Advances in the Treatment of Noninfectous Uveitis with Biologics: Anti-TNF and Beyond

Edited by
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Safety Issues: What to do Before Initiating and during Biological Therapy

Introduction

The rate of biologic therapies use in patients with non-infectious uveitis is rising rapidly [1]. The largest clinical experience exists with infliximab but most recently, an increasing number of reports of the effectiveness of other anti-TNF-α agents such as adalimumab [2] or golimumab [3], Anti-Interleukin (IL)-1 agents such as anakinra or gevokizumab, IL-6 blockers such as tocilizumab [4], and anti-CD 20 antibodies such as rituximab have appeared in the literature.

However, specific recommendations in terms of safety for their use in patients with intraocular inflammation are lacking. A rational approach is to extrapolate the accepted recommendations for biologics in patients with rheumatoid arthritis [5,6].

Before initiating and during therapy with this type of treatments it is important to keep in mind the main adverse events associated with their use such as infections, some hematologic and cardiac effects and the relationship with the development of certain types of malignancies.

In this chapter, we review the key points that physicians should take into account before starting and during treatment with biologic therapies. The majority of them will be in common for all biologic treatments except as indicated.

Before Initiating Biologics

The patient who will be treated with biologics should know the main signs and symptoms (“red flags”) of the adverse effects associated with their use. The recommended previous evaluations before initiating biologic treatment are described in the (Table 1).

<table>
<thead>
<tr>
<th>Before biologic therapy</th>
<th>Anti-TNFα agents</th>
<th>Anti-interleukin 1 agents</th>
<th>Interleukin-6 blocker</th>
<th>Anti-CD 20 antibody</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Infliximab</td>
<td>Etanercept, Golimumab</td>
<td>Tocilizumab</td>
<td>Rituximab</td>
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<tr>
<td>To rule out active infection including tuberculosis, malignancy, cardiac disease, and demyelinating disorder</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>To rule out close tuberculosis contacts</td>
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<td>Pregnancy discouraging</td>
<td>X</td>
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<td>Blood analysis including complete blood count, liver transaminase, and serum creatinine levels</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>Hepatitis B and C serology</td>
<td>X</td>
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<td>Chest radiograph</td>
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<td>Tuberculin skin test or interferon-γ-release assays</td>
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<tr>
<td>Pneumococcal and influenza vaccinations</td>
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</tbody>
</table>

Table 1: Monitoring patients under biologic therapy.
a) Blood analysis: When starting therapy with a biologic treatment, obtaining a complete blood count, liver transaminase levels, and serum creatinine levels for all biologic therapies.

b) Clinical examination: Before starting biologics a careful clinical examination is important in order to know some important data such as previous cardiac diseases, oncologic history or neurologic disorders. In fact, moderate or severe heart failure (New York Heart Association class III–IV with reduced ejection fraction of 50% or less [7]) is considered a contraindication for anti-TNF-α agents.

Regarding malignancies, anti-TNF-α agents were contraindicated in patients with prior lymphoproliferative disease that had been diagnosed and/or treated within the last 5 years [8]. The relationship between biologic agents and solid malignancies is scarce and controversial. If the patients have been treated for solid malignancies more than 5 years ago or have been treated for nonmelanoma skin cancer more than 5 years ago, the biologic agent could be initiated.

Some evidences from randomized controlled trials and observational studies [9] have demonstrated that anti-TNF-α agents have been associated with development of demyelinating disorders [10]. In fact, the duration from the introduction of anti-TNF-α therapy to the onset of demyelinating disorders was 5 months on average (range 1 week to 15 months) [11] or 12 months (range 2.5 months to 2 years) [9]. Therefore, they are contraindicated in cases of demyelinating disorders such as multiple sclerosis, optic neuritis, tranverse myelitis, and Guillain-Barré syndrome [12].

c) Active or latent infections: Given the high rate of serious bacterial infections associated with the use of biologic agents, an important point in the preliminary evaluation is to ensure the presence of active infection. In fact, bacterial infection or a bacterial infection currently requiring antibiotic therapy, active Tuberculosis (TB) or latent TB infection prior to starting preventive therapy, active herpes zoster infection, or active life-threatening fungal infections are reasons that contraindicate the therapy with biologic agents. It is mandatory to assess the patient’s medical history in order to identify risk factors for TB before initiating biologic therapy [13]. Some of these recognized risk factors are the close contacts of persons known or suspected to have active TB, foreign-born persons from areas that have a high incidence of active TB (e.g., Africa, Asia, Eastern Europe, Latin America, and Russia), persons who visit areas with a high prevalence of active TB, and infants, children, and adolescents exposed to adults who are at an increased risk for latent or active TB infection. Independently of the presence of any of these risk factors, tuberculin skin test or Interferon-γ Release Assays (IGRAs) are advisable as the initial test in all patients starting biologic agents [14]. If any of them are positive, chest radiograph should be performed and if there are signs of active TB, sputum culture is necessary in order to confirm the presence of active TB.

The majority of patients that will be candidate to initiate biologic treatment will be under conventional immunosuppressant therapy. In this context, they may have false-negative tuberculin skin test or IGRA results. If this immunosuppressed patient has risk factors for latent TB infection, the repetition of these tests 1–3 weeks after the initial negative screening is advisable. In cases where latent TB infection was confirmed, the recommendation is to start a 9-month course of daily isoniazid and delay the anti-TNF-α therapy at least one month later. In patients with active TB, biologic agents can be initiated only after completion of the treatment.

In the presence of acute hepatitis B or C, biologic agents were contraindicated. In those untreated chronic hepatitis B patients or with treated chronic hepatitis B with liver dysfunction (Child–Pugh class B and higher) biologic agents should not be initiated. There is some evidence that etanercept could be safe in patients with hepatitis C.

d) Vaccinations: Importantly, live vaccines (e.g., varicella-zoster vaccine, oral polio, rabies) are contraindicated during biologic therapy. Conversely, all killed (pneumococcal, influenza intramuscular, and hepatitis B), recombinant (human papillomavirus vaccine for cervical cancer), and live attenuated (herpes zoster) vaccinations should be undertaken before starting a biologic agent. In fact, periodic pneumococcal and annual influenza vaccinations are advisable for all patients receiving biologic treatment [14].

e) Pregnancy and breastfeeding: Pregnancy and breastfeeding should be discouraged in patients who will initiate biologic therapy.

**During Biologic Therapy**

Patients under biologic therapy should be monitored periodically. However, there is not a definitive recommendation of the frequency of testing and it will be performed according the biologic agent and the clinical situation. A rational approach could include a first control one month after start of treatment and thereafter each 1 to 4 months according the tolerance and response to the treatment [6].

Importantly, in each control a clinical examination and a blood analysis including complete blood count, liver transaminase, and serum creatinine levels are mandatory. The physician should rule out in every visit the presence of active infection, cardiac or pulmonary manifestations and neurological symptoms. In fact, it’s proved that patients with continuation of anti-TNF-α therapy even after the first appearance of neurological symptoms had a worst outcome when comparing with the patients that discontinued treatment, which most cases showed the partial or complete recovery of their neurological disorders [11]. One of the main points to keep in mind during anti-TNF-α therapy is the management of surgical operation due to the theoretically increased risk of infectious complications and/or delayed healing. However, this potential risk has not been clearly evaluated in the literature. The general recommendation in case of surgery not associated to high infection risk such as cataract is to discontinue the anti-TNF-α therapy for a period corresponding to two half-lives before the operation. Of note, if the surgery should be performed in a septic environment such as peritonitis the anti-TNF-α therapy should be discontinue for a time period close to the duration of bioavailability, which is five half-lives. In both cases, anti-TNF-α therapy could be reinitiated as soon as healing is confirmed and in the absence of infection [15].

**References**


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