<center>R E V I E W</center>

# Tuberculosis and TNF-α inhibitors in children: how to manage a fine balance

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**Abstract.** Since the introduction of biologic response modifiers (BRMs) in the management of children affected by the immune-mediated inflammatory disease, these patients substantially improved their quality of life. BRMs are generally well tolerated and effective in most children and adolescents refractory to conventional immunosuppressive therapy. On the other hand, patients receiving BRMs, especially TNF-α inhibitors, display an increased risk of primary infections or reactivations, i.e. due to *Mycobacterium tuberculosis*. *M. tuberculosis* can cause severe disease with consequent short- and long-term morbidity in children on anti-TNF-α treatment. The present paper analyses the increased risk of reactivation of latent tuberculosis infection (LTBI) or de novo TB infection in children treated with TNF-α inhibitors, with the purpose to provide recommendations for screening strategies and safety monitoring of paediatric patients. Special attention is also given to the currently available TB screening tools (IGRAs and TST) and their utility in the diagnosis of LTBI before starting the biologic therapy and during the treatment. Finally, the paper analyses the suggested TB-preventing therapies to adopt in these children and the correct timing to overlap anti-TB and anti-TNF-α treatment. (www.actabiomedica.it)

**Key words:** tuberculosis, latent tuberculosis, TNF-α inhibitors, children, immune-mediated disease

## Introduction

Biologic response modifiers (BRMs) are molecules targeted versus tumour necrosis factor α (TNF-α), versus interleukins (IL), including IL-1, IL-5, IL-6, IL-12, or IL-23, or versus other molecules able to interfere with the immune system response. BRMs are currently used in children affected by the chronic inflammatory disease, such as juvenile idiopathic arthritis (JIA), psoriatic arthritis (PA), inflammatory bowel disease (IBD) or uveitis.

Since the introduction of BRMs in the management of children affected by the immune-mediated inflammatory disease, these patients substantially im-

proved their quality of life (1). Treatment with BRMs is generally well tolerated and effective in most children and adolescents refractory to conventional immuno-suppressive therapy, such as steroids, methotrexate, aza-thioprine or other disease-modifying anti-rheumatic drugs (DMARDs) (1). BRMs in most children allowed rapid and prolonged clinical improvement and changed the natural history of chronic inflammatory diseases. In fact, due to BRMs, many patients can be weaned off steroids or, at least, can reduce the dose of steroids needed to control the underlying disease. Mainly in children affected by IBD, the reduced need for steroids and the remission of the disease result in improving lin-ear growth, often affected in this kind of patients (2).

On the other hand, patients receiving BRMs, es-pecially TNF-α inhibitors, display an increased risk of primary infections or reactivations, mainly due to *Mycobacterium tuberculosis* or viruses (herpes simplex, varicella-zoster, Epstein-Barr, hepatitis B). Weaker evidence is reported for fungal, non-tuberculous myco-bacteria or other intracellular pathogens infections (3). Regarding TNF-α antagonists, a "Black Box Warning" was issued in 2008 by the FDA after reports of seri-ous infections caused by viruses, fungi or bacteria that spread through the body, including disseminated tu-berculosis (TB) (4).

From the 2018 European Society of Clinical Mi-crobiology and Infectious Diseases consensus docu-ment, based on the review of meta-analyses, open-label extension studies, post-marketing registries and retrospective cohort studies, it results that anti-TNF-α therapy is associated with a two-to four-fold increase in the risk of TB reactivation in adults (5). Among the studies included, in Singh *et al.* Cochrane review of 2011, the overall OR of TB reactivation is 4.68 (95% CI: 1.18-18.60) among adults receiving BRMs of all classes, compared with adults receiving placebo (6). In Ai *et al.* review of 2016, the OR is to 17.1 (95% CI: 13.9-21.0) when adults are receiving anti-TNF-α therapy are compared to the general population; if the same population was receiving anti-TNF-α therapy was compared to patients affected by rheumatoid ar-thritis but not exposed to anti-TNF-α drugs, the OR of TB reactivation decline to 4.03 (95% CI: 2.36-6.88) (7). This last data highlight how the underlying in-flammatory condition alone involves an increased risk

of TB reactivation. In other studies, the increased risk of TB reactivation due to the underlying immune-me-diated inflammatory disease alone is estimated to be twice the baseline rate for the general population (8).

TNF-α antagonists were the first BRMs to be approved for children, and to date are still the more frequently used. To date, endorsed TNF-α antagonists for paediatric population are infliximab, adalimumab and etanercept. Golimumab and certolizumab pegol are approved only for adult patients and sometimes used as off-label therapy in children (9,10).

Infliximab was the first TNF-α inhibitor ap-proved for paediatric population (in 2006 for Crohn disease and 2011 for ulcerative colitis). It is a chimeric mouse-human monoclonal antibody. To date, it did not receive FDA-approved indications for JIA affect-ed children, for whom is sometimes used as off-label treatment (10). Adalimumab is a fully-humanised monoclonal antibody, approved for JIA patients, in-cluding enthesitis-related JIA patients, older than four years. From 2012 EMA approved adalimumab also for paediatric CD affected children older than six years (10). Etanercept is a soluble recombinant TNF recep-tor fusion protein and is approved in JIA patients, in-cluding enthesitis-related and psoriatic JIA patients, older than two years (10). To date, despite the use of biologics in thousands of children affected by JIA or IBD, studies regarding paediatric population treated with TNF-α antagonists included small numbers of subjects and mostly focused on treatment efficacy or serious adverse events. Therefore, strategies to prevent infections and monitor paediatric patients treated with TNF-α inhibitors continue to be extrapolated mainly from adult literature.

The present paper aims to explore further the in-creased risk of reactivation of latent tuberculosis in-fection (LTBI) or de novo TB infection in children treated with BRMs, with particular regards to TNF- α inhibitors.

**Pathogenesis of *Mycobacterium tuberculosis* infection in children on TNF-α inhibitors therapy**

The host response against *M. tuberculosis* depends on the interaction between infected macrophages and

CD4+ T-cells, which occurs in the regional lymph nodes (11). TNF-α is a pro-inflammatory cytokine secreted by monocytes, macrophages and T lymphocytes. Working in synergy with IFN-γ, it is fundamental to granuloma formation and maintenance (12). TNF- α and IFN-γ increase the expression of intercellular adhesion molecules (essential for the maintenance of granuloma) and stimulate the production of the bactericidal compound from nitrogen and oxygen intermediates. Thereby, the granuloma, composed of differentiated macrophages and lymphocytes, restricts the growth and spread of *M. tuberculosis*, resulting in a dynamic balance between pathogen and host and inducing latency of TB infection (12). The blockage of this cytokine disrupts the immune system ability to contain bacillary growth in protective granulomas (13,14). Also, according to Silva *et al.*, TNF-α inhibitors, *in vitro*, negatively modulated the production of Th1, Th17 and T-reg cytokines (11), which is fundamentally against active tuberculosis especially in lung environment (15).

On the other hand, in chronic inflammatory disease, TNF-α is produced in high concentration and leads to excessive inflammation and consequently to organ damage. Children affected by JIA or IBD have increased levels of pro-inflammatory cytokine in peripheral blood, synovial fluid or gastrointestinal mucosa. These processes lead to tissue damage and cartilage loss for JIA (16,17), and induction of apoptosis of the cells of the gut epithelial layer in IBD, compromising the barrier function of the gastrointestinal system (3). TNF-α antagonists prevent excessive inflammation and consequent damage to tissues.

**TNF-α inhibitors and LTBI**

LTBI is defined by the persistent immune response of the host to the antigenic stimulation of *M. tuberculosis*, without any evidence of clinically active TB. That involves that these patients have no symptoms and no chest X-ray signs of infection but persistent positivity of tuberculin skin test (TST) or Interferon-Gamma Release Assays (IGRA) (18). According to American Academy of Paediatrics and NICE guidelines, all patients candidate for therapy with an immunomodulating biologic agent should be tested for LTBI before starting the treatment, regardless of specific TB risk factors (9,10). This statement is endorsed by several paediatric studies that showed that treating LTBI before starting therapy with TNF-α inhibitors significantly reduces the risk of TB reactivation, strengthening the utility of TB screening in asymptomatic children (19,20). Toussi *et al.*, in a review of 2013, reported an increased risk of TB reactivation in children treated with TNF-α inhibitors (3).

Moreover, TB more frequently presented as severe disease in children on biologic therapy. Those data are confirmed in adults, for whom several studies showed a significant increase in the incidence of extrapulmonary and disseminated disease among patients receiving TNF-α antagonists compared with the expected background rate for adult TB, HIV-uninfected, patients (21). Besides, patients treated with biological therapies often undergo to other immunosuppressive treatment, such as steroid or methotrexate. Even though an increased risk of TB reactivation is reported in children, only a few paediatric patients, according to the included literature in Toussi *et al.* review, developed M. tuberculosis disease, since all patients in the USA were adequately screened for LTBI and treated before starting the TNF-α inhibitor therapy (3). These data are also confirmed by a more recent multi-centre study by Noguera *et al.*, involving sixty-six tertiary European healthcare institutions providing care for TB affected children (22). The study identified nineteen cases of active TB in children treated with anti-TNF-α therapy (22). The immune-based TB screening (TST and IGRAs) was performed in 15 over 19 children before commencing anti-TNF-α therapy, and only identified one LTBI case; of note that 13 of those children were already receiving other immunosuppressant therapies at the time, IGRAs/TST was performed. 32% of patients had new TB risk factors, occurred after commencing anti-TNF-α therapy, while in the remaining 68% of patients new risk factors could not be identified. All children were affected by the severe disease; 78% presented miliary TB, and one case was diagnosed post-mortem. 33% of active TB affected children, even if completed TB treatment, reported long-term sequelae (22). Several conclusions derive from these data: firstly, 74% of centres included in the study did not ex-

perience any patients diagnosed with active TB during biologic therapy, indicating that even in Europe TB disease may be a less common complication in children on anti-TNF-α therapy than in adults. This finding was further supported by various recent data from paediatric centres in low-burden TB areas (23,24,25) and is probably due to the implementation of LTBI screening before commencing anti-TNF-α therapy in paediatric settings. Also, Nagy et al., in a recent meta-analysis regarding children affected by JIA, reported only 3/221 patients with LTBI and no patient with active TB during the monitoring period (26). Anyway, has reported in Noguera et al. analysis, children who developed active TB, were often affected by the severe, disseminated or extra-pulmonary disease, highlighting the need for prompt diagnosis and management of TB (22). Finally, in the majority of children with active TB, risk factors could not be identified: all children are worthy of careful attention. Both Toussi et al. and Noguera et al. reviews do not report significant discrepancy among different anti-TNF-α drugs. In the adult population, etanercept showed a risk of TB reactivation of 39 per 100 000 person-years (18), lower than in patients treated with the other TNF-α antagonists (144 per 100 000 person-years for adalimumab and 136 per 100 000 person-year for infliximab) (27). Currently, no data are available for the paediatric population at this regard.

**How to screen children for LTBI**

To date, there is not a gold standard for the diagnosis of LTBI in children, since both the test currently available, the TST and IGRA assays, have suboptimal specificity and sensitivity (28). Therefore, the diagnosis of LTBI in children remains challenging for the paediatrician and If LTBI is suspected in children who are anticipated to be or are currently immunocompromised, the patient should be referred to a TB specialist (10). TST and IGRAs assays indirectly measure TB infection by detecting the presence of host memory T-cell sensitisation to M. tuberculosis antigens (29,30). TST shows a lower specificity in patients vaccinated with bacillus Calmette–Guérin (BCG), or in children who repeatedly undergo to TST (like immigrant chil-

dren from high TB-burden areas). On the other hand, it has reduced sensitivity in immunocompromised children (29). IGRAs measures in vitro responses of T-cells to M. tuberculosis antigens that are not present in BCG and most non-tuberculous mycobacteria, and thus specificity for M. tuberculosis is higher than with the TST.

On the other hand, IGRA assay showed suboptimal sensitivity in children younger than five years old and even more in children younger than two years old (29,30). In immune-mediated disease affected children, steroid treatment is considered to be the leading risk factor for indeterminate results of IGRA. The disease activity of chronic inflammatory disease has profound effects on the IGRA results (31,32). Hradsky et al. found that in IBD affected children, the status of active disease was associated with an indeterminate IGRA result with an OR of 5.52 (95% CI: 1.20–52), in addition to the use of medium-to-high doses of steroids at the time of QFT testing (31). In his cohort of patients, 10% of children showed an indeterminate result. Other studies reported a wide range of rate of indeterminate IGRA results, from 3 to 29%, in children affected by IBD (31). According to the American Academy of Paediatrics (AAP), the choice of the assay to perform should take into account the presence of risk factors for LTBI and the age of the child. Risk factors for LTBI are a previous TST positivity or a previous history of TB, the co-habitation with an active TB patient (even for a short period), and travelling to areas endemic for TB in the previous year (9). Even patients native of areas endemic for TB or whom parents are natives of those areas, should be considered at major risk for LTBI. In these patients, both TST and IGRA should be performed (9). For children without risk factors for LTBI, according to AAP, the decision about the screening method to use at baseline should be based on the age of the patient: TST for children younger than five years and IGRA for children older than five years. Because of the high number of discordant patients (TST+/IGRA- or TST-/IGRA+), especially among children moved from high TB-burden countries, other authors suggest that both IGRA and TST should be performed, especially in children younger than five years (28,33). NICE guidelines about tuberculosis recommend using IGRAs assays

alone in children and young people only if TST is not available or is impractical (34). This recommendation is even more applicable for children receiving biologic treatment, due to the higher risk for progression and poor outcome reported in these patients. Therefore, in children receiving TNF-α antagonists, testing with both IGRA and TST should be considered, in order to increase the accuracy of LTBI testing (35).

**How to treat children with LTBI**

Treatment of LTBI should be started if either test result is positive, once active TB has been ruled out. At this regard, chest radiography, in the post-anterior and lateral scan, should be performed in all patients IGRA or TST positive or having any risk factor associated with LTBI before starting anti-TNF-α treatment (3). Patients suspected or found with active TB should discontinue any immunosuppressive agent and be referred to infectious diseases specialist in order to exclude the diagnosis of active TB or, once the diagnosis is established, start the adequate therapy. According to Shim *et al.*, since the greater risk of TB reactivation in children on TNF-α antagonists therapy, LTBI treatment should be initiated immediately even after close contact with an active TB patient, without waiting the 8-12 weeks of the window period. TST and IGRAs should be repeated after the completion of the window period, and LTBI treatment should be continued if the immune assays result positive and stopped if they result in a negative (36). Routine annual retesting TST or IGRA is not recommended, but patients should be periodically asked about TB symptoms or risk factors such as a new contact with a TB disease case or travelling to a high TB prevalence country (3, 37). As already reported, it is fundamental to investigate about any variation in risk factors for TB that occurred after commencing anti-TNF-α therapy since active or disseminated TB cases in children negative for LTBI-screening before the commence of biologic treatment was reported in the literature (22). Moreover, in children contracting TB while already receiving anti-TNF-α treatment, TST or IGRA assays could provide a false-negative result since the immune system could be unable to respond to antigenic stimulation of *M.*

*tuberculosis*. Particular attention should also be taken in children receiving steroids or other immunosuppressive treatment (other than anti-TNF-α agents) at the moment of LTBI screening since false-negative results can also occur in this patients, as proven by a recent study that showed that both steroids and anti-TNF-α agents substantially impair the performance of these assays (38). All these data highlight how challenging it is to perform an early diagnosis in this kind of patients, for whom, at the same time, having a diagnosis as soon as possible in fundamental to avoid the poor outcomes deriving from the miliary or extra-pulmonary disease. Therefore, to decrease the possibility of false-negative results, it would be a good clinical practise to investigate for LTBI all patients with immune-mediated inflammatory conditions when the diagnosis is established, before commencing any medication (22), and children should be tested simultaneously with TST and IGRA, in order to achieve greater sensitivity. Also, from the product information data of infliximab, adalimumab and etanercept, it results that for patients with multiple or significant risk factors for TB, even if negative to TST/IGRA for LTBI, the anti-tubercular therapy should be considered before starting the TNF-α agent. Similarly, anti-tubercular therapy should also be evaluated in patients with a previous history of LTBI or active TB for whom it is not possible to assure adequate previous treatment. In conclusion, there is a consensus about the need for treating any suspected case of LTBI before starting TNF-αantagonists. LTBI therapy has efficacy of 60-90% in preventing the progression of the disease (39): do not forget that no chemoprophylaxis regimen is wholly effective and take into consideration any sign or symptom of TB during the whole course of anti-TNF-α therapy. On the other hand, at the time, there is no consensus regarding the timing of the initiation of biologic therapy while on TB-preventing therapy (22): is it safe to commence anti-TNF-α therapy one or two months after the starting of TB-preventive treatment or we should delay the start of the biologic drug until after the completion of TB-preventive therapy? Some studies in the adult population agree about the opportunity to start biological therapy after at least four weeks of TB-preventing therapy if the patient is strictly adhering to and tolerate the preventive regimen (40-42). Other authors suggest waiting periods

between the start of TB-preventive therapy and biological therapy varied between 3 weeks to 2 months, in adult patients (42). For the paediatric population, there are no data available at this time in the current literature. Therefore the clinical practices are still based on adult protocols. Nowadays, according to CDC recommendations published in 2020, different paediatric therapeutic regimens are available for LTBI treatment (43), and, in the general population, rifampicin-based shorter regimens are recommended. They include three months of once-weekly isoniazid plus rifapentine (only approved for children older than two years), or four months of daily rifampin, or three months of daily isoniazid plus rifampin. The last two are approved for all ages. Short regimens, in the general population, are preferred because of their effectiveness, safety, and high treatment completion rates. Alternative regimens consider 6 or 9 months of daily isoniazid and are approved for all ages. Although efficacious, they have higher toxicity risk and lower compliance, due to the longer duration (43). The possibility of adverse effects of LTBI treatment should be taken into account, especially in these patients, who suffer from comorbidities, immune-mediated organ damage, and who often need additional therapy to control the underlying disease. For this reason, there is concern about the adequate TB-preventive regimen in this kind of patients, mostly in order to avoid hepatic toxicity. The British Thoracic Society reported, in their recommendation of 2005 for the adult population, that the TB-preventive regimen of six months of isoniazid shows a hepatitis risk rate of about 280/100 000 treated patients, while the shorter regimen of rifampicin with isoniazid for three months cause serious hepatitis much more often (1800/100 000 treated patients). In the studies selection of this report, paediatric data were excluded since showing a low rate of drug reactions (44). On the contrary, the WHO guidelines for low tuberculosis burden countries (2015) reported, in adults, fewer hepatotoxicity events for the 3–4 months rifampicin regimen and the three months weekly isoniazid plus rifapentine regimen when compared to the six or 9-month isoniazid regimen (45). In children population, a randomised control trial of 2018 by Diallo et al., reported similar rates of safety and efficacy for the four months of rifampin regimen compared with the nine months of

treatment with isoniazid, and a higher rate of adherence (46). Regarding the 12-dose once-weekly isoniazid/rifapentine regimen, Cruz et al. reported only one child, over 80 patients receiving therapy, with mildly elevated transaminases and concluded that even the isoniazid/rifapentine regimen is safe and well-tolerated, with parallel higher completion rates than traditional LTBI regimens (47). Significant hepatotoxicity was not reported, defined as serum aspartate aminotransferase or alanine aminotransferase concentrations five times over the upper limit of normal in asymptomatic patients, or three times over the upper limit of normal in symptomatic patients (nausea, vomiting, jaundice or abdominal pain) (47). Anyway, no study analyse children on anti-TNF-α therapy.

Besides, the peripheral neuropathy correlated to isoniazid can effectively be prevented by simultaneous supplementation with pyridoxine (48), while patients taking rifampin should be warned of the orange/red colouration of body fluids. Other main side effects of rifampin are dizziness, headache, fatigue or nausea (49).

**Patients developing active TB while on anti-TNF-α treatment**

Diagnosing TB in children on TNF-α antagonists could be challenging. There are limited data on the performance of IGRA assay in children on long-term treatment with TNF-α inhibitors. In Noguera et al. multi-centre study, the sensitivities of TST and QFT assays in children diagnosed with active TB and already on anti-TNF-α treatment were 66.7% (95%CI: 29.6- 90.1%) and 55.6% (95%CI: 26.6-81.1%), respectively (22). On the contrary, in Gabriele et al. study, which analyses the rate of indeterminate results of QTF-IT assay in children affected by JIA or lupus and on DMARDs or anti-TNF-α therapy (adalimumab or etanercept), none of the children with indeterminate QFT-IT result was receiving anti-TNF-α drugs (50). Also, Vortia et al. reported a low rate of indeterminate IGRA results among IBD children on infliximab therapy, equal to 1.1% (51). The previous data suggest that paediatric patients with JIA or IBD on long-term therapy with anti-TNF-α drugs have an

adequate interferon-γ response to mitogen, and that IGRA assay should be used as a diagnostic tool for LTBI or active TB in children on anti-TNF-α treatment. In Noguera *et al.* study, false-negative results can occur, and the physician should not exclude TB only based on IGRA or TST result.

Patients found with active TB during anti-TNF-α treatment should stop biologic treatment and start anti-tubercular therapy; the biological treatment should be reintroduced, if possible, after TB therapy is completed. The treatment period for active TB is identical to that of ordinary TB affected children. Some studies, in adult patients, evaluated the possibility of a concomitant therapy, If TNF-α inhibitor therapy is urgent (45). Some authors suggest the possibility of restarting the treatment with TNF-α antagonists after the first two months of TB-treatment and the confirmation of favourable treatment responses (45). Further studies are needed to confirm the safety and efficacy of this approach, especially in the paediatric population, more vulnerable to TB infection (52).

### Other BMRs and TB risk in children

The other classes of BRMs consist of monoclonal antibodies which antagonise cytokines like IL-1, IL-5, IL-6, IL-12, and IL-23, or other molecules (like JAK3) taking part in the inflammatory cascade. Few data are available about the risk of reactivation of TB for these classes of drugs; anyway, for all of them, screening for LTBI is suggested by FDA, both for adult and children (9,10,53).

For example, abatacept, an anti-CTLA4 selective T-cell costimulation modulator protein, or tocilizumab, an IL-6 receptor antagonist, which are both approved for JIA affected children, have not been studied in children with a positive TB screen, and its safety in individuals with LTBI is unknown. FDA suggests to screen adult and paediatric patients for LTBI before starting the treatment and to begin TB-preventive therapy before abatacept or tocilizumab. In particular, according to Winthrop *et al.*, for adult patients on therapy with tocilizumab, the risk of TB reactivation or de novo infection resulted in being similar to that observed with anti-tumour necrosis factor-α agents (53).

Further studies are needed regarding the safety of these classes of BRMs in paediatric population since, to date, the management of children on therapy with these classes of drugs are based on data obtained from adult studies.

### Conclusions

Recommendations for screening strategies and safety monitoring of paediatric patients on TNF-α antagonists treatment are at the time largely extrapolated from adult studies. Recent paediatric data support the notion that TB disease is a relatively uncommon complication of anti-TNF-α therapy in children and adolescents compared to adult patients in low burden TB-countries when LTBI is investigated and treated before starting the biologic treatment (35-37). The disease severity and the short- and long-term morbidity observed in children affected by disseminated or extra-pulmonary TB underscores the need for LTBI screening programs in this high-risk patient population, even in low TB prevalence settings. The primary health care physician and the parents of the children receiving anti-TNF-α drugs need to be aware of the risks related to TB so that the primary-care paediatrician should initiate targeted investigations as soon as possible if the child has new risk factors or develops symptoms compatible with TB disease.

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