

Review

Adverse reactions of biological therapies in patients with psoriasis

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Abstract

Psoriasis is a chronic, immune-mediated disorder characterized by well demarcated, erythematous plaques covered by thick, silvery-white scales, most often located on the knees, elbows, sacral area and scalp. It has a significant impact on the patient's quality of life.

Biological therapies revolutionized the treatment of psoriasis vulgaris but there has been concern regarding the use of those agents due to severe adverse reactions reported in patients receiving TNF- α inhibitors for various inflammatory diseases.

The aim of this paper is to review the most important adverse reactions reported in patients receiving biological treatments. The most common and severe side effects associated with biologicals are infections, cardiac adverse reactions, neurologic adverse reactions, lymphomas, non-melanoma skin cancers and hepatobiliary disease.

Keywords: psoriasis, inflammatory disorders, TNF- α inhibitors, biological therapies, adverse reactions



Introduction

Psoriasis is a chronic, immune-mediated disorder characterized by well demarcated, erythematous plaques covered by thick, silvery-white scales, most often located on the knees, elbows, sacral area and scalp. Any region however can be involved. It has a worldwide distribution and a prevalence of approximately 2%. It can occur at any age but it presents two peaks of onset: one at 20-30 years and the second at 50-60 years. Psoriasis has a significant impact on the patient's quality of life. Several topical and systemic therapies are available nowadays for the treatment of psoriasis. Topical treatments are difficult to apply and time-consuming. Systemic conventional therapies are associated with severe adverse reactions. As a result, patient's compliance and adherence to treatment are low (1-3).

Biological therapies revolutionized the treatment of psoriasis vulgaris. In Romania, they are recommended for patients with moderate to severe plaque type psoriasis unresponsive or intolerant to conventional therapies. Three biologicals have been largely used so far: infliximab, adalimumab and etanercept. All of those are antibodies directed against tumor necrosis factor- α (TNF- α). In years recent, experience with ustekinumab, a human monoclonal antibody directed against interleukin (IL) 12 and 23, has also increased. Despite the very good results obtained with biological treatments, the clinician and the patient should be aware of possible adverse reactions (4).

Discussion

• Adverse events in patients receiving biological therapies

Local adverse reactions

Injection site reactions are the most frequently reported adverse events and occur in approximately 17.5% of patients treated with adalimumab and 22.4% of

patients receiving etanercept. They are mainly represented by erythema, edema, pruritus, hemorrhages, ecchymosis and low to moderate pain. The higher incidence of local adverse reactions in patients receiving etanercept is due to the more frequent administration of the drug. Injection site reactions are generally well tolerated and do not usually require interrupting the treatment. Topical corticosteroids and analgics are sometimes useful. Varying the injection site is recommended (5, 6).

Infusion reactions have been reported in approximately 17% of patients receiving infliximab and headache, dizziness, nausea, fever and pruritus are the most frequent symptoms. Life threatening adverse reactions such as convulsions and anaphylactic shock have been reported in approximately 0.5% of patients receiving infliximab. Infusion reactions can be acute or delayed. Acute reactions occur during the first hour and are represented by hives, rash, fever, bronchospasm, laryngopharyngeal edema, dyspnea and hypotension. Most cases only require decreasing the infusion rhythm or temporarily ceasing the infusion. Severe cases however necessitate stopping the treatment and stabilizing the patient. Delayed hypersensitivity reactions are represented by myalgia, arthralgia, fever, headaches, rash, fatigability and facial edema (5, 7).

Infections

Tuberculosis is one of the most important adverse events associated with biological therapies. Those can determine the reactivation of a latent tuberculosis or de novo infection. The risk of extrapulmonary tuberculosis is also higher in these patients. Given the high incidence of this infection in the general population, testing all patients prior to starting biological treatment is mandatory (8).

A study performed in Sweden by Askling et al. assessed the risk of developing tuberculosis of patients receiving TNF- α inhibitors and compared it to the risk

encountered in the general population. According to the authors, patients receiving biological therapies have a 4 fold higher risk of developing tuberculosis than patients who do not receive biological treatment (9).

Singh et al. conducted a meta-analysis of studies performed on patients receiving biological therapies. The authors included 163 randomized controlled studies with 50,010 participants and 46 extension studies with 11 954 participants. The authors showed that patients treated with TNF- α inhibitors had a higher risk of developing tuberculosis than patients in the control group (10).

Cutaneous infections like cellulitis, erysipelas or abscess have been reported in 0.1-7% of patients treated with biological therapies. Superficial fungal infections of the skin are also more frequent in patients receiving biologicals. Some cases of disseminated herpes simplex virus infection and reactivation of the varicella-zoster virus have also been reported. Strangfeld et al. performed a study in which they included 5,040 patients with rheumatoid arthritis who were treated with TNF- α inhibitors or with disease-modifying antirheumatic drugs (DMARDs). The authors observed that the risk of developing herpes zoster was high in patients receiving adalimumab and infliximab but not in patients receiving etanercept (11). Mc Donald et al. performed a retrospective study in which they included 20,357 patients treated for rheumatoid arthritis between 1998 and 2005 and found that the risk of developing herpes virus is higher in patients treated with biological treatments, patients receiving infliximab having the highest risk (12).

Opportunistic infections have been reported in patients receiving TNF- α inhibitors. Salmon-Ceron et al. performed a prospective study in which they aimed to describe opportunistic infections, other than tuberculosis, in patients with rheumatoid arthritis, inflammatory colitis, psoriasis vulgaris, ankylosing spondylitis and other inflammatory conditions treated

with biological agents. The most common opportunistic infections were listeriosis, nocardiosis, infections with atypical mycobacteria, atypical salmonellosis, pneumocystosis, aspergillosis, cryptococcosis, leishmaniosis and disseminated cytomegalovirus infection. Infliximab was associated with the highest risk of developing opportunistic infections while etanercept was associated with the lowest risk (13).

Lanternier et al. performed a prospective study between 2004 and 2007 in which they described the incidence of Legionella pneumophila pneumonia in patients treated with biological agents. The authors reported an annual incidence of 46.7 cases/100,000 patient-years and concluded that the incidence of Legionella pneumophila pneumonia is high in patients receiving biological therapies, especially infliximab and adalimumab (14).

Wissman et al. examined the pharyngeal exudate from 125 patients with rheumatological disorders, half of those being treated with infliximab. The authors demonstrated Pneumocystis jirovecii colonization in 25.6% of patients and concluded that infliximab treatment is an important risk factor for developing this infection (15).

Invasive fungal infections were reported in patients receiving TNF- α inhibitors. Tsiodras et al. performed a literature review and identified 281 cases of invasive fungal infections in patients treated with biological agents. 80% of those occurred in patients treated with infliximab, 16% in patients treated with etanercept and 4% in patients receiving adalimumab (16).

Cardiovascular adverse reactions

Various cardiovascular adverse events have been associated with biological therapies. Heart failure is one of the most important adverse reactions reported in the medical literature. Setoguchi et al. showed in a study performed between 1994 and 2004, which included 1002 patients treated with TNF- α inhibitors and 5593 patients

treated with methotrexate for rheumatoid arthritis, that patients receiving biological agents had a higher risk to develop cardiac insufficiency than patients treated with methotrexate (17). Curtis et al on the other hand performed a study in which they included young patients suffering from rheumatoid arthritis or Crohn's disease who received biological treatment or other treatments and noticed no significant difference regarding the rate of heart failure between patients receiving anti-TNF- α agents and patients receiving other treatments (18). Other authors, like Wolfe and Michaud, showed that biological therapies decrease the risk of cardiac insufficiency. The two scientists reached this conclusion after analyzing data from 13,171 patients with rheumatoid arthritis and 2,568 patients with osteoarthritis (19).

Arrhythmias were also reported in patients receiving infliximab. Lazzerini et al. performed a prospective placebo controlled study in which they included patients with ankylosing spondylitis and rheumatoid arthritis who were monitored during the infliximab infusion or placebo infusion, respectively. The authors showed that tachyarrhythmia and bradyarrhythmia were present in both examined groups and the difference was not statistically significant (20).

Data regarding the effect of biological therapies on the vascular system is contradictory. Some authors consider that they might improve endothelial function and reduce the rate of cardiovascular events while others consider that long-time treatment with infliximab is proatherogenic (21).

Cardiac output also seems to be decreased in patients treated with infliximab. Santos et al. performed a study in which they included 14 patients with rheumatoid arthritis with no history of cardiac insufficiency and measured a significant reduction of the cardiac output and stroke volume during the infliximab infusion (22).

Development of anti-drug antibodies

Biological therapies act as antigens after they are administered because of their protein structure. As a result, the immune system can create antibodies directed against them. The development of anti-drug antibodies was reported for all biological therapies. Two main types of anti-drug antibodies were described in the medical literature: neutralizing antibodies, which decrease or even annul the effect of the biological agent, and non-neutralizing antibodies, which do not influence the pharmacological proprieties of the drug (2, 23).

Infliximab is a chimeric mouse-human monoclonal antibody and its administration is frequently associated with the development of anti-drug antibodies which are generally neutralizing. Adalimumab is a fully human monoclonal antibody. For that reason, it was initially believed that it would not be recognized as non-self by the immune system. Recent studies however contradict this idea, as neutralizing antibodies directed against adalimumab were detected. Etanercept is a fusion protein produced by recombinant DNA technology. Anti-drug antibodies were described in patients treated with etanercept but these antibodies are not neutralizing (2).

A study performed by Van Schie et al. showed that more than 90% of the antibodies directed against adalimumab and infliximab are neutralizing as they interact with the portion responsible for binding TNF- α . The rest of the antibodies are non-neutralizing as they bind to other portions of the antibodies, which are not involved in binding TNF- α (24).

Kui et al. showed in a study performed on patients with psoriasis treated with TNF- α inhibitors that the presence of anti-drug antibodies is associated with higher severity of psoriasis and lower serum levels of TNF- α inhibitors (25). Murdaca et al. also showed that the presence of neutralizing antibodies against

adalimumab and infliximab decreases the chances of obtaining clinical remission of the disease, decreases the drug survival duration and increases the necessity to administer higher doses of biological agent (26).

The concomitant administration of biological agents with methotrexate and other immunosuppressives decreases the risk of developing anti-drug antibodies. Data regarding their usefulness in patients with psoriasis is contradictory and additional studies are needed to support the efficiency of the combined treatment (27).

Neurological adverse events

The most important neurological side-effects associated with biological therapies are demyelinating diseases of the central nervous system, optic neuritis, facial paresis, peripheral neuropathy, transverse myelitis, Guillain-Barré syndrome and infectious diseases (28, 29).

Progressive multifocal leukoencephalopathy (PML), a potentially fatal infectious disease determined by activation of the John Cunningham virus, was reported after the treatment with monoclonal antibodies, such as infliximab, adalimumab, etanercept, efalizumab, rituximab, etc. John Cunningham virus is a double stranded DNA polyomavirus. It is an ubiquitous neurotropic virus. Studies indicate that 50-90% of adults have been exposed to it. PML was initially described as a complication of chemotherapy in hematological patients. Nowadays, it is considered an important complication of HIV infection. If patients remain immunosuppressed, they die within months. Efalizumab was voluntarily pulled off the market after three patients with psoriasis died from PML, as it was considered that the benefits do not outweigh the risk. Cases of PML have also been reported in patients receiving infliximab, adalimumab and etanercept. The incidence of the disease

however is comparable to that found in the general population (29-31).

Non-melanoma skin cancers

TNF- α inhibitors are associated with higher rates of skin cancers, especially non-melanoma skin cancers. Askling et al. performed a meta-analysis in 2011 in which they included 74 randomized controlled studies which evaluated the short term risk of developing skin cancers. 15,418 patients were randomized to the group treated with TNF- α inhibitors and 7,486 patients were randomized to the control group. The authors concluded that patients receiving biological agents have a short term risk of 2.02% of developing non-melanoma skin cancer (32).

The concomitant or previous administration of other treatments such as methotrexate, cyclosporine or PUVA can increase the incidence of non-melanoma skin cancers in patients treated with biological agents. Those patients must therefore avoid sun exposure and be closely monitored for early detection of skin cancers (5).

Lymphomas

The occurrence of lymphomas has been described in patients receiving TNF- α inhibitors for various disorders. Until now, however, it has been impossible to say if biological therapies truly increase the risk of developing lymphomas as data from the specialty literature is contradictory. Some studies concluded that patients treated with adalimumab and infliximab have a higher risk of developing lymphomas than patients treated with etanercept. Other studies did not find higher risk of developing lymphomas in patients treated with biological agents. It is worth mentioning that most studies assessing the risk of lymphoma were performed on patients with rheumatoid arthritis. Rheumatoid arthritis itself is associated with a higher risk of developing lymphoma. Even though the risk of lymphoma does not seem to be higher in patients treated

with biological agents, continued vigilance is warranted (33, 34).

Hepatic adverse reactions

Autoimmune hepatitis, jaundice and drug-induced hepatic dysfunction can all be associated with the use of biological therapies. The administration of TNF- α inhibitors in patients with hepatitis B and hepatitis C is not an absolute contraindication. The clinician however must carefully assess the risk/benefit ratio before recommending these treatments to patients with hepatic disorders. Reactivation of hepatitis B in HBsAg carriers was reported after the administration of biological agents. TNF- α plays an important role in the eradication of hepatitis B virus. Perez et al. performed a review of the literature and noticed a 39% increase in the reactivation rate of HBV in HBsAg carriers treated with anti-TNF- α agents. The risk seems to be higher in patients treated with infliximab (35, 36).

TNF- α inhibitors seem to be safe in patients with hepatitis C. Studies show that TNF- α level is high in patients with hepatitis C and is associated with high levels of serum transaminases, histological changes and fibrosis. A study which included 216 patients with hepatitis C treated with TNF- α inhibitors showed that only 3 patients required terminating treatment due to hepatitis C reactivation. The viral load remains constant or even decreases after short term treatment with biological agents (37, 38). However, some cases of hepatocellular carcinoma were reported in patients with HCV who received long term treatment for psoriasis vulgaris. Regular follow-ups are therefore mandatory in those patients (38, 39).

- **Should safety data from other inflammatory disorders be extrapolated to psoriasis?**

Most data regarding the safety of biological therapies comes from patients treated for rheumatic diseases and from inflammatory bowel disease. These disorders are associated with comorbidities and require specific

treatments. Some authors therefore suggested that safety data from other inflammatory disorders should not be applied to patients with psoriasis. To support this idea, Garcia-Doval et al. compared data from two national drug safety registers: Biobadaser, the registry for rheumatic diseases and Biobadaderm, the registry for psoriasis. The authors showed that the risk of serious adverse events is almost two fold higher in patients with rheumatoid arthritis than in patients with psoriasis treated with anti-TNF α inhibitors. The authors also showed that patients receiving biological therapies for rheumatoid arthritis have a higher risk of developing infections, cardiac disorders, respiratory disorders, and infusion related reactions while patients receiving biologicals for psoriasis have a higher risk of developing skin and subcutaneous tissue disorders and hepatobiliary diseases (40).

A study which included 173 psoriasis patients who were prospectively followed for 5 years also showed that long-term treatment with biologicals is safe in this group of patients, the rate of malignancies, serious infections and serious cardiovascular events being comparable with the general population incidence rate. The authors also found that psoriatic patients treated with anti-TNF- α agents have a higher risk of developing skin malignancies, probably due to previous exposure to UV-therapies and immunosuppressive drugs, but also because these patients are more closely followed by dermatologists (41).

Conclusions

Psoriasis vulgaris is a chronic, inflammatory disease with a great impact on the patient's quality of life. TNF- α inhibitors have revolutionized the treatment of psoriasis but there has been some concern regarding the use of those agents due to severe adverse reactions reported in patients receiving biological therapies for various inflammatory diseases. The most important severe

adverse reactions associated with biologicals are infections, cardiac adverse reactions, neurologic adverse reactions, lymphomas, non-melanoma skin cancers and hepatobiliary disease. Most adverse events were reported in patients receiving anti-TNF α agents for rheumatic diseases and the safety data were extrapolated to psoriatic patients. New studies performed on psoriatic patients treated with biological agents are therefore required in order to establish the safety profile of the drugs in this particular group.

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