Review / *Derleme*

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The Risk of Tuberculosis and TNF-alpha Inhibitors

TNF-alfa İnhibitörleri ve Tüberküloz Riski

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Abstract

The clinical use of TNF-alpha inhibitors have been increasing in the treatment of autoimmune disorders. The most common anti-TNF-alpha agents on clinical use are ethanercept, infliximab and adalimumab. TNF-alpha is an important mediator in the pathogenesis of tuberculosis, therefore the use of TNFAI increases the risk of tuberculosis. Patients who are on anti-TNF alpha treatment should be carefully evaluated for tuberculosis risk before and during therapy. The recommended screening tools are detailed history, physical examination, tuberculin skin test and/or interferon gamma (IFN-γ) release assay and chest X-Ray every six months.

Keywords: TNF-alpha inhibitors, tuberculosis, screening

Özet

Otoimmün hastalıkların tedavisinde tümör nekroz faktörü-alfa (TNF-α) inhibitörlerinin kullanımı son yıllarda giderek artış göstermektedir. Klinikte en çok kullanılan TNF-α inhibitörleri; etanersept, infliksimab ve adalimumabtır. TNF-α; tüberküloz patogenezinde önemli yer tutan bir mediatör olduğundan, TNF-α inhibitörlerinin kullanımının tüberküloz gelişim riskini artırması şaşırtıcı değildir. Bu risk TNF-α inhibitörü ajanları içinde de farklılık göstermektedir. Bu nedenle TNF-α inhibitörü kullanımı adayı olan hastalar tedavi öncesi ve sırasında tüberküloz gelişimi açısından yakın takip edilmelidir. Tarama için altı ayda bir ayrıntılı anamnez, fizik muayene, tüberkülin deri testi ve/veya interferon gama (IFN-γ) salınım testi ile akciğer grafisi önerilmektedir.

Anahtar Kelimeler: TNF-alfa, inhibitörleri, tüberküloz, tarama

Introduction

Significant progress has been made in the treatment of numerous inflammatory diseases such as rheumatoid arthritis, seronegative spondylarthropathy and inflammatory bowel diseases with the clinical presentation of TNF-α inhibitors (TNFAI). Unlike many anti-inflammatory agents, TNFAI is effective with its target-specific treatment mechanism. However, many side effects associated with these drugs have been reported. These can be listed as mainly tuberculosis (TB), mycobacterial infections, bacterial, viral or other fungal infections, local reaction at the injection site, infusion reactions, triggering autoimmunity, demyelinating diseases, heart failure and malignancy (1).

Etanercept, infliximab and adalimumab are the most commonly used TNFAIs (Figure 1). Sertolizumab pegol and golimumab among the human monoclonal antibodies are newly developed agents, and there are not enough studies with regard to their clinical uses.

Infiximab, which is a chimeric (mouse/human) anti-TNF-α monoclonal antibody, shows high specificity and affinity for soluble and transmembrane forms of TNF-α. Similarly, adalimumab is also a fully human-induced monoclonal anti-TNF-α antibody and inhibits both soluble and transmembrane-localized TNF-α. Etanercept is a soluble TNF-α receptor fusion protein, which show its effect through the TNF-α receptors

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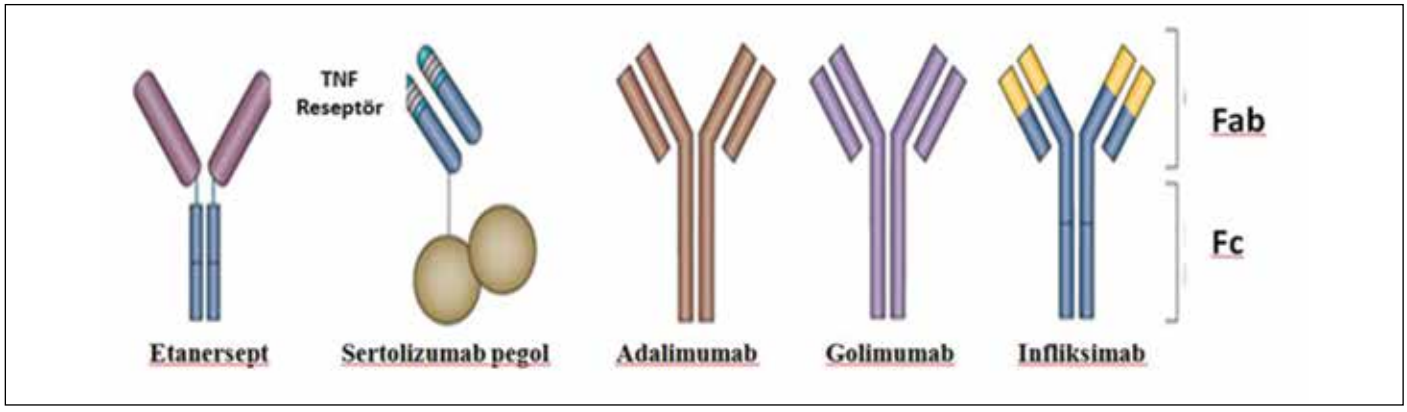

Figure 1. Clinical TNF-α inhibitors (2).

Table 1. Characteristics of TNFAI agents (3)

Biological agent (mode of administration)	Structure of the medicine	Half-life	Dose	Indication*
Infliksimab (remicade) (IV)	Chimeric IgG1 monoclonal antibody	8-9.5 days	Initially 3 mg/kg, then; 3 mg/kg at week 2 and 6. Maintenance: 3-6 mg/kg once in 8 weeks	There is no approval for JIA. ≥ 6 years moderate-serious CH and UC
Etanercept (enbrel) (subcutaneous)	Human; fusion protein	4.25 ± 1.25 days	0.8 mg/kg/week or 0.4 mg/kg/dose twice a week	≥ 2 years, moderate-severe polyarticular JIA There is no approval for IBH.
Adalimumab (humira) (subcutaneous)	100% human	10-20 days	JJIA: 15-29 kg; 20 mg once in two weeks ≥ 30 kg, 40 mg once in two weeks CH: Induction < 40 kg; 80 mg in day 1; 40 mg in day 14 > 40 kg; 160 mg in day 1; 80 mg in day 14 Maintenance: < 40 kg; 20 mg once in two weeks > 40 kg; 40 mg once in two weeks	≥ 4 years, moderate-severe polyarticular JIA There is no approval for pediatrics IBH

* Indication of use with FDA (Food and Drug Administration) approval.
CH: Crohn's Disease, JIA: Juvenile idiopathic arthritis, IBD: Inflammatory bowel disease, UC: Ulcerative colitis.

unlike other two agents. Its affinity for TNFR2 is higher than for TNFR1(2,3). TNFAI agents commonly used clinically are summarized in (Table 1).

TNF-α Inhibitors and Host Response

In animal models, TNF-α has been shown to have a number of protective roles against mycobacterial infections (4-6). Mycobacteria cannot be killed by the host when they enter into body, however, they are hidden in granulomas surrounded the by Langhans cells, lymphocytes and fibroblasts. TNF-α is very important in providing the inflammatory cell migration to granuloma structure and the continuity of granuloma structure (7,8). In addition, TNF-α also has several functions such as inducing antimicrobial activity in macrophages with interferon gamma, providing the migration of monocytes and circulating antigen-specific T cells to the infection site, managing leukocyte movement and facilitating its transmission through vascular endothelium, and activating cytotoxic T cells. TNF-α must be present at normal levels in the body and the tissues for the development of a healthy granuloma. Low levels of TNF-α create disorganized granulomas with high bacilli rates and inadequate macrophage activation where macrophages are over-stimulated and infected cells die, but the bacilli continue to multiply extracellularly within the granuloma where the levels of TNF-α are excessively high (9).

It is not surprising that TNFAIs increase tuberculosis development as a side effect while TNF-α has such important roles in TB pathophysiology. According to the American Food and Drug Adverse Effect Reporting System reports, the estimated TB rate was determined as 54-28/100.000 for patients

who used infliximab or etanercept in the United States between 1998 and 2002 and it was found to be higher than TB incidence (5.2-6.8/100.000) of the country in the same period (10). In a study on the 70 TB cases associated with infliximab, 64 cases were reported from countries that have low TB incidence, and TB development was determined to be the highest about 12 weeks after the treatment was started. Extrapulmonary tuberculosis rate was found to be 57.1% (11). In another study including 130 patients who had TB after infliximab intake between 2001 and 2006, risk factors facilitating TB recurrence have been identified as other accompanying immunosuppressive medication, latent or active TB history, born or lived for a long time in a TB endemic area (12).

Tuberculosis Risk for Different TNF-α Inhibitors

While it is often accepted that TNFAI facilitates TB development, studies have shown that the risk specified for these three drugs, which are increasingly used clinically, is not at the same level. In a study evaluating the incidence of TB in 10.000 patients who were received TNFAI treatment in the UK, TB development was shown to be higher than etanercept (39/100.000) during adalimumab (144/100.000) and infliximab (136/100.000) treatments (13). One of the hypotheses raised on this issue is that infliximab treatment is rapidly increasing to very high levels after intravenous bolus administration, however, blood drug levels show a steady state after subcutaneous administration of etanercept. However, this hypothesis does not explain why the risk is higher even though adalimumab pharmacokinetics is similar to etanercept (14). Another theory is that infliximab is forming large immune complexes with the binding of soluble trimeric TNF-α, and doing cell lysis through the complex system activation. Infliximab and adalimumab have been shown to lead to apoptosis-induced cell death in the lamina propria of patients with Crohn's disease (15). On the other hand, in a study, infliximab and adalimumab have been shown to reduce the TB response of CD4 cells by 70% and 50% and to reduce interferon (IFN) gamma production by 65% and 70%, however, etanercept has been shown to have no such effect (16). In addition, when the mechanisms of action of these agents are examined, adalimumab and infliximab directly inhibit TNF-α, and etanercept shows its effect by binding to receptors identified as TNF-R1 and TNF-R2. TNF-R1 receptor is known as the main reason of granuloma formation in tuberculosis pathophysiology. The lower affinity of etanercept on TNF-R1 seems likely to be associated with the lesser increase in the risk of tuberculosis (2).

The mean time required for TB development during the use of TNFAI also varies according to the drugs. Several studies have shown that TB development time after infliximab treatment is earlier than etanercept. The development of TB after infliximab treatment was found to be five and a half months shorter than etanercept (mean 13.4 months) and adalimumab (18.5 months) (11). In another study, 43% of infliximab-associated TB cases developed within the first 90 days of the treatment while this risk was homogeneously distributed for etanercept during the treatment (10).

In general, TB cases developed shortly after the initiation of TNFAI treatment are considered as reactivation whereas TB cases developed long after the initiation of the TNFAI treatment are considered as delayed reactivation or new TB infection. However, the issue that whether the tuberculosis, which is developed in regions with high risk of TB, is a latent TB activation or newly acquired TB infection can be only determined by DNA sequencing. Therefore, it would be more reasonable to interpret TB development as the reactivation of latent infection in TB endemic countries.

Latent Tuberculosis

Diagnosis of latent TB infection (LTBI) is very difficult. In particular, in countries such as Turkey, where BCG vaccination is routinely performed, it is necessary to evaluate several parameters to make a LTBI diagnosis. As the tuberculin skin test (TST) result may be positive depending on BCG vaccination, interferon-gamma release assays (IGRA) may give indeterminate results, the LTBE may show the immunologic memory TST and IGRA results of the recovered individuals as false positive, or on the contrary, IGRA/TST may be a false negative in individuals under immunosuppression (17,18).

The American Centers for Disease Control and Prevention (CDC) recommends screening all patients before the initiation of TNFAI treatment by detailed anamnesis, physical examination, TST or IGRA, and a chest X-Ray is also recommended to be taken if the patient is highly suspected with TB in physical examination or any other tests (19). However, chest X-Ray is recommended for LTBI screening since TB incidence is high in Turkey (20).

Similarly, CDC does not find the combination of TST and IGRA necessary for each patient on a routine basis. However, it is stated that it may be beneficial to perform both tests in the cases, whose first test is negative, and who have a risk of infection or progression, and whose the clinical course is predicted to be bad (19). Although IGRA is found to be negative, positive TST should be taken into consideration in the cases with the high risk of transformation to LTBI and active disease, and these patients should be carefully examined for the administration of isoniazid (INH). In these patients, INH administration should be considered when either of the IGRA or TST is positive.

Table 2. Recommendation for evaluating patients, who will use TNFAI treatment, before and after treatment in terms of TB (20)

1. TNFAI treatment is contraindicated if active TB is present and TNFAI treatment should not be started until tuberculosis treatment is completed.
2. TB screening should be performed to anyone who is a candidate for TNFAI treatment.
3. Recommendations for the screening are anamnesis, physical examination, chest X-Ray, tuberculin skin test.
4. Conservative treatment of TB is not required for patients, who have negative TST (< 5 mm), have no fibrotic/calcific lesions on chest X-Ray, and those who have not any close contact with a patient with active tuberculosis within a year.
5. In patients with fibrotic/calcific lesions on chest X-Ray, further investigation should be performed in terms of active TB.
6. Patients, who are excluded from active TB and who are starting TNFAI treatment, should be re-evaluated on the sixth and twelfth months of the treatment, and then once a year due to the possibility of active TB development through treatment.

In Turkey, TNFAI treatment is recommended for those whose TST is positive (≥ 5 mm), and for those who have fibrotic/calcific lesions in chest X-Rays, and TB preventive treatment is recommended for those who have close contact with a patient with active TB within the past year. Apart from these absolute indications, the physician may initiate the treatment by considering the risk-benefit ratio in patients with both initial and re-measured TST of 0 mm (21). According to the national guidelines, it is recommended to initiate TNFAI after taking isoniazid at least one month, and to use isoniazid at a dose of 300 mg/day for 9 months (Table 2) (20). The use of rifampicin for 4 months can be used as an alternative. Short-term combination of pyrazinamide and rifampicin is not recommended due to the high risk of hepatotoxicity. Although the preferred method is the initiation of TNFAI treatment after the latent TB therapy, it is accepted that it may be started 1-2 months after isoniazide treatment if necessary.

In patients with active TB during follow-up, TNFAI treatment should be ended immediately and active TB treatment should be initiated. In cases of which TNFAI treatment is stopped, there may be paradoxical deterioration at the beginning as part of the inflammatory response syndrome (22,23). In such a case, beneficial effects of corticosteroids have been shown (24).

Other Infections During TNFAI Treatment

Mild infections, particularly URTIs, are usually observed in patients using TNFAI, except of TB infection. The most common serious infections are sepsis, gastrointestinal system and soft tissue infections, and the most common viral agent is varicella-zoster virus. In studies, *listeria monocytogenes*, histoplasma, *pneumocystis jirovecii* infections have been reported (3).

Data on vaccination before TNFAI are inadequate. Recommended vaccinations are annual influenza vaccine, pneumococcal vaccine, Human Papilloma Virus and Hepatitis B vaccines. Patients should be evaluated for varicella and measles before the treatment, and they should get measles, mumps, rubella, and varicella (MMRV) vaccine (3).

In conclusion, more extensive studies are needed regarding the follow-up of patients using TNFAI. More extensive and updated guidelines, which are customized for Turkey, are needed for the evaluation of tuberculosis in these patients.

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