Tuberculosis: How to manage psoriasis in patients with positive tuberculosis test results?

This chapter is based on the previous chapter [1,2]. A systematic search was conducted, details of which can be found in the Methods & Evidence Report**.**

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 [3]

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 [3].

The sensitivity of **TST** for latent tuberculosis infection (LTBI) has been described as 74 % and the specificity of 89 % in a meta-analysis [4,5]. 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 [6] and urinalysis (pyuria) [7-9]. For details of differential diagnosis of latent versus active TB, please see respective guidelines and reviews [3,6,10]

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).	↑↑	 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 [11]. 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 [12].

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

Conventional treatments/Small molecules

Data on the reactivation risk with acitretin, ciclosporin (CsA), fumarates, methotrexate (MTX) and apremilast is scarce. Most published guidelines shave, thus far, not recommended TB screening for these drugs (except MTX and CsA)[13]. 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.[14]

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 [15]. The risk of latent TB reactivation seems to be lowest during treatment with anti-IL 17 and anti-IL 23 targeted treatments [12,16]

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 TNF antagonists. 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. [17].

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 recommenda-tion in line with SmPC	Comments
Conventional systemic agents	Acitretin	No	No cases of reactivation have been reported[18]
	Ciclosporin	No	Cases have been reported in organ transplant patients with high doses of CsA [18].
	Fumarates	No	No cases of reactivation have been reported [19,20]
	Methotrexate	Yes	Cases of reactivation have been reported [21].
Small molecules	Apremilast	No	Increased risk has not been reported. [22]

Anti-TNF alpha	Etanercept	Yes	Increased risk of reactivation has been reported [23,24]
	Infliximab	Yes	Increased risk of reactivation has been reported [23,24]
	Adalimumab	Yes	Increased risk of reactivation has been reported [23,24]
	Certolizumab	Yes	Increased risk of reactivation has been reported [18,23]
Anti-IL 12/23	Ustekinumab	Yes	Uncertain risk of reactivation (cases have been reported) [18,25]
Anti-IL 17	Secukinumab	Yes	Increased risk has not been reported in clinical trials [25,26]
	Ixekizumab	Yes	Increased risk has not been reported in clinical trials [25]
	Brodalumab	Yes	Increased risk has not been reported in clinical trials [25]
Anti-IL 23	Guselkumab	Yes	Increased risk has not been reported in clinical trials[27]
	Tildrakizumab	Yes	Increased risk has not been reported in clinical trials[28]
	Risankizumab	Yes	Increased risk has not been reported in clinical trials [29]
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** TNF alpha antagonists as a treatment for patients with latent TB unless there are no other suitable treatment options.	↓↓	STRONG CONSENSUS[1] 100 % Agreement EXPERT CONSENSUS
We **recommend** remaining alert to signs and symptoms of tuberculosis activation or re-infection during therapy.	↑↑	
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 antisporiatic treatment.	↑	

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

References

1. Nast A, Gisondi P, Ormerod AD *et al.* European S3-Guidelines on the systemic treatment of psoriasis vulgaris--Update 2015--Short version--EDF in cooperation with EADV and IPC. *Journal of the European Academy of Dermatology and Venereology : JEADV* 2015; **29**: 2277-94.
2. Nast A, Spuls PI, van der Kraaij G *et al.* European S3-Guideline on the systemic treatment of psoriasis vulgaris - Update Apremilast and Secukinumab - EDF in cooperation with EADV and IPC. *Journal of the European Academy of Dermatology and Venereology: JEADV* 2017; **31**: 1951-63.
3. 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.
4. Desai N, Raste Y, Cooke NT, Harland CC. QuantiFERON-TB Gold testing for tuberculosis in psoriasis patients commencing anti-tumour necrosis factor alpha therapy. *The British journal of dermatology* 2008; **158**: 1137-8.
5. Ehlers S. Tumor necrosis factor and its blockade in granulomatous infections: differential modes of action of infliximab and etanercept? *Clin Infect Dis* 2005; **41 Suppl 3**: S199-203.
6. World Health Organization. WHO Guidelines Approved by the Guidelines Review Committee. In: *Latent tuberculosis infection: updated and consolidated guidelines for programmatic management*. Geneva: World Health Organization (c) World Health Organization 2018. 2018.
7. Golden MP, Vikram HR. Extrapulmonary tuberculosis: an overview. *American family physician* 2005; **72**: 1761-8.
8. Christensen WI. Genitourinary tuberculosis: review of 102 cases. *Medicine* 1974; **53**: 377-90.
9. Simon HB, Weinstein AJ, Pasternak MS, Swartz MN, Kunz LJ. Genitourinary tuberculosis. Clinical features in a general hospital population. *The American journal of medicine* 1977; **63**: 410-20.
10. National Collaborating Centre for Chronic C, Centre for Clinical Practice at, Nice,,. National Institute for Health and Clinical Excellence: Guidance. In: *Tuberculosis: Clinical Diagnosis and Management of Tuberculosis, and Measures for Its Prevention and Control*. London: National Institute for Health and Clinical Excellence (UK) Royal College of Physicians of London. Updated text, Copyright (c) 2011, National Institute for Health and Clinical Excellence. 2011.
11. Schaberg T, Bauer T, Brinkmann F *et al.* [Tuberculosis Guideline for Adults - Guideline for Diagnosis and Treatment of Tuberculosis including LTBI Testing and Treatment of the German Central Committee (DZK) and the German Respiratory Society (DGP)]. *Pneumologie (Stuttgart, Germany)* 2017; **71**: 325-97.
12. Holroyd CR, Seth R, Bukhari M *et al.* The British Society for Rheumatology biologic DMARD safety guidelines in inflammatory arthritis. *Rheumatology* 2019; **58**: e3-e42.
13. Doherty SD, Van Voorhees A, Lebwohl MG *et al.* National Psoriasis Foundation consensus statement on screening for latent tuberculosis infection in patients with psoriasis treated with systemic and biologic agents. *J Am Acad Dermatol* 2008; **59**: 209-17.
14. Arias-Guillen M, Sanchez Menendez MM, Alperi M *et al.* High rates of tuberculin skin test positivity due to methotrexate therapy: False positive results? *Seminars in arthritis and rheumatism* 2018; **48**: 538-46.
15. Papp KA, Griffiths CE, Gordon K *et al.* Long-term safety of ustekinumab in patients with moderate-to-severe psoriasis: final results from 5 years of follow-up. *The British journal of dermatology* 2013; **168**: 844-54.
16. Cantini F, Nannini C, Niccoli L, Petrone L, Ippolito G, Goletti D. Risk of Tuberculosis Reactivation in Patients with Rheumatoid Arthritis, Ankylosing Spondylitis, and Psoriatic Arthritis Receiving Non-Anti-TNF-Targeted Biologics. *Mediators of inflammation* 2017; **2017**: 8909834.

17. Snast I, Bercovici E, Solomon-Cohen E *et al.* Active Tuberculosis in Patients with Psoriasis Receiving Biologic Therapy: A Systematic Review. *American journal of clinical dermatology* 2019; **20**: 483-91.
18. Kaushik SB, Lebwohl MG. Psoriasis: Which therapy for which patient: Focus on special populations and chronic infections. *J Am Acad Dermatol* 2019; **80**: 43-53.
19. Epstein DJ, Dunn J, Deresinski S. Infectious Complications of Multiple Sclerosis Therapies: Implications for Screening, Prophylaxis, and Management. *Open forum infectious diseases* 2018; **5**: ofy174.
20. Fox RJ, Kita M, Cohan SL *et al.* BG-12 (dimethyl fumarate): a review of mechanism of action, efficacy, and safety. *Current medical research and opinion* 2014; **30**: 251-62.
21. Cantini F, Niccoli L, Capone A, Petrone L, Goletti D. Risk of tuberculosis reactivation associated with traditional disease modifying anti-rheumatic drugs and non-anti-tumor necrosis factor biologics in patients with rheumatic disorders and suggestion for clinical practice. *Expert opinion on drug safety* 2019; **18**: 415-25.
22. Crowley J, Thaci D, Joly P *et al.* Long-term safety and tolerability of apremilast in patients with psoriasis: Pooled safety analysis for >=156 weeks from 2 phase 3, randomized, controlled trials (ESTEEM 1 and 2). *J Am Acad Dermatol* 2017; **77**: 310-7.e1.
23. Baddley JW, Cantini F, Goletti D *et al.* ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the safety of targeted and biological therapies: an infectious diseases perspective (Soluble immune effector molecules [I]: anti-tumor necrosis factor-alpha agents). *Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases* 2018; **24 Suppl 2**: S10-s20.
24. Cantini F, Niccoli L, Goletti D. Adalimumab, etanercept, infliximab, and the risk of tuberculosis: data from clinical trials, national registries, and postmarketing surveillance. *J Rheumatol Suppl* 2014; **91**: 47-55.
25. Winthrop KL, Mariette X, Silva JT *et al.* ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the safety of targeted and biological therapies: an infectious diseases perspective (Soluble immune effector molecules [II]: agents targeting interleukins, immunoglobulins and complement factors). *Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases* 2018; **24 Suppl 2**: S21-s40.
26. Elewski BE, Baddley JW, Deodhar AA *et al.* Association of Secukinumab Treatment With Tuberculosis Reactivation in Patients With Psoriasis, Psoriatic Arthritis, or Ankylosing Spondylitis. *JAMA dermatology* 2021; **157**: 43-51.
27. Crowley JJ, Warren RB, Cather JC. Safety of selective IL-23p19 inhibitors for the treatment of psoriasis. *Journal of the European Academy of Dermatology and Venereology : JEADV* 2019; **33**: 1676-84.
28. Lebwohl MG, Papp KA, Marangell LB *et al.* Psychiatric adverse events during treatment with brodalumab: Analysis of psoriasis clinical trials. *J Am Acad Dermatol* 2018; **78**: 81-9.e5.
29. Gordon KB, Strober B, Lebwohl M *et al.* Efficacy and safety of risankizumab in moderate-to-severe plaque psoriasis (UltIMMa-1 and UltIMMa-2): results from two double-blind, randomised, placebo-controlled and ustekinumab-controlled phase 3 trials. *Lancet* 2018; **392**: 650-61.