Tuberculosis: How to manage psoriasis in patients with positive interferon gamma release assay (IGRA) results?

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:

Comment: Depending on the prevalence of TB and on the health care situation, dermatologists may be in a position to interpret positive findings, to make further management decisions themselves or to directly refer patients to infectious disease specialists where interdisciplinary cooperation is common.

Interpretation of positive findings in IGRA/TST

Patients with active and latent tuberculosis (TB) can be identified using either the interferon gamma release assay (IGRA) or tuberculin skin test (TST). However, neither test can distinguish between the latent and active states of the disease [4].

IGRA is a specific blood test. The interpretation of IGRA test results (especially borderline results) can be limited due to issues in the cut-off values, shifting conversions and reversion rates over time, and varying test reproducibility. In case of borderline results, repeating the test may be advisable [4].

The sensitivity of **TST** for latent tuberculosis infection (LTBI) has been described as 74 % and the specificity of 89 % in a meta-analysis [5,6]. The positive predictive value for TB infection by the TST depends on the prevalence of TB within a given region/population and the possibility of cross-reactions.

False positive TST include those related to the administration of purified protein derivative (PPD) and its lecture (inexperience, high amount of antigen), and cross-reactions (BCG vaccination, and most environmental non-tuberculous mycobacteria). Although the TST would usually be, much higher if active TB is truly present.

Means to distinguish between active and latent TB commonly used in the guidelines group experts' setting include medical history (exposure risk), signs and symptoms (e.g. current cough, fever, weight loss, night sweats), chest x-ray [7] and urinalysis (pyuria) [8-10]. For details of differential diagnosis of latent versus active TB, please see respective guidelines and reviews [4,7,11]

We **recommend** discussing the decision to initiate immuno-suppressive therapies in patients with signs of latent tuberculosis with an infectious disease specialist (case-by-case basis).	↑↑	STRONG CONSENSUS[1]
As a commonly used procedure in case of latent TB, a treatment with isoniazid can be **recommended** with treatment initiation one month before the start of the immunosuppressive therapy and should be continued for 6 months (for alternatives see Table 1).	↑↑	100 % Agreement EXPERT CONSENSUS

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

Different treatment regimens are available for LTBI with duration depending on monotherapy or combinations. In clinical practice, the most widely accepted treatment are isoniazid (INH) for six months and INH + rifampicin (RIF) for three months, see Table 1 [12]. Patients should have regular check-ups during chemoprophylaxis treatment to detect any drug-related adverse events (e.g. hepatotoxicity) and to monitor for symptoms of TB during treatment with biologics, as reactivation has been reported even after screening and chemoprophylaxis for LTBI has been completed [13].

Table 1: Therapeutic regimens for LTBI

Drug	Dose	Treatment duration
INH alone (daily)	5 mg/kg; max dose: 300 mg	6-9 months
RIF alone (daily)	10mg/kg; max dose: 600 mg	3-4 months
INH + RIF (daily)	INH: 5 mg/kg; max dose: 300 mg RIF: 10mg/kg; max dose: 600 mg	3-4 months

INH = Isoniazide; RIF Rifampicin, Treatments with pyrazinamide should be avoided (high risk of hepatotoxicity). Based on WHO: Latent tuberculosis infection: updated and consolidated guidelines for programmatic management, 2018.

Risk of TBC reactivation with different treatments

The search conducted for this update did not provide robust evidence that would justify an adjustment of the current recommendations regarding TB management. Further research is needed to determine whether there are differences in risk of tuberculosis infection/ reactivation between the different classes of immunosuppressive agents (i.e. whether risks associated with IL17 and IL12/23 inhibition are equivalent to the established risks associated with TNFi).

Conventional treatments/Small molecules

Data on the reactivation risk with acitretin, ciclosporin (CsA), fumarates, methotrexate (MTX) and apremilast is scarce. Most published guidelines have, thus far, not recommended TB screening for these drugs (except MTX and CsA) [14]. Screening before treatment with MTX is recommended in the summary of products characteristics (SmPC).

The sensitivity of IGRA and TST may be influenced by conventional immunosuppressive treatments, so doing IGRA initially may be beneficial if a later switch, especially from MTX to other drug categories appears likely [15].

Biologics

A higher risk of latent TB reactivation under treatment with infliximab or adalimumb has been identified, with a lower risk of reactivation with etanercept. Cases of latent TB reactivation with ustekinumab have been reported in a long-term study of up to 5 years [16]. The risk of latent TB reactivation seems to be lowest during treatment with anti-IL 17 and anti-IL 23 targeted treatments [13,17].

In a systematic review by Snast et al., 78 patients who developed active TB during biologic treatment were analysed. Eighty percent of all cases were treated with adalimumab or infliximab, 12% were treated with etanercept. No case of active TB was identified with the anti–interleukin-17 agents (ixekizumab, secukinumab, and brodalumab); however, the total patient exposure years for these at the time of analysis were much shorter than for the TNFi. All patients in this review had initially been screened for TB. In the majority of cases of reactivation, patients presented with extra-pulmonary disease within the first six months of biologic therapy. [18].

Table 2 provides an overview of the screening practice based on reactivation risk during antipsoriatic treatments. The risk assessment may be biased due to the different time periods when the cases occurred. At the time of TNF alpha introduction, TBC screening was not always done, leading to less testing and higher numbers of patients with latent TB being exposed to the respective drugs. In addition to the reported cases of TB reactivation, pathophysiological considerations of the immune response to TB favor the group of anti-IL-17 and anti-IL-23 as treatment options. IL-12 has been reported to play a role in the anti TB immune response.

Table 2: LTBI screening indication based on different systemic treatments

Systemic treatments		Screening recommendation as provided in SmPC	Comments
Conventional systemic agents	Acitretin	No	No cases of reactivation have been reported[19]
	Ciclosporin	No	Cases have been reported in organ transplant patients with high doses of CsA [19]
	Fumarates	No	No cases of reactivation have been reported [20,21]

Systemic treatments		Screening recommendation as provided in SmPC	Comments
	Methotrexate	Yes	Cases of reactivation have been reported [22]
Phospho-diesterase 4 inhibitor	Apremilast	No	Increased risk has not been reported [23]
Tyrosine-kinase 2 inhibitor	Deucravacitinib	Yes	Uncertain risk of reactivation. No data available yet.
TNFi	Etanercept	Yes	Increased risk of reactivation has been reported [24,25]
	Infliximab	Yes	Increased risk of reactivation has been reported [24,25]
	Adalimumab	Yes	Increased risk of reactivation has been reported [24,25]
	Certolizumab	Yes	Increased risk of reactivation has been reported [19,24]
Anti-IL 12/23	Ustekinumab	Yes	Uncertain risk of reactivation (cases have been reported) [19,26,27]
Anti-IL 17	Secukinumab	Yes	Increased risk has not been reported in clinical trials [26,28]
	Ixekizumab	Yes	Increased risk has not been reported in clinical trials [26]
	Brodalumab	Yes	Increased risk has not been reported in clinical trials [26]
Anti-IL 23	Guselkumab	Yes	Increased risk has not been reported in clinical trials [29]
	Tildrakizumab	Yes	Increased risk has not been reported in clinical trials [30]
	Risankizumab	Yes	Increased risk has not been reported in clinical trials [31]
Reported cases need to be seen in correlation to approval date, especially with years and numbers of psoriasis patients exposed to the drug.			

We **recommend against** TNFi as a treatment for patients with latent TB unless there are no other suitable treatment options.	↓↓	STRONG CONSENSUS[1] 100 % Agreement
We **recommend** remaining alert to signs and symptoms of tuberculosis activation or re-infection during therapy.	↑↑	EXPERT CONSENSUS

We **suggest** acitretin, apremilast or fumarates or a treatment from the anti-IL-17 and anti-IL-23 group for patients with latent TB that require a systemic antipsoriatic treatment.	↑	

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

Review of the evidence on psoriasis and tuberculosis

What was the aim of this review?

The aim of this review was to inform the guideline development group about new evidence on the risk of tuberculosis (TB) in patients with psoriasis vulgaris who are about to be treated with a therapy other than TNFi. The goal was to potentially update the chapters on tuberculosis screening and tuberculosis management.

Research questions

1. Which antipsoriatic drugs (other than TNFi) are associated with a risk of activating latent tuberculosis?
2. How to screen for tuberculosis during biologic treatment?

The second research question will be addressed in the next update of the guideline.

Screening criteria

	Inclusion criteria	Exclusion criteria
Patients	Adult patients (psoriasis, psoriasis arthritis, inflammatory bowel disease, ankylosing spondylitis, rheumatic disease, rheumatoid arthritis or autoimmune disease) with primarily positive Quantiferon test (or equivalent) or Tuberkulin skin test in screening prior to initiation of immunsuppressive therapy and consecutive exclusion of active TB Secondary: Studies reporting TB activation as an adverse event in a population that did not have a positive quantiferone test, Studies reporting on efficacy and safety of TBC prophylaxis	Children Animal studies
Intervention	**conventional systemic treatment:** acitretin, apremilast, ciclosporin, fumarates, methotrexate **biologicals:** anti-IL12/23: ustekinumab anti-IL17: bimekizumab, brodalumab, ixekizumab, secukinumab	

	Inclusion criteria	Exclusion criteria
	anti-IL23: guselkumab, risankizumab, tildrakizumab **Small molecules:** PDE4i: Apremilast tyrosine kinase 2 (TYK2) inhibitor: deucravacitinib (new))	
Comparator	For RCTs: another included drug and/or placebo If TNFi is comparator, include as single-arm study or case series	
Outcomes	Cases of activation of tuberculosis (symptoms, tests) with or without TB prophylaxis	
Study Design	Primary: Systematic reviews	non-systematic reviews in-vitro studies expert opinions without primary data letters (if of narrative character or expert opinion only) 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, letters (if primary data is presented)

Information source and screening process

The search strategy was updated and the database MEDLINE via Ovid from 1946 was searched for all entries up until February 27, 2023. The full search strategy is shown below. Two methodologists conducted a topic specific screening of all identified systematic reviews (for filter see chapter “Search strategy”) independently. Included title/abstracts were then screened as full texts based on the above listed eligibility criteria by one methodologist and cross-checked by another one.

Methodological quality assessment

The AMSTAR-2-Tool was used for all systematic reviews that were included following title and abstract screening and had a “prioritized study design” and an “adequate research question”.

Search strategy (28.02.2023)

Filter for identification of systematic reviews and meta-analysis: 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)

Ovid-Link:
https://ovidsp.ovid.com/ovidweb.cgi?T=JS&NEWS=N&PAGE=main&SHAREDSEARCHID=4FP9vLrBf5mn1kqAkmV2x36pXm8QJXaWSatEThFz5bNdnPa5uPaRBT6jhSVjgpAiB

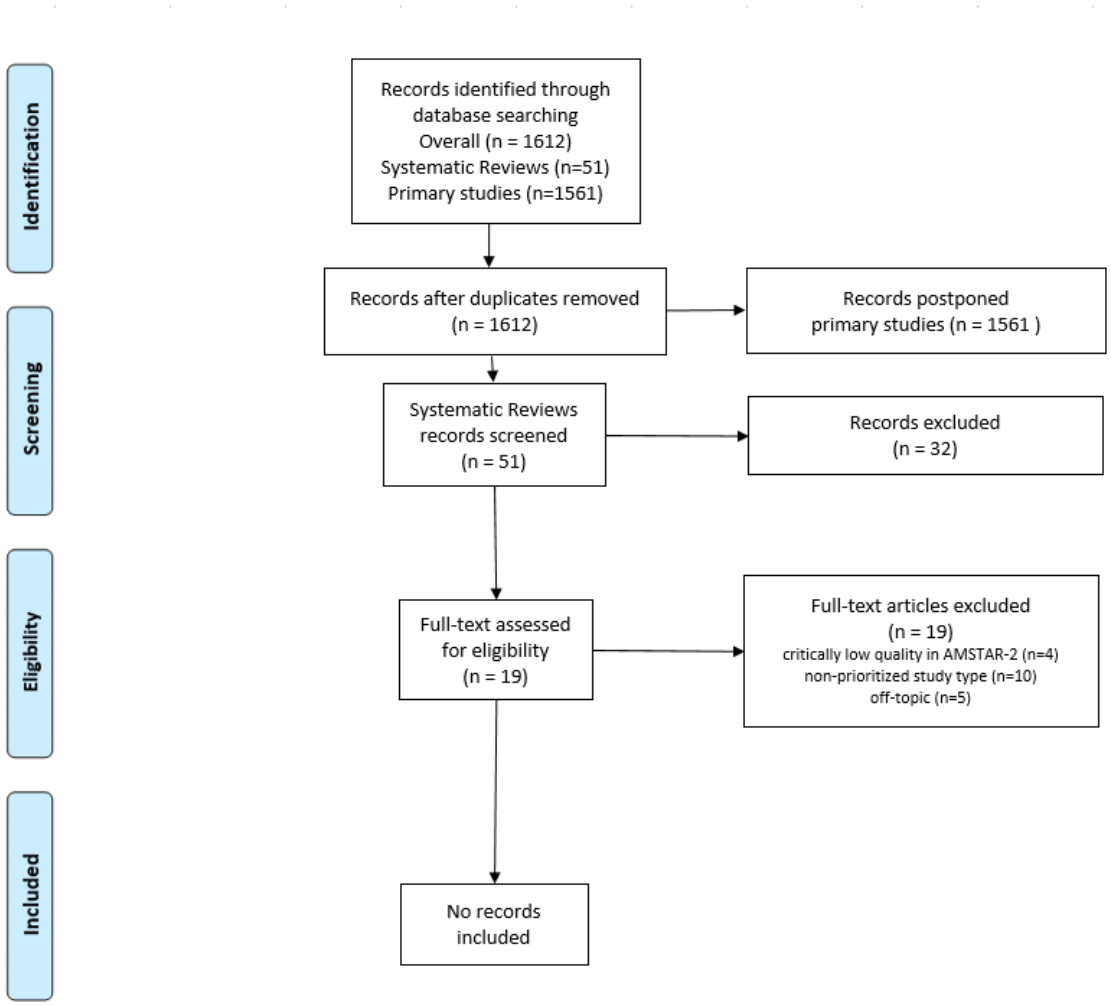
Ressource: Ovid MEDLINE(R) ALL <1946 to February 27, 2023>

No.	Search term	Result
1	exp Methotrexate/	40965
2	methotrexate$.mp.	59783
3	amethopterin.mp.	401
4	mtx.ti,ab.	14675
5	exp Fumarates/	5336
6	(fumar$ and esters).mp.	471
7	dimethylfumarate.mp.	207
8	fae.ti,ab.	1026
9	dmf.ti,ab.	9775
10	fumarate$1.mp.	20919
11	Acitretin/	1291
12	acitretin.mp.	2033
13	Ustekinumab.mp.	3013
14	secukinumab.mp.	1877
15	apremilast.mp.	1037
16	guselkumab.mp.	536
17	exp Interleukin-23/ or exp Interleukin-12/ or Interleukin-17/	30204
18	exp Interleukin-12 Subunit p40/ or p40 subunit.mp.	1902
19	Cyclosporine/	30502
20	(Ciclosporin* or cyclosporin*).mp.	61734
21	brodalumab.mp.	511
22	ixekizumab.mp.	949
23	tildrakizumab.mp.	249
24	bimekizumab.mp.	110
25	risankizumab.mp.	347
26	deucravacitinib.mp.	52
27	TYK2 Kinase/	615
28	(TYK2 or "tyrosine kinase 2").ti,ab.	2152
29	**or/1-28**	**188571**
30	exp Tuberculosis/	204867
31	Tuberculos*.ti,ab,kf.	234862
32	Mycobacterium tuberculosis/	56817
33	(TB or Tbc).ti,ab,kf.	72949
34	ltbi.ti,ab,kf.	2993

No.	Search term	Result
35	**or/30-34**	**300757**
36	cochrane database of systematic reviews.jn. or search.tw. or meta analysis.pt. or MEDLINE.tw. or systematic review.tw.	667197
37	exp animals/ not humans.sh.	5097167
38	29 and 35	2037
39	38 not 37	1612
40	**36 and 39**	**51**
41	**39 not 40**	**1561**

Results

Our update search yielded 1612 citations. No systematic reviews fulfilled the inclusion criteria. The detailed findings are presented in the PRISMA diagram provided below:



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