Psoriatic arthritis: How should psoriasis patients with concomitant psoriatic arthritis be managed?

This chapter is based on the corresponding chapter in the previous versions of the guideline [1,2]. An existing systematic review and meta-analysis was updated, details of which can be found below**.**

The aim of this updated review is to continuously inform the guideline development group about new evidence on the treatment of patients with plaque type psoriasis who also have psoriatic arthritis (PsA). Therefore, only treatments approved for plaque-type psoriasis and psoriatic arthritis are discussed. Please note that there are an increasing number of treatments available that are only approved for psoriatic arthritis and that clinical trials are increasingly distinguishing between different manifestations of PsA, namely peripheral arthritis, axial disease, enthesitis and dactylitis. Please consult the relevant guidelines and treatment recommendations, which focus primarily on PsA [3,4].

Results/Answer [5-8]:

We **recommend** interdisciplinary cooperation with a rheumatologist for the confirmation of the diagnosis of psoriatic arthritis and the selection of a suitable treatment whenever needed.	↑↑	STRONG CONSENSUS[1] 100 % Agreement EXPERT CONSENSUS

[1] due to personal-financial conflict of interest 4 abstentions

Treatments are usually categorized as NSAIDs (e. g. diclofenac), conventional synthetic disease modifying anti rheumatic drugs (csDMARDs) e. g. MTX, targeted synthetic (ts)DMARDS (e.g. apremilast) and biological (b)DMARDs (e. g. TNFi).

Head to head trials allowing direct comparison between the different groups or between the individual drugs are extremely rare. Indirect comparisons, e.g. network meta-analyses, are limited by the low number of trials for psoriatic arthritis. See **Table 1** for an overview of RCT data on psoriatic arthritis.

Table 1: Summary of the results for drugs approved for psoriasis of the skin and psoriatic arthritis (Dressler et al. [9] updated, see methods section, blue – new data/studies in March 2023

	Patients achieving ARC20 after 12-24 weeks			Patients with at least one adverse event		
	RR	95% CI	Certainty Evidence (GRADE)	RR	95% CI	Certainty Evidence (GRADE)
Head-to-head comparisons:						
ADA 40 mg Q2W+ MTX 15 mg p.o./s.c. QW vs. MTX up to 20-25 mg p.o./s.c. or highest tolerable dose QW	2.06	1.55 to 2.73	LOW	1.08	0.88 to 1.32	VERY LOW
ADA 40mg EOW (1) vs. SEC 300mg LD then Q4W	0.92	0.82 to 1.02	MODERATE	1.02	0.95 to 1.10	MODERATE
APR vs. MTX (no dosage given)	0.83	0.42 to 1.66	VERY LOW	0.53	0.16 to 1.76	VERY LOW
ETA 50mg QW + MTX up to 20mg QW vs. MTX up to 20mg QW	1.28	1.11 to 1.48	LOW	1.01	0.92 to 1.11	MODERATE
INF 5mg/kg w0, 2, 6, 14 + MTX 15mg QW vs. MTX 15mg/ QW	1.40	1.07 to 1.84	VERY LOW	1.65	1.08 to 2.52	VERY LOW
IXE 80mg Q2W (LD 160mg w0) vs. ADA 40mg EOW (1)	1.08	0.86 to 1.36	LOW	1.02*	0.83 to 1.25	MODERATE
Placebo comparisons:						
ADA 40mg EOW (2)	2.08	1.52 to 2.86	MODERATE	1.07	0.83 to 1.39	MODERATE
APR 30mg BID	2.01	1.69 to 2.40	MODERATE	1.24	1.12 to 1.36	LOW
CZP 400mg LD then 200mg Q2W	2.71	1.95 to 3.76	MODERATE	1.01*	0.86 to 1.19	MODERATE
CZP 400mg LD then 400mg Q4W (3)	2.36	1.68 to 3.31	MODERATE	1.05*	0.90 to 1.23	MODERATE
ETA 25mg BIW	5.47	3.27 to 9.16	LOW	no data		
GUS 100mg LD then Q8W (4)	2.13	1.82 to 2.50	HIGH	0.99	0.87 to 1.13	HIGH
INF 5mg/kg w0, 2, 6, 14	4.38	2.24 to 8.56	MODERATE	1.13	0.87 to 1.47	LOW
IXE 80mg Q2W (LD160mg w0)	2.21	1.71 to 2.86	MODERATE	1.39*	1.09 to 1.78	LOW
MTX 7.5mg to 10mg to 15mg	1.82	0.97 to 3.40	LOW	no data		
RZB 150mg w0, 4, 16	1.76	1.56 to 2.00	HIGH	1.03*	0.92 to 1.15	HIGH
SEC 300mg + LD vs. PBO (ACR20 w16-24)	2.55	2.09 to 3.10	MODERATE	1.01	0.91 to 1.11	MODERATE
SEC 300mg + LD vs. PBO (ACR20 w12)	2.74	1.93 to 3.89	MODERATE	0.83	0.65 to 1.06	LOW
UST 45mg	1.95	1.52 to 2.50	HIGH	no data		
UST 90mg (5)	2.26	1.80 to 2.82	MODERATE	0.96	0.75 to 1.24	VERY LOW

1 - 80mg LD only for pts. with moderate-to-severe PsO
2 - No LD of 80mg (this would be the case for PsO)
3 - For psoriasis vulgaris, 400mg Q2W can also be considered
4 - For patients at high risk of joint damage according to clinical judgement, a dose of 100 mg every 4 weeks may be considered (SMPc)
5- For Pso patient with >=100kg (dosis not licensed for PsA); one study reported induction dose of QW (weeks 0-3).
*treatment emergent adverse events

Abbreviations: ACR20 = 20% improvement in American College of Rheumatology response criteria; RR = risk ratio; 95% CI = 95% confidence interval; ETA = etanercept; MTX = methotrexate; mg = milligrams; QW= once a week; INF = infliximab; kg = kilograms IXE = ixekizumab; ADA = adalimumab; Q2W = once every 2 weeks; EOW = every other week; PBO = placebo; APR = apremilast; BID = twice a day; CZP = certolizumab pegol; Q4W = once every 4 weeks; BIW = twice a week; W = week; Sec = secukinumab; LD = loading dose; RZB: risankizumab; GUS: Guselkumab, UST = ustekinumab; Q12W = every 12 weeks.

Non-steroidal anti-inflammatory drugs (NSAIDs)

The role of NSAIDs is usually in the relief of symptoms of psoriatic arthritis for patients with mild and non-erosive articular and para-articular involvement. Treatment of NSAIDs should be limited to the lowest required dose for the shortest period as needed [10].

Treatment initiation

We **recommend** starting treatment early to prevent progression of disease and erosive destruction of joints.	↑↑	STRONG CONSENSUS[1] 100 % Agreement EXPERT CONSENSUS

[1] due to personal-financial conflict of interest 4 abstentions

Peripheral active joint involvement (PsA) despite the use of NSAIDs or glucocorticoid site injections (if applicable) and/or polyarthritis increased inflammatory markers and erosive changes, and extra-articular musculoskeletal manifestations are indicators that systemic therapy is needed.

Conventional synthetic DMARDs (e.g., MTX)

We **suggest** monotherapy with a synthetic DMARD (e.g. MTX) as first-line treatment for most patients with moderate to severe psoriasis of the skin and active joint involvement (PsA).	↑	STRONG CONSENSUS[1] 100 % Agreement EVIDENCE AND EXPERT CONSENSUS TABLE **1**

[1] due to personal-financial conflict of interest 4 abstentions

This recommendation takes account of the label/price/reimbursement situation in most European countries, the efficacy on skin and peripheral joints, the safety profile and the long-term experience.

Biological DMARDs

For patients with an inadequate response after at least one synthetic DMARD, we **recommend** using a biological DMARD as monotherapy or in combination with a synthetic DMARD. In cases of severe active joint involvement (PsA) where a sufficient response cannot be expected with the use of a conventional treatment, we recommend using a biologic as first-line therapy.	↑↑	STRONG CONSENSUS[1]  EVIDENCE AND EXPERT CONSENSUS TABLE **1**
When choosing a bDMARD for patients with moderate to severe psoriasis of the skin and active joint involvement (PsA), we **recommend** taking into account aspects of efficacy with regard to skin and the joints, comorbidity, practicability and safety.	↑↑	STRONG CONSENSUS[1]  EXPERT CONSENSUS

[1] due to personal-financial conflict of interest 4 abstentions

The following drugs have been approved for the treatment of psoriatic arthritis by the European Medicines Agency: the TNFi adalimumab, certolizumab – pegol, etanercept, and infliximab; the IL-17 antagonists ixekizumab and secukinumab; the IL-23 antagonists guselkumab and risankizumab and the IL12/23p40 antagonist ustekinumab. For the available evidence see Table 1.

Previous guidelines have given preference to TNFi over other bDMARDs. The available evidence does not support this approach any longer and shows that other drugs approved by the European Medicines Agency for PsA might be equally effective. Biological DMARDs can be used as monotherapy or in combination with a conventional synthetic DMARD.

Small molecules

Apremilast is the only small molecule currently approved for both plaque type psoriasis and psoriatic arthritis. There are no head-to-head trials comparing apremilast with biological DMARDs. A head–to-head trial with MTX showed comparable efficacy [11].

We **suggest** using apremilast for patients with moderate to severe psoriasis of the skin and active joint involvement (PsA) if an oral treatment is desired or if other systemic agents have led to an inadequate response or if they are contraindicated or not tolerated.	↑	STRONG CONSENSUS[1]  EVIDENCE AND EXPERT CONSENSUS TABLE **1**

[1] due to personal-financial conflict of interest 4 abstentions

In line with the inclusion criteria of this guideline, for this chapter we included only drugs licensed for both, plaque type psoriasis and PsA. Be aware that updacitinib and tofacitinib are licensed and approved for use in psoriatic arthritis, and can show benefit in psoriasis, although they have not been systematically assessed in the scope of this guideline.

Other treatment options

Local injection of glucocorticoids can be recommended in patients with active mono- or oligoarthritis, dactylitis and in entheseal areas (enthesitis).

Systemic use of glucocorticoids should not be standard for the treatment of psoriatic arthritis, but if needed, e. g. during flares, "systemic steroids at the lowest effective dose may be used with caution" [12]. Tapering of glucocorticoids should be done slowly and in a step-wise manner when feasible.

Axial spondyloarthritis

We **suggest** using TNFi or IL-17 antagonists for patients with moderate to severe psoriasis of the skin and concomitant PsA manifestation in the form of axial involvement or enthesitis.	↑	STRONG CONSENSUS[1] 100 % Agreement EXPERT CONSENSUS

[1] due to personal-financial conflict of interest 4 abstentions

Living systematic review of treatments for psoriasis vulgaris patients with concomitant psoriatic arthritis

History

Version	Search Date	Database	Included drugs	Number of new studies	Number of studies included in total	Implications for conclusion
Update 3 for living systematic review	16 Nov 2022	CENTRAL	ADA, APR, CZP, ETA, INF, MTX, UST, IXE, RZB, SEC,GUS	3	35	The conclusion that bDMARDS and tsDMARDs are generally effective remains unchanged.
Update 2 for living systematic review	1 Feb 2022	CENTRAL	ADA, APR, CZP, ETA, INF, MTX, UST, IXE, RZB, SEC,GUS	5 studies: 1 study on APR vs. MTX, 1 study on GUS vs. PBO 2 studies on RZB, 1 study SEC vs. PBO	32	Risankizumab is now also licensed for PsO and PsA. The conclusion that bDMARDS and tsDMARDs are generally effective remains unchanged.
Update 1 for living systematic review	4 May 2021	CENTRAL	ADA, APR, CZP, ETA, INF, MTX, UST, IXE, SEC,GUS	5 studies: 3 studies on GUS, 1 study ADA vs SEC, 1 study ADA vs PBO (+upa)	27	Guselkumab is now also licensed for PsO and PsA. The conclusion that bDMARDS and tsDMARDs are generally effective remains unchanged.
Original Chapter: based on Dressler et al 2017 and Pham et al 2017	25 Oct 2019	Medline only	ADA, APR, CZP, ETA, GOL, INF, IXE, LEF, MTX, SEC, SSZ and UST (CSA, TOF - 0 RCTS)	14 studies included by Avila in the original update for the EuroGuiDerm Pso GL (10 were newly found and 4 studies had previously been excluded by Dressler et al.)		Generally, on ACR20 the bDMARDs and tsDMARDs have an effect after a treatment period of 12 to 24 weeks. There are no or few concerns regarding the safety outcome. Few trials are available for each comparison

Content

Executive summaries of updates

Update 3 (November 2022)

Authors: A. Pennitz, I. Vader (Update 3)

What was the aim of this systematic review?

The aim of this review update is to continuously inform the guideline development group of new evidence on treatments for patients with **psoriasis vulgaris who also have psoriasis arthritis**.

The working group conducted two systematic reviews on psoriasis arthritis in 2017 [9,13]. These were updated in 2019 to inform the original version of the EuroGuiDerm psoriasis guideline. The guideline is now being updated regularly at shorter intervals as a living guideline. The first of these updates for the psoriasis arthritis chapter of the guideline was published in August 2021 (see Update 1 (August 2021) below), the second update for the psoriasis arthritis chapter of the guideline was conducted in February 2022.

This section of document reports the results of the **third update** of the systematic review for the psoriasis arthritis chapter of the guideline.

What did we do?

The search strategy and eligibility criteria specified that the only drugs (and dosages) to be included were those licensed for psoriasis vulgaris and psoriasis arthritis at the time of the literature search (16 November 2022). We considered the two relevant outcomes to be ACR20 (i.e., a >=20% improvement in the modified American College of Rheumatology Response Criteria) and the number of patients with at least one adverse event. We evaluated the certainty of evidence for each outcome (for details, see **Methods and results** below, and also the Methods Report of the main guideline).

What are the main results of the review?

We included three new studies. A total of 35 trials are now included in this review (see included studies table, available upon request).

For an overview of the results, see Table 2.

New head-to-head comparisons:

- Adalimumab and methotrexate vs. methotrexate dose escalation (up to 25 mg / week): Adalimumab and methotrexate may be more effective than methotrexate dose escalation alone with regard to efficacy. We are uncertain whether there are differences between adalimumab and methotrexate 15 mg vs. methotrexate dose escalation with regard to adverse events.

(The reporting of the results is worded in line with the recommendations of the Cochrane Consumers and Communication group, which take effect size and certainty of evidence into account.)

New or updated placebo comparisons concerning efficacy (ACR20):

For all of the drugs listed below, a statistically significant difference was found when compared to placebo. The results are based on pairwise comparisons against placebo, which do not allow for direct comparisons between the drugs.

- Risanzkizumab improves psoriatic arthritis (outcome assessed at 16 or 24 weeks).
- Secukinumab improves psoriatic arthritis (outcome assessed at 16 or 24 weeks).

(The reporting of the results is worded in line with the recommendations of the Cochrane Consumers and Communication group, which take effect size and certainty of evidence into account.)

New or updated placebo comparisons concerning safety (patients with at least one adverse event):

- There is little or no difference in adverse events when comparing risankizumab to placebo.
- There is little or no difference in adverse events when comparing secukinumab to placebo.

(The reporting of the results is worded in line with the recommendations of the Cochrane Consumers and Communication group, which take effect size and certainty of evidence into account.)

Key message

We included 35 trials on interventions licensed for psoriasis vulgaris and psoriatic arthritis. A total of 16 placebo comparisons are available, with a certainty of evidence from very low to high. Only six head-to-head comparisons could be included – the certainty of evidence was very low to moderate.

The evidence generally indicated that for ACR20 the bDMARDs and tsDMARDs have an effect after a treatment period of 12 to 24 weeks. There are no or few concerns regarding the safety outcome.

How up-to-date is this review?

16 November 2022

Table 2: Effect size and GRADE evaluation for ACR20 and adverse events (blue – new study/data as of November 2022)

				Patients achieving ARC20 after 12-24 weeks				Patients with at least one adverse event					
	RCTs	N	weeks	RR	95% CI	Risk difference with comparator	Certainty Evidence (GRADE)	RCTs	N	RR	95% CI	Risk difference with comparator	Certainty Evidence (GRADE)
Head-to-head comparisons:													
ADA 40 mg Q2W+ MTX 15 mg p.o./s.c. QW vs. MTX up to 20-25 mg p.o./s.c. or highest tolerable dose QW	1	245	16	2.06	1.55 to 2.73	ADA+MTX: 348 more per 1000 (from 180 more to 567 more)	LOW	1	245	1.08	0.88 to 1.32	ADA+MTX: 46 more per 1000 (from 69 fewer to 184 more)	VERY LOW
ADA 40mg EOW (1) vs. SEC 300mg LD then Q4W	1	853	12	0.92	0.82 to 1.02	ADA: 50 fewer per 1000 (from 113 fewer to 13 more)	MODERATE	1	853	1.02	0.95 to 1.10	ADA: 15 more per 1000 (from 39 fewer to 77 more)	MODERATE
APR vs. MTX (no dosage given)	1	31	24	0.83	0.42 to 1.66	APR: 96 fewer per 1000 (from 326 fewer to 371 more)	VERY LOW	1	31	0.53	0.16 to 1.76	APR: 176 fewer per 1000 (from 315 fewer to 85 more)	VERY LOW
ETA 50mg QW + MTX up to 20mg QW vs. MTX up to 20mg QW	1	567	24	1.28	1.11 to 1.48	ETA+MTX: 142 more per 1000 (from 56 more to 243 more)	LOW	1	567	1.01	0.92 to 1.11	ETA+MTX: 8 more per 1000 (from 60 more to 83 more)	MODERATE
INF 5mg/kg w0,2,6,14 + MTX 15mg QW vs. MTX 15mg/ QW	1	115	16	1.40	1.07 to 1.84	INF+MTX: 221 more per 1000 (from 39 more to 463 more)	VERY LOW	1	111	1.65	1.08 to 2.52	INF+MTX: 229 more per 1000 (from 28 more to 535 more)	VERY LOW
IXE 80mg Q2W (LD 160mg w0) vs. ADA 40mg EOW (1)	1	204	24	1.08	0.86 to 1.36	IXE: 46 more per 1000 (from 80 fewer to 207 more)	LOW	1	203	1.02*	0.83 to 1.25	IXE: 13 more per 1000 (from 109 fewer to 161 more)	MODERATE
Placebo comparisons													
ADA 40mg EOW (2)	5	1687	12	2.08	1.52 to 2.86	320 more per 1000 (from 154 more to 551 more)	MODERATE	4	1370	1.07	0.83 to 1.39	39 more per 1000 (from 94 fewer to 216 more)	MODERATE
APR 30mg BID	5	1472	16	2.01	1.69 to 2.40	185 more per 1000 (from 126 more to 256 more)	MODERATE	5	1477	1.24	1.12 to 1.36	117 more per1000 (from 58 more to 175 more)	LOW
CZP 400mg LD then 200mg Q2W	1	274	24	2.71	1.95 to 3.76	402 more per 1.000 (from 224 more to 649 more)	MODERATE	1	274	1.01*	0.86 to 1.19	7 more per 1.000 (from 95 fewer to 129 more)	MODERATE
CZP 400mg LD then 400mg Q4W (3)	1	271	24	2.36	1.68 to 3.31	320 more per 1000 (from 160 more to 544 more)	MODERATE	1	271	1.05*	0.90 to 1.23	34 more per 1000 (from 68 fewer to 156 more)	MODERATE
ETA 25mg BIW	2	265	12	5.47	3.27 to 9.16	467 more per 1000 (from 237 more to 853 more)	LOW	no data					
GUS 100mg LD then Q8W (4)	4	1183	24	2.13	1.82 to 2.50	297 more per 1000 (from 215 more to 394 more)	HIGH	4	1181	0.99	0.87 to 1.13	5 fewer per 1000 (from 60 fewer to 60 more)	HIGH
INF 5mg/kg w0,2,6,14	2	304	16-24	4.38	2.24 to 8.56	467 more per 1000 (from 171 more to 1000 more)	MODERATE	1	103	1.13	0.87 to 1.47	84 more per 1000 (from 84 fewer to 304 more)	LOW
IXE 80mg Q2W (LD160mg w0)	2	449	24	2.21	1.71 to 2.86	297 more per 1000 (from 174 more to 457 more)	MODERATE	1	208	1.39*	1.09 to 1.78	184 more per 1000 (from 42 more to 368 more)	LOW
MTX 7.5mg to 10mg to 15mg	1	221	24	1.82	0.97 to 3.40	95 more per 1000 (from 3 fewer to 279 more)	LOW	no data					
RZB 150mg w0, 4, 16	3	1491	16-24	1.76	1.56 to 2.00	240 more per 1000 (from 177 more to 315 more)	HIGH	2	1407	1.03	0.92 to 1.15	13 more per 1000 (from 35 fewer to 66 more)	HIGH
SEC 300mg + LD vs. PBO	4	1183	16-24	2.55	2.09 to 3.10	351 more per 1000 (from 247 more to 475 more)	HIGH	4	1183	1.01	0.91 to 1.11	6 more per 1000 (from 53 fewer to 65 more)	HIGH
SEC 300mg + LD vs. PBO	1	328	12	2.74	1.93 to 3.89	329 more per 1000 (from 176 more to 546 more)	MODERATE	1	333	0.83	0.65 to 1.06	82 fewer per 1000 (from 169 fewer to 29 more)	LOW
UST 45mg	2	463	24	1.95	1.52 to 2.50	206 more per 1000 (from 90 more to 371 more)	HIGH	no data					
UST 90mg (5)	3	765	12-24	2.26	1.80 to 2.82	259 more per 1000 (from 164 more to 374 more)	MODERATE	1	90	0.96	0.75 to1.24	25 fewer per1000 (from157 fewer to 151 more)	VERY LOW

Update 2 (February 2022)

Authors: M. Gaskins, C. Dressler

What was the aim of this systematic review?

The aim of this review update is to continuously inform the guideline development group of new evidence on treatments for patients with psoriasis vulgaris who also have psoriasis arthritis.

The working group conducted two systematic reviews on psoriasis arthritis in 2017 [9,13]. These were updated in 2019 to inform the original version of the EuroGuiDerm psoriasis guideline. The guideline is now being updated regularly at shorter intervals as a living guideline. The first of these updates for the psoriasis arthritis chapter of the guideline was published in August 2021 (see Update 1 (August 2021) below).

This section of document reports the results of the second update of the systematic review for the psoriasis arthritis chapter of the guideline.

What did we do?

The search strategy and eligibility criteria specified that the only drugs (and dosages) to be included were those licensed for psoriasis vulgaris and psoriasis arthritis at the time of the literature search (1 February 2022). We considered the two relevant outcomes to be ACR20 (i.e., a >=20% improvement in the modified American College of Rheumatology Response Criteria) and the number of patients with at least one adverse event. We evaluated the certainty of evidence for each outcome (for details, see Methods and results below, and also the Methods Report of the main guideline).

What are the main results of the review?

We included five new studies. A total of0 trials are now included in this review (see included studies table, available upon request).

For an overview of the results, see Table 3.

New head-to-head comparisons:

- We are uncertain whether there are differences between apremilast and methotrexate with regard to efficacy and adverse events.

(The reporting of the results is worded in line with the recommendations of the Cochrane Consumers and Communication group, which take effect size and certainty of evidence into account.)

New or updated placebo comparisons concerning efficacy (ACR20):

For all of the drugs listed below, a statistically significant difference was found when compared to placebo. The results are based on pairwise comparisons against placebo, which do not allow for direct comparisons between the drugs.

- Guselkumab improves psoriatic arthritis (outcome assessed at 24 weeks).

- Risazkizumab improves psoriatic arthritis (outcome assessed at 24 weeks).
- Secukinumab improves psoriatic arthritis (outcome assessed at 16 or 24 weeks; data from Update 1) and probably does so by week 12 (data from new study added in Update 2).

(The reporting of the results is worded in line with the recommendations of the Cochrane Consumers and Communication group, which take effect size and certainty of evidence into account.)

New or updated placebo comparisons concerning safety (patients with at least one adverse event):

- There is little or no difference in adverse events when comparing guselkumab to placebo
- There is little or no difference in adverse events when comparing risankizumab to placebo.
- There is little or no difference in adverse events when comparing secukinumab to placebo

(The reporting of the results is worded in line with the recommendations of the Cochrane Consumers and Communication group, which take effect size and certainty of evidence into account.)

Key message

We included 32 trials on interventions licensed for psoriasis vulgaris and psoriatic arthritis. A total of 14 placebo comparisons are available, with a certainty of evidence from very low to high. Only five head-to-head comparisons could be included – the certainty of evidence was very low to moderate.

The evidence generally indicated that for ACR20 the bDMARDs and tsDMARDs have an effect after a treatment period of 12 to 24 weeks. There are no or few concerns regarding the safety outcome.

How up-to-date is this review?

1 February 2022

Table 3: Effect size and GRADE evaluation for ACR20 and adverse events (blue – new study/data as of 1 February 2022)

				Patients achieving ARC20 after 12-24 weeks				Patients with at least one adverse event					
	RCTs	N	weeks	RR	95% CI	Risk difference with comparator	Certainty Evidence (GRADE)	RCTs	N	RR	95% CI	Risk difference with comparator	Certainty Evidence (GRADE)
Head-to-head comparisons:													
ADA 40mg EOW (1) vs. SEC 300mg LD then Q4W	1	853	12	0.92	0.82 to 1.02	ADA: 50 fewer per 1000 (from 113 fewer to 13 more)	MODERATE	1	853	1.02	0.95 to 1.10	ADA: 15 more per 1000 (from 39 fewer to 77 more)	MODERATE
APR vs. MTX (no dosage given)	1	31	24	0.83	0.42 to 1.66	APR: 96 fewer per 1000 (from 326 fewer to 371 more)	VERY LOW	1	31	0.53	0.16 to 1.76	APR: 176 fewer per 1000 (from 315 fewer to 85 more)	VERY LOW
ETA 50mg QW + MTX up to 20mg QW vs. MTX up to 20mg QW	1	567	24	1.28	1.11 to 1.48	ETA+MTX: 142 more per 1000 (from 56 more to 243 more)	LOW	1	567	1.01	0.92 to 1.11	ETA+MTX: 8 more per 1000 (from 60 more to 83 more)	MODERATE
INF 5mg/kg w0,2,6,14 + MTX 15mg QW vs. MTX 15mg/ QW	1	115	16	1.40	1.07 to 1.84	INF+MTX: 221 more per 1000 (from 39 more to 463 more)	VERY LOW	1	111	1.65	1.08 to 2.52	INF+MTX: 229 more per 1000 (from 28 more to 535 more)	VERY LOW
IXE 80mg Q2W (LD 160mg w0) vs. ADA 40mg EOW (1)	1	204	24	1.08	0.86 to 1.36	IXE: 46 more per 1000 (from 80 fewer to 207 more)	LOW	1	203	1.02*	0.83 to 1.25	IXE: 13 more per 1000 (from 109 fewer to 161 more)	MODERATE
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CZP 400mg LD then 400mg Q4W (3)	1	271	24	2.36	1.68 to 3.31	320 more per 1000 (from 160 more to 544 more)	MODERATE	1	271	1.05*	0.90 to 1.23	34 more per 1000 (from 68 fewer to 156 more)	MODERATE
ETA 25mg BIW	2	265	12	5.47	3.27 to 9.16	467 more per 1000 (from 237 more to 853 more)	LOW	no data					
GUS 100mg LD then Q8W (4)	4	1183	24	2.13	1.82 to 2.50	297 more per 1000 (from 215 more to 394 more)	HIGH	4	1181	0.99	0.87 to 1.13	5 fewer per 1000 (from 60 fewer to 60 more)	HIGH
INF 5mg/kg w0,2,6,14	2	304	16-24	4.38	2.24 to 8.56	467 more per 1000 (from 171 more to 1000 more)	MODERATE	1	103	1.13	0.87 to 1.47	84 more per 1000 (from 84 fewer to 304 more)	LOW
IXE 80mg Q2W (LD160mg w0)	2	449	24	2.21	1.71 to 2.86	297 more per 1000 (from 174 more to 457 more)	MODERATE	1	208	1.39*	1.09 to 1.78	184 more per 1000 (from 42 more to 368 more)	LOW
MTX 7.5mg to 10mg to 15mg	1	221	24	1.82	0.97 to 3.40	95 more per 1000 (from 3 fewer to 279 more)	LOW	no data					
RZB 150mg w0, 4, 16	2	1408	24	1.77	1.56 to 2.01	241 more per 1000 (from 175 more to 316 more)	HIGH	2	1407	1.03*	0.92 to 1.15	13 more per 1000 (from 35 fewer to 66 more)	HIGH
SEC 300mg + LD vs. PBO	3	1028	16-24	2.69	2.06 to 3.52	382 more per 1000 (from 239 more to 569 more)	HIGH	3	1028	1.00	0.9 to 1.1	0 fewer per 1000 (from 60 fewer to 60 more)	HIGH
SEC 300mg + LD vs. PBO	1	328	12	2.74	1.93 to 3.89	329 more per 1000 (from 176 more to 546 more)	MODERATE	1	333	0.83	0.65 to 1.06	82 fewer per 1000 (from 169 fewer to 29 more)	LOW
UST 45mg	2	463	24	1.95	1.52 to 2.50	206 more per 1000 (from 90 more to 371 more)	HIGH	no data					
UST 90mg (5)	3	765	12-24	2.26	1.80 to 2.82	259 more per 1000 (from 164 more to 374 more)	MODERATE	1	90	0.96	0.75 to1.24	25 fewer per1000 (from 157 fewer to 151 more)	VERY LOW

Update 1 (August 2021)

Authors: C.Dressler, G. Avila Valles

What was the aim of this systematic review?

The aim of this review update was to continuously inform the guideline development group of new evidence on treatments for patients with psoriasis vulgaris who also have psoriasis arthritis.

We updated two systematic reviews published in 2017, once in 2019 to inform the original version of the EuroGuiDerm psoriasis guideline. We update the review again in 2021.

What did we do?

The search strategy as well as the eligibility criteria specified that only those drugs (and dosages) that are licensed for psoriasis vulgaris and psoriasis arthritis are included. We considered ACR 20 - a >=20% improvement in the modified American College of Rheumatology Response Criteria and the number of patients with at least one adverse event as the two relevant outcomes. We evaluated the certainty of evidence. For details, see Methods Report.

What are the main results of the review?

We included 5 new studies. A total of 27 trials are now included in this review (see included studies table).

For an overview of the results, see Table 4.

Head-to-head comparisons:

- There is probably little or no difference between adalimumab and secukinumab.
- Etanercept combined with methotrexate may improve psoriatic arthritis slightly compared to methotrexate alone (ACR20), but there is little or no difference when looking at the adverse events.
- We are uncertain whether there is an effect considering infliximab combined with methotrexate versus methotrexate alone.
- There is very low certainty evidence that ixekizumab was equally effective as adalimumab. There is probably little or no difference when considering adverse events.

(The reporting of the results is worded in line with the recommendations of the Cochrane Consumers and Communication group, which take effect size and certainty of evidence into account.)

Placebo comparisons concerning efficacy (ACR20):

For all of the below listed drugs except MTX, a statistically significant difference was found when compared to placebo. The results are based on pairwise comparisons against placebo, which do not allow for direct comparisons between the drugs.

- Guselkumab, secukinumab and ustekinumab 45mg improve psoriatic arthritis.
- Adalimumab, apremilast, certolizumab pegol, infliximab, ixekizumab and ustekinumab 90mg probably improve psoriatic arthritis.

- Etanercept may improve psoriatic arthritis.
- Methotrexate may make little or no difference.

(The reporting of the results is worded in line with the recommendations of the Cochrane Consumers and Communication group, which take effect size and certainty of evidence into account.)

Placebo comparisons concerning safety (patients with at least one adverse event):

- There is probably little or no difference in adverse events when comparing adalimunab, certolizumab pegol or guselkumab versus placebo.
- Infliximab and secukinumab may make little or no difference.
- Apremilast, ixekizumab may increase the number of patients with adverse events slightly
- We are uncertain whether ustekinumab 90mg effects the outcome.
- This outcome was not reported in the trials comparing etanercept, methotrexate and ustekinumab 45mg versus placebo.

(The reporting of the results is worded in line with the recommendations of the Cochrane Consumers and Communication group, which take effect size and certainty of evidence into account.)

Key message

We included 27 trials on interventions licensed for psoriasis vulgaris and psoriatic arthritis. A total of 12 placebo comparison are available, with a certainty of evidence from very low to high. Only four head-to-head comparisons could be included – the certainty of evidence was very low to moderate.

The evidence generally indicated that for ACR20 the bDMARDs and tsDMARDs have an effect after a treatment period of 12 to 24 weeks. There are no or few concerns regarding the safety outcome.

How up-to-date is this review?

4 May 2021

Table 4: Effect size and GRADE evaluation for ACR20 and adverse events (blue – new study/data as of 4 May 2021

				Patients achieving ARC20 after 12-24 weeks				Patients with at least one adverse event					
	RCTs	N	weeks	RR	95% CI	Risk difference with comparator	Certainty Evidence (GRADE)	RCTs	N	RR	95% CI	Risk difference with comparator	Certainty Evidence (GRADE)
Head-to-head comparisons:													
ADA 40mg EOW (1) vs. SEC 300mg LD then Q4W	1	853	12	0.92	0.82 to 1.02	50 fewer per 1.000 (from 113 fewer to 13 more)	MODERATE	1	853	1.02	0.95 to 1.10	15 more per 1.000 (from 39 fewer to 77 more)	MODERATE
ETA 50mg QW + MTX up to 20mg QW vs. MTX up to 20mg QW	1	567	24	1.28	1.11 to 1.48	ETA+MTX: 142 more per 1.000 (from 56 more to 243 more)	LOW	1	567	1.01	0.92 to 1.11	ETA+MTX: 8 more per 1.000 (from 60 more to 83 more)	MODERATE
INF 5mg/kg w0,2,6,14 + MTX 15mg QW vs. MTX 15mg/ QW	1	115	16	1.40	1.07 to 1.84	INF+MTX: 221 more per 1.000 (from 39 more to 463 more)	VERY LOW	1	111	1.65	1.08 to 2.52	229 more per 1.000 (from 28 more to 535 more)	VERY LOW
IXE 80mg Q2W (LD 160mg w0) vs. ADA 40mg EOW (1)	1	204	24	1.08	0.86 to 1.36	IXE: 46 more per 1.000 (from 80 fewer to 207 more)	VERY LOW	1	203	1.02*	0.83 to 1.25	IXE: 13 more per 1.000 (from 109 fewer to 161 more)	MODERATE
Placebo comparisons													
ADA 40mg EOW (2) vs. PBO	5	1687	12	2.08	1.52-2.86	320 more per 1.000 (from 154 more to 551 more)	MODERATE	4	1370	1.07	0.83 to 1.39	39 more per 1.000 (from 94 fewer to 216 more)	MODERATE
APR 30mg BID	5	1472	16	2.01	1.69 to 2.40	185 more per 1.000 (from 126 more to 256 more)	MODERATE	5	1477	1.24	1.12 to 1.36	117 more per1.000 (from 58 more to 175 more)	LOW
CZP 400mg LD then 200mg Q2W	1	274	24	2.71	1.95 to 3.76	402 more per 1.000 (from 224 more to 649 more)	MODERATE	1	274	1.01*	0.86 to 1.19	7 more per 1.000 (from 95 fewer to 129 more)	MODERATE
CZP 400mg LD then 400mg Q4W (3)	1	271	24	2.36	1.68 to 3.31	320 more per 1.000 (from 160 more to 544 more)	MODERATE	1	271	1.05*	0.90 to 1.23	34 more per 1.000 (from 68 fewer to 156 more)	MODERATE
ETA 25mg BIW	2	265	12	5.47	3.27 to 9.16	467 more per 1.000 (from 237 more to 853 more)	LOW	no data					
GUS 100mg LD then Q8W (4)	3	898	24	2.20	1.75 to 2.78	333 more per 1.000 (from 208 more to 494 more)	HIGH	3	896	1.02	0.87 to 1.20	9 more per 1.000 (from 59 fewer to 91 more)	MODERATE
INF 5mg/kg w0,2,6,14	2	304	16-24	4.38	2.24 to 8.56	467 more per 1.000 (from 171 more to 1.000 more)	MODERATE	1	103	1.13	0.87 to 1.47	84 more per 1.000 (from 84 fewer to 304 more)	LOW
IXE 80mg Q2W (LD160mg w0)	2	449	24	2.21	1.71 to 2.86	297 more per 1.000 (from 174 more to 457 more)	MODERATE	1	208	1.39*	1.09 to 1.78	184 more per 1.000 (from 42 more to 368 more)	LOW
MTX 7.5mg to 10mg to 15mg	1	221	24	1.82	0.97 to 3.40	95 more per 1.000 (from 3 fewer to 279 more)	LOW	no data					
SEC 300mg + LD vs. PBO	3	1028	16-24	2.69	2.06 to 3.52	382 more per 1.000 (from 239 more to 569 more)	HIGH	1	276	0.97	0.79 to 1.20	17 fewer per 1.000 (from 118 fewer to 112 more)	LOW
UST 45mg	2	463	24	1.95	1.52 to 2.50	206 more per 1.000 (from 90 more to 371 more)	HIGH	0					
UST 90mg (5)	3	765	12-24	2.26	1.80 to 2.82	259 more per 1.000 (from 164 more to 374 more)	MODERATE	1	90	0.96	0.75 to1.24	25 less per1.000 (from157 less to 151 more)	VERY LOW

Abbreviations: ACR20 = 20% improvement in American College of Rheumatology response criteria; RR = risk ratio; 95% CI = 95% confidence interval; ETA = Etanercept; MTX = Methotrexate; mg = milligrams; QW= once a week; INF = Infliximab; kg = kilograms IXE = Ixekizumab; ADA = Adalimumab; Q2W = once every 2 weeks; EOW = every other week; PBO = placebo; APR = Apremilast; BID = twice a day; CZP = Certolizumab Pegol; Q4W = once every 4 weeks; BIW = twice a week; W = week; Sec = Secukinumab; LD = loading dose; UST = Ustekinumab; Q12W = every 12 weeks.

1- 80mg LD only for pts. with moderate-to-severe PsO
2- No LD of 80mg (this would be the case for PsO)
3- for psoriasis vulgaris, 400mg Q2W can also be considered
4- For patients at high risk for joint damage according to clinical judgement, a dose of 100 mg every 4 weeks may be considered (SMPc)
5- For Pso patient with >=100kg (dosis not licensed for PsA)
*treatment emergent adverse events

Methods and results

Update 3 (November 2022)

In November 2022, we performed a further update of the systematic review and meta-analysis conducted for the psoriasis arthritis chapter of the Living EuroGuiDerm Guideline for the systemic treatment of psoriasis vulgaris.

Inclusion criteria

Same as for Update 2.

Information sources

We searched CENTRAL: CENTRAL is comprised of randomized controlled trial (RCT) and quasi-RCT records systematically and continuously retrieved from PubMed/MEDLINE, Embase, CINAHL, ClinicalTrials.gov, WHO's ICTRP, KoreaMed, all Cochrane Review Groups' Specialized Registers, and records identified by handsearching various biomedical.

The search was conducted on 16 November 2022. The search strategy is shown in Appendix 1 of this update.

Data collection, statistical analysis and study evaluation

Same as for Updates 1 and 2 (see below).

GRADE Assessment

Same as for Updates 1 and 2 (see below).

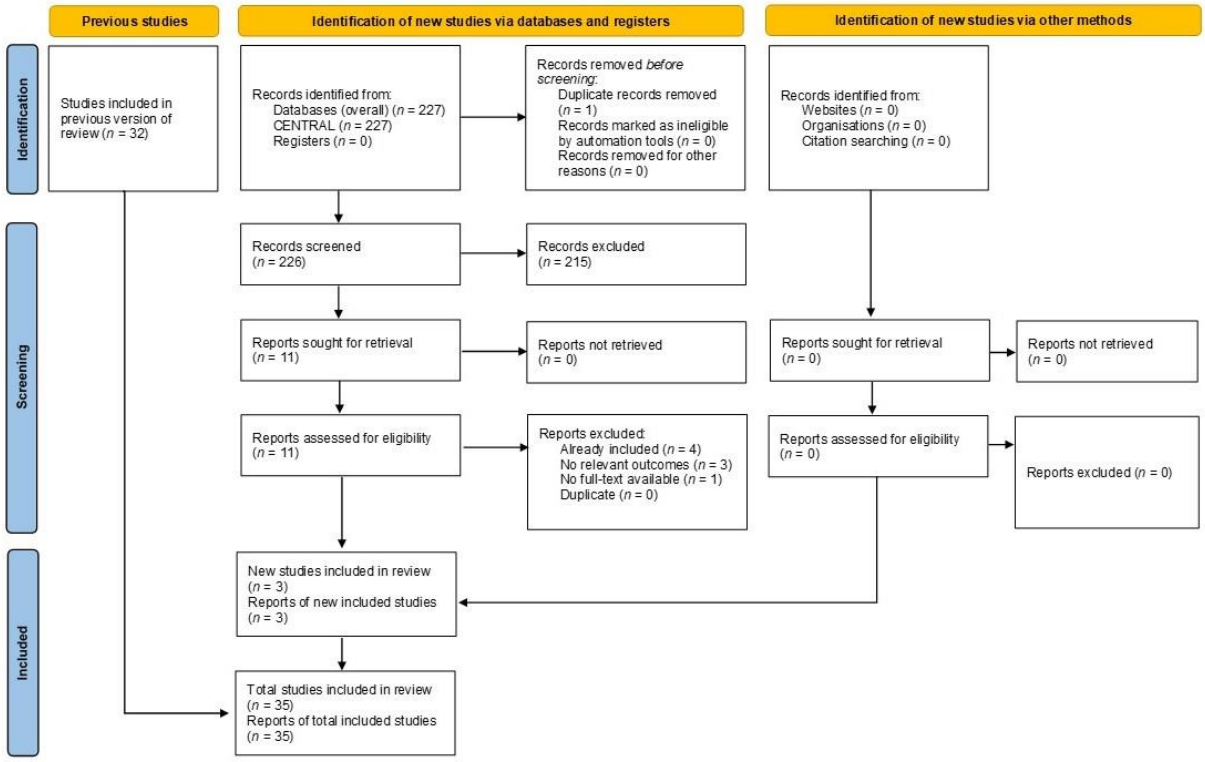
Inclusion criteria

Same as for Updates 1 and 2.

Results

We identified a total of 227 records, one of which was a duplicate. After screening the titles and abstracts of the remaining 226 records, we identified 11 publications as potentially meeting our inclusion criteria. After obtaining and screening the full texts of these, we identified three publications that met our inclusion criteria: one study compared adalimumab with methotrexate dose escalation [14], one study compared risankizumab with placebo [15] and one study compared secukinumab with placebo [16] (see study selection flowchart, Figure 1).

Figure 1: Study selection flowchart for the selection of studies for the review update 3 on psoriasis vulgaris patients with concomitant psoriatic arthritis



A total of 35 studies are included in this update (see 'included studies table'). Only six head-to-head comparisons could be included, for which the certainty of evidence was very low to moderate. A total of 14 placebo comparisons were evaluated, for which the certainty of evidence was very low to high (see Table 2). For the description of the results and the key messages, see 'summary'.

Update 2 (February 2022)

In February 2022, we performed a further update of the systematic review and meta-analysis conducted for the psoriasis arthritis chapter of the Living EuroGuiDerm Guideline for the systemic treatment of psoriasis vulgaris.

Inclusion criteria

Same as for Update 1 but with the inclusion of risankizumab in the category of biological (b)DMARDs.

Information sources

We searched CENTRAL: CENTRAL is comprised of randomized controlled trial (RCT) and quasi-RCT records systematically and continuously retrieved from PubMed/MEDLINE, Embase, CINAHL, ClinicalTrials.gov, WHO's ICTRP, KoreaMed, all Cochrane Review Groups' Specialized Registers, and records identified by handsearching various biomedical.

The search was conducted on 1 February 2022. The search strategy is shown in Appendix 1 of this update.

Data collection, statistical analysis and study evaluation

Same as for Update 1 (see below).

GRADE Assessment

Same as for Update 1 (see below).

Results

We identified a total of 156 records, three of which were duplicates. After screening the titles and abstracts of the remaining 153 records, we identified 24 publications as potentially meeting our inclusion criteria. After obtaining and screening the full texts of these, we identified five publications that met our inclusion criteria: one study compared apremilast with methotrexate [11], one study compared guselkumab with placebo [17], two studies compared risankizumab with placebo [18,19], and one study compared secukinumab with placebo [20].

A total of 32 studies are included in this update (see 'included studies table'). Only five head-to-head comparisons could be included, for which the certainty of evidence was very low to moderate. A total of 14 placebo comparisons were evaluated, for which the certainty of evidence was very low to high (see Table 3). For the description of the results and the key messages, see 'summary'.

Update 1 (August 2021)

We updated two systematic reviews published in 2017, once in 2019 and again in 2021. The search strategy as well as the eligibility criteria specified that only those drugs (and dosages) that are licensed for psoriasis vulgaris (PsO) and psoriasis arthritis (PsA) are included.

Inclusion criteria

Patients:

- Adult patients with diagnosis of PsA, Pso w/ PsA (at least 80% of the included patient population with PsA where no subgroup analysis was conducted), adults,

Drugs approved for Psoriasis vulgaris and psoriasis arthritis included are:

- conventional synthetic disease modifying anti rheumatic drugs (csDMARDs): methotrexate (MTX; ususal dose 5.5mg – 15mg taken once weekly).
- small molecules (tsDMARDs) : apremilast (APR; 30mg BID with initial titration)
- biological (b)DMARDs:
    - TNFi: adalimumab (ADA; 40mg every other week (loading dose of 80mg only for PsO patients) , certolizumab pegol (CZP; loading dose 400mg week 0, 2 and 4, then 200mg every other week, 400mg every 4 weeks can be considered; for PsO 400mg every 2 weeks can be considered if insufficient response (week 16)), etanercept (ETA; 25mg twice a week or 50mg once a week, for PsO patients 50mg twice a week up to week 12, alternatively), infliximab INF (5mg/kg bodyweight then week2, week 6, then every 8 weeks)
    - anti-IL12/23: ustekinumab 45mg and 90mg (for PsO patients >= 100kg body weight) UST
    - anti-IL17: ixekuzumab (IXE; recommended for PsA with concomitant PsO: 160mg week 0 then every other week until week 12, then every 4 weeks), secukinumab (SEC, 300mg week 0, 1, 2, 3,4 then every 4 weeks)
    - anti-IL23: guselkumab (GUS; 100mg week0, 4 then every 8 weeks; For patients at high risk for joint damage according to clinical judgement, a dose of 100 mg every 4 weeks may be considered).

Outcomes:

At least 1 of the following outcomes at one time point within 12-24 weeks:

- Efficacy outcomes: ACR 20
- Safety outcomes: percentage of patients with at least one AE

Study Design:

- randomized controlled trials with more than 15 patients per arm.

Information sources

We searched CENTRAL: CENTRAL is comprised of randomized controlled trial (RCT) and quasi-RCT records systematically and continuously retrieved from PubMed/MEDLINE, Embase, CINAHL, ClinicalTrials.gov, WHO's ICTRP, KoreaMed, all Cochrane Review Groups' Specialized Registers, and records identified by handsearching various biomedical sources.

The original search was conducted on 4 May 2021. The search strategy is shown in Appendix 1 of this update.

Data collection, statistical analysis and study evaluation

We extracted data for number of patients achieving a >= 20% improvement in the modified American Colleague of Rheumatology (ACR20) and number of patients with at least one adverse event. Where percentages were reported we calculated absolute numbers using either the number of patients randomized or those analysed, as stated in the publication. We calculated risk ratios and 95% confidence intervals using Review Manager 5.4.1.

We continue to use the Cochrane Risk of Bias Tool [21].

GRADE Assessment

(section identical to the manuscript Dressler et al. 2017)

1. Risk of bias: downgraded in cases were one or more risk of bias category was high, or several categories were rated as unclear;
2. Inconsistency: downgraded if only one study available, if I^2 was larger than 60% or when estimates differed widely and the estimate of one study was not included in the confidence interval of another study;
3. Indirectness: downgraded if there were differences regarding study population or when the time of the outcome assessments differed;
4. Imprecision: downgraded when confidence intervals were very wide and when the confidence interval crossed the minimal clinical important difference (MID) threshold (s).
    - For the dichotomous outcomes ACR20/50 and adverse events/serious adverse events, the MIDs were set to be greater than 25% benefit (1.25) and greater than 25% harm (0.75).
    - For the Health Assessment Questionnaire Disability Index the MID is reported to be ±0.3 [22];
    - The MID for the Short Form Health Survey is ±3.5 for SF-36 PC and MC domains [22,23].
5. Publication bias: we did not assess publication bias (GRADE option “undetected”).

Results

We identified 315 records, 29 of which were duplicates. 286 title/abstracts were screened, of which we obtained the fulltext for the 14 hits that we included. Finally, 4 hits were included plus one study that had been excluded in 2019 (guselkumab).

We included 5 new studies: three studies evaluated guselkumab [24,25], one study compared adalimumab with placebo and upadaticinib (not included here) [26], and one study compared adalimumab and secukinumab [27]. A total of 27 studies are included in this update, see ‘included studies table’:

- 4 studies including head to head comparisons (one of which also includes a placebo arm)
- 5 studies on ADA vs. placebo (additional arms in one study evaluated TOF and in a second study UPA - not relevant here; and one study also included IXE)
- 5 studies on APR versus placebo

- 1 study on CERTO P vs. placebo
- 3 studies on GUS (new in 2021),
- 3 studies on ETA (one of which is a head-to-head trial comparing ETA vs. MTX)
- 3 studies on INF (one of which is a head-to-head comparing INF vs. MTX)
- 2 studies on IXE (one also includes ADA)
- 3 studies on MTX (two of which are head-to-head studies)
- 3 studies on UST vs. placebo
- 4 studies on SEC (one is head-to-head study vs. ADA)

Only four head-to-head comparisons could be included – the certainty of evidence was very low to moderate. A total of 12 placebo comparison were evaluated – the certainty of evidence was very low to high, see Table 4.

Original review (October 2019)

Methods

We adhered to the methods as reported in both of the above mentioned reviews. However, we modified the inclusion criteria from Dressler et al. The assessment time of the efficacy outcome modified American College of Rheumatology (ACR) criteria, was not only after 24 weeks but after 12 to 24 weeks since the start of treatment. Hence, studies that were excluded before were also reviewed for inclusion. Studies that were included in both systematic reviews were included in the update.

As safety outcome, we used the proportion of participants with at least one adverse events. We did not take into account guselkumab, bimekizumab and abatacept, because the European Medicines Agency (EMA) has not approved them for the treatment of psoriatic arthritis. We only included randomized controlled trials (RCTs) reporting efficacy outcome and/or safety outcome. The eligibility criteria can be seen in table below.

Inclusion criteria

Patients	Inclusion: diagnosis of PsA, Pso w/ PsA (at least 80% of the included patient population with PsA where no subgroup analysis was conducted) Adults Exclusion: Other diagnoses e.g. RA Inpatients ≤ 15 patients per study arm at point of randomization
Intervention	Inclusion: DMARDs: methotrexate (MTX), sulfasalazin (SSZ), cyclosporine (CSA) or leflunomide (LEF) Biologics: adalimumab (ADA), etanercept (ETA), golimumab (GOL), infliximab (INF), ustekinumab (UST), secukinumab (SEC), ixekizumab (anti IL17), certolizumab pegol (CZ), including biosimilars for ADA, ETA, GOL and INF Others: apremilast (APR) or tofacitinib (TOF) Exclusion: Guselkumab, bimekizumab and abatacept
Comparator	Inclusion: Comparisons with another included drug and/or placebo Dose comparison studies Exclusion: Comparison with same systematic drug and only different topical drug (in case of patients with primary plaque type psoriasis with sub-analysis for joints)
Outcomes	Inclusion: At least 1 of the following efficacy or safety outcomes at one time point within 12-24 weeks: Efficacy outcomes: 20% improvement in the ACR criteria Safety outcomes: percentage of patients with at least one AE

Study Design	Inclusion: Only RCTs (cross-over, parallel, cluster, factorial) Exclusion: Observational studies Abstracts

Information sources

We searched Medline (via Ovid) using the search strategy from Pham et al [13]. The update was run the 25 October 2019. The search contained subject headings and terms for psoriatic arthritis and drugs see end of this section.

Data collection, statistical analysis and study evaluation

Duplicates were removed. First, every hit underwent title and abstract screening. Secondly, records underwent full-text screening, both in accordance with the eligibility criteria. Only one reviewer conducted the update.

All records identified were managed with Endnote X8. Data was then extracted using a shorter version of the standardized extraction sheet, as displayed below.

First author	Drug	Study characteristic							Inclusion criteria		Baseline data					Withdrawals			Induction (16-24w): ACR20/50/70					SAE	
		Number (n) randomized	Study duration [w]	Extension	Number of AE withdrawals	Lost to follow-up	discontinuation due to other reasons	Concurrent treatment	Washout phase	Inclusion criteria as defined in the paper	Age	Age mean ±SD/ median (range)	TJC mean ±SD/ median	SJC mean ±SD / median (interquartile range)	HAQ mean±SD / median (interquartile range)	Female n [%]	Weight [kg mean±SD, median(range)]	Number of AE withdrawals	Lost to follow-up	discontinuation due to other reasons	Time of assessment [w]	N	ACR 20 n (%)	ACR 50 n (%)	ACR 70 n (%)	Time of assessment [w]	N (%) of patients with at least one SAE

One reviewer using the Cochrane risk of bias tool assessed the risk of bias of the included studies [28]. Each study was evaluated according to the following categories: random sequence generation, allocation concealment, building of participant and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias.

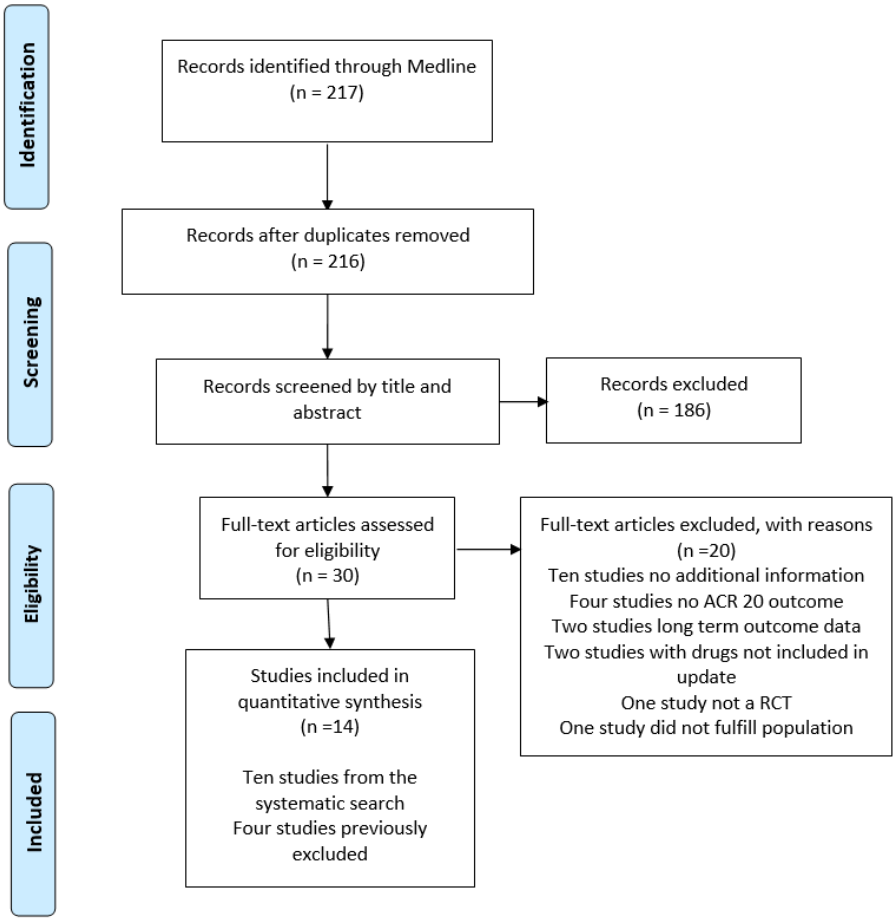
We extracted data from the number of participants as intention to treat(ITT) or modified ITT if available. Review manager 5.3 (RevMan) was used to calculate risk ratios as effect measure for dichotomous

outcomes and to estimate 95% confidence intervals. For meta-analyses, data was pooled using random effects model and heterogeneity was assessed with I2.

We utilized the GRADE approach [29] to assess the quality of evidence. Gradepro GDT was used to generate summary of findings table and data was imported from RevMan. We evaluated ACR20 and safety outcomes for each treatment comparison.

Results

The search yielded 217 records, 14 new studies were included.



Evidence to decision framework

We updated existing systematic reviews from Dressler et al. [9] and Pham et al.[13] , which had been developed by the same working group in parallel.

For the guideline, the recommendations focus on treatment options suitable and licensed for both conditions as the target group of this guideline are dermatologists, treating patients with moderate to severe psoriasis. The systematic review, however, was done for all treatment options licenced for psoriatic arthritis.

First we report the evidence to decision framework, thereafter the details of the systematic review update.

For patients with moderate to severe plaque type psoriasis and concomitant psoriatic arthritis, what are the clinical efficacy, safety and tolerability of approved (for both plaque type psoriasis and psoriatic arthritis) conventionals (methotrexate), biologics (adalimumab, brodalumab, certolizumab pegol, etanercept, infliximab, ixekizumab, secukinumab, ustekinumab) or small molecules (apremilast) compared with each other or with placebo?	
POPULATION:	Patients with moderate to severe psoriasis vulgaris and concomitant psoriatic arthritis
INTERVENTION:	Considered for the guideline recommendation(s): only systemic treatments approved for both plaque type psoriasis and psoriatic arthritis • conventional synthetic disease modifying anti rheumatic drugs (csDMARDs): MTX, • targeted synthetic (ts)DMARDS: apremilast, • biological (b)DMARDs: ADA, CZP, ETA, INF, UST, IXE, SEC
COMPARISON:	One of the above or placebo
MAIN OUTCOMES:	- Efficacy outcomes: 20% improvement in the mACR criteria - Safety outcomes: proportion of patients with at least one AE
SETTING:	- Region: Europe (study inclusion not limited to studies done in Europe) - Setting: clinical and practice (private and public) dermatologists
PERSPECTIVE:	- Population perspective
BACKGROUND:	- Concomitant psoriatic arthritis is frequent in patients with moderate to severe plaque type psoriasis. - Several new treatments have been developed and approved since the last version of the guideline, additional evidence is available as further studies have been performed and published. - Access to specialist care is limited and in many countries long waiting periods are required for specialist appointments, appropriate treatment choice from dermatologists for patients with concomitant psoriatic arthritis needs to be ensured. - It is important to note that specific subtypes of psoriatic arthritis exist (e.g. peripheral, axial, enthesitis, dactylitis) and that response rates to drugs may vary based on the subtype. Evidence synthesis updated based on Dressler et al and Pham et al.[9,13]
CONFLICT OF INTERESTS:	Less than 50% of the guideline development committee declared to have personal-financial conflicts of interests (see Methods & Evidence report of this guideline).

Needs Assessment

RESEARCH EVIDENCE

- Access to specialist care is limited and in many countries long waiting periods are required for specialist appointments, appropriate treatment choice from dermatologists for patients with concomitant psoriatic arthritis needs to be ensured.

Desirable Effects

How substantial are the desirable anticipated effects?

RESEARCH EVIDENCE

For details of systematic review, see below.
Psoriatic arthritis: Update of a systematic review on the systemic treatment of psoriatic arthritis

Summary of the results for drugs approved for psoriasis of the skin and psoriatic arthritis (Dressler et al [9] updated, below)

	Patients achieving ACR20		
	RR	95% CI	Quality of the Evidence (GRADE)
Head-to-head comparisons			
ETA 50mg + MTX vs. MTX 20mg QW	1.28	1.11 to 1.48	LOW
INF 5mg/kg W 0,2,6,14 + MTX vs. MTX 15mg QW	1.40	1.07 to 1.84	VERY LOW
IXE 80mg Q2W vs. ADA 40mg Q2W	1.08	0.86 to 1.36	LOW
IXE 80mg Q4W vs. ADA 40mg Q2W	0.96	0.86 to 1.06	LOW
Placebo comparisons			
ADA 40mg EOW vs. PBO	3.35	2.24 to 4.99	MODERATE
APR 30mg BID vs. PBO	1.94	1.59 to 2.38	MODERATE
APR 20mg BID vs PBO	1.86	1.49 to 2.31	MODERATE
CZP 400mg Q4W vs. PBO	2.36	1.68 to 3.31	MODERATE
CZP 200mg Q2W vs. PBO	2.71	1.95 to 3.76	MODERATE
ETA 25mg BIW vs. PBO	4.05	2.56 to 6.40	LOW
INF 5mg/kg W0,2,6,14vs. PBO	4.38	2.24 to 8.56	MODERATE
IXE 80mg Q2W vs. PBO	2.21	1.71 to 2.86	MODERATE
IXE 80mg Q4W vs. PBO	2.25	1.59 to 3.18	MODERATE
MTX 7.5mg QW vs. PBO	1.82	0.97 to 3.40	LOW
SEC 150mg Q4W vs. PBO	2.44	2.10 to 2.84	HIGH
SEC 150mg Q4W+ LD vs. PBO	2.06	1.70 to 2.49	HIGH
SEC 300mg Q4W + LD vs. PBO	2.28	1.87 to 2.80	MODERATE
UST 45mg W0,4, Q12W vs PBO	1.95	1.52 to 2.50	HIGH
UST 90mg W0,4, Q12W vs PBO	2.26	1.80 to 2.82	MODERATE

One study (Gottlieb et al. 2009) reported induction dose of QW (weeks 0-3). Abbreviations: ACR20 = 20% improvement in American College of Rheumatology response criteria; RR = risk ratio; 95% CI = 95% confidence interval; ETA = Etanercept; MTX = Methotrexate; mg = milligrams; QW= once a week; INF = Infliximab; kg = kilograms IXE = Ixekizumab; ADA = Adalimumab; Q2W = once every 2 weeks; EOW = every other week;

PBO = placebo; APR = Apremilast; BID = twice a day; CZP = Certolizumab Pegol; Q4W = once every 4 weeks; BIW = twice a week; W = week; Sec = Secukinumab; LD = loading dose; UST = Ustekinumab; Q12W = every 12 weeks.

Effects with regard to ACR 20 response from included treatment options versus placebo were considered as relevant. Difference in the effects of TNFi versus IL 17 antagonists with regard to ACR 20 were considered as irrelevant or of minor importance (indirect comparisons with relevant methodological limitations).

Undesirable Effects

How substantial are the undesirable anticipated effects?

RESEARCH EVIDENCE

For details of systematic review, see below.
Psoriatic arthritis: Update of a systematic review on the systemic treatment of psoriatic arthritis

Summary of the results for drugs approved for psoriasis of the skin and psoriatic arthritis (Dressler et al [9] updated, below)

	Patients with at least one adverse event		
	RR	95% CI	Quality of the Evidence (GRADE)
Head-to-head comparisons			
ETA 50mg + MTX vs. MTX 20mg QW	1.01	0.92 to 1.11	MODERATE
INF 5mg/kg W 0, 2, 6, 14 + MTX vs. MTX 15mg QW. MTX 15mg QW	1.65	1.08 to 2.52	VERY LOW
IXE 80mg Q2W vs. ADA 40mg Q2W	1.02	0.83 to 1.25	MODERATE
IXE 80mg Q4W vs. ADA 40mg Q2W	1.14	1.01 to 1.28	VERY LOW
Placebo comparisons			
ADA 40mg EOW vs. PBO	0.67	0.50 to 0.89	VERY LOW
APR 30mg BID vs. PBO	1.24	1.12 to 1.36	LOW
APR 20mg BID vs PBO	1.27	1.15 to1.41	LOW
CZP 400mg Q4W vs. PBO	1.05	0.90 to 1.23	MODERATE
CZP 200mg Q2W vs. PBO	1.01	0.86 to 1.19	MODERATE
ETA 25mg BIW vs. PBO	n.d.		
INF 5mg/kg W 0, 2, 6, 14 vs. PBO	1.13	0.87 to 1.47	LOW
IXE 80mg Q2W vs. PBO	1.39	1.09 to 1.78	LOW
IXE 80mg Q4W vs. PBO	1.41	1.10 to 1.79	LOW
MTX 7.5mg QW vs. PBO	n.d.		
SEC 150mg Q4W vs. PBO	1.03	0.95 to 1.12	HIGH
SEC 150mg Q4W **+ LD vs. PBO**	1.01	0.89 to 1.15	MODERATE
SEC 300mg Q4W **+ LD vs. PBO**	1.02	0.89 to 1.16	MODERATE
UST 45mg W 0, 4 and Q12W vs PBO	n.d.		
UST 90mg W 0, 4 and Q12W* **vs PBO**	0.96	0.75 to1.24	VERY LOW

*One study (Gottlieb et al. 2009) reported induction dose of QW (weeks 0-3). Abbreviations: RR = risk ratio; 95% CI = 95% confidence interval; ETA = Etanercept; MTX = Methotrexate; mg = milligrams; QW= once a week; INF = Infliximab; kg = kilograms IXE = Ixekizumab; ADA =

Adalimumab; Q2W = once every 2 weeks; EOW = every other week; PBO = placebo; APR = Apremilast; BID = twice a day; CZP = Certolizumab Pegol; Q4W = once every 4 weeks; BIW = twice a week; W = week; Sec = Secukinumab; LD = loading dose; UST = Ustekinumab; Q12W = every 12 weeks.

Assessment of undesirable effects was limited due to limited direct comparability of safety results and safety reporting. The assessments of undesirable effect with regard to the available data on "Patients with at least one adverse event" were considered not to be specific enough to guide general treatment recommendations. A treatment safety profile needs to be individually matched to a specific patient (see also other chapters on comorbid situations).

Certainty of evidence

What is the overall certainty of the evidence of effects?

	ACR20 - induction							Adverse Events - induction						
	Certainty assessment							Certainty assessment						
Comparison	№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Head-to-head comparisons:														
Etanercept 50mg+ MTX vs. Methotrexate 20 mg QW +PBO	1	RCT	not serious	not serious	serious[a]	serious[b]	none	1	RCT	not serious	not serious	serious[a]	not serious	none
	a. only 1 study available; b. 95% confidence limit crosses MID threshold (1.25) uncertain whether it is clinical important													
Infliximab 5mg/kg + MTX 15mg/w vs Methotrexate 15mg/w	1	RCT	serious[a]	serious[b]	not serious	serious[c]	none	1	RCT	serious[a]	serious[b]	not serious	serious[d]	none
	a. open-label RCT; small sample size; b. only one study available; c. 95% confidence limit crosses MID (1.25); statistically significant but clinical importance uncertain; d 95% confidence limit crosses line of appreciable harm (1.25); statistically significant but clinical importance uncertain													
Ixekizumab 80mg Q2W vs Adalimumab 40mg Q2W	1	RCT	not serious	serious[a]	not serious	serious[b]	none	1	RCT	not serious	serious[a]	not serious	not serious	none
	a. only one study available; b. 95% CI crosses line of no effect and MID threshold (1.25); uncertain whether there is any difference													
Ixekizumab 80mg Q4W vs. Adalimumab	1	RCT	very serious[a]	not serious	serious[b]	not serious	none	1	RCT	very serious[a]	not serious	serious[b]	serious[c]	none
	a. Open label RCT (RoB= high for allocation concealment and blinding); b. Only one study; c. 95% confidence limit crosses MID threshold (1.25); statistically significant but clinical importance uncertain													
Placebo comparisons:														
Adalimumab 40mg EOW vs. placebo	2	RCT	serious[a]	not serious	not serious	not serious	none	1	RCT	serious[b]	not serious	serious[c]	serious[d]	none
	a. unclear allocation concealment, randomization method and blinding (RoB = unclear 2/2), b. unclear blinding of personnel and patients (RoB=unclear 1/1) ,c. Only one study ,d. 95% confidence limit crosses lines of MID (0.75); uncertain whether it is clinical significant													
Apremilast 30mg BID vs. placebo	5	RCT	serious[a]	not serious	not serious	not serious	none	5	RCT	serious[a]	not serious	not serious	serious[b]	none

	a. unclear allocation concealment and randomization methods in 4 of 5 RCTs (ROB = unclear 5/5 RCTs);b. 95% confidence limit crosses MID threshold (1.25); statistically significant but clinical importance uncertain													
Apremilast 20mg BID vs. placebo	4	RCT	serious[a]	not serious	not serious	not serious	none	4	RCT	serious[a]	not serious	not serious	serious[b]	none
	a. unclear allocation concealment and randomization methods in 3 of 4 RCTs (RoB=unclear 4/4); b. 95% confidence limit crosses MID threshold (1.25); statistically significant but clinical importance uncertain													
Certolizumab pegol 400mg Q4W vs placebo	1	RCT	not serious	serious[a]	not serious	not serious	none	1	RCT	not serious	serious[a]	not serious	not serious	none
	a. only one study available													
Certolizumab pegol 200mg Q2W vs placebo	1	RCT	not serious	serious[a]	not serious	not serious	none	1	RCT	not serious	serious[a]	not serious	not serious	none
	a. only one study available													
Etanercept 25mg BIW vs. placebo	2	RCT	very serious[a]	not serious	not serious	not serious	none	no data	no data	no data	no data	no data	no data	no data
	a. unclear randomization and allocation concealment, and high incomplete outcome data (RoB= unclear 1/2 and high 1/2)													
Infliximab 5mg/kg W0, 2, 6, 14 vs placebo	2	RCT	not serious	not serious	serious[a]	not serious	none	1	RCT	not serious	serious[b]	not serious	serious[c]	none
	a. data was pooled across 16 and 24 weeks (IMPACT: 16weeks, IMPACT2: 24 weeks, the latter included early escape options and hence more NRI for early escapers); b. only one study available; c. 95% confidence limit crossed lines of no effect and appreciable harm; uncertain whether there is any difference													
Ixekizumab 80mg Q2W vs placebo	2	RCT	not serious	not serious	serious[a]	not serious	none	1	RCT	not serious	serious[b]	not serious	serious[c]	none
	a. different inclusion criteria (bDMARD naive vs. non-responder to 1 or 2 anti TNF alpha); b. only one study available; c. 95% confidence limit crosses MID (1.25); statisticially significant but clinical importance uncertain													
Ixekizumab 80mg Q4W vs placebo	2	RCT	not serious	not serious	serious[a]	not serious	none	1	RCT	not serious	serious[b]	not serious	serious[c]	none
	a. different inclusion criteria (bDMARD naive vs. non-responder to 1 or 2 anti TNF alpha); b. only one study available; c. 95% confidence limit crosses MID threshold (1.25); statistically significant but clinical importance uncertain													
Methotrexate 7.5mg/w vs placebo	1	RCT	not serious	serious[a]	not serious	serious[b]	none	no data	no data	no data	no data	no data	no data	no data
	a. only one study available; b. 95% confidence limit crosses lines of no effect and MID threshold (1.25); uncertain whether there is any difference													
Sekucinumab 150mg vs. placebo	5	RCT	not serious	not serious	not serious	not serious	none	4	RCT	not serious	not serious	not serious	not serious	none
Secukinumab 150mg+LD vs. placebo	2	RCT	not serious	not serious	not serious	not serious	none	1	RCT	not serious	not serious	serious[a]	not serious	none
	a. Only one study													
Secukinumab 300mg+LD vs. placebo	1	RCT	not serious	not serious	serious[a]	not serious	none	1	RCT	not serious	not serious	serious[a]	not serious	none
	a. Only one study													
Ustekinumab 45mg W0, 4 and Q12W vs placebo	2	RCT	not serious	not serious	not serious	not serious	none	no data	no data	no data	no data	no data	no data	no data
Ustekinumab 90mg W0, 4 and Q12W vs placebo	3	RCT	serious[a]	not serious	not serious	not serious	none	1	RCT	serious[a]	not serious	serious[b]	serious[c]	none
	a. unclear selective outcome reporting 1 of 3 RCTs (RoB = unclear 1/3 and low 2/3); b. only one study; c. 95% confidence interval crosses line of no effect and (0.75), wide confidence interval													

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

ACR 20 reflects on a minimum response of 20% improvement to baseline. Higher improvement percentages will be valued more. ACR is a composite score measuring number of tender and number of swollen joints but also includes patient/physician global assessment as well as pain and functional ability. A stronger focus on patient reported outcomes and quality of life measurements may be valued more by some people.

For safety outcomes see above. In general, direct comparison for safety are hampered by a lack of standardised importance and people may value adverse events and safety profile very differently

Balance of effects

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

Indirect evidence for this from above (evidence to decision table for Plaque type psoriasis) can be taken into consideration for this.

Equity

What would be the impact on health equity?

RESEARCH EVIDENCE

- Costs remain barrier to prescribing biologics [30]
- In addition, national regulations and reimbursement situation need to be taken into consideration and treatment algorithms need to be adapted to regional or national specific circumstances.

Acceptability

Is the intervention acceptable to key stakeholders?

RESEARCH EVIDENCE

- Patients are first interested in safety followed by efficacy of treatments, with some variations [31]
- Sociodemographic factors play a role; access and delivery are important attributes
- Costs and drug licencing limit the use of expensive treatment of treatments having a “second line label”.

Recommendations

See main guideline

Justification

Recommendations were drafted along the line of drug licensing, taking practical aspect of reimbursement into account. National societies may develop different recommendations reflecting the national reimbursement situation.

For most patients MTX is considered as the first treatment option.(recommendation based on label, long term experience, price, efficacy, safety). .

In case of non-response, TNFs, anti IL12/23 and anti IL17 are considered the alternatives (recommendation based on label, price, efficacy, safety).

Previously, guidelines have given a preference to TNF alpha antagonists over other bDMARDs. In the guideline group's view, a preference for inhibitors of TNF treatments for PsA is no longer mandatory, since the IL-17A antibody treatments might be equally effective, however more data are needed for its real-life long term efficacy, safety and co-medication.

For the selection of a treatment among the anti TNF alpha antagonists and the anti IL17 directed antibodies, no clear hierarchy has been decided upon by the guideline group.

Subgroup considerations

This is already a subgroup, other comorbid conditions are discussed in other chapters.

Implementation considerations

The main barrier to implementation may be the national/local limitation to drug reimbursement, making the prescription of costly treatments difficult.

Monitoring and evaluation

Monitoring and evaluation is to be done on national levels.

- Change in practice performance
- Change in health outcomes
- Change in end-user knowledge and understanding

As an example for national monitoring and evaluation strategies, see BAD [32]or for an example of a cross sectional survey about psoriasis patient care [33]

Research priorities

- -Which treatment is most suitable for specific subtypes of psoriatic arthritis exist (e.g. peripheral, axial, enthesitis, dactylitis)
- How can treatment response be predicted?
- -What is the role of therapeutic drug monitoring?

- -When should a treatment be stopped in case of ceased pain?
- -Which treatments can be combined safely and lead to improved efficacy?

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Appendix 1

Search Name: PsA update search 11/2022
Date Run: 16/11/2022
Comment: including Deucra

ID	Search	Hits
#1	(arthritis psoriatic):ti,ab,kw	
#2	MeSH descriptor: [Arthritis, Psoriatic] explode all trees	
#3	(psoria* NEAR/3 arthr*):ti,ab,kw	
#4	#1 or #2 or #3	2828
#5	MeSH descriptor: [Adalimumab] explode all trees	
#6	(adalimumab):ti,ab,kw	3670
#7	(apremilast):ti,ab,kw	526
#8	MeSH descriptor: [Certolizumab Pegol] explode all trees	
#9	("certolizumab pegol"):ti,ab,kw	
#10	MeSH descriptor: [Etanercept] explode all trees	
#11	(etanercept):ti,ab,kw	
#12	MeSH descriptor: [Infliximab] explode all trees	
#13	(infliximab):ti,ab,kw	
#14	(ixekizumab):ti,ab,kw	
#15	MeSH descriptor: [Methotrexate] explode all trees	
#16	(methotrexate):ti,ab,kw	
#17	(MTX):ti,ab,kw	
#18	(secukinumab):ti,ab,kw	
#19	MeSH descriptor: [Ustekinumab] explode all trees	
#20	(ustekinumab):ti,ab,kw	
#21	(risankizumab):ti,ab,kw	
#22	(guselkumab):ti,ab,kw	
#23	#5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22	
#24	#4 and #23 with Cochrane Library publication date Between Feb 2022 and Nov 2022	
#25	(deucravacitinib):ti,ab,kw	
#26	#4 and #25	
#27	#24 or #26	

Appendix 2

Search strategy CENTRAL for Update 2 (February 2022)

ID	Search	Hits
#1	(arthritis psoriatic):ti,ab,kw	
#2	MeSH descriptor: [Arthritis, Psoriatic] explode all trees	
#3	(psoria* NEAR/3 arthr*):ti,ab,kw	
#4	#1 or #2 or #3	2574
#5	MeSH descriptor: [Adalimumab] explode all trees	
#6	(adalimumab):ti,ab,kw	
#7	(apremilast):ti,ab,kw	
#8	MeSH descriptor: [Certolizumab Pegol] explode all trees	
#9	("certolizumab pegol"):ti,ab,kw	
#10	MeSH descriptor: [Etanercept] explode all trees	
#11	(etanercept):ti,ab,kw	
#12	MeSH descriptor: [Infliximab] explode all trees	
#13	(infliximab):ti,ab,kw	
#14	(ixekizumab):ti,ab,kw	
#15	MeSH descriptor: [Methotrexate] explode all trees	
#16	(methotrexate):ti,ab,kw	
#17	(MTX):ti,ab,kw	
#18	(secukinumab):ti,ab,kw	
#19	MeSH descriptor: [Ustekinumab] explode all trees	
#20	(ustekinumab):ti,ab,kw	
#21	(guselkumab):ti,ab,kw	
#22	(risankizumab):ti,ab,kw	
#23	#5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22	
#24	#4 and #23	

Appendix 3

Search strategy CENTRAL for Update 1 (May 2021)

ID	Search
#1	(arthritis psoriatic):ti,ab,kw (Word variations have been searched)
#2	MeSH descriptor: [Arthritis, Psoriatic] explode all trees
#3	(psoria* adj. arthr*):ti,ab,kw (Word variations have been searched)
#4	(psoria* NEAR/3 arthr*):ti,ab,kw (Word variations have been searched)
#5	#1 or #2 or #3 #4
#6	MeSH descriptor: [Adalimumab] explode all trees
#7	(adalimumab):ti,ab,kw
#8	(apremilast):ti,ab,kw
#9	MeSH descriptor: [Certolizumab Pegol] explode all trees
#10	(Certolizumab Pegol):ti,ab,kw
#11	MeSH descriptor: [Etanercept] explode all trees
#12	("etanercept"):ti,ab,kw
#13	(guselkumab):ti,ab,kw
#14	MeSH descriptor: [Infliximab] explode all trees
#15	(infliximab):ti,ab,kw
#16	(Ixekizumab):ti,ab,kw
#17	MeSH descriptor: [Methotrexate] explode all trees
#18	("methotrexate"):ti,ab,kw
#19	(MTX):ti,ab,kw
#20	(Secukinumab):ti,ab,kw
#21	MeSH descriptor: [Ustekinumab] explode all trees
#22	("ustekinumab"):ti,ab,kw
#23	#6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22
#24	#5 and #23
#25	#24 with Publication Year from 2019 to 2021, in Trials

Appendix 4

Search strategy for 2019 update (MEDLINE only) to inform development of EuroGuiDerm guideline

The results are summarized below. Full data extraction tables of the studies including during this update are available upon request from euroguiderm@debm.de

Search strategy for the review on psoriasis arthritis: MEDLINE OVID; from Pham et al 2019

#	Searches		
1	exp Arthritis, Psoriatic/	32	30 and 31
2	(Psoria* adj3 arthr*).ab,ti.	33	Randomized Controlled Trials as Topic/
3	exp Antibodies, Monoclonal/	34	randomized controlled trial/
4	exp Adalimumab/	35	Random Allocation/
5	adalimumab.ab,ti.	36	Double Blind Method/
6	exp Certolizumab Pegol/	37	Single Blind Method/
7	certolizumab pegol.ab,ti.	38	clinical trial/
8	exp Ustekinumab/	39	clinical trial, phase i.pt.
9	ustekinumab.ab,ti.	40	clinical trial, phase ii.pt.
10	exp Infliximab/	41	clinical trial, phase iii.pt.
11	infliximab.ab,ti.	42	clinical trial, phase iv.pt.
12	exp Etanercept/	43	controlled clinical trial.pt.
13	etanercept.ab,ti.	44	randomized controlled trial.pt.
14	golimumab.ab,ti.	45	multicenter study.pt.
15	secukinumab.ab,ti.	46	clinical trial.pt.
16	guselkumab.ab,ti.	47	exp Clinical Trials as topic/
17	ixekizumab.ab,ti.	48	or/33-47
18	apremilast.ab,ti.	49	(clinical adj trial$).tw.
19	tofacitinib.ab,ti.	50	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.
20	biologic*.ab,ti.	51	PLACEBOS/
21	(DMARD* or diseas* modif* anti?rheuma* drug* or (anti?rheuma* adj2 drug*) or (anti?rheuma* adj2 agent*) or (monoclonal adj2 antibod*)).ab,ti.	52	placebo$.tw.
22	exp Antirheumatic Agents/	53	randomly allocated.tw.
23	exp Methotrexate/	54	(allocated adj2 random$).tw.
24	(MTX* or methotrexat*).ab,ti.	55	or/49-54
25	exp Sulfasalazine/	56	48 or 55
26	(sulfazalazin* or sulphasalazin* or sulphazalazin* or sulfasalazin* or SSZ*).ab,ti.	57	case report.tw.
27	exp Cyclosporine/	58	letter/
28	(cyclosporin* or ciclosporin* or csa*).ab,ti.	59	historical article/
29	(leflunomid* or lef*).ab,ti.	60	or/57-59
30	1 or 2	61	56 not 60
31	3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29	62	32 and 61

Excluded full-texts with reasons:

Author	Year	Title	Reason for exclusion
I. B. McInnes, et al.	2017	Secukinumab sustains improvement in signs and symptoms of psoriatic arthritis: 2 year results from the phase 3 FUTURE 2 study	(no additional information, same study)
D. van der Heijde, et al.	2018	4-year results from the RAPID-PsA phase 3 randomised placebo-controlled trial of certolizumab pegol in psoriatic arthritis	(no additional information)
D. van der Heijde, et al.	2018	Efficacy and Safety of Ixekizumab in Patients with Active Psoriatic Arthritis: 52-week Results from a Phase III Study (SPIRIT-P1)	(no additional information)
J. A. Walsh, et al.	2018	Efficacy of certolizumab pegol with and without concomitant use of disease-modifying anti-rheumatic drugs over 4 years in psoriatic arthritis patients: results from the RAPID-PsA randomized controlled trial	(long term data study already included by dressler)
L. C. Coates, et al.	2018	Secukinumab provides sustained PASDAS-defined remission in psoriatic arthritis and improves health-related quality of life in patients achieving remission: 2-year results from the phase III FUTURE 2 study	(no additional information)
S. Cohen, et al.	2019	Decreased Injection Site Pain Associated with Phosphate-Free Etanercept Formulation in Rheumatoid Arthritis or Psoriatic Arthritis Patients: A Randomized Controlled Trial	(no ACR20 outcome)
S. Dauth, et al.	2018	[Value of combining biologics with methotrexate for treatment of psoriatic arthritis-questions remain]	(no RCT)
H. M. Y. de Jong, et al.	2019	Sustained remission with methotrexate monotherapy after 22-week induction treatment with TNF-alpha inhibitor and methotrexate in early psoriatic arthritis: an open-label extension of a randomized placebo-controlled trial	(no ACR20 outcome)
A. Deodhar, et al.	2018	Efficacy and safety of guselkumab in patients with active psoriatic arthritis: a randomised, double-blind, placebo-controlled, phase 2 study	(not approved by EMA for PsA)
M. C. Genovese, et al.	2018	Safety and efficacy of ixekizumab in patients with PsA and previous inadequate response to TNF inhibitors: week 52 results from SPIRIT-P2	(no additional information)
S. Glatt, et al.	2018	Dual IL-17A and IL-17F neutralisation by bimekizumab in psoriatic arthritis: evidence from preclinical experiments and a randomised placebo-controlled clinical trial that IL-17F contributes to human chronic tissue inflammation	(not approved by EMA for PsA)
A. B. Gottlieb, et al.	2018	Ixekizumab improves patient-reported outcomes up to 52 weeks in bDMARD-naive patients with active psoriatic arthritis (SPIRIT-P1)	(no additional info)
M. Haroon, et al.	2018	Inflammatory back pain in psoriatic arthritis is significantly more responsive to corticosteroids compared to back pain in ankylosing spondylitis: a prospective, open-labelled, controlled pilot study	(no ACR20 outcome, pilot study)

A. Kavanaugh, et al.	2019	Radiographic Progression Inhibition with Intravenous Golimumab in Psoriatic Arthritis: Week 24 Results of a Phase III, Randomized, Double-blind, Placebo-controlled Trial	(no additional info)
A. Kavanaugh, et al.	2019	Ixekizumab improves patient-reported outcomes in patients with active psoriatic arthritis and inadequate response to tumour necrosis factor inhibitors: SPIRIT-P2 results to 52 weeks	(no additional info SPIRIT p2)
I. B. McInnes, et al.	2018	Secukinumab provides rapid and sustained pain relief in psoriatic arthritis over 2 years: results from the FUTURE 2 study	(no additional info)
M. Ohtsuki, et al.	2019	Efficacy and safety of risankizumab in Japanese patients with moderate to severe plaque psoriasis: Results from the SustaIMM phase 2/3 trial	(Fewer than 20% of patients in any treatment group had psoriatic arthritis)
V. Strand, et al.	2019	Effect of tofacitinib on patient-reported outcomes in patients with active psoriatic arthritis and an inadequate response to tumour necrosis factor inhibitors in the phase III, randomised controlled trial: OPAL Beyond	(a same trial opal beyond data in ANN no outcome of interest)
V. Strand, et al.	2019	Tofacitinib or adalimumab versus placebo: patient-reported outcomes from OPAL Broaden-a phase III study of active psoriatic arthritis in patients with an inadequate response to conventional synthetic disease-modifying antirheumatic drugs	(no additional info same trial OPAL Broaden ANN)
D. van der Heijde, et al.	2019	Secukinumab provides sustained low rates of radiographic progression in psoriatic arthritis: 52-week results from a phase 3 study, FUTURE 5	(long term outcomes)
M. L. M. Mulder et al.	2022	Comparing methotrexate monotherapy with methotrexate plus leflunomide combination therapy in psoriatic arthritis (COMPLETE-PsA): a double-blind, placebo-controlled, randomised, trial	(no full-text available
I. B. McInnes et al.	2022	Long-Term Efficacy and Safety of Guselkumab, a Monoclonal Antibody Specific to the p19 Subunit of Interleukin-23, Through Two Years: results From a Phase III, Randomized, Double-Blind, Placebo-Controlled Study Conducted in Biologic-Naive Patients With Active Psoriatic Arthritis	(no relevant outcomes)
J. Ruwaard et al.	2022	Interval prolongation of etanercept in rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis: a randomized controlled trial	(no relevant outcomes)
S. W. Syversen et al.	2022	Effect of Therapeutic Drug Monitoring vs Standard Therapy During Maintenance Infliximab Therapy on Disease Control in Patients With Immune-Mediated Inflammatory Diseases: a Randomized Clinical Trial	(no relevant outcomes)
L. C. Coates et al.	2022	Efficacy and safety of guselkumab in patients with active psoriatic arthritis who are inadequate responders to tumour necrosis factor inhibitors: results through one year of a phase IIIb, randomised, controlled study (COSMOS)	(already included)
L. E. Kristensen	2022	Efficacy and safety of risankizumab for active psoriatic arthritis: 24-week results from the randomised, double-blind, phase 3 KEEPsAKE 2 trial	(already included)
A. Östör	2022	Efficacy and safety of risankizumab for active psoriatic arthritis: 24-week results from the randomised, double-blind, phase 3 KEEPsAKE 2 trial	(already included)
A. F. Wells	2022	Apremilast monotherapy for long-term treatment of active psoriatic arthritis in DMARD-naïve patients	(already included)