Cancer: How should psoriasis patients with a history of malignancies be managed?

This chapter is based on the corresponding chapter in the previous versions of the guideline[1-3]. A search was conducted, details of which can be found below**.**

Results/Answer:

Theoretically, immunomodulatory therapies used for psoriasis have the potential to affect the course of a malignant disease, and the safety of using them in this context is uncertain.

In clinical practice, different scenarios are associated with different risks and the answer might not be the same for each of them. Patients can present with pre-cancer (such as cervical dysplasia, colonic polyps or Barrett's esophagus), low risk cancer (NMSC, cancer with a long period of non-recurrence, usually defined as more than 5 years), or high-risk cancer (active cancer, recent aggressive cancer).

Available evidence to guide clinicians in these situations is scarce. Patients with malignancies are excluded from randomized clinical trials, so RCTs will not provide valid answers. Information about patients with previous cancer can only come from observational studies, which are less valid, as they are commonly affected by confounding by indication. There are techniques that can help control for this type of confounding, but these kinds of analyses require large numbers of patients that are difficult to enroll. This power issue is the reason for results usually being given for different cancers merged and also for different drugs grouped.

Most of the data available is of marginal relevance to this question:

Overall risk of cancer in psoriasis:

Psoriasis is associated with increased mortality due to many diseases, including an increased risk of cancer. It is not clear whether this is due to the disease itself, or is influenced by lifestyle factors (mainly alcohol and smoking) or therapy [4].

A recent systematic review and meta-analysis of 112 observational cohort studies of patients with psoriasis and psoriatic arthritis revealed a slightly increased risk of several cancer types, particularly keratinocyte cancer and lymphoma [5].

Association of therapy and incident cancer in psoriasis and other immune-mediated disease:

Some studies have studied the possible association of the use of systemic therapies for psoriasis and incident of cancer (in patients without previous history of cancer).

A systematic review of RCTs and observational studies exploring the risk of cancer in psoriasis patients treated with biologics described an increased risk of non-melanoma skin cancer in those patients being treated with TNFi. However, included studies lacked adjustment for highly relevant confounding factors such as prior phototherapy. Data on other cancers do not show a risk associated with exposure to drugs. However, the studies are likely to be underpowered to ascertain the risk of individual types of cancer.[6] The chapter authors also consider extensive light damage resulting from repeated and prolonged sunbathing as a significant confounding factor, as per their perspective.

Vaengebjerg et al did not find increased risk of cancer in patients with psoriasis and psoriatic arthritis on biologics compared with other systemic therapies [5]. Similarly, recent data has not shown an increase in the incidence of cancer in patients treated with secukinumab [7]or tildrakizumab, but these studies are based on RCT patients and do not have untreated comparison populations.[8]

There are also some studies describing the risk of cancer associated with systemic therapy for other immune-mediated disorders, mainly rheumatoid arthritis, other rheumatic disorders and inflammatory bowel disease. Results in these disorders might not be appropriately extrapolated to psoriasis patients, as psoriatic patients receive less immunosuppressive therapy (specially corticosteroids) and the associated disorders are different [9].

Most studies are reassuring and did not find a relationship between exposure to TNFi and risk of incident cancer in rheumatoid arthritis and psoriatic arthritis [10]. Luo et al, analyzing data from nine cohorts, described an increased risk of cancer in psoriatic arthritis patients treated with disease modifying antirheumatic drugs, which was not seen in patients receiving biologics. However, this increase was due to NMSC and included studies have not considered the likely effect of previous PUVA therapy [11]. SmPCs of TNFi contain information regarding the risk of lymphoma/leukemia. However, these are rare events and data supporting this association are conflicting. So far no such association have been shown for psoriasis patients [6].

Risk of cancer recurrence in patients exposed to systemic therapy for psoriasis:

Few studies provide information that is relevant for answering this question.

Regarding patients with precancerous conditions (data available only for cervical dysplasia), a study using routine data of women with rheumatoid arthritis (RA), describe that initiation of therapy with a biological disease-modifying anti-rheumatic drug (bDMARD) was associated with an increased, but not statistically significant, risk of high-grade cervical dysplasia or cervical cancer compared to initiation of a nonbiological (nb)DMARD [12]. Conversely, a review analyzing 238 women with RA and a history of cervical carcinoma in situ, no genital cancer was observed in the TNFi-treated group over a median of 5.2 years of follow-up compared with two incidents of genital cancer in the nbDMARD-treated group, during a median follow-up of 3.9 years [13].

A systematic review of patients with a history of cancer and exposed to TNFi therapy assessing for the risk of the occurrence of new cancer or cancer re-ocurrence compared to non-biologic disease modifying antirheumatic drugs (DMARD), included nine studies with 11679 patients. None of them where studies on psoriasis. The outcome measures were heterogeneous, with many studies focused on describing NMSC. Overall, the study did not find an increased risk of recurrence in patients treated with TNFi compared to nbDMARD [14].

A retrospective study, based on routine data, of patients with rheumatoid arthritis and inflammatory bowel disease, and a previous NMSC, described an increased risk of a second NMSC in patients treated with methotrexate that was higher with longer exposures. TNFi use was also associated with an increased risk, mostly in a subgroup (patients with RA and concomitant use of methotrexate). [15]

Another systematic review analyzed the risk of cancer recurrence in patients with immune-mediated diseases exposed to immune-suppressive therapies. They included 16 observational studies with 11702 participants after a cancer diagnosis and with 1698 new or recurrent cases of cancer. Only one very small study, and not contributing to the final analysis, was focused on psoriasis patients. Overall, rates of cancer recurrence were similar among participants receiving TNFi therapy, immune-modulator therapy or no immunosuppression, but was higher among patients receiving combination immune suppression [16].

French guidelines have reviewed the risk of cancer associated with systemic therapies. Ciclosporine has been clearly linked to an increased risk of cancer and a recommendation to avoid it has been issued. Evidence from larger patient cohort over long periods of time on the risk of the newer drugs such as the anti IL 17, anti 23 antibodies and apremilast is still very scarce. [17] From a theoretical point of view, acitretin has lower efficacy but might also have the lowest risk in these patients. Phototherapy is associated with skin cancer, but not with other cancers. Although evidence is not strong, there does

not seem to be a difference in risk with methotrexate and TNFi, except for a possible increase in risk of NMSC for methotrexate [17].

We **recommend** taking the burden of psoriasis, and the risk of cancer worsening or recurrence (pre-cancer vs low risk vs high risk) into account for shared therapeutic decision making.	↑↑	
For patients with recent malignancy we **recommend** topical therapies, phototherapy (narrow band UVB) * and/or acitretin. *except patients with a recent, and/or high risk of cutaneous malignancy	↑↑	
We **recommend** to discuss the decision to initiate immunosuppressive therapies, in psoriasis patients with a current or recent diagnosis of cancer in the previous five years case-by-case with cancer specialists and to reach an informed decision, respecting the patient's preference.	↑↑	
In case of inadequate response to topical therapies, phototherapy, (narrow band UVB) and/or acitretin we **suggest** using MTX in psoriasis patients with a previous history of cancer.* *(*for patients with history of non melanoma skin cancer, see background text)*	↑	STRONG CONSENSUS[1] 100 % Agreement EXPERT CONSENSUS
We **suggest** apremilast can be used in psoriasis patients with a previous history of cancer despite the lack of long term experience based on pathophysiological considerations on a case-by-case basis including discussion with cancer specialist	↑	
We **suggested against** using ciclosporin in psoriasis patients with a previous history of cancer.	↓	
We **suggest** TNFi, ustekinumab can be used based on existing safety data on a case-by-case basis including discussion with cancer specialist. We **suggest** anti-IL17, anti-IL23 can be used in psoriasis patients with a previous history of cancer despite the lack of long term experience based on pathophysiological considerations on a case-by-case basis including discussion with a cancer specialist.	↑	

[1] due to personal-financial conflict of interest 3 abstentions

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Review of the evidence on psoriasis and cancer

Methods

Inclusion criteria

Patients	Inclusion: adult patients with a clinical diagnosis of psoriasis and ▪ No malignancy in history ▪ pre-cancer (such as cervical dysplasia, colonic polyps or Barrett's esophagus), ▪ low risk cancer (NMSC, cancer with a long period of non-recurrence, usually defined as more than 5 years), ▪ high-risk cancer (active cancer, recent aggressive cancer), ▪ or history of malignancy
Intervention	Conventional systemic treatment (acitretin, apremilast, ciclosporin, fumarates, methotrexate) and biologicals (anti TNF alpha: adalimumab, etanercept, certolizumab pegol, infliximab; anti-IL12/23: ustekinumab; anti-IL17: bimekizumab, brodalumab, ixekizumab, secukinumab; anti-IL23: guselkumab, risankizumab, tildrakizumab; tyrosine kinase 2 (TYK2) inhibitor: deucravacitinib (new))
Comparator	Comparisons with another included drug and/or placebo
Outcomes	Incidence of cancer Risk of cancer recurrence Other safety concerns
Study Design	Inclusion: Systematic reviews, guidelines Exclusion: randomized controlled trials, clinical trials (with and without comparison group), cohort studies, case control studies and cross sectional studies, case series, case reports, retrospective studies with less than 100 patients, non-systematic reviews, letter, comments

Information source and screening process

The search strategy was updated and the database MEDLINE via Ovid (from 1946) was searched for the period September 2019 to 11 January 2023. One methodologist conducted a topic specific but non-systematic screening. Afterwards, the authors of the chapter screened full texts based on the above listed eligibility criteria.

Search strategy

Filter for detecting systematic reviews: Wong SSL, Wilczynski NL, Haynes RB. Comparison of top-performing search strategies for detecting clinically sound treatment studies and systematic reviews

in MEDLINE and EMBASE. J Med Libr Assoc 2006; 94(4): 451-455. https://pubmed.ncbi.nlm.nih.gov/17082841/ (High specificity strategy)

Filter for detecting guidelines: Lunny C, Salzwedel D M, Liu T, Ramasubbu C, Gerrish S, Puil L, Mintzes B, Wright J M. Validation of five search filters for retrieval of clinical practice guidelines produced low precision. J Clin Epidemiol 2019. 117:109-116. https://pubmed.ncbi.nlm.nih.gov/31610216/ (CADTH narrow – see Publication appendix 1)

Ressource: Ovid MEDLINE(R) ALL <1946 to January 11, 2023>

ID	Search term	Result
1	exp Neoplasms/	3779499
2	neoplasm.ti,ab.	64174
3	malignan*.ti,ab.	663610
4	malignom*.ti,ab.	796
5	cancer*.ti,ab.	2137123
6	lymphom*.ti,ab.	200257
7	carcinom*.ti,ab.	743752
8	tumor*.ti,ab.	1685080
9	tumour*.ti,ab.	298690
10	**or/1-9**	**4930505**
11	exp Psoriasis/	46840
12	Psoria*.ti,ab.	57169
13	palmoplantar$ pustulosis.ti,ab.	664
14	pustulosis palmaris et plantaris.ti,ab.	173
15	(pustulosis and palms and soles).ti,ab.	107
16	**or/11-15**	**63906**
17	10 and 16	10014
18	("201909*" or "201910*" or "201911*" or "201912*" or "2020*" or "2021*" or "2022*" or "2023*").dt.	5093719
19	17 and 18	1802
20	cochrane database of systematic reviews.jn. or search.tw. or meta analysis.pt. or MEDLINE.tw. or systematic review.tw.	657794
21	(guideline or practice guideline or consensus development conference or consensus development conference, NIH).pt. or (guideline* or standards or consensus* or recommendat*).ti. or (practice parameter* or position statement* or policy statement* or CPG or CPGs or best practice*).ti. or (care adj2 (path or paths or pathway or pathways or map or maps or plan or plans or standard)).ti. or ((critical or clinical or practice) adj2 (path or paths or pathway or pathways or protocol*)).ti. or (algorithm* and (pharmacotherap* or chemotherap* or chemotreatment* or therap* or treatment* or intervention*)).ti. or (algorithm* and (screening or examination or test or tested or testing or assessment* or diagnosis or diagnoses or diagnosed or diagnosing)).ti.	239503

ID	Search term	Result
22	**20 or 21**	**883463**
23	**19 and 22**	**166**

Documented search for guidelines on psoriasis and cancer

We did not identify guidelines with our search in PubMed. Guidelines, which were cited in the previous version of the EuroGuiDerm Psoriasis, have not been updated yet. Therefore, we conducted a documented search in guideline databases and interdisciplinary guideline providers.

Update search for guidelines already cited in previous version (February 2022)

Search date: 16 January 2023

Amatore F, Villani AP, Tauber M, et al. French guidelines on the use of systemic treatments for moderate-to-severe psoriasis in adults. J Eur Acad Dermatol Venereol 2019;33(3):464-83. doi: 10.1111/jdv.15340 [published Online First: 02/22]

- Search in https://www.sfdermato.org/page-24-recommandations: no update identified

Holroyd CR, Seth R, Bukhari M, et al. The British Society for Rheumatology biologic DMARD safety guidelines in inflammatory arthritis. Rheumatology 2018;58(2):e3-e42. doi: 10.1093/rheumatology/key208

- Search in https://www.rheumatology.org.uk/practice-quality/guidelines: no update identified

Lewinsohn DM, Leonard MK, LoBue PA et al. Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention Clinical Practice Guidelines: Diagnosis of Tuberculosis in Adults and Children. Clin Infect Dis 2017; 64: 111-5

- Search in https://www.cdc.gov/tb/publications/guidelines/testing.htm: no update identified

Documented guideline search

Search terms

Psoriasis, inflammatory bowel disease, rheumatoid arthritis, ankylosing spondylitis, psoriasis arthritis

Explanation: A search for other disease than psoriasis was conducted to identify information on a possible association between drugs, prescribed for different conditions, and the risk of malignancy.

Search date

18 January 2023

Limits

Published after 2019

List of guideline databases and interdisciplinary guideline providers

- Guidelines Central, US
    - Hits per search term: 17/ 17/ 10/ 6 /7; 3 included:
    - Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with awareness and attention to comorbidities (https://www.jaad.org/article/S0190-9622(18)33002-0/fulltext), p. 1098

  - Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with biologics (https://www.jaad.org/article/S0190-9622(18)33001-9/fulltext), e.g. pp. 1043, 1048, 1053, 1054
  - Joint American Academy of Dermatology - National Psoriasis Foundation guidelines of care for the management of psoriasis with systemic nonbiologic therapies (https://pubmed.ncbi.nlm.nih.gov/32119894/), e.g. pp 1463, 1472

- Tripdatabase (UK)
  - Only search terms psoriasis (n=99, 0 included) and psoriasis arthritis (n=57, 1 included):
  - Brazilian Society of Rheumatology 2020 guidelines for psoriatic arthritis (https://advancesinrheumatology.biomedcentral.com/articles/10.1186/s42358-021-00219-y), p. 20, ref. [196]
- Canadian Medical Association (CPG Infobase), CA
  - 0 hits for all search terms
- ECRI-Guidelines Trust, US
  - 3 hits, 0 included
- Guidelines International Network (GIN), AUS
  - 27 hits, 0 included
- National Institute for Health and Clinical Excellence (NICE), GB
  - Hits per search term: 8/ 20/ 14/ 3/ 9; 0 included
- Scottish Intercollegiate Guidelines Network (SIGN)
  - List of guidelines checked, 0 included
- In German language only: Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF), DE
  - Total number of hits not presented; list of hits checked; 3 included
  - S3-Leitlinie Colitis ulcerosa (https://register.awmf.org/de/leitlinien/detail/021-009); p. 32/85; ref. [358]
  - S3-Leitlinie Diagnostik und Therapie des Morbus Crohn (https://register.awmf.org/de/leitlinien/detail/021-004) P. 38/87; ref. [490]; p. 56/87 ref. [750-753]
  - S3-Leitlinie Management der frühen rheumatoiden Arthritis (https://register.awmf.org/de/leitlinien/detail/060-002) P. 40/123 ref. [209, 221, 222, 225-228, 229-231]

Flow chart