

## Biological Therapies and Tuberculosis Infection in Dermatology

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### ABSTRACT

After contact with a case of transmissible tuberculosis (TB), some of the exposed individuals may be infected and develop an immune reaction against *Mycobacterium tuberculosis* (Mtb), the causative agent of the disease. The replication of mycobacteria is usually stopped within cellular structures called granulomas, whose integrity relies on a complex interplay between cells and cytokines, the most prominent of them being TNF. In case of deficiency or inhibition of the activity of TNF, the granulomas may disrupt and release the surviving mycobacteria which may multiply, disseminate and lead to active TB disease.

Several immune-mediated inflammatory diseases, among which rheumatoid arthritis, Crohn's disease, ankylosing spondylitis and psoriasis can be treated by biological therapies acting by the inhibition of TNF or cytokines like IL-17 and IL-23. If these therapies, in particular TNF-inhibitors, are administered to people infected by Mtb, there is a risk of decreasing the integrity of granulomas and increasing the probability of multiplication of mycobacteria and TB reactivation.

Therefore, in persons with rheumatological, gastro-enterological and dermatological diseases candidate to biological therapies there is a general recommendation of screening for TB infection (TBI) at baseline. The screening should include also a search for history of prior TB or contact with TB, a test for the presence of TBI, and if scored positive, a chest X-Ray.

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About one quarter of the world population is estimated to have developed an immune reaction against *Mycobacterium tuberculosis* (Mtb) after having been in contact with it [1]. The vast majority of infected people do not develop tuberculosis (TB) diseases and remain in a state of infection (TBI), their immune system being able to contain the replication of mycobacteria within granulomas. In most cases, it is assumed that the mycobacteria are finally eliminated and the TB infection is manifested only by a lasting immunological reaction. In rare cases, living mycobacteria may persist within the tissues and replicate at a later stage causing tissue damage (usually in the lung) and the clinical disease. TBI is not a disease but an unstable stage in which the mycobacteria is in a dormant or non-replicating status and characterized by a positive specific immune response. A minority of the subjects with TBI may progress to active disease if the immune response does not control the mycobacteria eventually present in the tissue [2-4]. Within the TBI definition today there are also individuals who eliminated the mycobacteria and that show only a positive response to the immune-based tests [5-7].

One of the main factors responsible for the integrity of the granulomas enclosing the mycobacteria and the control of

mycobacterial replication and the risk of active TB after infection, is Tumor Necrosis Factor (TNF), a cytokine released from infected alveolar macrophages and T cells and involved in cell recruitment, granuloma formation and clearance of mycobacterial infection [8,9].

As TNF has potent pro-inflammatory activities and plays a key role in many immune and auto-immune diseases, inhibition of TNF has emerged as one of the most efficient therapy in several severe inflammatory diseases like rheumatoid arthritis, ankylosing spondylitis, inflammatory bowel diseases and psoriasis [10-16].

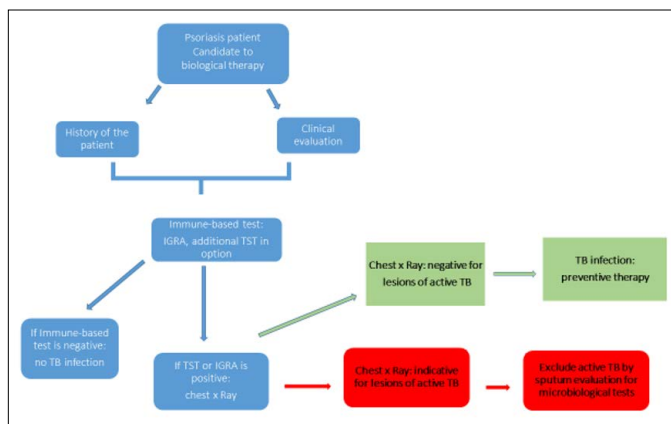
### Risk of TB in Immune-Mediated Inflammatory Diseases

Patients with some chronic inflammatory diseases like rheumatoid arthritis have a relative risk of developing TB, estimated to be 2 to 16 times higher than the risk in the local population, due to the disease itself and the use of non-biological treatments with an impact on immune defense mechanisms (for instance methotrexate and steroids) [17]. Some of the TNF-inhibitors may further increase the risk of TB up to 20 times the risk in the general population, the risk being variable and related to the drug used [18-20]. The highest risk seems to be associated with the use of infliximab and adalimumab, particularly if the patients receive simultaneously other immunomodulating drugs [21-23].

## TNF-Inhibitors and Risk of TB

In patients under TNF-inhibitors developing TB, the disease progresses rapidly and is frequently disseminated, involving several organs in addition to the lungs, and may be life-threatening, for instance if the central nervous system or the pericardium are involved [24]. The mechanism involved is the reactivation of TBI following the disruption of the granulomas and the dissemination of mycobacteria [25]. An extensive review of the risks associated with TNF-inhibitors therapies has been published by the European Society of Clinical Microbiology and Infectious Diseases [26].

Following the recognition of the risk of TB in patients receiving TNF-inhibitors, an extensive review of the risk and proposals for the screening of patients at risk was published [27]. Consequently, many national guidelines recommend the screening of all patient eligible for biological therapies with TNF-inhibitors for the presence of TBI and the prescription of a preventive therapy in those with a documented infection [28-30]. The screening should comprise a detailed history about prior TB or exposure to TB patients and an immune-based tests for TBI detection like the tuberculin skin test (TST) or Interferon- $\gamma$  Release Assay (IGRA) (alone or combined). In those scored positive to a TBI test, a chest X-ray shall be performed to exclude incipient or active TB disease (Figure 1). Patients with TBI diagnosis (positive immune-based test and a chest X-Ray without lesions suggestive of TB) should receive an adequate preventive treatment before starting TNF-inhibitors. The evidence generated so far has shown that a systematic screening for TBI and administration of a preventive therapy was followed by a dramatic decrease in the number of incident TB cases [18-31], in the patients candidate to biological treatment.



**Figure 1:** Algorithm for screening and prescription of preventive therapy in patients eligible for biological therapy

The risk of TB associated with biological or immunomodulating treatments other than TNF-inhibitors is considered lower than the risk of using TNF-inhibitors but the conclusions of the available studies are controversial. Some studies conclude that the risk of TB in patients receiving IL-17 and IL-23 blocking drugs is negligible and that screening is not mandatory before treatment [32-33]. A prospective study by the British Association of Dermatologists Biologic Intervention Register (BADBIR) concluded that there was no significant increase in the risk of TB in patients receiving etanercept, adalimumab or ustekinumab compared with non-biologic systemic therapies or methotrexate [34]. On the other side, a recent analysis concluded that the evidence for a lower risk is partly biased by the fact that many studies excluded patients with TBI or included patients with TBI who received a preventive treatment, thus not allowing a correct evaluation of the risk for TB reactivation [33-35].

## Risk of TB in Patients with Psoriasis under Biological Therapies

In the field of dermatology, an increased risk of severe infections, including TB, in patients with psoriasis has also been reported [34, 36, 37]. The risk seems to be low and comparable to the risk in the local population for patients receiving non-biological therapies, including methotrexate, and for the TNF-inhibitors etanercept or for the IL-12/IL-23 inhibitor ustekinumab. The risk seems to be increased for patients receiving infliximab (2.49/100 patient/year) or adalimumab (1.97/100 patient/year) compared with methotrexate (1.28/100 patient/year) or non-biologic treatments, retinoids or phototherapy (1.05/100 patient/year) [38]. Globally, the risk of infection associated with TNF-inhibitors treatment seems to be lower for patients with psoriasis than for patients with rheumatoid arthritis, possibly because the latter patients frequently receive a combination therapy including other immunosuppressive medications (like steroids and metotrexate) which may increase the risk for TB reactivation [23].

Recommendations have been issued regarding the need for screening patients with psoriasis for active disease and TBI, prescription of preventive therapy in patients with documented infection prior to the initiation of TNF-inhibitors therapy and due attention during and after the biological treatment, some cases of TB appearing late or with atypical clinical presentation [16]. The 2009 Guidelines of the British Association of Dermatologists recommend the screening for TBI, including a detailed a history of TB or TB exposure, a chest-Xray and a tuberculin skin test (or an IGRA in patients under immunosuppressive therapy and in other patients if available), and the consideration of preventive therapy two months before the initiation of biological therapy initiation in those diagnosed with TBI [39, 16].

In patients under long-term biological therapy with a negative initial test (and not receiving a preventive treatment), the repetition of screening test for TB is recommended if the patient reports contacts with TB patients and/or travels in endemic TB areas. Continuous attention to the possible emergence of signs of active TB is recommended, as some rare patients present a conversion of the screening test or develop an active TB in spite of preventive treatment [40-42]. The 2017 Guidelines of the British Association of Dermatologists recommends the use of ustekinumab, adalimumab or secukinumab as first-line therapy in adults with psoriasis eligible for biological therapy, reserving infliximab for patients with very severe disease or where other agents cannot be used and adalimumab, etanercept or ustekinumab for children [43]. In the 2020 update, screening with an IGRA alone or supplemented with a TST is recommended in all patients eligible for biologic therapy, with chest X-ray to rule out abnormalities suggestive of active TB [44].

## Screening Procedure and Controversies

One of the controversial issues is the performance of the test for the detection of TBI and the selection of the most appropriate test. TST has been used for many years as a traditional test for the detection of infection but several studies have demonstrated that the sensitivity of the test in patients with immunological disorders like rheumatoid arthritis may be reduced and that the specificity is influenced by prior vaccination with BCG or contact with non-tuberculous mycobacteria [45-49].

Therefore, the replacement of TST by more sensitive and more specific tests like IGRAs (QuantiFERON or T-SPOT.TB) is frequently advocated. This may allow a better targeting of the patients at risk for TB and eligible for preventive therapy and

improve the selection of the patients who will benefit from the treatment [27, 28, 50, 51]. The latest Guidelines of the British Dermatologist Association recommend to assess patients with psoriasis about the risk of past exposure to or current TB, to screen for TB infection with an IGRA and monitoring the possible occurrence of signs or symptoms of TB during or after treatment with TNF-inhibitors.

Another controversy exists about the need for screening for TBI in patients receiving non-TNF-inhibitors biological treatment. Considering that the conclusions of many studies on risk of TB associated with non-TNF-inhibitors drugs are potentially biased by the exclusion of patients with TBI or inclusion of patients under preventive treatment, the German Committee against TB (DZK), the German Society of Rheumatologist (DGRh) and the German Dermatologist Society (DDG) considered that the same recommendations for screening should be applied for patients receiving TNF-inhibitors and non-TNF-inhibitors biologic [35, 46]. According to this statement, screening is indicated in all patients receiving a biological treatment, followed by a careful evaluation of the indication for preventive therapy in patients with a positive IGRA and/or TST result, taking into account the type of disease and the choice of the biological treatment considered.

As no immune-based test can prove the presence of living mycobacteria in the tissues, there is currently an over-treatment of TBI subjects receiving a preventive therapy, as more patients receive a preventive treatment than what is strictly needed to prevent the occurrence of a case of clinical TB [52]. Several studies have demonstrated that the number needed to treat can be reduced to a minimum by using a specific screening test (avoiding false positive test results due to prior BCG vaccination or contact with non-tuberculous mycobacteria) and by taking into account the individual risk factors for reactivation like the intensity of contact, the time lapse since the infection (if known), the age and the intensity of the test response [47, 53-55].

Recently, the rationale for the repetition of the screening test in patients with a negative test result before the initiation of TNF-inhibitors therapy has been questioned, due to the observation of transitory IGRA conversions in persons without any exposure to TB [6]. The repetition of the test should be reserved for persons with a negative initial screening test who have been exposed to a case of TB or who live in or travel to an environment with a high risk of exposure to TB after the completion of the first test [6].

Furthermore, considering the current availability of non-TNF-inhibitors targeted biologicals, these drugs should be proposed as a first option to all patients in need of a biological treatment but with prior exposure to TB, evidence of TB or an elevated risk of TB reactivation [33].

### Learning points

1. The development of TB in patients with a prior infection receiving a biological treatment with TNF-inhibitors drugs is a rare but serious event.
2. It seems to be more prevalent in patients with rheumatoid arthritis than in patients with psoriasis and is particularly frequent in patients receiving infliximab and adalimumab.
3. Due to the severity of the disease (rapidly progressive and disseminated form), a screening for TB active disease or TBI is recommended before the initiation of TNF-inhibitors therapy, followed by an evaluation of the risk of TB reactivation.
4. In addition to clinical examination, assessment of the risk

5. factors for TB (prior TB or TB exposure) and screening for the presence of TBI (IGRA and/or TST) should be performed
5. Patients with a positive response to the immune-based tests for TBI and without lung lesions identified by a chest X-Ray, should receive a preventive TB treatment before the initiation of TNF-inhibitors therapy or should receive biological drugs with the lowest risk, whenever possible.

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