TNF-α Inhibitors and Vaccinations

Subjects: Dermatology

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This entry is a up-to-dated review of the current indications for vaccination in patients on anti-TNF-a therapy. Live attenuated vaccines are always contraindicated, while inactivated vaccines can be safely administered.

TNF-α inhibitors

1. Introduction

TNF-α inhibitors are an important treatment option for moderate-to-severe plaque psoriasis [1]. The evaluation of safety and efficacy in developing an adequate immune response to pneumococcal polysaccharide and inactivated influenza vaccine has been conducted in patients with rheumatoid arthritis and psoriatic arthritis [2][3][4][5][6][7]. Treatment with etanercept, adalimumab and infliximab was shown not to affect the response to the pneumococcal vaccine. Concomitant use of methotrexate (MTX) or disease-modifying antirheumatic drugs (DMARDs) may result in a lower antibody response to the pneumococcal polysaccharide vaccine, although they do not alter the response to the inactivated influenza vaccine [2][8]. These two vaccinations are very important in patients receiving anti-TNF therapy to reduce complications related to those infections.

The administration of live attenuated vaccines is contraindicated in concomitance with TNF-α inhibitors due to the increased infectious risk and lack of available data. However, one study by Suissa et al. [9] showed a possible protective role of etanercept in exacerbations of chronic obstructive pulmonary disease, making it the first choice in patients at particularly high infectious risk or receiving a live attenuated vaccine.

Transplacental passage of IgG occurs in pregnant women on anti-TNF-α therapy during the third trimester and anti-TNF-α IgG has been found up to 6 months after birth in an infant [10]. For this reason, live attenuated vaccines should be avoided for the first six months in infants of mothers treated with TNF-α inhibitors [11], with the exception of certolizumab pegol [12]. In fact, one death from disseminated tuberculosis occurred in an infant exposed to infliximab and vaccinated with Bacillus Calmette–Guérin [13]. TNF-α inhibitors that can cross the blood-placental barrier can also be excreted in breast milk, so breastfeeding should be avoided if therapy cannot be discontinued [14]. The newborn vaccination schedule should be re-evaluated in the event of exposure to anti-TNF-α therapy, possibly by assessing the serum level of the biologic considered prior to administration of a live-attenuated vaccine [15].

2. Certolizumab

Certolizumab pegol is a pegylated Fab fragment of a monoclonal antibody targeting TNF-α, indicated in moderate-to-severe plaque psoriasis [16]. In the literature, a randomized phase IV trial on 224 subjects confirmed the efficacy and safety of inactivated trivalent influenza and polysaccharide pneumococcal vaccination in patients with rheumatoid arthritis treated with certolizumab pegol, reporting a humoral response comparable to placebo patients. Lower antibody responses were seen in patients treated with anti-TNF-α and concomitant DMARD (MTX) [17].

3. Adalimumab

Adalimumab is a monoclonal antibody that inhibits the action of TNF-a. In the literature, a randomized, multi-center, double-blind clinical trial involving 226 adult subjects with rheumatoid arthritis reported similar antibody responses to trivalent influenza virus vaccine and 23-valent pneumococcal vaccine in subjects treated with adalimumab or placebo [3]. This underlines the efficacy and safety of vaccination with both pneumococcal capsular polysaccharide antigens and inactivated influenza vaccine.

In a study by Burmester et al. [18], 15,132 patients with rheumatoid arthritis treated with adalimumab were analyzed. Of these, 351 patients received influenza vaccination, reporting fewer infection-related adverse effects than unvaccinated subjects.

No data are available on secondary transmission of infection from live vaccines in patients receiving adalimumab but, given the increased risk of infection, administration is not recommended [19].

As for pediatric patients, it is recommended to administer adalimumab after having performed the vaccinations required for age. Administration of live and live-attenuated vaccines to children exposed to adalimumab in utero is not recommended until five months after the last administration of adalimumab to the mother during pregnancy [20] [21].

4. Etanercept

Etanercept is a dimer consisting of a protein corresponding to the extracellular domain of TNF-a receptor 2 and the Fc fraction of human IgG1 immunoglobulin. [22]

Since no studies are available concerning the infectious risk from live vaccines, their administration in patients receiving etanercept is not recommended. In a randomised,[22] double-blind, placebo-controlled clinical trial in patients with psoriatic arthritis, 184 patients received a multivalent polysaccharide pneumococcal vaccine at week 4 of etanercept treatment. In this study, most patients treated with etanercept were able to produce an effective B-cell immune response to the pneumococcal polysaccharide vaccine.

In a study by *Rákóczi et al* [23], the 4- and 8-week immunogenicity of a 13-valent pneumococcal vaccine was evaluated in rheumatoid arthritis patients treated with etanercept and methotrexate (15) or with etanercept alone

(7) or with NSAIDs alone (24), confirming the efficacy of the antibody response and the safety of the vaccine in all patients treated with etanercept.

5. Infliximab

Infliximab is a IgG1 monoclonal antibody that bind TNF-a. The concomitant administration of live vaccines with infliximab is not recommended. In infants exposed in utero to infliximab, a fatal outcome due to disseminated bacillus Calmette-Guérin (BCG) infection has been reported after administration of BCG vaccine after birth. A waiting period of at least six months after birth is recommended before administering live vaccines to infants exposed in utero to infliximab. [24]

In a study concerning pneumococcal vaccination (pneumovax) in rheumatoid arthritis patients treated with infliximab and methotrexate it was shown that infliximab did not alter the antibody response, although in all patients treated with methotrexate the antibody title was lower than in untreated subjects. [25]

A randomised study by *deBruyn et al*. [26] in 134 patients with inflammatory bowel disease (IBD) treated with infliximab confirms that infliximab does not alter the antibody response of the influenza vaccine, even in relation to the timing of infusion. Recently, *Caldera et al*. [27] showed an increased antibody response in IBD patients treated with infliximab following a high dose influenza vaccine compared to the standard dose.

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