IBD REVIEWS

Scientific and technological research article

Review article: Adverse effects caused by Anti-TNF therapy in adults with inflammatory bowel disease

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Introduction

Crohn's Disease (CD) and Ulcerative Colitis (UC), the most common forms of Inflammatory Bowel Disease (IBD) have presented worldwide an increase in both incidence and prevalence in recent decades. #, # Likewise, Latin America is not excluded from this epidemiological phenomenon. #, # Biological therapy, specifically anti-TNF, was introduced for the first time in the USA in the year 98, this marked a before and after in the treatment of CD and CU since it allowed to change the natural evolution of the disease. # The first anti-TNF molecule used was Infliximab, an IgG1 type chimeric monoclonal antibody, which is effective in inducing and maintaining remission in CD # and CU # Then fully humanized monoclonal antibodies such as Adalimumab were developed, which also proved to be effective in the treatment of both CD#,# and CU ##. As well as Golimumab and Certolizumab, which is a fab pegylated fragment of a humanized monoclonal antibody. Both are effective in inducing and maintaining remission in CU ##, ## and CD ##, ## respectively. However, the use of anti-TNFs may be associated with serious adverse effects, of which most of these are class effects.

Objectives and methods

The objective of this review is to identify and classify the adverse effects of the use of biological anti-TNFs in adults with inflammatory bowel disease, to be able to recognize them early in daily clinical practice and when possible avoid them. For this, a search of articles in PubMed was conducted, that focus on the adverse effects of anti-TNF in adult patients with inflammatory bowel disease, for which a search was conducted using the following terms: ¨anti-TNF¨ combined with ¨ adverse effects¨ and ¨ Inflammatory bowel disease¨. Only articles in English were included and articles with pediatric patients were discarded.

1. Hypersensitivity reactions

Hypersensitivity reactions may be acute, when it occurs at the time of infusion of the biological or within the first 24 hours or may be late when these occur between 24 hours to 14 days of infusion. Clinically acute reactions are manifested as rash, pruritus, headache, flushing and even being able to reach anaphylactic reactions, while late reactions are presented as myalgia, arthralgia, fatigue and fever. ## Acute reactions in the case of Infliximab, occur in 9-11% of cases and late reactions in 1.7% and hypersensitivity reactions occur more frequently in patients who develop antibodies against Infliximab 35- 50% vs. 9.7%. # In the case of Adalimumab, the percentage of hypersensitivity reactions is only 1.6%, with the formation of antibodies against Adalimumab 0.04 to 2.9%, this consequence of which it is a totally human anti-TNF and that its route of administration is subcutaneous, on the other hand, cases of reactions at the puncture site such as flushing or pain range from 12 - 38%. #, ## Also with Golimumab, being a fully human antibody and subcutaneous administration, the main complication is the reaction at the injection site 3.4%. ## Finally, in the case of Certolizumab Pegol, also because its subcutaneous route of administration, there is a reaction at the injection site in just 1%. ##

2. Immune-mediated inflammatory disorders and Autoimmunity phenomena.

2a. Joint compromise

It consists of joint manifestations that occur in patients receiving anti-TNF, without prior rheumatic disease or in patients with spondylitis who develop peripheral joint manifestations, which clinically manifests as arthralgia sometimes disabling or arthritis. These types of manifestations occur in up to 11% who receive Infliximab and apparently are not related to medication levels or anti-Infliximab antibody titres. These manifestations usually occur with an average duration of anti-TNF of 12 months and the exact mechanism that originates these manifestations is not yet known, but it is possible that it is related to autoimmunity phenomena, since up to 50% of these patients are show high titers of antinuclear antibodies. ##

2b. Lupus-Like Syndrome

Approximately 44% of patients with IBD treated with anti-TNFs have antinuclear antibody (ANA) formation and 15.6% double-chain anti-DNA antibody formation. ## However, only 2.1 - 8.9% of these patients have clinical manifestations such as arthralgia, myalgia, fever, serositis and malarial erythema in butterfly wings (Lupus-Like), most of which are women, ## related to the formation of these autoantibodies. ##, ##, ## This type of reaction is not a class effect, since when rotating with another anti-TNF, the possibility that it develops again is low 7%. ##

2c. Hematological non-neoplastic effects

Anemia. Anemia is considered an activity marker in both CD and UC. ## In addition, only 33.6% of patients with IBD who have anemia and who are being treated with anti-TNF and iron have an improvement in this. ## Therefore, ruling out some case of hemolytic anemia, ## it seems that anemia, rather than an adverse effect of the use of anti-TNF, is a consequence of IBD itself.

Neutropenia. It is defined as the neutrophil count in blood less than 1500 cel / mm³, the risk of infections increases significantly when the neutrophil count is <1000 cel / mm³. ## Likewise, there are few cases reported in the world literature on neutropenia due to the use of anti-TNF, mainly in CDs in which although the cause of this reaction is not yet defined, the presence of anti-neutrophil antibodies was detected, which could cause an increase in the destruction of peripheral neutrophils. ##

Thrombocytopenia. It is defined as the platelet count in blood less than 150000 cel / mm³, ## there are few reported cases and possibly caused by anti-platelet antibodies. ##

Hypercoagulability. Patients with IBD have an increased risk of thromboembolic events, usually when the disease is active and when patients are subject to risk factors such as tobacco use, immobilization, surgery, hospitalization or use of oral contraceptives. The direct association of the use of anti-TNF and the development of thromboembolic events is therefore a complex diagnosis. There are also few cases of thromboembolic events reported by the use of anti-TNF, most of which were venous thrombosis and possibly related to the development of antiphospholipid and anticardiolipin antibodies. ##

2d. Non-neoplastic, non-infectious skin compromise

Psoriasis. The exact mechanism of why psoriasis develops in a patient with IBD in treatment with anti-TNF remains unknown, but possibly due to the blockage of TNF can cause an increase in the release of IFNα, a cytokin for the induction of psoriasis produced in dermal plasmocytoid dendritic cells. ## This effect occurs in 1.6-5.3% of patients treated with anti-TNF. Tobacco, CD and female sex are risk factors. ##, ## In addition approximately 60% of patients have recurrence when rotating to another anti-TNF. ## The areas of the body with the highest psoriasis involvement are plants, palms and scalp 53% and most 88% occur in 2 or more areas. ## There is no relationship between the development of psoriasis and the level of anti-Infliximab antibodies or Infliximab levels. ##

Other manifestations. Other cutaneous manifestations include: cutaneous vasculitis, which is the main form of presentation 87% and of which leukocytoclastic vasculitis is the main form. Clinically the most frequent finding is the palpable purpura. ## The possible mechanism of these manifestations could be due to the deposition of immunocomplexes (anti-TNF / anti-TNF antibody) in the blood vessels inducing complement activation, that is, type III Hypersensitivity reaction. ## Eczema, with red, scaly and scab lesions involving the scalp, trunk, genitals, face and flexures. The possible mechanism could be similar to psoriasis. ## Other less common manifestations reported as isolated cases are alopecia, vitiligo, lichen, acne, granuloma annulare, interstitial granulomatous dermatitis, erythema nodosum, dermatitis herpetiformis, pemphigus vulgaris, pyoderma gangrenosum. ##

2e. Lung effects, Non-Infectious

Lung damage induced by anti-TNF is a rare (0.6%), but potentially fatal adverse effect. It is a non-infectious interstitial pneumopathy, which clinically manifests itself with symptoms such as dyspnea, cough and fever. In the images predominates the bilateral infiltrates and in tarnished glass. For the diagnosis it is required that there are no lung lesions prior to the use of anti-TNF, rule out infections or other lung diseases and resolution of symptoms and radiological manifestations after removing the anti-TNF. ##

2e. Non-infectious neurological effects.

Cases of demyelinating disorders have been reported 0.05-0.2%, with the use of anti-TNF, which most affect the central nervous system, with 70% optic neuritis followed by multiple sclerosis. In addition, cases of peripheral nervous system may occur, of which the most prevalent is Guillain-Barre syndrome 45%. ## The clinical manifestations of these adverse effects are so varied that they depend on the site where demyelination occurs. The mechanism of why anti-TNF induces demyelinating processes is not yet known. Other non-infectious neurological manifestations not associated with demyelinating disorders are secondary to vasculitis or ischemic (hypercoagulability).

2f. Non-infectious Hepatobiliary effects.

Up to 6% of patients with IBD who begin using anti-TNF have some degree of elevation of ALT without prior alteration to its use, of which approximately 50% is directly related to the use of anti-TNF. The mechanism of this adverse effect is not yet known, but it is very possible that it is an autoimmune mechanism, since it has been seen in most patients with elevation of ANA and ASMA levels, in addition to liver biopsies similar to of an autoimmune hepatitis, that is, active hepatitis with interface activity and plasma cells. Most cases occur in women and are transient and mild. ## There are very isolated cases in which patients with anti-TNF use debut with acute liver failure, which even require liver transplantation. The clinical and histological characteristics are not compatible with autoimmunity phenomena, possibly being the effect of idiosyncratic reactions. ##

3. Cardiac effects.

In a study, which was designed to demonstrate the usefulness of Infliximab in the treatment of heart failure with NYHA III or IV functional stages, it was demonstrated not only that it has no benefit, but that this clinical condition worsens with high doses of infliximab 10mg / kg ## It has also been seen that the use of Anti-TNF not only worsens heart failure, but can also precipitate it. In a study of 47 patients who developed heart failure with the use of anti-TNF, 80% had no history of known heart disease. ## The mechanism of this phenomenon is unknown.

4. Cancer

The use of anti-TNF has been associated with the development of some malignant tumors such as melanoma, non-melanoma skin cancer, solid organ tumors and lymphoproliferative tumors. ## However, it is difficult to establish a causal relationship since many of the patients who have undergone the use of anti-TNF, have previously been or are jointly treated with immunomodulators such as thiopurines, the same as if they are related to an increase in the risk of developing lymphoproliferative tumors. ## A study of 666 patients with IBD treated with thiopurines and anti-TNF showed that in the group of patients treated with thiopurines they developed more malignant tumors than patients treated with anti-TNF 7% vs. 2%, and that in both groups the majority of the tumors appeared in> 50 years. ##

4a. Lymphoma

The data obtained from the TREAT registry (Therapy, Resource, Evaluation and Assessment Tool) for CD, show that there is no increase in the risk of lymphoma development among patients treated with anti-TNF compared to patients treated with other drugs 0, 05 vs 0.06 events per 100 patients / year respectively. ## It is possible

that the reported cases of lymphomas in patients with IBD in the use of anti-TNF are more related to the previous or simultaneous use of thiopurines since in a study with more than 16,000 patients with IBD it was observed that the use of anti-TNF more thiopurines were associated with an increased risk of lymphoma. ##

4b. Non melanoma skin cancer

Patients with IBD who are being treated with anti-TNF are not related to a significant increase in the risk of developing non-melanoma skin cancer, but if anti-TNF is combined with thiopurines, there is a significant increase in risk (OR, 3 , 89; 95% CI, 2.33-646). It should be noted that patients who are exposed as monotherapy with anti-TNF have generally been previously exposed to thiopurines. ## Once again it is difficult to ensure whether anti-TNF is the associated factor in the development of nonmelanoma skin cancer or if it is thiopurines.

4c. Melanoma.

IBD has an increased risk of melanoma (37%), independent of the use of anti-TNF. ## There are also reports that this risk increases more with the use of anti-TNF, in a study with 108,579 patients with IBD, the use of anti-TNF was associated with melanoma (OR, 1.88, 95% CI, 1 , 08 - 3.29) ##

4d. Not colon - solid organ cancer, nor associated with infections.

In a cohort study of more than 56,000 patients with IBD, an increased risk of cancer was not found in patients exposed to anti-TNF. ## However, there was a slight increase in the risk of urinary tract cancer (OR, 1.60; 95% CI, 0.61-4.19). Similarly, in another study it was observed that among patients who received anti-TNF more incidence of urinary tract cancer was observed compared to those who received only thiopurines. ##

5. Infections

5a. Tuberculosis.

TNF-α is important in the Th1 cell-mediated immune response, activating macrophages so that they can destroy intracellular mycobacteria and limiting their spread with granuloma formation. [48] In a Spanish retrospective study, 15 patients out of 25 on treatment with anti-TNF developed TbP (OR 7.45; p = 0.001). [49] Another retrospective Asian study of 376 patients with IBD who were receiving anti-TNF, identified that latent Tb infection (OR = 5.76, P = 0.008) and leukocyte count <5000 mm³ (OR = 4.5, P = 0.007) they were independent risk factors for the development of active Tb. [50] Another risk factor for the development of active Tb is the combination of anti-TNF with immunomodulatory therapy (OR 54; P <0.001). [51]

5b. Hepatitis B and C.

TNF-α is produced by cytotoxic T lymphocytes in response to the recognition of hepatitis B virus antigens, this allows some pathways to induce viral lysis. ## The reactivation of hepatitis B virus in chronic patients (HbsAg +, undetectable HBV DNA, Normal liver function tests) and to a lesser extent in hidden carriers of hepatitis B virus (HbcAg + and HbsAg -), occurs with the anti-TNF treatment. ## On the other hand, in the case of chronic carriers of the hepatitis C virus, the use of anti-TNF has an acceptable safety profile. ##

5c. HIV infection.

As with HCV infection, TNF-α is involved in the pathogenesis of HIV and may even promote viral replication. ## This is why the use of anti-TNF has a minimal impact on the viral load of HIV and the CD4 count. The problem is that the use of anti-TNF in patients with HIV without treatment, with a high viral load and with a CD4 count <200 / mm³ could be associated with a greater probability of opportunistic polymicrobial infections. ##

5 d. Infections by members of the herpes virus family.

Reactivations of virus infections such as Cytomegalovirus, Herpes virus-1 and Varicella Zoster virus have been described in patients treated with anti-TNF. ## Few cases of herpes simplex virus reactivation have been published in the literature, including a case of herpes virus esophagitis. ## Also the reactivation of Varicella Zoster virus has been documented in patients under treatment with anti-TNF, a reactivation incidence has been seen in 3% of patients with rheumatoid arthritis treated with anti-TNF, most of whom received together treatment with corticosteroids. ## Likewise, herpes zoster in this patient group is usually more severe. ## With regard to infection or reactivation of CMV infections, there are few cases reported in the literature, most of them treated with anti-TNF, but concomitantly with corticosteroids and immunosuppressants. ##

5e. Fungal infections.

Histoplasmosis is the most commonly reported fungal infection in patients undergoing anti-TNF. The incidence is 18 per 100,000 patients receiving infliximab, most cases occur in endemic areas and with concomitant use of immunosuppressants. ## Other fungal infections less frequently associated with the use of anti-TNF are caused by Coccidioidomycosis and Blastomycosis, also the majority associated with use in conjunction with immunosuppressants and endemic areas. ##

5f. Bacterial Infections.

Patients with IBD being treated with anti-TNF are at a higher risk of developing serious bacterial infections, with an incidence of 18.9 per 1000 patients / year, mainly pulmonary, gastrointestinal, urinary and musculoskeletal infections, and this risk increases with concomitant use with immunosuppressants and the age of patients ≥65 years. ##

Conclusion

The use of biologicals, specifically anti-TNFs, currently have a leading role in the induction and maintenance of remission in IBD. Although they have a good safety profile, with more than 15 years of use in IBD, it has been shown that they are associated with a series of multisystem adverse effects, some of them preventable, which are mostly class effects, that is, counteract the effects of TNF-α or anti-TNF antibody formation product. It is imperative to recognize these adverse events, since their detection and timely treatment reduce the risk of complications on fatal occasions. Lately, new biological molecules have been developed with a different mechanism of action that have a better safety profile, mainly with less association to the development of infections.

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