | Nº of participants (studies) Follow-up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute Risk with no add-on intervention | effects Risk difference with add-on CSA | | |
| | | participants (studies) | evidence | effect | Risk with no add-on | Risk difference | | |
| | Outcomes | participants (studies) Follow-up | evidence (GRADE) | effect (95% CI) RR 8.88 (0.57 to | Risk with no add-on intervention | Risk difference with add-on CSA 0 fewer per 1.000 | | |

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

| Outcomes | № of participants (studies) Follow-up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute e | Risk difference with add-on CSA |
|-------------------------------|--|---------------------------------------|---------------------------------|------------------------|---|
| complete suppression - w12 | 35 (1 RCT) | ⊕○○○ VERY LOW a,b,c | RR 11.42 (0.74 to 175.71) | 0 per 1.000 | 0 fewer per 1.000 (0 fewer to 0 fewer) |

- unclear method of randomiz ation and allocation concealment; no blinding; > 10% loss to follow-up
- CI crossed line of no effect and MID threshold(s): uncertain whether there is any difference b)
- c) d) 4. CI crosses MID threshold: statistically significant difference of uncertain clinical importance

Undesirable Effects

How substantial are the undesirable anticipated effects?

| JUDGEMENT | RESEARCH EVIDENCE | | | | | |
|--|------------------------------|--|---------------------------------------|--------------------------------|-------------------------|--|
| o Large o Moderate o Small Trivial o Varies | Outcomes | № of participants (studies) Follow-up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute ef | ffects Risk difference with add-on CSA |
| O Don't know | withdrawal due to AE - w4 | 29 (1 RCT) | ⊕⊕⊕⊕ HIGH | not estimable | 0 per 1.000 | 0 fewer per 1.000 (0 fewer to 0 fewer) |

Values and overall certainty of the evidence

| JUDGEMENT | RESEARCH EVIDENCE | | | | | | |
|------------|---|---|---------------|--|--|--|--|
| • Very low | The relative importance or values of the main outcomes of interest: | | | | | | |
| | Outcome | Outcome Relative importance Certainty of the evidence (GRADE) | | | | | |
| | complete suppression - w1 | critical | ⊕○○○ VERY LOW | | | | |
| | complete suppression – w4 | critical | ⊕○○○ VERY LOW | | | | |

| complete suppression - w1 | critical | ⊕○○○ VERY LOW |
|-----------------------------------|----------|---------------|
| complete suppression – w4 | critical | ⊕○○○ VERY LOW |
| complete suppression – w12 | critical | ⊕○○○ VERY LOW |
| good or excellent response - w1-2 | critical | ⊕⊕○○ LOW |
| good or excellent response – w4 | critical | ⊕⊕○○ LOW |
| mean change UAS7 –w4 | critical | ⊕⊕⊕○ MODERATE |
| withdrawal due to AE – w4 | critical | ФФФНIGH |

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT RESEARCH EVIDENCE

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

| Favors the comparison | Summary of finding | s: | | | |
|--|--------------------------------------|-----------------------------|--|---|----------------------------------|
| o Probably favors the comparison | Outcome | With no add-on intervention | With add-on CSA | Difference (95% CI) | Relative effect (RR) (95% CI) |
| o Does not favor either the | complete suppression - w1 | 0 per 1.000 | 0 per 1.000 (0 to 0) | 0 fewer per 1.000 (from 0 fewer to 0 fewer) | RR 11.42 (0.74 to 175.71) |
| intervention or the comparison o Probably | complete suppression - w4 | 0 per 1.000 | 0 per 1.000 (0 to 0) | 0 fewer per 1.000 (from 0 fewer to 0 fewer) | RR 8.88 (0.57 to 138.71) |
| favors the intervention o Favors the | complete suppression - w12 | 0 per 1.000 | 0 per 1.000 (0 to 0) | 0 fewer per 1.000 (from 0 fewer to 0 fewer) | RR 11.42 (0.74 to 175.71) |
| intervention o Varies • Don't know | good or excellent response - w1-2 | 0 per 1.000 | 0 per 1.000 (0 to 0) | 0 fewer per 1.000 (from 0 fewer to 0 fewer) | RR 14.11 (2.05 to 97.04) |
| | good or excellent response - w4 | 0 per 1.000 | 0 per 1.000 (0 to 0) | 0 fewer per 1.000 (from 0 fewer to 0 fewer) | RR 8.90 (0.57 to 140.31) |
| | mean change in UAS7 - w4 | | The mean change in UAS7 in the intervention group was 10,4 points lower (18,68 lower to 2,12 lower) | MD 10.4 lower (18.68 lower to 2.12 lower) | - |
| | withdrawal due to AE - w4 | 0 per 1.000 | 0 per 1.000 (0 to 0) | | not estimable |

Feasibility

Is the intervention feasible to implement?

| JUDGEMENT | RESEARCH EVIDENCE |
|---|---|
| O No O Probably no O Probably yes O Yes | Feasibility, costs, equity and acceptability of the intervention need to be considered in the context of the local health care systems. |
| VariesDon't know | |

Summary

No difference was found for 'complete suppression' (very low) and 'good or excellent response - w4' (low quality) and for 'withdrawal due to AE' (high quality).

Add-on CSA was superior to no add-on treatment based on 'good or excellent response - w1-2' (low quality) and 'mean change UAS7' (moderate quality).

No evidence was found for CSA as add-on treatment versus other interventions as add-on.

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

Montelukast + 2nd gen H1-AH versus 2nd gen H1-AH 1-fold or 2-fold or placebo

| POPULATION: | Patients wtih chronic urticaria , who failed to respond to 1-fold 2 nd gen H1-AH |
|---------------|---|
| INTERVENTION: | montelukast+ 2 nd gen H1-AH |
| COMPARISON: | 2 nd gen H1-AH 1-fold, 2 nd gen H1-AH 2 fold, placebo |
| BIBLIOGRAPHY | Di Lorenzo 2004, Wan 2009 |
| | Erbagci 2002, Nettis 2004, DiLorenzo 2004 |
| | Sarkar 2017* |
| | *studies added in the 2020 update |
| | |

Assessment

| JUDGEME NT | RESEARCH EVIDENCE | | | | | | | |
|--|---|--|--------------------------|----------------------------------|------------------------------|--|--|--|
| o Trivial o Small | 1) Montelukast+ | 2 nd gen H1-Al | H 1-fold compa | red to placebo | | | | |
| o Modera te | | Nº of | Quality of the | | Anticipated absolute effects | | | |
| o Large ● Varies o Don't know | Outcomes | participants (studies) Follow-up | evidence (GRADE) | Relative effect (95% CI) | Risk with placebo | Risk difference with montelukast + H1-AH | | |
| | mean change in TSS) - w6 | 80 (1 RCT) | ⊕⊕⊜ LOW a,b | - | | MD 1.76 lower (1.87 lower to 1.64 higher) | | |
| | good or excellent response w4 | 60 (1 RCT) | ⊕○○○ VERY LOW a,b,c,d | RR 17.00 (1.03 to 281.91) | 0 per 1.000 | 0 fewer per 1.000 (0 fewer to 0 fewer) | | |
| | a. unclear method of randomiz ation and allocation concealment b. all patients with CU were included (not only non-responders to H1-AH) c. Cl crosses MID threshold: statistically significant difference of uncertain clinical importance d. wide Cl 2) Montelukast+2 nd gen H1-AH 1-fold compared to 2 nd gen H1-AH 1-fold | | | | | | | |

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

| Outcomes | (studies) | Quality of the evidence effect (GRADE) (95% CI) | | Anticip | ated absolute | effects |
|----------------------------|----------------|---|-------------------------------|-------------------------------|--|--------------------------------|
| | | | | Risk with placebo + H1- AH | Risk differen | ce with montelukast - H1-AH |
| excellent response - w6 | 96 (2 RCTs) | ⊕⊕⊖⊖ LOW a,b | RR 4.77 (1.95 to 11.66) | 83 per 1.000 | 314 more per (79 more to 8 | |
| mean change in TSS | 80 (1 RCT) | LOW a,b | - | | MD 0.01 high (0.13 higher to | |

- a. unclear method of randomization and allocation concealment
- **b.** all patients with CSU were included (not only non-responders)

3) Montelukast+levocetirizin 1-fold compared to levocetirizin 2-fold

| Outcomes | Nº of participants | Certainty of the evidence | Relative effect | Anticipated absolute effects* (95% CI) | | |
|----------------------|------------------------|-----------------------------------|-------------------------|--|---|--|
| | (studies) Follow up | (GRADE) | (95% CI) | Risk with levocetirizin 2- fold | Risk difference with montelukast+levocetirizin 1-fold | |
| good or excellent | 120 (1 RCT) | ⊕⊕⊜⊝ LOW ^{a,b} | RR 1.04 (0.69 to | Study population | | |
| response w4 | | | 1.55) | 433 per 1.000 | 17 more per 1.000 (134 fewer to 238 more) | |
| UAS w2 | 103 (1 RCT) | ⊕⊖⊖⊖ VERY LOW ^{a,b,c} | - | | MD 0.15 higher (0.48 lower to 0.78 higher) | |
| UAS w4 | 103 (1 RCT) | ⊕⊕⊜⊖ LoWa,c | - | | MD 0.12 higher (0.51 lower to 0.75 higher) | |
| DLQI w4 | 103 (1 RCT) | ⊕⊖⊖⊖ VERY LOWa,c,d | - | | MD 4.08 lower (5.91 lower to 2.25 lower) | |

- a. 25-30% of patients had inducable urticaria
- b. CI crossed MID and line of no effect: uncertain whether there is any difference
- c. LOCF for continous outcomes
- d. CI crossed MID: statistically significant of uncertain clinical importance

Undesirable Effects

How substantial are the undesirable anticipated effects?

| JUDGEME | RESEARCH EVIDENCE |
|---------|-------------------|
| NT | |

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

o Large o Modera te

te o Small

Trivial Varies Don't

know

1) Montelukast+2nd gen H1-AH 1-fold compared to placebo

No evidence

2) Montelukast+2nd gen H1-AH 1-fold compared to 2nd gen H1-AH 1-fold

| | Nº of participants | Quality of the | Relative effect | Anticipated absolut | | |
|----------------------------------|------------------------|--------------------|---|-------------------------|-----------------------------------|--|
| Outcomes | (studies) Follow-up | tudies) (GRADE) | | Risk with placebo + H1- | Risk diffe | |
| patients with at least 1 AE - w6 | 54 (1 RCT) | ⊕⊕⊜ LOW a,b | not estimable (zero in both groups) | 0 per 1.000 | 0 fewer per (0 fewer to | |
| withdrawal due to AE - w6 | 42 (1 RCT) | ⊕⊕⊕○ MODERATE a | not estimable (zero in both groups) | 0 per 1.000 | 0 fewer per (0 fewer to | |

- a. unclear method of randomization and allocation concealment
- b. all patients with CSU were included (not only non-responders)

3) Montelukast+levocetirizin 1-fold compared to levocetirizin 2-fold

No evidence

Values and certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEME NT

RESEARCH EVIDENCE

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

| • | Very |
|----|------|
| lo | w |

1) Montelukast+2nd gen H1-AH 1-fold compared to placebo

| Outcome | Relative importance | Certainty of the evidence (GRADE) |
|---------------------------------|---------------------|-----------------------------------|
| TSS- w6 | critical | ⊕⊕○○ Low |
| good or excellent response - w4 | critical | ⊕○○○ VERY LOW |

2) Montelukast+2nd gen H1-AH 1-fold compared to 2nd gen H1-AH 1-fold

| Outcome | Relative importance | Certainty of the evidence (GRADE) |
|----------------------------------|---------------------|-----------------------------------|
| excellent response - w6 | critical | ⊕⊕○○ LOW |
| TSS | critical | ⊕⊕○○ LOW |
| patients with at least 1 AE - w6 | critical | ⊕⊕○○ LOW |
| withdrawal due to AE - w6 | critical | ⊕⊕⊕○ MODERATE |

3) Montelukast+levocetirizin 1-fold compared to levocetirizin 2-fold

| Outcome | Relative importance | Certainty of the evidence (GRADE) |
|----------------------------|---------------------|-----------------------------------|
| Good or excellent response | critical | ⊕⊕○○ LOW |
| UAS w2 | critical | ⊕○○○ VERY LOW |
| UAS w4 | critical | ⊕⊕○○ LOW |
| DLQI w4 | critical | ⊕○○○ VERY LOW |

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

| JUDGEME NT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---------------|--------------------|--------------------------------------|
| o Favors | 1) Montalukast 2nd | Ten H1-AH 1-fold compared to placeho |

the comparis on o Probabl y favors the comparis

• Does not favor either the interventi on or the comparis

o Probabl y favors the interventi

he comparis With

| Οι | ıtcome | With placebo | With montelukast + H1-AH | Difference (95% CI) | Relative effect (RR) (95% CI) |
|----|---------------------------|----------------|--|--|----------------------------------|
| TS | SS - w6 | | The mean difference in TSS in the intervention group was 1,76 points lower (1,87 lower to 1,64 higher) | MD 1.76 lower (1.87 lower to 1.64 higher) | - |
| " | or excellent onse - w4 | 0 per 1.000 | 0 per 1.000 (0 to 0) | 0 fewer per 1.000 (from 0 fewer to 0 fewer) | RR 17.00 (1.03 to 281.91) |

2) Montelukast+2nd gen H1-AH 1-fold compared to 2nd gen H1-AH 1-fold

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

on
o Favors
the
interventi
on
o Varies
o Don't
know

| Outcome | With placebo + H1-AH | With montelukast + H1-AH | Difference (95% CI) | Relative effect (RR) (95% CI) |
|-------------------------------------|-------------------------|---|--|----------------------------------|
| excellent response - w6 | 83 per 1.000 | 397 per 1.000 (162 to 972) | 314 more per 1.000 (from 79 more to 888 more) | RR 4.77 (1.95 to 11.66) |
| TSS | | The mean difference in TSS in the intervention group was 0,01 points higher (0,13 higher to 0,09 lower) | MD 0.01 higher (0.13 higher to 0.09 lower) | - |
| patients with at least 1 AE - w6 | 0 per 1.000 | 0 per 1.000 (0 to 0) | | not estimable |
| withdrawal due to AE - w6 | 0 per 1.000 | 0 per 1.000 (0 to 0) | | not estimable |

3) Montelukast+levocetirizin 1-fold compared to levocetirizin 2-fold

| Outcomes | With levocetirizin 2-fold | With montelukast+levocetirizin 1-fold | Difference | Relative effect (95% CI) |
|----------------------------------|---------------------------------|---|--|-------------------------------|
| good or excellent response w4 | 433 per 1.000 | 416 per 1.000 (273 to 633) | 17 fewer per 1.000 (160 fewer to 199 more) | RR 0.96 (0.63 to 1.46) |
| UAS w2 | The mean UAS w2 was 0 | The mean UAS in the intervention group was 0,15 points higher (0,48 lower to 0,78 higher) | MD 0.15 higher (0.48 lower to 0.78 higher) | - |
| UAS w4 | The mean UAS w4 was 0 | The mean UAS in the intervention group was 0,12 points higher (0,51 lower to 0,75 higher) | MD 0.12 higher (0.51 lower to 0.75 higher) | - |
| DLQI w4 | The mean DLQI w4 was 0 | The mean DLQI in the intervention group was 4,08 points lower (5,91 lower to 2,25 lower) | MD 4.08 lower (5.91 lower to 2.25 lower) | - |

Feasibility

Is the intervention feasible to implement?

| JUDGEME | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---------|-------------------|---------------------------|
| NT | | |

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

| O No O Probabl y no O Probabl | Feasibility, costs, equity and acceptability of the intervention need to be considered in the context of the local health care systems. |
|--|---|
| y yes o Yes | |
| • Varies | |
| o Don't | |
| know | |
| | |
| | |

Summary

(Differences to 2016 marked in purple)

1) COMPARISON: MONTELUKAST + 2ND GENERATION H1-AH 1-FOLD vs. PLACEBO

No new data added in 2020

Efficacy

No difference was found for the outcomes: 'mean difference in total symptom score' (low quality) and 'good or excellent response' (very low quality).

Safety

No safety data were available.

2) COMPARISON: MONTELUKAST + 2ND GENERATION H1-AH 1-FOLD vs. 2ND GENERATION H1-AH 1-FOLD

No new data added in 2020

Efficacy

Montelukast + 2nd generation H1-AH 1-fold was superior to 2nd generation H1-AH 1-fold for the outcome: 'excellent response' (low quality).

No difference was found for the outcome: 'mean difference in TSS' (low quality).

Safety

No difference was found for: 'withdrawal due to adverse event' (moderate quality) and 'patients with at least one adverse event' (low quality).

3) COMPARISON: MONTELUKAST + LEVOCETIRIZIN 1-FOLD vs. LEVOCETIRIZIN 2-FOLDData added in 2020 update from 1 new study

Efficacy

Montelukast + levocetirizine 1-fold was superior to levocetirizine 2-fold for the outcome: 'DLQI' (very low quality).

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

No difference was found for the outcome: 'good or excellent response' (low quality) or 'UAS' (very low to low quality).

Safety

No safety data were available.

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

Should oral corticosteroids be used as add-on treatment in the treatment of urticaria?

No evidence identified

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

NB-UVB versus PUVA

| POPULATION: | patients with chronic spontanious urticaria |
|---------------|--|
| INTERVENTION: | NB-UVB |
| COMPARISON: | PUVA |
| BIBLIOGRAPHY | Bishnoi 2017*, Khafagy 2013, * studies added in the update 2020 |

Assessment

| UDGEMENT | RESEARCH EVIDENCE | | | | | | | |
|--|---|--------------------|----------------------------|--------------------|-------------------------|--|--|--|
| TrivialSmallModerate | Outcomes | Nº of participants | | Relative effect | Anticipated (95% CI) | Anticipated absolute effects* (95% CI) | | |
| Large Varies | | | | (95% CI) | Risk with PUVA | Risk difference with NB-UVB | | |
| Don't know | complete suppression | | $\Theta\ThetaOO$ | RR 3.00 | Study popula | ation | | |
| | 90d* | (1 RCT) | LOW ^{a,b} | (0.13 to 70.30) | 0 per 1.000 | 0 fewer per 1.000 (0 fewer to 0 fewer) | | |
| | good or excellent | 50 (1 RCT) | ⊕⊕⊕⊜ MODERATE® | RR 1.04 | Study population | | | |
| | response -90d* | | | (0.91 to 1.20) | 920 per 1.000 | 37 more per 1.000 (83 fewer to 184 more) | | |
| | mean change in TSS - w3 | 24 (1 RCT) | ⊕⊕⊖⊖ LOW ^{b,c} | - | | MD 0.75 lower (5.09 lower to 3.59 higher) | | |
| | UAS7 - d90* | 50 (1 RCT) | ⊕⊕⊖ LOW ^{a, d} | - | | MD 0.5 lower (0.89 lower to 0.11 lower) | | |
| | a. concomitant treatment: levocetirizine 10mg QD (Bishnoi 2017) b. Cl crossed line of no effect and MID threshold(s): uncertain whether there is any difference c. unclear/high risk of bias d. patients not blinded | | | | | | | |

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

| o Large |
|------------|
| <u> </u> |
| o Moderate |

- o Small
- Trivial o Varies o Don't know

| | participants | evidence | Relative effect (95% CI) | Anticipated absolute effects (95% CI) | |
|--|---|--------------------|---|---------------------------------------|--|
| | | Risk with PUVA | Risk difference with NB-UVB | | |
| patients with at least | | | Study popula | ation | |
| 1 AE - w3 | (1 RCT) | LOW ^{b,c} | (0.93 to 7.69) | 250 per 1.000 | 418 more per 1.000 (17 fewer to 1.673 more) |
| withdrawal due to AE | 74 | ⊕⊕⊕○ | not pooled | Study population | |
| * | (2 RCTs) MODERATE ^a (zero in both groups) | | not pooled | not pooled | |
| relapse (back to | \cdot | Study popula | ation | | |
| baseline UAS)* (1 RCT) LOW ^a (0.1 | (0.13 to 70.30) | 0 per 1.000 | 0 fewer per 1.000 (0 fewer to 0 fewer) | | |

- a. concomitant treatment: levocetirizine 10mg QD (Bishnoi 2017)
 b. Cl crossed line of no effect and MID threshold(s): uncertain whether there is any difference
- unclear/high risk of bias
- wide CI

Values and overall certainty of the evidence

| JUDGEMENT | RESEARCH EVIDENCE | | | | |
|-----------|-------------------------------------|-----------------------|---------------------------------|--|--|
| • Low | The relative importance or values o | f the main outcomes o | of interest: | | |
| | Outcome | Relative importance | Certainty of the evidence (GRAD | | |

| Outcome | Relative importance | Certainty of the evidence (GRADE) |
|---------------------------------|---------------------|-----------------------------------|
| complete suppression – 90d | critical | ⊕⊕○○ LOW |
| good or excellent response -90d | critical | ⊕⊕⊕○ MODERATE |
| mean change in TSS –w3 | critical | ⊕⊕○○ LOW |
| UAS7- 90d | critical | ⊕⊕○○ LOW |
| Patients with at least 1 AE -w3 | critical | ⊕⊕○○ LOW |
| withdrawal due to AE - w2 | critical | ⊕⊕⊕○ MODERATE |
| relapse | important | ⊕⊕⊜○ LOW |

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT RESEARCH EVIDENCE

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

| o Favors the comparison o Probably | Outcomes | With PUVA | With NB-UVB | Difference | Relative effect |
|---|---|------------------|---|---|-------------------------------|
| favors the comparison o Does not | | FOVA | | | (95% CI) |
| favor either the intervention or the | complete suppression - 90d* | 0 per 1.000 | 0 per 1.000 (0 to 0) | 0 fewer per 1.000 (0 fewer to 0 fewer) | RR 3.00 (0.13 to 70.30) |
| comparison o Probably favors the intervention | good or excellent response -90d* | 920 per 1.000 | 957 per 1.000 (837 to 1.000) | 37 more per 1.000 (83 fewer to 184 more) | RR 1.04 (0.91 to 1.20) |
| Favors the interventionO VariesO Don't know | mean change in TSS - w3 | | The mean mean change in TSS - in the intervention group was 0,75 points lower (5,09 lower to 3,59 higher) | MD 0.75 points lower (5.09 lower to 3.59 higher) | - |
| | UAS7 - d90* | | The mean UAS7 in the intervention group was 0,5 points lower (0,89 lower to 0,11 lower) | MD 0.5 lower (0.89 lower to 0.11 lower) | - |
| | withdrawal due to AE - w3 | 0 per 1.000 | 0 per 1.000 (0 to 0) | 0 fewer per 1.000 (0 fewer to 0 fewer) | not estimable |
| | patients with at least 1 AE - w3 | 250 per 1.000 | 668 per 1.000 (233 to 1.000) | 418 more per 1.000 (17 fewer to 1.673 more) | RR 2.67 (0.93 to 7.69) |
| | withdrawal due to AE - during treatment* | not pooled | not pooled | not pooled | not pooled |
| | relapse (back to baseline UAS)* | 0 per 1.000 | 0 per 1.000 (0 to 0) | 0 fewer per 1.000 (0 fewer to 0 fewer) | RR 3.00 (0.13 to 70.30) |

Feasibility

Is the intervention feasible to implement?

| JUDGEMENT | RESEARCH EVIDENCE |
|--|---|
| o No o Probably no o Probably yes o Yes | Feasibility, costs, equity and acceptability of the intervention need to be considered in the context of the local health care systems. |
| Varies | |
| o Don't know | |

Summary:

COMPARISON: NB-UVB vs. PUVA

Data added in 2020 update from 1 new study (differences to 2016 marked in purple)

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

Efficacy

NB-UVB was superior to PUVA for the outcome: 'UAS7' (low quality).

No difference was found for the outcomes: 'complete supression' (low quality), 'good/excellent response' (moderate quality), 'mean change in TSS' (low quality) and relapse (low quality).

Safety

No difference was found for the outcomes: 'withdrawal due to adverse event' (moderate quality) and 'patients with at least one adverse event' (low quality).

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

NB-UVB versus 2nd gen H1-AH

| POPULATION: | patients with chronic spontaneous urticaria |
|---------------|--|
| INTERVENTION: | 2nd gen H1-AH + NB-UVB (2 or 3 times per week) |
| COMPARISON: | 2nd gen H1-Ah (1 or 2-fold) |
| BIBLIOGRAPHY | Sheikh 2019* |
| | Engin 2008b |
| | Zuo 2011 |
| | *- studies added in the 2020 update |
| | |

Assessment

| UDGEMENT | RESEARCH EVIDEN | RESEARCH EVIDENCE | | | | | | | |
|--|-----------------------------------|---|---------------------------------|--------------------|------------------------------------|---|--|--|--|
| o Small o Moderate o Large o Varies o Don't know | 1) UB UVB BIW + | Floratadine 19mg | g QD compared t | o loratadine | 10mg QD | | | | |
| | Outcomes | Nº of participants | Certainty of the evidence | Relative effect | Anticipated absol | ute effects* (95% CI) | | | |
| | | (studies) Follow up | (GRADE) | (95% CI) | Risk with loratadine 10mg QD | Risk difference with UB- NBV + loratadine 10mg QD | | | |
| | urticaria activity score - w 4 | 72 (1 observational study) | ⊕○○○ VERY LOW ^{a,b} | - | | MD 10.36 lower (13.57 lower to 7.15 lower) | | | |
| | urticaria activity score – w8 | 72 (1 observational study) | ⊕○○○ VERY LOW ^a | - | | MD 14.74 lower (18.65 lower to 10.83 lower) | | | |
| | b. CI crosse c. CI interva | I evaluation: critical is MID threshold: statis al crossed line of no efficiency of the control | fect and MID threshol | d: uncertain wh | ether there is any differe | | | | |
| | | participants (studies) | evidence (GRADE) | effect (95% CI) | Risk with levocetirizine | Risk difference with levocetirizine + NB-UVB | | | |
| | | Follow-up | | | | | | | |

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

| mean change in UAS7 - w7 | 78 (1 RCT) | ⊕⊕⊕⊜ MODERATE a | | | MD 4.02 lower (7.22 lower to 0.82 lower |
|-----------------------------|---------------|--------------------|--|--|--|
|-----------------------------|---------------|--------------------|--|--|--|

a. unclear/high risk of bias

3) NB UVB TIW + mizolastine 10mg QD compared to mizolastine 10mg QD

| Outcomes | Nº of | Quality of the Relative Antic | | of Quality of the Relative Anticipat | | | olute effects |
|--|--|-------------------------------|--------------------|--------------------------------------|---|--|---------------|
| | participants (studies) Follow-up | evidence (GRADE) | effect (95% CI) | Risk with minolastine alone | Risk difference with mizolastine + NB-UVB | | |
| change in mean total symptom score (MTSS) - w4 | 81 (1 RCT) | ⊕⊕⊕○ MODERATE ª | - | | MD 3.46 lower (4.14 lower to 2.78 lower) | | |
| change in mean total symptom score (MTSS) - w8 | 81 (1 RCT) | ⊕⊕⊕○ MODERATE ª | - | | MD 3.73 lower (4.23 lower to 3.23 lower) | | |

a. unclear risk of bias

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT | RESEARCH EVIDENCE

- o Largeo Moderateo Small
- TrivialVariesDon't

know

1) UB UVB BIW + loratadine 19mg QD compared to loratadine 10mg QD

| Outcomes | № of participants | Certainty of the evidence | Relative effect | Anticipated absolute effects* (95% CI) | | |
|--|----------------------------------|-------------------------------|-------------------------|--|--|--|
| | (studies) Follow up | (GRADE) | (GRADE) (95% CI) | | Risk difference with UB-NBV + loratadine 10mg QD | |
| patients with at least 1 AE | 72 (1 observational | ФООО | RR 2.84 (0.12 to 67.53) | Study population | | |
| | study) | VERY LOW ^{a,c} | | 0 per 1.000 | 0 fewer per 1.000 (0 fewer to 0 fewer) | |
| relapse (change in UAS7 4w after treatment was finished) | 72 (1 observational study) | ⊕○○○ VERY LOW ^a | - | | MD 23.84 lower (27.6 lower to 20.08 lower) | |

- a. ROBINS-I evaluation: critical
- b. CI crosses MID threshold: statistically significant of unclear clinical importance
- c. CI interval crossed line of no effect and MID threshold: uncertain whether there is any difference

2) NB UVB TIW + levocetirizine 10mg QD compared to levocetirizine 10mg QD

No evidence

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

3) NB UVB TIW + mizolastine 10mg QD compared to mizolastine 10mg QD

| Outcomes | Nº of participants | Quality of the | Relative effect (95% CI) | Anticipated absolute effects | |
|------------------------------|------------------------|--------------------|--|------------------------------|---|
| | (studies) Follow-up | (GRADE) | (33% CI) | Risk with minolastine alone | Risk difference with mizolastine + NB-UVB |
| withdrawal due to AE - w8 | 81 (1 RCT) | ⊕⊕⊕⊜ MODERATE ª | not estimable (zero events in both groups) | 0 per 1.000 | 0 fewer per 1.000 (0 fewer to 0 fewer) |

a. unclear risk of bias

Values and overall certainty of evidence

■ Very low O Low O Moderate O High O NO included studies ■ Very low O Low UAS – w4 UAS – w8

1) UB UVB BIW + loratadine 19mg QD compared to loratadine 10mg QD

| Outcome | Relative importance | Certainty of the evidence (GRADE) |
|-----------------------------|---------------------|-----------------------------------|
| UAS – w4 | critical | ⊕○○○ VERY LOW ^a |
| UAS – w8 | critical | ⊕○○○ VERY LOW ^a |
| patients with at least 1 AE | important | ⊕○○○ VERY LOW ^a |
| relapse | imporant | ⊕○○○ VERY LOW³ |

2) NB UVB TIW + levocetirizine 10mg QD compared to levocetirizine 10mg QD

| Outcome | Relative importance | Certainty of the evidence (GRADE) |
|--------------------------|---------------------|-----------------------------------|
| mean change in UAS7 w3 | critical | ⊕⊕⊕○ MODERATE |
| mean change in UAS7 - w7 | critical | ⊕⊕⊕⊜ MODERATE |

3) NB UVB TIW + mizolastine 10mg QD compared to mizolastine 10mg QD

| Outcome | Relative importance | Certainty of the evidence (GRADE) |
|--|---------------------|-----------------------------------|
| change in mean total symptom score (MTSS) -w4 | critical | ⊕⊕⊕○ MODERATE |
| change in mean total symptom score (MTSS) - w8 | critical | ⊕⊕⊕○ MODERATE |
| withdrawal due to AE - w8 | critical | ⊕⊕⊕⊜ MODERATE |

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT | RESEARCH EVIDENCE

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

o Favors the comparison o Probably favors the comparison Does not favor either intervention or the comparison o Probably favors the intervention o Favors the intervention o Varies o Don't know

Summary of finding:

1) UB UVB BIW + loratadine 19mg QD compared to loratadine 10mg QD

| Outcomes | With loratadine 10mg QD | With UB-NBV + loratadine 10mg QD | Difference | Relative effect (95% CI) |
|---|-------------------------------|--|--|--------------------------------|
| urticaria activity score – w4 | | The mean urticaria activity score in the intervention group was 10,36 points lower (13,57 lower to 7,15 lower) | MD 10.36 lower (13.57 lower to 7.15 lower) | - |
| urticaria activity score – w8 | | The mean urticaria activity score in the intervention group was 14,74 points lower (18,65 lower to 10,83 lower) | MD 14.74 lower (18.65 lower to 10.83 lower) | - |
| patients with at least 1 AE | 0 per 1.000 | 0 per 1.000 (0 to 0) | 0 fewer per 1.000 (0 fewer to 0 fewer) | RR 2.84 (0.12 to 67.53) |
| relapse (change in UAS7 4w after treatment was finished) | | The mean change in UAS7 4w after treatment relapse) in the intervention group was 23,84 points lower (27,6 lower to 20,08 lower) | MD 23.84 lower (27.6 lower to 20.08 lower) | - |

2) NB UVB TIW + levocetirizine 10mg QD compared to levocetirizine 10mg QD

| Outcome | With levocetirizine | With levocetirizine + NB-UVB | Difference (95% CI) | Relative effect (RR) (95% CI) |
|-----------------------------|---------------------|--|--|----------------------------------|
| mean change in UAS7 - w3 | | The mean change in UAS7 in the intervention group was 4,68 points lower (7,22 lower to 2,14 lower) | MD 4.49 lower (8.03 lower to 2.95 lower) | - |
| mean change in UAS7 - w7 | | The mean change in UAS7 in the intervention group was 4,02 points lower (7,22 lower to 0,82 lower) | MD 4.02 lower (7.22 lower to 0.82 lower) | - |

3) NB UVB TIW + mizolastine 10mg QD compared to mizolastine 10mg QD

| Outcome | With minolastine alone | With mizolastine + NB-UVB | Difference (95% CI) | Relative effect (RR) (95% CI) |
|--|------------------------------|--|---|----------------------------------|
| change in mean total symptom score (MTSS) - w4 | | The change in mean total symptom score (MTSS) in the intervention group was 3,46 points lower (4,13 lower to 2,79 lower) | MD 3.46 lower (4.14 lower to 2.78 lower) | - |

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

| change in mean total symptom score (MTSS) - w8 | The change in mean total symptom score (MTSS) in the intervention group was 3,73 points lower (4,22 lower to 3,24 lower) | MD 3.73 lower (4.23 lower to 3.23 lower) | - |
|--|--|---|----------|
| withdrawal due to 0 per 1.000 | 0 per 1.000 | | not |
| AE - w8 | (0 to 0) | | estimabl |

| | Feasibility s the intervention feasible to implement? | | | | |
|---|---|--|--|--|--|
| JUDGEMENT | RESEARCH EVIDENCE | | | | |
| o No o Probably no o Probably yes o Yes ● Varies o Don't know | Feasibility, costs, equity and acceptability of the intervention need to be considered in the context of the local health care systems. | | | | |

Summary

(Differences to 2016 marked in purple)

1) COMPARISON: NB-UVB BIW + LORATADINE 10MG QD vs. LORATADINE 10MG QD Data added in 2020 update from 1 new study

Efficacy

Safety

2) COMPARISON: NB-UVB TIW + LEVOCETIRIZINE 10MG (2-FOLD) QD vs. LEVOCETIRIZINE 10MG (2-FOLD) QD

No new data added in 2020

NB-UVB TIW + levocetirizine 10mg (2-fold) QD was superior to levocetirizine 10mg (2-fold) for the outcome: 'mean change in USS7' (moderate quality, but of uncertain clinical importance).

No further evidence could be identified.

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

Autologeous whole blood injections versus placebo

| Should AWB | Should AWB injection vs. placebo be used for urticaria - KQ19* update 2020? | | |
|---------------|---|--|--|
| POPULATION: | patients with CSU | | |
| INTERVENTION: | AWB injection | | |
| COMPARISON: | placebo | | |
| BIBLIOGRAPHY | Staubach 2006, Adolnezhadaian 2016* | | |
| | *- studies added in 2020 update | | |

Assessment

| UDGEMENT | RESEARCH EVIDENCE | | | | | | |
|--|---|--------------------|----------------------------|---------------------------|---|--|--|
| Trivial Small Moderate Large Varies Don't know | Outcomes | Nº of | Certainty of the | Relative | Anticipated a | ubsolute effects* (95% | |
| | participants evidence (studies) (GRADE) | effect (95% CI) | CI) | | | | |
| | | Follow up | | | Risk with placebo | Risk difference with AWB injection | |
| | clear* | 51 (1 RCT) | ⊕⊕⊜⊝ LOW ^{a,b} | not estimable | e Study population | | |
| | | | (zero in both groups) | 0 per 1,000 | 0 fewer per 1,000 (0 fewer to 0 fewer) | | |
| | good or excellent response-w9* | 51 (1 RCT) | ⊕⊕⊜⊝ LOWa,b | RR 3.89 (0.22 to | Study popula | population | |
| | | | | 68.11) | 0 per 1,000 | 0 fewer per 1,000 (0 fewer to 0 fewer) | |
| | good or excellent response - w12 | 56 (1 RCT) | ⊕⊕⊕⊖ MODERATE° | RR 0.64 (0.33 to 1.24) | Study popula | itudy population | |
| | | | | | 500 per 1,000 | 180 fewer per 1,000 (335 fewer to 120 more) | |
| | TSS - w9* | 50 (1 RCT) | ⊕⊕⊜⊖ LoW ^{a,b} | - | | MD 0.73 lower (2.62 lower to 1.16 higher) | |

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

- unclear risk of bias
- b.
- H1-AH non-responders
 CI crossed line of no effect and MID threshold(s): uncertain whether there is any difference

Undesirable Effects

How substantial are the undesirable anticipated effects?

| JUDGEMENT | RESEARCH EVIDENCE |
|--|-------------------|
| o Large o Moderate o Small o Trivial o Varies • Don't know | no evidence |

Values and overall certainty of evidence

| JUDGEMENT | RESEARCH EVIDENCE ADDITIONAL CONSIDERATIONS | | | | |
|--|---|------------|---------------------|-----------------------------------|--|
| o Very low • Low o Moderate o High o No included studies | The relative importance or values of the main outcomes of interest: | | | | |
| | Outo | ome | Relative importance | Certainty of the evidence (GRADE) | |
| | Clear | | critical | ⊕⊕○○ LOW | |
| | good or excellent resp | onse - w19 | critical | ⊕⊕⊜⊜ LOW | |
| | good or excellent resp | onse - w12 | critical | ⊕⊕⊕○ MODERATE | |
| | TSS – w9 | | critical | ⊕⊕○○ LOW | |
| | | | | | |

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

| JUDGEMENT | RESEARCH EVIDENCE | | | | |
|--|-----------------------------------|-----------------|--------------------------------|--|--------------------------------|
| o Favors the comparison | Summary of findings: | | | | |
| o Probably favors the comparison o Does not favor either | Outcomes | With placebo | With AWB injection | Difference | Relative effect (95% CI) |
| the intervention or the comparison o Probably | clear* | 0 per 1,000 | 0 per 1,000 (0 to 0) | 0 fewer per 1,000 (0 fewer to 0 fewer) | not estimable |
| favors the intervention o Favors the intervention o Varies | good or excellent response-w9* | 0 per 1,000 | 0 per 1,000 (0 to 0) | 0 fewer per 1,000 (0 fewer to 0 fewer) | RR 3.89 (0.22 to 68.11) |

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

| ● Don't know | good or excellent response - w12 | 500 per 1,000 | 320 per 1,000 (165 to 620) | 180 fewer per 1,000 (335 fewer to 120 more) | RR 0.64 (0.33 to 1.24) |
|--------------|-------------------------------------|------------------|---|--|------------------------------|
| | TSS - w9* | | The mean TSS - w9* in the intervention group was MD 0.73 lower (2.62 lower to 1.16 higher) | MD 0.73 lower (2.62 lower to 1.16 higher) | - |
| Feasibility | y ion feasible to implement? | | | | |

Feasibility, costs, equity and acceptability of the intervention need to be considered in

Summary

Data added in 2020 update from 1 new study (differences to 2016 marked in purple)

the context of the local health care systems.

Efficacy

o No

o Probably no

o Probably yeso Yes• Varieso Don't know

No difference was found for the outcome: 'clear' (low quality), 'good or excellent response' (low/moderate quality) or 'total symptom score' (low quality).

No further evidence could be identified.

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

Hydroxychloroquine versus placebo

Should hydroxychloroquine + H1-AH vs. placebo + H1-AH be used for chronic urticaria - KQ19?

POPULATION: patients with CSU unresponsive to H1-AH

INTERVENTION: hydroxychloroquine + H1-AH

COMPARISON: placebo + H1-AH

BIBLIOGRAPHY Boonpiyathad 2017*

*additional data added in 2020 update/ outcome with new data added 2020

Assessment

| JUDGEMENT | RESEARCH EVIDEN | NCE | | | | |
|---|--|---------------------|---------------------------|--------------------|--|--|
| TrivialSmall | | | | | | |
| o Moderate o Large | Outcomes | Nº of participants | Certainty of the evidence | Relative effect | Anticipated absolu | te effects* (95% CI) |
| o Varies o Don't know | (studies) (GRADE) Follow up | | (GRADE) | (95% CI) | Risk with placebo + H1-AH | Risk difference with hydroxychloroquine + H1-AH |
| | mean change in USS - w12* | 39 (1 RCT) | ⊕⊖⊖⊖ VERY LOW³,c | - | The mean mean change in USS - w12* was 0 | MD 24.57 lower (33.85 lower to 15.29 lower) |
| | mean change in DLQI - w12* | 39 (1 RCT) | ⊕⊖⊖⊖ VERY LOW³,c | - | The mean mean change in DLQI - w12* was 0 | MD 5.83 lower (9.31 lower to 2.35 lower) |
| | a. high risk of bias b. CI crosses MID threshold and line of no effect: uncertain whether there is any difference c. reporting of errors bars unclear (assumption made that these are SDs) | | | | | |
| | | g or cirors bars an | | | | |
| | | | offects? | | | |
| How substant | c. reporting | ble anticipated e | ffects? | | | |
| UDGEMENT Large Moderate | c. reporting the control of the cont | ble anticipated e | Certainty of the evidence | Relative effect | Anticipated abso | olute effects* (95% CI) |
| | c. reporting the control of the cont | ble anticipated e | Certainty of the | | Anticipated absorbed Risk with placebo + H1-AH | Plute effects* (95% CI) Risk difference with hydroxychloroquine + H1-AH |

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

| patients with at least 1 AE* 55 VERY LOW ^{a,b} | RR 1.61 (0.42 to 6.08) | 111 per 1.000 | 68 more per 1.000 (64 fewer to 564 more) |
|---|------------------------------|---------------|---|
|---|------------------------------|---------------|---|

- a. high risk of bias
- b. CI crosses MID threshold and line of no effect: uncertain whether there is any difference
- c. reporting of errors bars unclear (assumption made that these are SDs)

Values and overall certainty of evidence

JUDGEMENT RESEARCH EVIDENCE The relative importance or values of the main outcomes of interest: Very low o Low Certainty of the evidence o Moderate Outcomes Importance (GRADE) o High o No USS critical ⊕○○○ VERY LOW included studies DLQI critical ⊕○○○ VERY LOW Patients with at least 1 AE $\bigoplus\bigcirc\bigcirc\bigcirc$ VERY LOW important

Balance of effects

JUDGEMENT RESEARCH EVIDENCE

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

| JODGEWIENT | RESEARCH EVIDENCE | | | | | | |
|---|-------------------------------|---|---|---|--------------------------------|--|--|
| o Favors the comparison | Summary of findings: | | | | | | |
| o Probably favors the comparison o Does not favor either the | Outcomes | With placebo + H1-AH | With hydroxychloroquine + H1-AH | Difference | Relative effect (95% CI) | | |
| intervention or the comparison o Probably favors the | patients with at least 1 AE* | 111 per 1.000 | 179 per 1.000 (47 to 676) | 68 more per 1.000 (64 fewer to 564 more) | RR 1.61 (0.42 to 6.08) | | |
| intervention o Favors the intervention o Varies • Don't know | mean change in USS - w12* | | The mean mean change in USS in the intervention group was 24,57 points lower (33,85 lower to 15,29 lower) | MD 24.57 lower (33.85 lower to 15.29 lower) | - | | |
| | mean change in DLQI - w12* | The mean mean change in DLQI - w12* was 0 | The mean mean change in DLQI in the intervention group was 5,83 points lower (9,31 lower to 2,35 lower) | MD 5.83 lower (9.31 lower to 2.35 lower) | - | | |

Feasibility

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

| Is the interver | s the intervention feasible to implement? | | | | |
|---|---|--|--|--|--|
| JUDGEMENT | RESEARCH EVIDENCE | | | | |
| o No o Probably no o Probably yes o Yes • Varies o Don't know | Feasibility, costs, equity and acceptability of the intervention need to be considered in the context of the local health care systems. | | | | |

Summary:

COMPARISON: HYDROXYCHLOROQUINE AS ADD-ON TO H1-AH vs. PLACEBO + H1-AH

Data added in 2020 update from 1 new study (an extension of study included in 2016)

Efficacy

Hydroxychloroquine as add-on to H1-AH was superior to placebo + H1-AH for the outcome: 'mean change in USS' (very low quality).

No difference was found for: 'mean change in DLQI' (very low quality).

Safety

No difference was found for: 'patients with at least one AE' (very low quality).

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

Methotrexate versus placebo

Should MTX + H1-AH vs. placebo + H1-AH be used for chronic urticaria - KQ19? POPULATION: patients with CSU unresponsive to standard or two-fold H1-AH INTERVENTION: MTX + H1-AH COMPARISON: placebo + H1-AH BIBLIOGRAPHY Leducq 2019* *additional data added in 2020 update/ outcome with new data added 2020

| JUDGEMENT | RESEARCH EVIDEN | NCE | | | | |
|---|------------------------------|--|---|--------------------------------|--|--|
| • Trivial o Small o Moderate o Large o Varies | Outcomes | № of participants (studies) Follow up | Certainty of the evidence (GRADE) | Relative effect (95% CI) | Median change from baseline (IQR) with MTX+H1-AH | Median change from baseline (IQR) with H1-AH |
| o Don't know | median change in DLQI w8* | 72 (1 RCT) | ⊕○○○ VERY LOW ^{a,c} | - | 8.5 (4.8, 12.3) | 5.7 (2.9, 11.9) |
| | al are the undesirate | | fects? | | | |
| o Large o Moderate o Small | No data availabl | e | | | | |
| o Trivial o Varies ● Don't know | | | | | | |

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

| • Very low • Low | The relative imp | ortance or val | ues of the main ou | itcomes of i | interest: | | |
|--|--|---|---|--------------------------------|---|---------|--|
| o Moderate o High | | Outcomes | | In | nportance | Cert | ainty of the evidence (GRADE) |
| o No included | DLQI | | | | critical \oplus | | OO VERY LOW |
| studies | | | | ' | | | ' |
| | of effects nce between desirab | e between desirable and undesirable effects favor the intervention or the comparison? | | | | | |
| JUDGEMENT | RESEARCH EVIDEN | ICE | | | | | |
| o Favors the comparison | Summary of finding | igs: | | | | | |
| o Probably favors the comparison o Does not favor either | Outcomes | № of participants (studies) Follow up | Certainty of the evidence (GRADE) | Relative effect (95% CI) | Median change fro baseline (IQR) with MTX+H1-AH | | Median change from baseline (IQR) with H1-AH |
| the intervention or the comparison o Probably | median change in DLQI w8* | 72 (1 RCT) | VERY LOW ^{a,c} | - | 8.5 (4.8, 12.3) | | 5.7 (2.9, 11.9) |
| favors the intervention o Favors the intervention o Varies • Don't know | | | | | | | |
| Feasibilit | | 1 | | | | | |
| JUDGEMENT | tion feasible to implement? RESEARCH EVIDENCE | | | | | | |
| o No o Probably no o Probably yes o Yes • Varies o Don't know | Feasibility, co | sts, equity a | nd acceptabilit | - | ntervention nee | ed to k | pe considered in |

Summary:

COMPARISON: METHOTREXATE AS ADD-ON TO H1-AH vs. PLACEBO + H1-AH

Data added in 2020 update from 1 new study (differences to 2016 marked in purple)

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

Efficacy

No difference was found for the outcome: 'median change in DLQI' (very low quality).

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

Dapsone

| POPULATION: | patients with chronic spontanious urticaria |
|---------------|---|
| INTERVENTION: | dapsone 100mg QD + existing therapy |
| COMPARISON: | placebo QD + existing therapy |
| BIBLIOGRAPHY | Morgan 2014 Engine 2008a |

| IUDGEMENT | RESEARCH EVIDENCE | | | | | | | |
|-------------------------------------|--|---|---------------------------------|--|---|--|--|--|
| o Trivial o Small | 1) Dapsone 100mg QD + existing therapy vs existing therapy alone | | | | | | | |
| oModerate | Outcomes | Nº of | Quality of the | Relative | Anticipated absolute effects | | | |
| o Large o Varies ● Don't know | | participants (studies) Follow-up | evidence (GRADE) | effect (95% CI) | Risk with placebo QD + existing therapy | Risk difference with dapsone 100mg QD + existing therapy | | |
| | complete suppression - w6 | 22 (1 RCT) | ⊕⊕⊖⊖ LOW ^{a,b} | RR 8.27 (0.48 to 143.35) | 0 per 1.000 | 0 fewer per 1.000 (0 fewer to 0 fewer) | | |
| | | le CI | | old(s): uncerta | in whether there is any c | | | |
| | b. wid | + dapsone cor | mpared to deslo | old(s): uncertai | Anticipated abso | olute effects Risk difference with | | |
| | b. wid | + dapsone cor Nº of participants | Quality of the evidence | ratadine Relative effect | Anticipated abso | olute effects | | |
| | b. wid | + dapsone cor No of participants (studies) | Quality of the evidence | ratadine Relative effect | Anticipated abso | olute effects Risk difference with | | |
| | b. wic 2) Desloratadine Outcomes complete | + dapsone con Nº of participants (studies) Follow-up 65 | Quality of the evidence (GRADE) | ratadine Relative effect (95% CI) RR 6.46 (0.36 to | Anticipated absorbed Risk with desloratadine | Risk difference with desloratadine + dapsone | | |

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

o Trivial o Small

1) Dapsone 100mg QD + existing therapy vs existing therapy alone

oModerate
o Large
o Varies

• Don't know

| Outcomes | Nº of | Quality of the | Relative | Anticipated absolut | te effects |
|-------------------------------------|--|---------------------|------------------------------|---|--|
| | participants (studies) Follow-up | evidence (GRADE) | effect (95% CI) | Risk with placebo QD + existing therapy | Risk difference with dapsone 100mg QD + existing therapy |
| withdrawal due to AE - w6 | 22 (1 RCT) | ⊕⊕⊕⊕ ніGн | not estimable | 0 per 1.000 | 0 fewer per 1.000 (0 fewer to 0 fewer) |
| patients with at least 1 AE - w6 | 21 (1 RCT) | ⊕⊕⊕○ MODERATE ª | RR 1.47 (0.43 to 5.01) | 273 per 1.000 | 128 more per 1.000 (155 fewer to 1.094 more) |

- a. CI crossed line of no effect and MID threshold(s): uncertain whether there is any difference
- b. wide C

2) Desloratadine + dapsone compared to desloratadine

| Outcomes | № of participants (studies) Follow-up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolu Risk with desloratadine | Risk difference with desloratadine + dapsone |
|------------------------------|--|---------------------------------------|--------------------------------|--|--|
| withdrawal due to AE - w4 | 65 (1 RCT) | ⊕○○○ VERY LOW ^{1,2,3} | RR 3.59 (0.18 to 71.91) | 0 per 1.000 | 0 fewer per 1.000 (0 fewer to 0 fewer) |

- a. unclear/high risk of bias
- b. wide CI
- c. CI crossed line of no effect and MID threshold(s): uncertain whether there is any difference

Values and overall certainty of the evidence

| UDGEMENT | RESEARCH EVIDENCE | | | | | |
|----------|---|----------------------|-----------------------------------|--|--|--|
| Low/Very | The relative importance or values of the main outcomes of interest: | | | | | |
| | 1) Dapsone 100mg QD + existing therapy vs existing therapy alone | | | | | |
| | Outcome | Relative importance | Certainty of the evidence (GRADE) | | | |
| | complete suppression – w6 | critical | ⊕⊕○○ LOW | | | |
| | withdrawal due to AE - w6 | critical | ⊕⊕⊕ нібн | | | |
| | patients with at least 1 AE – w6 | important | ⊕⊕⊕○ MODERATE | | | |
| | 2) Desloratadine + dapsone compa | red to desloratadine | | | | |
| | Outcome | Relative importance | Certainty of the evidence (GRADE) | | | |

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

| mean change in UAS7 w4 | critical | ⊕⊕⊕○ MODERATE |
|-------------------------|----------|------------------|
| withdrawal due to AE w4 | critical | ⊕○○○ VERY LOW |

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

| o Favors the |
|----------------------------|
| comparison |
| o Probably |
| favors the |
| comparison |
| Does not |

favor either

JUDGEMENT

RESEARCH EVIDENCE Summary of findings:

- 1) Dapsone 100mg QD + existing therapy vs existing therapy alone
- the intervention or the comparison o Probably favors the intervention o Favors the intervention o Varies

o Don't know

| Outcome | With placebo QD + existing therapy | With dapsone 100mg QD + existing therapy | Difference (95% CI) | Relative effect (RR) |
|------------------------------------|------------------------------------|--|--|-----------------------------|
| complete suppression - w6 | 0 per 1.000 | 0 per 1.000 (0 to 0) | 0 fewer per 1.000 (from 0 fewer to 0 fewer) | RR 8.27 (0.48 to 143.35) |
| withdrawal due to AE -w6 | 0 per 1.000 | 0 per 1.000 (0 to 0) | | not estimable |
| patients with at least 1 AE -w6 | 273 per 1.000 | 401 per 1.000 (117 to 1.000) | 128 more per 1.000 (from 155 fewer to 1.000 more) | RR 1.47 (0.43 to 5.01) |

2) Desloratadine + dapsone compared to desloratadine

| Outcome | With desloratadine | With desloratadine + dapsone | Difference (95% CI) | Relative effect (RR) (95% CI) |
|------------------------------|--------------------|--|--|----------------------------------|
| complete suppression - w4 | 0 per 1.000 | 0 per 1.000 (0 to 0) | 0 fewer per 1.000 (from 0 fewer to 0 fewer) | RR 6.46 (0.36 to 115.24) |
| mean change in UAS7 - w4 | | The mean change in UAS7 in the intervention group was 1,23 points lower (1,54 lower to 0,92 lower) | MD 1.23 lower (1.54 lower to 0.92 lower) | - |
| withdrawal due to AE - w4 | 0 per 1.000 | 0 per 1.000 (0 to 0) | 0 fewer per 1.000 (from 0 fewer to 0 fewer) | RR 3.59 (0.18 to 71.91) |

Feasibility

Is the intervention feasible to implement?

| JUDGEMENT | RESEARCH EVIDENCE |
|--|---|
| o No o Probably no o Probably yes o Yes | Feasibility, costs, equity and acceptability of the intervention need to be considered in the context of the local health care systems. |
| Varieso Don't know | |

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

Summary:

1) Dapsone 100mg Qd + existing therapy vs existing therapy alone

No difference was found for 'complete suppression' (low quality), 'withdrawal due to AE' (high quality) and 'patients with at least one AE' (moderate quality).

2) Desloratadine + dapsone compared to desloratadine

Desloratadine plus daspone was superior to desloratadine alone based on 'mean change in UAS7' (moderate quality, but of uncertain clinical importance). No difference was found for 'complete suppression' (very low quality) and 'withdrawal due to AE' (very low quality).

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

Motelukast versus montelukast + desloratadine

| POPULATION: | patients with chronic spontanious urticaria |
|---------------|---|
| INTERVENTION: | Montelukast (+ placebo) |
| COMPARISON: | Montelukast + desloratadine, |
| BIBLIOGRAPHY | DiLorenzo 2004 |
| | |

| JUDGEMENT | RESEARCH EVIDENCE | | | | | | | | |
|--|--|--|---------------------------------------|--------------------------------|---|---|--|--|--|
| • Trivial • Small | Montelukast (+pla | Montelukast (+placebo) vs. montelukast + desloratadine | | | | | | | |
| oModerate o Large o Varies o Don't know | Outcomes | № of participants (studies) Follow-up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated ab Risk with montelukast 10mg QD + desloratadine 5mg QD | Risk difference with montelukast 10mg QD + placebo | | | |
| | mean difference (mean change in TSS) | 80 (1 RCT) | ⊕⊕⊕○ MODERATE ^a | - | 0 | MD 1.14 points higher (1.03 higher to 1.26 higher) | | | |
| | ble Effects al are the undesirable | anticipated effe | cts? | | | | | | |
| | | anticipated effe | cts? | | | | | | |
| How substantia | RESEARCH EVIDENC | E | | oratadine | | | | | |
| How substantia JUDGEMENT o Trivial | al are the undesirable | E | | oratadine | | | | | |
| JUDGEMENT O Trivial O Small OModerate O Large O Varies | RESEARCH EVIDENC | E | | oratadine | | | | | |
| JUDGEMENT O Trivial O Small OModerate O Large | RESEARCH EVIDENC Montelukast (+pl | E | | oratadine | | | | | |
| JUDGEMENT O Trivial O Small OModerate O Large O Varies Don't know | RESEARCH EVIDENC Montelukast (+pl | E acebo) vs. mo | ntelukast + desl | | | | | | |
| JUDGEMENT o Trivial o Small oModerate o Large o Varies o Don't know | RESEARCH EVIDENCE Montelukast (+pl No data available | acebo) vs. mo | ntelukast + desl | | | | | | |
| JUDGEMENT O Trivial O Small OModerate O Large O Varies Don't know | RESEARCH EVIDENCE Montelukast (+pl No data available nd overall cer | acebo) vs. mo | ntelukast + desl | ce | of interest: | | | | |

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

| | | Outcome | Relative importance | Certaint | ty of the evidenc | e (GRADE) | |
|--|---|---|--|------------|---|-------------------------------------|--|
| | mean difference (m | ean change in TSS) | critical | ⊕⊕⊕○ M | ODERATE | | |
| Balance o | | and undesirable effects favo | or the intervention or the cor | nparison? | | | |
| JUDGEMENT | RESEARCH EVIDENCE | | | | | | |
| o Favors the comparison o Probably favors the comparison | Summary of findings: Montelukast (+placebo) vs. montelukast + desloratadine | | | | | | |
| o Does not favor either the intervention | Outcome | With desloratadine 5mg QD + montelukast 10mg QD | With placebo + monteluka | st 10mg QD | Difference (95% CI) | Relative effect (RR) (95% CI) | |
| or the comparison o Probably favors the intervention | mean difference (mean change in TSS) | | The(mean change in TS intervention group was 1, higher (1,03 higher to 1,2 | 14 points | MD 1.14 points higher (1.03 higher to 1.26 higher) | - | |
| o Favors the intervention o Varies Don't know | | | | | | | |
| Feasibility Is the interventi | / on feasible to implem | ent? | | | | | |
| JUDGEMENT | RESEARCH EVIDENCE | | | | | | |
| o No o Probably no o Probably yes o Yes ■ Varies o Don't know | Feasibility, costs, equity and acceptability of the intervention need to be considered in the context of the local health care systems. | | | | | | |

Summary:

Montelukast (+placebo) vs. montelukast + desloratadine

Montelukast was inferior to montelukast plus desloratedine based on 'mean difference/mean change in total symptom score' (moderate quality). No further evidence could be identified.

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

PART II: CINDU

Symptomatic dermographism (3 comparisons in total)

1) BETAMETHASONE 2MG + CETIRIZINE HCl 10MG QD vs. CETIRIZINE HCl 10MG QD (No new data added in 2020)

| POPULATION: | patients with symptomatic dermographism |
|------------------|--|
| INTERVENTION(S): | betamethasone 2mg + cetirizine HCl 10mg QD |
| COMPARISON: | cetirizine HCl 10mg QD |
| BIBLIOGRAPHY | Kumar 2002 |

| EMENT | RESEARCH EVIDENCE | | | | | | |
|---|--------------------------|------------------------|---------------------------------|-------------------------|--|---|--|
| rial nall | Outcomes | № of participants | Certainty of the evidence | Relative effect | Anticipated absolute effects* (95% CI) | | |
| Moderate .arge /aries Don't know | | (studies) Follow up | (GRADE) | (95% CI) | Risk with betamethasone 2mg + cetirizine HCl 10mg QD | Risk difference with cetirizine HCI 10mg | |
| | complete remission w4 | 16 (1 RCT) | ⊕○○○ VERY LOW ^{a,b} | RR 1.44 (0.88 to | Study population | | |
| | | | | 2.35) | 667 per 1,000 | 293 more per 1,000 (80 fewer to 900 more) | |
| | ≥90% relief w4 | 16 (1 RCT) | ⊕○○○ VERY LOW ^{a,b} | RR 1.25 (0.84 to | Study population | | |
| | | | | 1.86) | 778 per 1,000 | 194 more per 1,000 (124 fewer to 669 more) | |

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

| IUDGEMENT | RESEARCH EVIDE | NCE | | | | | |
|--|--------------------------------|--|---------------------------|----------------------|--|------------------|--|
| o Large o Moderate | Outcomes | Nº of participants | Certainty of the evidence | Relative effect | Anticipated absolute effects* (95% CI) | | |
| o Small ● Trivial o Varies o Don't know | | (studies) Follow up | (GRADE) | (95% CI) | Risk with betamethasone 2mg + cetirizine HCl 10mg QD | | Risk difference wit cetirizine HCl 10mg QD |
| | withdrawal due to AE w4 | 16 (1 RCT) | DOM ₃ | not estimable | Study popul | lation | ' |
| | | | | | 0 per 1,000 | | 0 fewer per 1,000 (0 fewer to 0 fewer |
| | a. CCT | | | | | | |
| | a. CCT nd overall ce | | f the evide | nce | | | |
| UDGEMENT • Very low | nd overall co | ENCE | f the evide | | s of interest: | | |
| UDGEMENT • Very low • Low • Moderate • High | nd overall co | ENCE | | | | Certainty of | f the evidence RADE) |
| UDGEMENT • Very low • Low • Moderate | RESEARCH EVIDE | ENCE | alues of the ma | in outcomes | nce | Certainty of (GF | |
| Very low Down Moderate High No included | RESEARCH EVIDE | ence oportance or va Outcomes | alues of the ma | in outcomes | ı | Certainty of (GF | RADE) |
| Very low Low Moderate High No included | RESEARCH EVIDE The relative im | ence operance or va Outcomes nplete remission | alues of the ma | in outcomes Importar | nce I | Certainty of (GF | VERY LOW ^{a,b} |

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

| o Favors the comparison o Probably favors the comparison | Outcomes | With betamethasone 2mg + cetirizine HCI 10mg QD | With cetirizine HCl 10mg QD | Difference | Relative effect (95% CI) |
|--|-------------------------|---|-------------------------------------|--|--------------------------------|
| • Does not favor either the intervention or the comparison | complete remission w4 | 667 per 1,000 | 960 per 1,000 (587 to 1,000) | 293 more per 1,000 (80 fewer to 900 more) | RR 1.44 (0.88 to 2.35) |
| o Probably favors the intervention o Favors the intervention | ≥90% relief w4 | 778 per 1,000 | 972 per 1,000 (653 to 1,000) | 194 more per 1,000 (124 fewer to 669 more) | RR 1.25 (0.84 to 1.86) |
| o Varies o Don't know | withdrawal due to AE w4 | 0 per 1,000 | 0 per 1,000 (0 to 0) | 0 fewer per 1,000 (0 fewer to 0 fewer) | not estimable |

Feasibility

Is the intervention feasible to implement?

| JUDGEMENT | RESEARCH EVIDENCE |
|--|---|
| o No o Probably no o Probably yes o Yes | Feasibility, costs, equity and acceptability of the intervention need to be considered in the context of the local health care systems. |
| VariesDon't know | |

Summary:

1) COMPARISON: BETAMETHASONE 2MG + CETIRIZINE HCI 10MG QD vs. CETIRIZINE HCI 10MG QD FOR DERMOGRAPHISM

No new data added in 2020

Efficacy

No difference was found for the outcomes: 'complete remission' (very low quality) and '>=90% relief' (very low quality).

Safety

No difference was found for the outcome: 'withdrawal due to adverse event' (low quality).

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

2) COMPARISON: omalizumab 300MG vs. placebo

3) COMPARISON: omalizumab 150mg vs. placebo

POPULATION: patients with symptomatic dermographism

INTERVENTION(S): 2) omalizumab 300mg every 4w, 3) omalizumab 150mg every 4w

COMPARISON: placebo

BIBLIOGRAPHY Maurer 2017*

*New study in 2020 update

| Desirable How substantial | Effects are the desirable anticipated effects? |
|----------------------------------|--|
| JUDGEMENT | RESEARCH EVIDENCE |

|) malizumab | 2) omalizumab 300mg 6 | 2) omalizumab 300mg every 4w compared to placebo | | | | | | | | | |
|--|---|--|---------------------------------|-------------------------|--|--|--|--|--|--|--|
| 300mg every 4w vs. placebo ⊙ Trivial ● Small | Outcomes | № of participants | Certainty of the evidence | Relative effect | Anticipated absolute effects* (95% CI) | | | | | | |
| | | (studies) Follow up | (GRADE) | (95% CI) | Risk with placebo | Risk difference with omalizumab 300mg every 4w | | | | | |
| Moderate Large Varies | complete response w10 | 42 (1 RCT) | ФФОО | RR 5.00 (1.24 to | Study popu | Study population | | | | | |
| Don't know | | , | LOW ^{a,b} | 20.12) | 95 per 1,000 | 381 more per 1,000 (23 more to 1,821 more) | | | | | |
| | change in trigger threshold from baseline w10 | 42 (1 RCT) | ⊕○○○ VERY LOW ^{b,d} | - | | MD 1.4 lower (2.38 lower to 0.42 lower) | | | | | |
| | DLQI w10 | 38 (1 RCT) | ⊕○○○ VERY LOW ^{c,d} | - | | MD 3.25 lower (6.73 lower to 0.23 higher | | | | | |
| | a. Several risk-of-bias items unclear b. CI crosses MID threshold: statistically significant difference of uncertain clinical importance c. CI crossed line of no effect and MID threshold(s): uncertain whether there is any difference d. High risk of bias due to incomplete outcome data | | | | | | | | | | |
| nalizumab | | | | | | | | | | | |

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

150mg every 4w vs. placebo

- o Trivial
- Small o Moderate
- o Large o Varies o Don't know

3) omalizumab 150mg every 4w compared to placebo

| Outcomes | Nº of participants | Certainty of the evidence | Relative effect | Anticipated absolute effects* (95% CI) | | |
|---|------------------------|---------------------------------|-------------------------|--|--|--|
| | (studies) Follow up | (GRADE) | (95% CI) | Risk with placebo | Risk difference with omalizumab 150mg every 4w | |
| complete response w10 | 40 (1 RCT) | @ | RR 4.42 (1.07 to | Study population | | |
| | | LOW ^{a,b} | 18.29) | 95 per 1,000 | 326 more per 1,000 (7 more to 1,647 more) | |
| change in trigger threshold from baseline w10 | 40 (1 RCT) | ⊕○○○ VERY LOW ^{b,d} | - | | MD 1.2 lower (2.17 lower to 0.23 lower) | |
| DLQI w10 | 37 (1 RCT) | ⊕⊕⊖⊖ LOW,d | - | | MD 4.27 lower (8.16 lower to 0.38 lower) | |

- Several risk-of-bias items unclear
- b. CI crosses MID threshold: statistically significant difference of uncertain clinical importance
- CI crossed line of no effect and MID threshold(s): uncertain whether there is any difference
- d. High risk of bias due to incomplete outcome data

Undesirable Effects

How substantial are the undesirable anticipated effects? RESEARCH EVIDENCE

| 2) |
|-------------|
| omalizumab |
| 300mg every |
| 4w vs. |
| placebo |

JUDGEMENT

- o Large o Moderate o Small
- Trivial o Varies o Don't know

2) omalizumab 300mg every 4w compared to placebo

| | № of participants | Certainty of the evidence | Relative effect | Anticipated absolute effects* (95% CI) | | |
|------------------------------------|------------------------|---|--|--|--|--|
| Outcomes | (studies) Follow up | (GRADE) | (95% CI) | Risk with placebo | Risk difference with omalizumab 300mg every 4w | |
| withdrawal due to AE w10 | 42 (1 RCT) | ӨӨӨ | not estimable | Study popula | tion | |
| | | MODERATE ^a (zero in both groups) | 1 ' | 0 per 1,000 | 0 fewer per 1,000 (0 fewer to 0 fewer) | |
| patients with at least 1 AE w10 | 42 (1 RCT) | ФФОО | RR 0.89 (0.70 to 1.15) | Study popula | ation | |
| | LOW ^{a,b} | 905 per 1,000 | 100 fewer per 1,000 (271 fewer to 136 more) | | | |

Several risk-of-bias items unclear

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

 \bigoplus \bigcirc \bigcirc \bigcirc VERY LOW

 $\oplus \oplus \oplus \bigcirc$ moderate

Centre for Guideline Development

| 3) omalizumab 150mg every | 3) omalizumab 150mg every 4w compared to placebo | | | | | | | | |
|---|--|---|---------------------------|---------------------------|-------------------|--|--|--|--|
| 4w vs. | Outcomes | Nº of participants | Certainty of the evidence | Relative effect | Anticipated | absolute effects* (95% CI) | | | |
| o Large o Moderate o Small | | 100000000000000000000000000000000000000 | | (95% CI) | Risk with placebo | Risk difference with omalizumab 150mg every 4w | | | |
| TrivialVariesDon't know | withdrawal due to AE w10 | 40 (1 RCT) | ⊕⊕⊕○ | not estimable | Study popula | ation | | | |
| o Don e know | | , | MODERATE ^a | (zero in both groups) | 0 per 1,000 | 0 fewer per 1,000 (0 fewer to 0 fewer) | | | |
| | patients with at least 1 AE w10 | • | ()() | RR 0.99 (0.80 to 1.22) | Study population | | | | |
| | | | | | 905 per 1,000 | 9 fewer per 1,000 (181 fewer to 199 more) | | | |
| | b. CI crossed I | | MID threshold(s): unc | ertain whether ther | e is any differen | ce | | | |
| Values an | d overall cert | ainty of th | e evidence | | | | | | |
| UDGEMENT | RESEARCH EVIDENCE | Ē | | | | | | | |
| 2) & 3) omalizumab 300mg or 150mg every | The relative impor 2) omalizumab 300 | | | | est: | | | | |
| olacebo Very low | | Outcome | 5 | Impo | rtance | Certainty of the evidence (GRADE) | | | |
| ● Low ○ Moderate ○ High | | complete respon | se w10 | crit | tical | ⊕⊕○○ LOW | | | |
| O No included studies | change in t | rigger threshold | from baseline w10 | crit | tical | ⊕○○○ VERY LOW | | | |
| | | DLQI w10 | <u> </u> | crit | tical | • | | | |

CI crossed line of no effect and MID threshold(s): uncertain whether there is any difference

critical

withdrawal due to AE w10

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

| | patients with at least 1 AE w10 | | AE w10 | important | ФФОО і | .OW | |
|---|--|-----------------|-----------------------------|---|--|--------------------------------|--|
| | 3) omalizumab 150mg eve | ry 4w con | npared to placebo | 1 | | | |
| | 0 | | Importance | Certainty of the evidence (GRADE) | | | |
| | complete response w10 | | | critical | |) | |
| | change in trigger threshold from baseline w10 DLQI w10 withdrawal due to AE w10 patients with at least 1 AE w10 | | | critical | ⊕○○○ VERY LOW | | |
| | | | | critical | ⊕⊕⊕ MODERATE | | |
| | | | | critical | | | |
| | | | | important | ⊕⊕○○ LOW | | |
| Balance o | f effects te between desirable and undes | irable effec | ts favor the intervention (| or the comparison? | | | |
| JUDGEMENT | RESEARCH EVIDENCE | | | | | | |
| 2) omalizumab | 2) omalizumab 300mg eve | ry 4w con | npared to placebo | | | | |
| 300mg every 4w vs. placebo o Favors the | Outcomes | With placebo | With omalizumab 3 | 300mg every 4w | Difference | Relative effect (95% CI) | |
| comparison O Probably favors the comparison O Does not favor either | complete response - w10 | 95 per 1,000 | 476 per (118 to 1 | 381 more per 1,000 (23 more to 1,821 more) | RR 5.00 (1.24 to 20.12) | | |
| the intervention or the comparison o Probably favors the | change in trigger threshold from baseline - w10 baseline - w10 baseline - w10 1.4 points lower (2.3 bly) | | | ervention group was | MD 1.4 lower (2.38 lower to 0.42 lower) | - | |
| intervention o Favors the intervention | | | | | | | |

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

| o Varies ● Don't know | DLQI - w10 | | The mean DLQI - w10 in the intervention group was 3.25 points lower (18.42 lower to 11.92 higher) | MD 3.25 lower (18.42 lower to 11.92 higher) | - |
|------------------------|--------------------------------------|------------------|---|--|------------------------------|
| | withdrawal due to AE - w10 | 0 per 1,000 | 0 per 1,000 (0 to 0) | 0 fewer per 1,000 (0 fewer to 0 fewer) | not estimable |
| | patients with at least 1 AE - w10 | 905 per 1,000 | 805 per 1,000 (633 to 1,000) | 100 fewer per 1,000 (271 fewer to 136 more) | RR 0.89 (0.70 to 1.15) |

3) omalizumab 150mg every 4w compared to placebo

| 150mg every 4w vs. placebo |
|----------------------------------|
| o Favors the |
| comparison |
| o Probably |
| favors the |
| comparison |
| o Does not |
| favor either |
| the |
| intervention |
| or the |
| comparison |
| Probably |
| favors the |

3) omalizumab

• Don't know

intervention o Favors the intervention o Varies

| Outcomes | With placebo | With omalizumab 150mg every 4w | Difference | Relative effect (95% CI) |
|--|------------------|--|--|--------------------------------|
| complete response w10 | 95 per 1,000 | 421 per 1,000 (102 to 1,000) | 326 more per 1,000 (7 more to 1,647 more) | RR 4.42 (1.07 to 18.29) |
| change in trigger threshold from baseline w10 | | The mean change in trigger threshold from baseline w10 in the intervention group was 1.2 points lower (2.17 lower to 0.23 lower) | MD 1.2 lower (2.17 lower to 0.23 lower) | - |
| DLQI w10 | | The mean DLQI w10 in the intervention group was 4.27 points lower (20.86 lower to 12.32 higher) | MD 4.27 lower (20.86 lower to 12.32 higher) | - |
| withdrawal due to AE w10 | 0 per 1,000 | 0 per 1,000 (0 to 0) | 0 fewer per 1,000 (0 fewer to 0 fewer) | not estimable |
| patients with at least 1 AE w10 | 905 per 1,000 | 896 per 1,000 (724 to 1,000) | 9 fewer per 1,000 (181 fewer to 199 more) | RR 0.99 (0.80 to 1.22) |

Feasibility

Is the intervention feasible to implement?

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

| JUDGEMENT | RESEARCH EVIDENCE |
|--|---|
| 2) & 3) omalizumab 300mg or 150mg every 4w vs. | 2) & 3) omalizumab 300mg or 150mg every 4w vs. placebo Feasibility, costs, equity and acceptability of the intervention need to be considered in the context of the local health care systems. |
| placebo | |
| o No o Probably no o Probably yes o Yes | |
| VariesDon't know | |

Summary:

(Differences to 2016 marked in purple.)

2) COMPARISON: OMALIZUMAB 300MG EVERY 4 WEEKS vs. PLACEBO FOR DERMOGRAPHISM

Data added in 2020 update from 1 new study

Efficacy

Omalizumab 300mg every 4 weeks was superior to placebo for the outcomes: 'complete response' (low quality) and 'change in trigger threshhold from baseline' (very low quality).

No difference was found for the outcome: 'DLQI' (very low quality).

Safety

No difference was found for the outcome: 'withdrawal due to adverse event' (moderate quality) and 'patients with at least one adverse event' (low quality).

3) COMPARISON: OMALIZUMAB 150MG EVERY 4 WEEKS vs. PLACEBO FOR DERMOGRAPHISM

Data added in 2020 update from 1 new study

Efficacy

Omalizumab 150mg every 4 weeks was superior to placebo for the outcomes: 'complete response' (low quality) and 'change in trigger threshhold from baseline' (very low quality).

No difference was found for the outcome: 'DLQI' (very low quality).

Safety

No difference was found for the outcomes: 'withdrawal due to adverse event' (moderate quality) and 'patients with at least one adverse event' (low quality).

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

Cold urticaria (8 comparisons in total)

1) Comparison: 2nd gen H1-AH: high dose vs. low dose (No new data added in 2020)

Are 2nd gen H1-AH (high dose) more effective and safer than 2nd gen H1-AH (low dose) in patients with cold urticaria?

POPULATION: patients with cold urticaria

COMPARISON: 2nd gen H1-AH (low dose)

2nd gen H1-AH (high dose)

Krause 2013, Magerl 2012, Kaplan2010/Siebenhaar 2009, Abajian 2016

Assessment

INTERVENTION:

| DGEMENT | RESEARCH EVIDENCE | | | | | | | | | |
|--|---|--|---------------------|-------------------------------|--|--|--|--|--|--|
| Trivial | 2nd gen AH 2-fold compared to 2nd gen AH 1-2-fold for cold urticaria | | | | | | | | | |
| Small Moderate | Outcomes | Nº of | Quality of the | e Relative | Anticipated absolute | e effects | | | | |
| o Large o Varies o Don't know | | participants (studies) Follow-up | evidence (GRADE) | effect (95% CI) | Risk with 2nd gen AH (different dosage) | Risk difference with 2nd gen AH | | | | |
| | symptom free - 2nd gen Al 2-fold vs. 1-fold (1w) | H 40 (1 RCT) | LOW a,b | RR 1.57 (0.77 to 3.22) | 350 per 1.000 | 200 more per 1.000 (80 fewer to 777 more) | | | | |
| | symptom free - 2nd gen Al 1 to 2-fold increase vs. 1- fold (4w) | H 27 (1 RCT) | ⊕⊕⊖⊖ LOW b,c | RR 4.06 (0.21 to 77.37) | 0 per 1.000 | 0 fewer per 1.00 (0 fewer to 0 fewer) | | | | |
| | 2nd gen AH 4-fold comp | ared to 2nd ge | n AH 1-fold for | cold urticari | ia Anticipated absolute e | ffects | | | | |
| | | participants (studies) Follow-up | evidence (GRADE) | effect (95% CI) | Risk with 2nd gen AH (different dosage) | Risk difference with 2nd gen AH | | | | |
| | symptom free - 2nd gen AH 4-fold vs. 1-fold (1w) | 100 (2 RCTs) | ⊕⊕○○ LOW a,c | RR 1.90 (1.15 to 3.16) | 280 per 1.000 | 252 more per 1.000 (42 more to 605 more) | | | | |

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

| Outcomes | № of participants (studies) Follow-up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute e Risk with 2nd gen AH (different dosage) | Risk difference with 2nd gen AH |
|---|--|---------------------------------------|--------------------------------|--|--|
| symptom free - 2nd gen AH 4-fold vs. 2-fold (1w) | 85 (2 RCTs) | ⊕⊕⊖⊖ LOW a,c | RR 1.16 (0.77 to 1.76) | 465 per 1.000 | 74 more per 1.000 (107 fewer to 353 more) |

- a. unclear risk of bias
- b. CI crossed line of no effect and MID threshold(s): uncertain whether there is any difference
- c. wide C
- d. CI crosses MID threshold: statistically significant difference of uncertain clinical importance

Undesirable Effects

How substantial are the undesirable anticipated effects?

| JUDGEMENT | RESEARCH EVIDENCE | | | | | | | | |
|--|---|--|---------------------|------------------------------|---|---|--|--|--|
| o Large o Moderate | 2nd gen AH 2-fold compa | 2nd gen AH 2-fold compared to 2nd gen AH 1-2-fold for cold urticaria | | | | | | | |
| • Small | Outcomes | Nº of | Quality of the | Relative | Anticipated absolute effects | | | | |
| o Trivial o Varies o Don't know | | participants (studies) Follow-up | evidence (GRADE) | effect (95% CI) | Risk with 2nd gen AH (different dosage) | Risk difference with 2nd gen AH | | | |
| | patients with at least 1 AE - 2nd gen AH 2-fold vs. 1-fold (w1) | 40 (1 RCT) | LOM a'p | RR 1.40 (0.53 to 3.68) | 250 per 1.000 | 100 more per 1.000 (118 fewer to 670 more) | | | |

2nd gen AH 4-fold compared to 2nd gen AH 1-fold for cold urticaria

| Outcomes | № of participants (studies) Follow-up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute Risk with 2nd gen AH (different dosage) | effects Risk difference with 2nd gen AH |
|---|--|---------------------------------------|--------------------------------|--|---|
| patients with at least 1 AE - 2nd gen AH 4-fold vs. 1-fold (1w) | 40 (1 RCT) | LOM a'p | RR 0.80 (0.25 to 2.55) | 250 per 1.000 | 50 fewer per 1.000 (188 fewer to 387 more) |

2nd gen AH 4-fold compared to 2nd gen AH 2-fold for cold urticaria

| Outcomes | № of participants (studies) Follow-up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute Risk with 2nd gen AH (different dosage) | Risk difference with 2nd gen AH |
|--|--|---------------------------------------|--------------------------------|--|---|
| withdrawal due to AE - 2nd gen AH 1 to 4-fold increase vs. 2-fold (6w) | 28 (1 RCT) | ⊕⊕⊕⊕ нібн | not estimable | 0 per 1.000 | 0 fewer per 1.000 (0 fewer to 0 fewer) |

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

| patients with at least 1 AE - 2nd gen AH 4-fold vs. 2-fold | 86 (2 RCTs) | ⊕⊕⊜⊝ LOW a,b | RR 1.02 (0.38 to | 326 per 1.000 | 7 more per 1.000 (202 fewer to |
|---|----------------|-----------------|-------------------------|---------------|---------------------------------------|
| (1w) | | | 2.73) | | 563 more) |

- a. unclear risk of bias
- b. CI crossed line of no effect and MID threshold(s): uncertain whether there is any difference
- c. wide C
- d. CI crosses MID threshold: statistically significant difference of uncertain clinical importance

Values and overall certainty of evidence

JUDGEMENT RESEARCH EVIDENCE

o Very low

The relative importance or values of the main outcomes of interest:

LowModerateHighNoincluded

studies

| Relative importance | Certainty of the evidence (GRADE) |
|------------------------|---|
| critical | ⊕⊕○○ LOW |
| critical | ⊕⊕⊕⊕ ніGн |
| important | ⊕⊕⊜⊜ LOW |
| important | ⊕⊕○○ LOW |
| important | ⊕⊕○○ LOW |
| | importance critical critical critical critical critical important |

Balance of effects

JUDGEMENT | RESEARCH EVIDENCE

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

| o Favors the comparison | Summary of findings: | | | | |
|---|--|------------------------------------|---|---|---------------------------------|
| o Probably favors the comparison | Outcome | With 2nd gen AH (different dosage) | With 2nd gen AH | Difference (95% CI) | Relative effect (RR (95% CI) |
| o Does not favor either the intervention | symptom free - 2nd gen AH 2-fold vs. 1-fold (1w) | 350 per 1.000 | 550 per 1.000 (269 to 1.000) | 200 more per 1.000 (from 80 fewer to 777 more) | RR 1.57 (0.77 to 3.22) |
| or the comparison o Probably favors the | symptom free - 2nd gen AH 1 to 2-fold increase vs. 1-fold (4w) | 0 per 1.000 | 0 per 1.000 (0 to 0) | 0 fewer per 1.000 (from 0 fewer to 0 fewer) | RR 4.06 (0.21 to 77.37) |
| intervention O Favors the intervention O Varies | symptom free - 2nd gen AH 4-fold vs. 1-fold (1w) | 280 per 1.000 | 532 per 1.000 (322 to 885) | 252 more per 1.000 (from 42 more to 605 more) | RR 1.90 (1.15 to 3.16) |

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

| know | symptom free - 2nd gen AH 4-fold vs. 2-fold (1w) | 465 per 1.000 | 540 per 1.000 (358 to 819) | 74 more per 1.000 (from 107 fewer to 353 more) | RR 1.16 (0.77 to 1.76) |
|------|---|---------------|---|--|-------------------------------|
| | withdrawal due to AE - 2nd gen AH 1 to 4-fold increase vs. 2-fold (6w) | 0 per 1.000 | 0 per 1.000 (0 to 0) | | not estimable |
| | patients with at least 1 AE - 2nd gen AH 2-fold vs. 1-fold (w1) | 250 per 1.000 | 350 per 1.000 (133 to 920) | 100 more per 1.000 (from 118 fewer to 670 more) | RR 1.40 (0.53 to 3.68) |
| | patients with at least 1 AE - 2nd gen AH 4-fold vs. 1-fold (1w) | 250 per 1.000 | 200 per 1.000 (63 to 638) | 50 fewer per 1.000 (from 188 fewer to 387 more) | RR 0.80 (0.25 to 2.55) |
| | patients with at least 1 AE - 2nd gen AH 4-fold vs. 2-fold (1w) | 326 per 1.000 | 332 per 1.000 (124 to 889) | 7 more per 1.000 (from 202 fewer to 563 more) | RR 1.02 (0.38 to 2.73) |

Feasibility

Is the intervention feasible to implement?

| is the interven | ition feasible to implement? |
|--|---|
| JUDGEMENT | RESEARCH EVIDENCE |
| o No o Probably no o Probably yes o Yes | Feasibility, costs, equity and acceptability of the intervention need to be considered in the context of the local health care systems. |
| ● Varies o Don't know | |

Summary:

1) COMPARISON: 2ND GENERATION H1-AH (HIGH DOSE) vs. 2ND GENERATION H1-AH (LOW DOSE) FOR COLD URTICARIA

No new data added in 2020

Efficacy

2nd generation H1-AH (high dose) was superior to 2nd generation H1-AH (low dose) for the outcome: 'symptom free' (low quality).

Safety

No difference was found for the outcomes: 'patients with at least one adverse event' (low quality) and (for 4-fold vs. 2-fold only) 'withdrawal due to adverse event' (high).

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

2) COMPARISON: 2ND GENERATION H1-AH vs. 1ST GENERATION H1-AH

(No new data added in 2020)

Are 2nd gen H1-AH more effective and safer than 1st gen H1-AH in patients with cold urticaria?

POPULATION: patients with cold urticaria

INTERVENTION: 2nd gen H1-AH

COMPARISON: 1st gen H1-AH

BIBLIOGRAPHY Villas Martinez 1992

| JUDGEMENT | RESEARCH EVIDE | NCE | | | | | | |
|--|--|--------------------------------------|---------------|-----------------------------|------------------------------|-----------|-----------------------------|---|
| o Trivial ● Small o Moderate o Large o Varies o Don't know | 2nd gen AH compared to 1st gen AH for cold urticaria | | | | | | | |
| | Outcomes | Nº of | Qua | ity of the | Relative | Anti | cipated absolu | te effects |
| | | participar (studies) Follow-up | (GR | ence ADE) | effect (95% CI) | Risk | | Risk difference with 2nd |
| | symptom free (2w) | 20 (1 RCT) | | OO 'LOW ^{a,b,c} | RR 0.86 (0.30 to 2.49) | 667 | • | 93 fewer per 1.000 467 fewer to 993 more) |
| | | | | | | | ences ere is any differe | nce |
| | c. CI cro | ossed line of CI | no effect and | | | | | nce |
| | c. Cl cro d. wide | ossed line of CI ble anticipat | no effect and | | | | | nce |
| How substant UUDGEMENT D Large | c. Cl cro d. wide | ossed line of CI ble anticipat | no effect and | vID threshold(s |): uncertain wh | | | nce |
| How substant JUDGEMENT D Large Moderate D Small | c. Cl cro d. wide | ossed line of CI ble anticipat | no effect and | vID threshold(s | nria | | ere is any differe | absolute effects |
| How substant UDGEMENT D Large Moderate | c. Cl cro d. wide | ossed line of CI ble anticipat | ted effects? | or cold urtica | aria of the Relieffe | ether the | ere is any differe | absolute effects |

The International EAACI/GA2LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

| drowsiness (time unclear) 19 (1 RCT) WERY LOW a,c,d | RR 0.32 (0.06 to 1.80) | 600 per 1.000 | 408 fewer per 1.000 (564 fewer to 480 more) |
|---|-------------------------------|------------------|--|
|---|-------------------------------|------------------|--|

- unclear risk of bias
- statistical heterogeneity ($I^2 = 40\%$) maybe due to methodological differences
- CI crossed line of no effect and MID threshold(s): uncertain whether there is any difference

Values and overall certainty of evidence

JUDGEMENT | RESEARCH EVIDENCE

The relative importance or values of the main outcomes of interest:

| • very low |
|------------|
| o Low |
| o Moderate |
| o High |
| o No |
| included |
| studies |
| |

| Outcome | Relative importance | Certainty of the evidence (GRADE) |
|--|---------------------|-----------------------------------|
| symptom free (2w) | critical | ⊕○○○ VERY LOW |
| patients with at least one AE (time unclear) | important | ⊕○○○ VERY LOW |
| drowsiness (time unclear) | important | ⊕○○○ VERY LOW |

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

| HIDGEMENT | D |
|-----------|---|

JUDGEMENT | RESEARCH EVIDENCE

o Favors the com o Pr

know

Summary of findings:

| comparison | | | | | |
|--|--|--------------------|---|---|----------------------------------|
| o Probably favors the | Outcome | With 1st gen AH | With 2nd gen AH | Difference (95% CI) | Relative effect (RR) (95% CI) |
| comparison o Does not favor either the intervention | symptom free (2w) | 667 per 1.000 | 573 per 1.000 (200 to 1.000) | 93 fewer per 1.000 (from 467 fewer to 993 more) | RR 0.86 (0.30 to 2.49) |
| or the comparison o Probably | patients with at least one AE (time unclear) | 600 per 1.000 | 222 per 1.000 (60 to 834) | 378 fewer per 1.000 (from 234 more to 540 fewer) | RR 0.37 (0.10 to 1.39) |
| favors the intervention o Favors the intervention o Varies | drowsiness (time unclear) | 600 per 1.000 | 192 per 1.000 (36 to 1.000) | 408 fewer per 1.000 (from 480 more to 564 fewer) | RR 0.32 (0.06 to 1.80) |
| ● Don't | | | | | |

Feasibility

Is the intervention feasible to implement?

JUDGEMENT

RESEARCH EVIDENCE

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

| O No O Probably no O Probably yes O Yes | Feasibility, costs, equity and acceptability of the intervention need to be considered in the context of the local health care systems. |
|---|---|
| Varies | |
| o Don't | |
| know | |
| | |
| KIIOW | |

Summary:

2) COMPARISON: 2ND GENERATION H1-AH vs. 1ST GENERATION H1-AH FOR COLD URTICARIA

No new data added in 2020

Efficacy

No difference was found for the outcome: 'symptom free' (very low quality).

Safety

No difference was found for the outcomes: 'patients with at least one adverse event' (very low quality) and 'drowsiness' (very low quality).

3) COMPARISON: 2ND GENERATION H1-AH 1-4 FOLD vs. PLACEBO

(No new data added in 2020)

| Are 2nd gen H1-AH more effective and safer than 1st gen H1-AH in patients with cold urticaria? | | | | | |
|--|--|--|--|--|--|
| POPULATION: | patients with cold urticaria | | | | |
| INTERVENTION: | 2nd gen H1-AH 1-4 fold | | | | |
| COMPARISON: | placebo | | | | |
| BIBLIOGRAPHY | Krause 2013, Dubertret 2003, Kaplan2010/Siebenhaar 2009, Metz 2010, Abajian 2016 | | | | |

| Desirable How substanti | e Effects al are the desirable anticipated effects? |
|--------------------------------|---|
| JUDGEMENT | RESEARCH EVIDENCE |

The International EAACI/GA2LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

| | | | placebo | |
|--------------------|--------------------|--------------------------------|---|---|
| ee 268 (4 RCTs) | ⊕⊕⊕○ MODERATE ª | RR 4.33 (2.11 to 8.85) | 61 per 1.000 | 202 more per 1.000 (67 more to 476 more) |
| | | (4 RCTs) MODERATE ^a | (4 RCTs) MODERATE ^a (2.11 to 8.85) | (4 RCTs) MODERATE ^a (2.11 to 8.85) 1.000 |

Undesirable Effects

How substantial are the undesirable anticipated effects?

| JUDGEMENT | RESEARCH EVIDEN | CE | | | | |
|--|----------------------------|-------------------------------------|-------------------------------|------------------------------|---------------------|--|
| o Large o Moderate | Outcomes | Nº of | Quality of the | Relative effect | Anticipated ab | solute effects |
| SmallTrivialVaries | | (studies) Follow-up | (GRADE) | (95% CI) | Risk with placebo | Risk difference with 2nd gen H1-AH 1-4 fold |
| o Don't know | withdrawal due to AE | 96 (2 RCTs) | ⊕⊕⊕⊜ MODERATE ^a | not pooled | not pooled | not pooled |
| | patients with at least 1AE | 199 (3 RCTs) | LOW a,b | RR 1.63 (0.92 to 2.89) | 162 per 1.000 | 102 more per 1.000 (13 fewer to 306 more) |
| | | risk of bias ed line of no effec | ct and MID threshold | (s): uncertain wh | nether there is any | difference |

Values and overall certainty of evidence

JUDGEMENT RESEARCH EVIDENCE o Very low The relative importance or values of the main outcomes of interest: o Low Moderate Outcome **Relative importance** Certainty of the evidence (GRADE) o High $\oplus \oplus \oplus \bigcirc \mathsf{MODERATE}$ symptom free critical o No included withdrawal due to AE critical $\oplus \oplus \oplus \bigcirc$ MODERATE studies $\oplus\oplus\bigcirc\bigcirc$ LOW patients with at least 1AE important

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

| JUDGEMENT RES | SEARCH EVIDENCE |
|---------------|-----------------|
|---------------|-----------------|

CI crossed line of no effect and MID threshold(s): uncertain whether there is any difference

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

| o Favors the comparison | Summary of findings: | | | | |
|---|--|------------------|-----------------------------------|---|----------------------------------|
| o Probably favors the | Outcome | With placebo | With 2nd gen AH (1-4 fold) | Difference (95% CI) | Relative effect (RR) (95% CI) |
| comparison o Does not favor either the | symptom free | 61 per 1.000 | 262 per 1.000 (128 to 536) | 202 more per 1.000 (from 67 more to 476 more) | RR 4.33 (2.11 to 8.85) |
| intervention or the comparison | withdrawal due to AE | 0 per 1.000 | 0 per 1.000 (0 to 0) | | not pooled |
| Probably favors the intervention | patients with at least 1AE | 162 per 1.000 | 264 per 1.000 (149 to 468) | 102 more per 1.000 (from 13 fewer to 306 more) | RR 1.63 (0.92 to 2.89) |
| o Favors the intervention o Varies o Don't know | | | | | |
| Feasibilits the interver | ty ntion feasible to implement | :? | | | |
| JUDGEMENT | RESEARCH EVIDENCE | | | | |
| ○ No ○ Probably no | Feasibility, costs, e | | · · | intervention need to | be considered in |

Summary:

3) COMPARISON: 2ND GENERATION H1-AH 1-4 FOLD vs. PLACEBO FOR COLD URTICARIA No new data added in 2020

Efficacy

o Don't know

2nd generation H1-AH 1-4 fold were superior to placebo based on the outcome: 'symptom free' (moderate quality).

Safety

No difference was found for the outcomes: 'patients with at least one adverse event' (low quality) and 'withdrawal due to adverse event' (moderate quality).

4) COMPARISON: DOXEPINE vs. PLACEBO

(No new data added in 2020)

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

| Is doxepine mo | s doxepine more effective and safer than placebo in patients with cold urticaria? | | | | | |
|----------------|---|--|--|--|--|--|
| POPULATION: | patients with cold urticaria | | | | | |
| INTERVENTION: | doxepine | | | | | |
| COMPARISON: | placebo | | | | | |
| BIBLIOGRAPHY | Neittaanmäki 1984, Neittaanmäki 1984 | | | | | |

| | e Effects ial are the desirable | e anticipated effe | octs? | | | | | | | |
|---|---|--|--|---------------------------------|------------------------------|---|--|--|--|--|
| JUDGEMENT | RESEARCH EVIDENCE | | | | | | | | | |
| o Trivial o Small | Doxepine compared to placebo for cold urticaria | | | | | | | | | |
| Moderate | Outcomes | Nº of | Quality of the | Relative | Anticipated absolute effects | | | | | |
| LargeVariesDon'tknow | | participants (studies) Follow-up | evidence (GRADE) | effect (95% CI) | Risk with placebo | Risk difference with doxepine | | | | |
| | very effective- 1w | 44 (2 RCTs) | ⊕⊕⊜⊖ LOW a,b | RR 14.90 (2.13 to 104.08) | 0 per 1.000 | 0 fewer per 1.000 (0 fewer to 0 fewer) | | | | |
| | a. unclea b. wide 0 | r risk of bias | | | | | | | | |
| | able Effects ial are the undesira | | ffects? | | | | | | | |
| o Large o Moderate o Small o Trivial o Varies • Don't know | No evidence | | | | | | | | | |
| Values a | nd overall o | ertainty o | f evidence | | | | | | | |
| values a | | | | | JUDGEMENT RESEARCH EVIDENCE | | | | | |
| JUDGEMENT | RESEARCH EVIDE | NCE | | | | | | | | |
| JUDGEMENT O Very low | | _ | ues of the main out | comes of inter | est: | | | | | |
| JUDGEMENT | | portance or va | ues of the main out Relative importan | | | e evidence (GRADE) | | | | |

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

| JUDGEMENT | RESEARCH EVIDENCE | | | | | | | | |
|---|---|--------------|-----------------------------|--|-------------------------------|--|--|--|--|
| o Favors the | Summary of findings: | | | | | | | | |
| comparison O Probably | Outcome | With placebo | With doxepine | Difference (95% CI) | Relative effect (RR) (95% CI) | | | | |
| avors the comparison of Does not favor either the intervention or the comparison of Probably favors the intervention of Favors the intervention of Varies Don't know | very effective-1w | 0 per 1.000 | 0 per 1.000 (0 to 0) | 0 fewer per 1.000 (from 0 fewer to 0 fewer) | RR 14.90 (2.13 to 104.08) | | | | |
| Feasibilist the interver | ty tion feasible to implem | ent? | | | | | | | |
| o No o Probably no o Probably yes o Yes ■ Varies o Don't | Feasibility, costs the context of th | | | of the intervention ned | ed to be considered in | | | | |

Summary:

4) COMPARISON: DOXEPINE vs. PLACEBO FOR COLD URTICARIA

No new data added in 2020

Efficacy

Doxepine was superior to placebo based on the outcome: 'very effective' (low quality).

<u>Safety</u>

No safety data were available.

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

5) COMPARISON: HYDROXYZINE vs. DOXEPINE

(No new data added in 2020)

| Is hydroxyzin | Is hydroxyzine more effective and safer than doxepine in patients with cold urticaria? | | | | | |
|---------------|--|--|--|--|--|--|
| POPULATION: | patients with cold urticaria | | | | | |
| INTERVENTION: | hydroxyzine | | | | | |
| COMPARISON: | doxepine | | | | | |
| BIBLIOGRAPHY | Neittaanmäki 1984 | | | | | |

| | e Effects ial are the desira | able anticipated e | ffects? | | | | | | |
|--|---|--|------------------------|------------------------------|------------------------------|--|--|--|--|
| JUDGEMENT | RESEARCH EV | | | | | | | | |
| o Trivial o Small | Hydroxyzine compared to doxepine for cold urticaria | | | | | | | | |
| o Moderate o Large o Varies • Don't know | Outcomes | Nº of | Quality of the | Relative | Anticipated absolute effects | | | | |
| | | participants (studies) Follow-up | evidence (GRADE) | effect (95% CI) | Risk with doxepine | Risk difference with hydroxyzine | | | |
| | very effective | 24 (1 RCT) | ⊕○○○ VERY LOW a,b,c | RR 0.33 (0.08 to 1.33) | 500 per 1.000 | 335 fewer per 1.000 (460 fewer to 165 more) | | | |
| | c. Cl | crossed line of no | effect and MID thresho | ld(s): uncertain w | hether there is any di | fference | | | |
| | able Effect | | | ld(s): uncertain w | hether there is any di | fference | | | |
| | able Effect | ts sirable anticipated | | ld(s): uncertain w | hether there is any di | fference | | | |
| JUDGEMENT O Large O Moderate O Small O Trivial | able Effect | ts sirable anticipated IDENCE | | ld(s): uncertain w | hether there is any di | fference | | | |
| How substanti | able Effectial are the undes | ts sirable anticipated IDENCE | | ld(s): uncertain w | hether there is any di | fference | | | |
| JUDGEMENT O Large O Moderate O Small O Trivial O Varies Don't know | RESEARCH EVI | ts sirable anticipated IDENCE CE | | ld(s): uncertain w | rhether there is any di | fference | | | |

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

| Moderate | Outcom | e l | Relative importance | Certainty of the | e evidence (GRADE) | |
|---|---|---------------|----------------------------------|---|------------------------------|--|
| High No ncluded tudies | very effect | ive | critical | ⊕○○○ VERY LOW | | |
| | of effects nce between desira | | ble effects favor the | intervention or the comparison? | | |
| Favors the comparison | Summary of | findings: | | | | |
| o Probably | Outcome | With doxepine | With hydroxyzine | Difference (95% CI) | Relative effect (RR) (95% CI | |
| favors the comparison O Does not | very effective | 500 per 1.000 | 165 per 1.000 (40 to 665) | 335 fewer per 1.000 (from 165 more to 460 fewer) | RR 0.33 | |
| o Probably favors the intervention o Favors the intervention o Varies O Don't know | | | | | | |
| Feasibili s the interver | | plement? | | | | |
| | RESEARCH EVIDE | NCE | | | | |
| JUDGEMENT | RESEARCH EVIDENCE Feasibility, costs, equity and acceptability of the intervention need to be considered in the context of the local health care systems. | | | | | |

Summary:

5) COMPARISON: HYDROXYZINE vs. DOXEPINE FOR COLD URTICARIA

No new data added in 2020

Efficacy

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

No difference was found for the outcome: 'very effective' (very low quality).

Safety

No safety data were available.

6) COMPARISON: HYDROXYZINE vs. PLACEBO

(No new data added in 2020)

| Is hydroxyzine more effective and safer than placebo in patients with cold urticaria? | | | | | |
|---|------------------------------|--|--|--|--|
| POPULATION: | patients with cold urticaria | | | | |
| INTERVENTION: | hydroxyzine | | | | |
| COMPARISON: | placebo | | | | |
| BIBLIOGRAPHY | Neittaanmäki 1984 | | | | |

| JUDGEMENT | RESEARCH EVIDENCE | | | | | |
|----------------------|---|--|-----------------------------------|--------------------------------|------------------------------|---|
| o Trivial o Small | Hydroxyzine | compared to p | lacebo for cold urti | caria | | |
| o Moderate | Outcomes | Nº of Quality of the participants evidence (studies) (GRADE) Follow-up | Quality of the | Relative | Anticipated absolute effects | |
| | | | | effect (95% CI) | Risk with placebo | Risk difference with hydroxyzine |
| | very effective | 24 (1 RCT) | ⊕○○○ VERY LOW ^{a,b,c} | RR 5.00 (0.27 to 94.34) | 0 per 1.000 | O fewer per 1.000 (0 fewer to 0 fewer) |
| | a. unclear risk of bias b. CI crossed line of no effect and MID threshold(s): uncertain whether there is any difference c. wide CI able Effects ial are the undesirable anticipated effects? | | | | | |
| | RESEARCH EVIDENCE | | | | | |
| JUDGEMENT | | | | | | |

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

| • Don't know | | | | | | | |
|---|---|------------------|---------------------------------------|---------------------------------------|----------------|--------------------------------|--|
| | | | | | | | |
| | nd overall coverall coverall certainty of the | | | | | | |
| JUDGEMENT | RESEARCH EVIDEN | NCE | | | | | |
| • Very low | The relative imp | oortance or val | ues of the main ou | tcomes of interes | t: | | |
| LowModerate | Outcome | | Relative importance | Ce | ertainty of tl | he evidence (GRADE) | |
| o High o No | very effective | ve | critical | ⊕○○○ VE | ERY LOW | | |
| included studies | | | | | | | |
| | of effects nce between desiral | ble and undesira | ble effects favor the in | ntervention or the co | omparison? | | |
| JUDGEMENT | RESEARCH EVIDEN | NCE | | | | | |
| o Favors the comparison | Summary of findings: | | | | | | |
| o Probably favors the | Outcome | With placebo | With hydroxyzine | Difference (95 | 5% CI) | Relative effect (RR) (95% CI) | |
| comparison o Does not | very effective | 0 per 1.000 | 0 per 1.000 (0 to 0) | 0 fewer per 1 (from 0 fewer to | | RR 5.00 (0.27 to 94.34) | |
| favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention o Varies Don't know | | | | | | | |
| Feasibility Is the interver | ty ntion feasible to imp | lement? | | | | | |
| JUDGEMENT | RESEARCH EVIDEN | NCE | | | | | |
| o No o Probably no o Probably yes o Yes • Varies | - | | and acceptability ealth care syste | | ention ne | ed to be considered in | |

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

| know | | |
|------|--|--|
| | | |
| | | |

Summary:

6) COMPARISON: HYDROXYZINE vs. PLACEBO FOR COLD URTICARIA

No new data added in 2020

Efficacy

No difference was found for the outcome: 'very effective' (very low quality).

<u>Safety</u>

No safety data were available.

7) COMPARISON: OMALIZUMAB 300mg EVERY 4 WEEKS vs. PLACEBO

8) COMPARISON: OMALIZUMAB 150mg EVERY 4 WEEKS vs. PLACEBO

| POPULATION: | patients with cold urticaria |
|------------------|--|
| INTERVENTION(S): | omalizumab 300mg every 4w, omalizumab 150mg every 4w |
| COMPARISON: | placebo |
| BIBLIOGRAPHY | Metz 2017* |
| | *New study in 2020 update |

| | Desirable Effects How substantial are the desirable anticipated effects? | | | | |
|---|---|--|--|--|--|
| JUDGEMENT | RESEARCH EVIDENCE | | | | |
| 7) omalizumab 300mg every 4w vs. placebo o Trivial o Small | 7) omalizumab 300mg every 4w compared to placebo | | | | |
| o Moderate o Large | | | | | |

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

| Varies |
|--------------------------|
| o Don't know |

omalizumab 150mg every 4w vs. placebo

o Trivialo Smallo Moderate

o Large◆ Varieso Don't know

| Outcomes | № of participants (studies) Follow up | Certainty of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects* (95% CI) | | |
|---|--|---|----------------------------------|--|--|--|
| | | | | Risk with placebo | Risk difference with omalizumab 300mg every 4w | |
| complete response w10 | 21 (1 RCT) | ⊕⊕⊕○ MODERATE ^{a,b} | RR 11.70 (0.71 to 192.98) | Study population | | |
| | | | | 0 per 1,000 | 0 fewer per 1,000 (0 fewer to 0 fewer) | |
| change in trigger threshold from baseline w10 | 21 (1 RCT) | ⊕⊕⊕⊕ нібн | - | | MD 10.1 lower (16.63 lower to 3.57 lower) | |

- a. Wide confidence interval
- b. CI crossed line of no effect and MID threshold(s): uncertain whether there is any difference

8) omalizumab 150mg every 4w compared to placebo

| Outcomes | Nº of participants | Certainty of the evidence | Relative effect | Anticipated absolute effects* (95% CI) | | |
|---|--------------------|---------------------------|--|--|---|--|
| (studies) (GRADE) (95% CI) Follow up | | Risk with placebo | Risk difference with omalizumab 150mg every 4w | | | |
| complete response w10 | 22 (1 RCT) | ⊕⊕⊕○ | RR 10.64 (0.64 to | Study population | | |
| | | MODERATE ^{a,b} | 176.54) | 0 per 1,000 | 0 fewer per 1,000 (0 fewer to 0 fewer) | |
| change in trigger threshold from baseline w10 | 22 (1 RCT) | ⊕⊕⊕⊕ нібн | - | | MD 10.3 lower (15.5 lower to 5.1 lower) | |

- a. Wide confidence interval
- b. CI crossed line of no effect and MID threshold(s): uncertain whether there is any difference

Undesirable Effects

How substantial are the undesirable anticipated effects?

| JUDGEMENT | RESEARCH EVIDENCE |
|--|--|
| 7) omalizumab 300mg every 4w vs. placebo | 7) omalizumab 300mg every 4w compared to placebo |
| o Large o Moderate o Small ● Trivial | |

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

| ries n't know | Outcomes | Nº of Certainty of the participants evidence | evidence | Relative effect | Anticipated : | absolute effects* (95% CI) | | |
|-----------------------------------|---|--|-------------------------------|--|-------------------|--|--|--|
| | | (studies) Follow up | (GRADE) | (95% CI) | Risk with placebo | Risk difference with omalizumab 300mg even | | |
| | withdrawal due to AE w10 | $\Phi \Phi \Phi \Phi$ | | not estimable | Study popula | ation | | |
| | | | | (zero in both groups) | 0 per 1,000 | 0 fewer per 1,000 (0 fewer to 0 fewer) | | |
| | patients with at least 1 AE w10 | 21 (1 RCT) | 0000 | RR 1.04 (0.64 to 1.67) | Study population | | | |
| lizumab mg every rs. ebo | | | MODERATE ^a | | 750 per 1,000 | 30 more per 1,000 (270 fewer to 502 more) | | |
| | a. CI crossed line of no effect and MID threshold(s): uncertain whether there is any difference | | | | | | | |
| te | 8) omalizumab | 150mg ever | ry 4w compare | d to placebo | | | | |
| | Outcomes | Certainty of the evidence | Relative effect | Anticipated absolute effects* (95% CI) | | | | |
| know | | (studies) Follow up | (GRADE) | (95% CI) | Risk with placebo | Risk difference with omalizumab 150mg ever | | |
| | withdrawal due to AE w10 | 22 (1 RCT) | ⊕⊕⊕⊕ нібн | not estimable | Study population | | | |
| | | | nign | (zero in both groups) | 0 per 1,000 | 0 fewer per 1,000 (0 fewer to 0 fewer) | | |
| | | | | | Study population | | | |
| | patients with at least 1 AE w10 | 22 (1 RCT) | ⊕⊕⊕○ MODERATE ^b | RR 0.93 (0.55 to 1.57) | Study popula | ation | | |

- a. Wide confidence interval
- b. CI crossed line of no effect and MID threshold(s): uncertain whether there is any difference

750 per

1,000

52 fewer per 1,000

(337 fewer to 428 more)

Values and overall certainty of the evidence

| JUDGEMENT | RESEARCH EVIDENCE |
|-------------------------|---|
| 7) & 8) omalizumab | The relative importance or values of the main outcomes of interest: |
| 300mg or 150mg every | 7) omalizumab 300mg every 4w compared to placebo |
| 4w vs. | |
| placebo | |
| | |

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

| Very low |
|----------------------------|
| o Low |
| Moderate |
| o High |
| o No included |
| studies |

| Outcomes | Importance | Certainty of the evidence (GRADE) |
|---|------------|--------------------------------------|
| complete response w10 | critical | ⊕⊕⊕○ MODERATE |
| change in trigger threshold from baseline w10 | critical | ⊕⊕⊕⊕ ніGн |
| withdrawal due to AE w10 | critical | ⊕⊕⊕⊕ ні с н |
| patients with at least 1 AE w10 | important | ⊕⊕⊕○ MODERATE |

8) omalizumab 150mg every 4w compared to placebo

| Outcomes | Importance | Certainty of the evidence (GRADE) |
|---|------------|--------------------------------------|
| complete response w10 | critical | ⊕⊕⊕○ MODERATE |
| withdrawal due to AE w10 | critical | ⊕⊕⊕⊕ ні G н |
| patients with at least 1 AE w10 | critical | ⊕⊕⊕○ MODERATE |
| change in trigger threshold from baseline w10 | important | ⊕⊕⊕⊕ ні G н |

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

| 7) omalizumab 300mg every 4w vs. placebo o Favors the comparison | 7) omalizumab 300mg every 4w compared to placebo | | | | | | | |
|---|--|----------------|--|---|----------------------------------|--|--|--|
| | Outcomes With placebo With omalizumab 300mg every 4w | | Difference | Relative effect (95% CI) | | | | |
| o Probably favors the comparison o Does not favor either the | complete response w10 | 0 per 1,000 | 0 per 1,000 (0 to 0) | 0 fewer per 1,000 (0 fewer to 0 fewer) | RR 11.70 (0.71 to 192.98) | | | |
| intervention or the comparison o Probably favors the intervention | change in trigger threshold from baseline w10 | | The mean change in trigger threshold from baseline w10 in the intervention group was 10.1 points lower (16.63 lower to 3.57 lower) | MD 10.1 lower (16.63 lower to 3.57 lower) | - | | | |
| o Favors the intervention | withdrawal due to AE w10 | 0 per 1,000 | 0 per 1,000 (0 to 0) | 0 fewer per 1,000 | not estimable | | | |

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

| Varies Don't know | | | | (0 fewer to 0 fewer) | |
|--|--|------------------|--|---|----------------------------------|
| | patients with at least 1 AE w10 | 750 per 1,000 | 780 per 1,000 (480 to 1,000) | 30 more per 1,000 (270 fewer to 502 more) | RR 1.04 (0.64 to 1.67) |
| nalizumab | 8) omalizumab 150mg eve | ery 4w con | npared to placebo | | |
| Omg every vs. cebo | Outcomes | With placebo | With omalizumab 150mg every 4w | Difference | Relative effect (95% CI) |
| comparison O Probably favors the comparison O Does not favor either the intervention or the comparison O Probably favors the intervention O Favors the intervention O Varies | complete response w10 | 0 per 1,000 | 0 per 1,000 (0 to 0) | 0 fewer per 1,000 (0 fewer to 0 fewer) | RR 10.64 (0.64 to 176.54) |
| | withdrawal due to AE w10 | 0 per 1,000 | 0 per 1,000 (0 to 0) | 0 fewer per 1,000 (0 fewer to 0 fewer) | not estimable |
| | patients with at least 1 AE w10 | 750 per 1,000 | 698 per 1,000 (413 to 1,000) | 52 fewer per 1,000 (337 fewer to 428 more) | RR 0.93 (0.55 to 1.57) |
| Oon't know | change in trigger threshold from baseline w10 | | The mean change in trigger threshold from baseline w10 in the intervention group was 10.3 points lower (15.5 lower to 5.1 lower) | MD 10.3 lower (15.5 lower to 5.1 lower) | - |

Feasibility

Is the intervention feasible to implement?

| JUDGEMENT | RESEARCH EVIDENCE |
|--|---|
| 7) & 8) omalizumab | 7) & 8) omalizumab 300mg or 150mg every 4w vs. placebo |
| 300mg or 150mg every 4w vs. placebo | Feasibility, costs, equity and acceptability of the intervention need to be considered in the context of the local health care systems. |
| o No o Probably no o Probably yes o Yes | |

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

| Varies |
|--------------------------|
| Don't know |
| |

Summary:

(Differences to 2016 marked in purple.)

7) & 8) COMPARISON: OMALIZUMAB 300mg OR 150mg EVERY 4 WEEKS vs. PLACEBO FOR COLD URTICARIA

Data added in 2020 update from 1 new study

Efficacy

Omalizumab 300mg or 150mg every 4 weeks was superior to placebo for the outcome: 'change in trigger threshhold from baseline' (high quality).

No difference was found for the outcome: 'complete response' (moderate quality).

Safety

No difference was found for the outcomes: 'withdrawal due to adverse event' (high quality) or 'patients with at least one adverse event' (moderate quality).

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

Cholinergic urticaria (1 comparison)

1) Comparison: OMALIZUMAB 300mg vs. PLACEBO

| POPULATION: | patients with cholinergic urticaria |
|------------------|-------------------------------------|
| INTERVENTION(S): | omalizumab 300mg every 4w |
| COMPARISON: | placebo |
| BIBLIOGRAPHY | Gastaminza 2019* |
| | *New study in 2020 update |

| JDGEMENT | RESEARCH EVIDENCE | RESEARCH EVIDENCE | | | | | | | |
|---|---|------------------------|----------------------------|--------------------------------|--|--|--|--|--|
| Trivial Small Moderate Large Varies Don't know | Outcomes | Nº of participants | Certainty of the evidence | Relative effect (95% CI) | Anticipated absolute effects* (95% CI) | | | | |
| | | (studies) Follow up | (GRADE) | | Risk with placebo | Risk difference with omalizumab 300mg every 4w | | | |
| | symptom free with UCOL exercise challenge | 23 (1 RCT) | ⊕⊕⊕○ MODERATE® | RR 0.38 (0.04 to 3.67) | Study population | | | | |
| | | | | | 200 per 1,000 | 124 fewer per 1,000 (192 fewer to 534 more) | | | |
| | CU2QoL | 22 (1 RCT) | ⊕⊕⊖⊖ LOW ^{a,b} | - | | MD 7 lower (19.52 lower to 5.52 higher) | | | |
| | a. CI crossed line of no effect and MID threshold(s): uncertain whether there is any difference b. Mean and SD were estimated based on median and 25th and 75th quartile values according to Wan 2014 | | | | | | | | |

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

| Trivial Small Moderate Large Varies Don't know | Outcomes | № of participants (studies) Follow up | Certainty of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects* (95% CI) | | |
|--|-----------------------------------|--|---|---|---|--|--|
| | | | | | Risk with placebo | Risk difference with omalizumab 300mg every 4w | |
| | patients with at least 1 AE | 22 (1 RCT) | ФФФ○ MODERATE ^a | RR 1.56 (0.69 to 3.52) | Study popula | tion | |
| | least I AE (I NCI) MODERATE (0.05 | | 444 per 1,000 | 249 more per 1,000 (138 fewer to 1,120 more) | | | |
| | withdrawal due to AE | 23 (1 RCT) | ⊕⊕⊕⊕ HIGH | not estimable | Study popula | tion | |
| | | | (zero in both groups) | 0 per 1,000 | 0 fewer per 1,000 (0 fewer to 0 fewer) | | |

a. CI crossed line of no effect and MID threshold(s): uncertain whether there is any difference

Values and overall certainty of the evidence

| JUDGEMENT | RESEARCH EVIDENCE | | | | | | | |
|---|---|------------|--------------------------------------|--|--|--|--|--|
| o Very low o Low | The relative importance or values of the main outcomes of interest: | | | | | | | |
| ModerateHighNo included | Outcomes | Importance | Certainty of the evidence (GRADE) | | | | | |
| studies | symptom free with UCOL exercise challenge | critical | ⊕⊕⊕○ MODERATE | | | | | |
| | CU2QoL | critical | Ф⊕○○ LOW | | | | | |
| | withdrawal due to AE | critical | ⊕⊕⊕⊕ ні с н | | | | | |
| | patients with at least 1 AE | important | ⊕⊕⊕○ MODERATE | | | | | |

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

| JUDGEMENT | RESEARCH EVIDENCE | | | | | | | |
|--|--|------------------|-----------------------------------|--|--------------------------------|--|--|--|
| o Favors the comparison o Probably favors the comparison | Outcomes | With placebo | With omalizumab 300mg every 4w | Difference | Relative effect (95% CI) | | | |
| • Does not favor either the intervention or the comparison | symptom free with UCOL exercise challenge | 200 per 1,000 | 76 per 1,000 (8 to 734) | 124 fewer per 1,000 (192 fewer to 534 more) | RR 0.38 (0.04 to 3.67) | | | |

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

| o Probably favors the intervention o Favors the intervention o Varies o Don't know | patients with at least 1 AE | 444 per 1,000 | 693 per 1,000 (307 to 1,000) | 249 more per 1,000 (138 fewer to 1,120 more) | RR 1.56 (0.69 to 3.52) |
|--|-----------------------------|------------------|---|---|-------------------------------|
| | withdrawal due to AE | 0 per 1,000 | 0 per 1,000 (0 to 0) | 0 fewer per 1,000 (0 fewer to 0 fewer) | not estimable |
| | CU2QoL | | The mean cU2QoL in the intervention group was 7 points lower (19.52 lower to 5.52 higher) | MD 7 lower (19.52 lower to 5.52 higher) | - |

Feasibility

Is the intervention feasible to implement?

| JUDGEMENT | RESEARCH EVIDENCE |
|--|---|
| o No o Probably no o Probably yes o Yes | Feasibility, costs, equity and acceptability of the intervention need to be considered in the context of the local health care systems. |
| VariesDon't know | |

Summary:

(Differences to 2016 marked in purple.)

COMPARISON: OMALIZUMAB 300mg EVERY 4 WEEKS vs. PLACEBO FOR CHOLINERGIC URTICARIA

Data added in 2020 update from 1 new study

Efficacy

No difference was found for the outcomes: 'symptom free with UCOL exercise challenge' (moderate quality) and 'CU2QoL' (low quality)

Safety

No difference was found for the outcomes: 'withdrawal due to adverse event' (high quality) and 'patients with at least one adverse event' (moderate quality).

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

EuroGuiDerm

Centre for Guideline Development

Solar urticaria/vibratory AE/aquagenic urticaria/contact urticaria

No evidence identified