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REVIEW

Infliximab and biosimilar infliximab in psoriasis: efficacy, loss of efficacy, and adverse events

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Abstract: Psoriasis is a chronic immune-mediated skin disease affecting multiple systems, and tumor necrosis factor-α (TNF-α) plays a significant role in the initiation and progression of the disease process. Psoriasis has a high prevalence rate in the Western world, especially in the USA and Australia; in China, although the prevalence rate is much lower, there is still a large number of patients suffering from psoriasis and its comorbidities. As TNF-α is thought to be crucial in the pathogenesis of psoriasis, specific therapy blocking TNF-α may be beneficial in the treatment of this disease. Infliximab, a murine–human monoclonal antibody, is highly efficacious in the treatment of moderate-to-severe psoriasis, with better skin clearance and faster onset of action than topical medications such as methotrexate, narrow-band ultraviolet B, and calcipotriol. Lack of adherence to infliximab therapy is mainly due to loss of response (LOR) over time and adverse events, particularly because infusion reactions are usually encountered. Anti-infliximab antibody is thought to be responsible for the LOR and infusion reactions. However, the mechanism underlying the formation of anti-infliximab antibody and its side effects remains unclear. Further studies identifying patients at risk for LOR will probably help clinicians to select the right patients for anti-TNF-α therapy and to increase the durability of the treatment. This review discusses the efficacy of infliximab as demonstrated by various clinical trials, LOR to infliximab, combatting LOR, as well as the adverse events usually faced during the use of infliximab therapy and the infliximab biosimilar Remsima®. We hope that we can discover a better way to use infliximab in the therapy of psoriasis from the current research data.

Keywords: anti-infliximab antibody, infliximab, psoriasis, TNF-α, treatment

Introduction

Psoriasis is a common, chronic inflammatory skin disease, which cannot be cured.[1] The prevalence rates of psoriasis are around 0.73–2.9% in Europe, 0.7–2.6% in America, 2.30–6.6% in Australia, and about 0.47% in China.[2,3] The different types of psoriasis include plaque psoriasis (psoriasis vulgaris), inverse psoriasis, pustular psoriasis, guttate psoriasis, erythrodermic psoriasis, nail psoriasis and psoriatic arthritis. Plaque psoriasis is the most common type, accounting for 90% of all cases of psoriasis.[1,4] With advances in the knowledge of psoriasis, it is now regarded as an autoimmune T-cell-mediated disease.[5] Pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-22 (IL-22), IL-23, and IL-17, produced by T cells and dendritic cells, are necessary for the induction and maintenance of disease activity in psoriasis.[6] Psoriasis, being a chronic disease, requires long-term treatment to alleviate both physical symptoms and psychological stress. Many biological agents have been approved for the treatment of moderate-to-severe plaque psoriasis. The most commonly used biologics

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include TNF-α antagonists (etanercept, infliximab, and adalimumab), IL-12/23p40 antagonist (ustekinumab), IL-23p19 antagonist (guselkumab), IL-17A antagonists (secukinumab and ixekizumab), and IL-17RA antagonist (brodalumab). TNF-α antagonists were used as the earliest treatment for psoriasis. Infliximab, a mouse–human IgG_1 chimeric monoclonal antibody, has been used for many years in psoriasis. Infliximab is well tolerated by most patients and has satisfactory effects, but loss of response (LOR) over time is a major problem. The chronicity of psoriasis demands proper adherence to the treatment to achieve better clinical results; a lack of adherence may lead to treatment failure and vice versa. Hence, it is important to identify those patients at risk for loss of efficacy and the predictors for drug survival, to increase adherence to infliximab therapy.

Infliximab and its efficacy

Infliximab is an IgG_1 murine–human monoclonal antibody that binds with both the soluble subunit and transmembrane precursor of TNF-α.[7] It binds with high specificity, affinity, and avidity to TNF-α and, through its inhibitory, neutralizing, and cytotoxic activities, interferes with the pathological mechanism of psoriasis and other inflammatory diseases that are characterized by TNF overproduction.[8] It was approved by the US Food and Drug Administration (FDA) in 2006 for the treatment of severe plaque psoriasis.[7] Infliximab is effective in both the induction and maintenance phases of treatment. Various clinical trials have demonstrated the efficacy of infliximab in moderate-to-severe psoriasis. Infliximab not only clears the skin lesion but also significantly improves the health-related quality of life. Table 1 shows the results of some important studies published since 2010, demonstrating the efficacy of infliximab in plaque psoriasis. The time until the onset of action for infliximab is shorter (3.5 weeks) than that for other biologics such as adalimumab, ustekinumab, etanercept, and alefacept.[9] Infliximab showed a rapid and significantly higher level of efficacy until week 24 compared to etanercept.[10] Infliximab not only clears the skin lesions but is also effective in improving joint symptoms in patients with psoriatic arthritis.[11,12] Infliximab, although not cost effective, is an ideal treatment option for patients with moderate-to-severe psoriasis recalcitrant to other treatment modalities. In addition, infliximab as continuous infusion seems to be more effective than as-needed infusion. In the RESTORE2 study, which was a long-term extension of RESTORE1, patients were randomized to receive either continuous infusion every 8 weeks or intermittent infusion. Patient in the intermittent infusion group received infliximab treatment when their PsoriasisArea and Severity Index (PASI) score showed >50% loss of the PASI improvement that had been gained during RESTORE1. The PASI 75% response (PASI 75) was attained by a significantly greater number of patients in the continuous group than in the intermittent group.[13] In another study, Menter et al found that PASI responses were better maintained by continuous therapy than by intermittent treatment. In this study, patients who achieved PASI 75 response at week 10 after induction were randomized at week 14 to receive either continuous or intermittent infliximab infusion. Patients in the continuous therapy group received infliximab infusion (3 or 5 mg/kg) every 8 weeks and patients in the intermittent therapy group received infliximab when the observed improvement in PASI from baseline was less than 75% (3 or 5 mg/kg). Up to week 50, the PASI 75 response was better maintained in the continuous therapy group than in the intermittent group, and it was also found that 5 mg/kg was more effective than 3 mg/kg[14] (Table 1).

Adverse effects of infliximab

Although infliximab is generally well tolerated, there are some adverse effects associated with its use. Adverse events are a major reason for discontinuation of infliximab therapy in patients with psoriasis. A Canadian multicenter retrospective study showed that 15% of patients withdrew from infliximab therapy owing to adverse effects.[15] The adverse events encountered with infliximab use as described in the following subsections.

Infusion reactions

Infusion reactions occur in about 3–22% of patients of psoriasis treated with infliximab.[16] Infusion reactions can be classified as acute or delayed, depending on time of onset, and as mild, moderate, or severe, depending on the severity of the symptoms.[17,18] Most of these reactions are mild or moderate and only a few are severe.[17] Infusion reactions occurring during and within 24 hours of infusion are categorized as acute infusion reactions, and the symptoms include headache, flushing, hypotension/hypertension, dizziness, shortness of breath, nausea, sweating, rise in temperature, and other symptoms of anaphylaxis, such as urticaria and rash.[19,20] Delayed infusion reactions occur between 24 hours and 14 days after an infusion and are generally characterized by myalgia, arthralgia, fever, urticarial rash, and malaise.[19,21] Although the exact mechanism of infusion reactions is not known, the development of antibodies to infliximab (ATIs) may play a significant role.

Table 1 Efficacy of infliximab in some pivotal studies

Study	Design of the study	Treatment regimen	Efficacy
Shear et al (REALITY)[45]	Prospective, observational, open-label, multicenter study N=521 in treatment phase (week 0–50) N=169 in extended treatment phase (week 50–98)	Infliximab 5 mg/kg induction at 0, 2, and 6 weeks, and maintenance every 8 weeks up to 98 weeks	PASI 75 response at week 50, 56.8% PASI 75 response at week 98, 66.3%
Torii and Nakagawa[79]	Multicenter, open-label, uncontrolled study N=37 (plaque psoriasis)	Infliximab 5 mg/kg induction at 0, 2, and 6 weeks, and then every 8 weeks up to week 46	PASI 75 response at week 10, 72.2% PASI 75 response at week 50, 53.6%
Barker et al[80]	Open-label, active-controlled, randomized trial N=868	Infliximab 5 mg/kg induction at 0, 2, and 6 weeks, and every 8 weeks up to week 22 or MTX 15 mg weekly for the first 6 weeks and could increase to 20 mg/weekly if PASI improvement was <25% from baseline	PASI 75 response at week 16, 78% in infliximab group and 42% in MTX group PASI 75 response at week 26, 77% in infliximab group and 31% in MTX group
Torii and Nakagawa[57]	Randomized, double-blind, placebo-controlled, multicenter trial N=54	Infliximab 0 or 5 mg/kg induction at 0, 2, and 6 weeks, and then every 8 weeks up to week 62	PASI 75 response at week 10, 68.6% in infliximab group and 0.0% in placebo group PASI 75 and PASI 90 response at week 66, 76.7% and 56.7%, respectively, in infliximab group

Abbreviations: MTX, methotrexate; N, total number of case studies; PASI, Psoriasis Area and Severity Index; PASI 75, PASI 75% response; PASI 90, PASI 90% response; REALITY,Real-World Assessment of Long-Term Infliximab Therapy for Psoriasis.

The presence of ATIs is associated with an increased incidence of infusion reactions.[22–24]

Concomitant use of immunosuppressives, such as methotrexate (MTX), is thought to reduce both the immunogenicity of infliximab and the occurrence of infusion reactions. However, there are no well-documented studies combining immunosuppressive drugs with infliximab in psoriasis. A prospective study by Vermeire et al, in patients with Crohn's disease, found that infusion reactions occurred more often in patients not taking concomitant MTX (40%) than in patients taking concomitant MTX (16%).[25] Infliximab therapy with a loading dose at 0, 2, and 6 weeks seems to be less immunogenic than one single starting dose.[26] In addition, maintenance treatment at 8-week intervals is associated with a lower rate of infusion reactions than on-demand or intermittent infusion.[13,14]

The management of infusion reactions is symptomatic. Acute reactions can be managed by slowing the infusion rate, administering intravenous fluids, and administering paracetamol and anti-histamines. Paracetamol, anti-histamines, and, if necessary, steroids are advised in cases of delayed infusion reactions.[17] Treatment can be continued after symptomatic management of mild or moderate infusion reactions, but in cases of severe infusion reactions the pros and cons of a new infusion should be carefully deliberated.[17]

Infection

A risk of infection is associated with the use of all TNF-α antagonists, with upper respiratory tract infection being the most common.[27] Serious infections are not common, but patients with underlying predisposing factors may be at risk for serious infection.[1] A high rate of infections, both serious and non-serious, with the use of anti-TNF agents has been reported in other indications, including rheumatoid arthritis and inflammatory bowel disease, but this may not be the same in the psoriatic population as anti-TNF agents are generally used as monotherapy in psoriasis, whereas they are generally used with other immune-modulating drugs such as MTX or corticosteroids, or both, in other indications.[1,20]

TNF-α has a central role both in the host immune response to *Mycobacterium tuberculosis* infection and in the immunopathology of tuberculosis (TB).[28] Anti-TNF therapies increase the risk of granulomatous infection by interfering with granuloma formation or by weakening the integrity of established granulomas.[29] Thus, patients on anti-TNF therapy have an increased risk for reactivation or exacerbation of granulomatous infections, in particular TB, and mostly in TB-endemic areas.[8] The risk of TB is higher in patients receiving monoclonal antibodies (infliximab followed by adalimumab) than in patients receiving soluble-receptor anti-TNF therapy (etanercept).[30] A study by Wallis revealed that more than 20% of latent tuberculosis infection (LTBI) is reactivated each month by infliximab treatment, which is 12.1 times more than with etanercept treatment.[31] This study also revealed that both drugs, ie, infliximab and etanercept, appeared to pose a high risk of progression of new *M. tuberculosis* infection to active TB.[31] Careful screening and proper treatment of LTBI may reduce the risk of reactivation of LTBI progressing to active TB. Patients who need to be treated with infliximab and other TNF antagonists should be properly screened with a tuberculin skin test and chest radiography, and assessed for symptoms of cough and weight loss. Two novel tests, the QuantiFERON®-TB Gold test and ELISPOT-based T-Spot®.TB, offer advantages over the tuberculin test as they are not affected by previous vaccination with bacille Calmette–Guérin (BCG) or by infection with commonly encountered non-tuberculous mycobacteria.[8]

The British Association of Dermatologists recommends 3 months of isoniazid (with pyridoxine) and rifampicin, or 6 months of isoniazid (with pyridoxine), with the aim of completing 2 months of treatment before commencing biologic therapy in people who require treatment for LTBI.[32] The National Psoriasis Foundation recommends LTBI prophylaxis with 9 months of isoniazid. Although it is preferable to complete the 9 months of therapy, immunosuppressive/immunomodulatory therapy may be initiated after 1–2 months if required by the patient's clinical condition, as long as he or she is strictly adhering to and tolerating treatment with isoniazid.[33] French guidelines suggest that LTBI prophylaxis should be started at least 3 weeks before the initiation of TNF blockers.[34] According to British Thoracic Society guidelines, patients with active TB, either pulmonary or non-pulmonary, should receive standard chemotherapy for a minimum of 2 months, directed by a specialist in TB, before starting anti-TNF treatment.[35] Histoplasmosis, listeriosis, aspergillosis, coccidioidomycosis, and candidiasis have been associated with TNF-α antagonists, but the causative relationship is not clear.[36] Male gender, steroid use, and the number of comorbidities can be factors predictive of serious infections.[37]

Anti-nuclear antibodies (ANAs) and lupus-like symptoms

Although 50% or more of patients treated with anti-TNF-α may develop ANAs, anti-TNF-α-induced lupus is rare.[8,38] In a follow-up study by Poulalhon et al, in 28 patients receiving infliximab for severe, recalcitrant forms of psoriasis, ANA positivity increased from 12% at baseline to 72% at week 22. IgM double-stranded DNA (anti-dsDNA) antibodies were raised to 68% at week 22 from 0% at baseline.[39] Gottlieb et al reported that 23.9% of patients were newly positive for ANAs and 3.8% of patients were newly positive for anti-dsDNA antibodies while on infliximab therapy, but no patients developed drug-induced lupus or lupus-like syndrome.[40] However, some cases of lupus-like syndrome, with malar rash, arthralgia, diffuse joint swelling, photosensitivity, mouth ulcers, and increased ANAs, have been reported with infliximab use for the treatment of psoriasis.[41,42]

Malignancy

The risk of malignancy with the use of biologics is not clearly understood, but many studies examining the carcinogenic risk suggest that TNF-α inhibitors may cause a slightly increased risk of cancer, including non-melanoma skin cancer and hematological malignancies.[43] Fiorentino et al found that long-term (≥12 months) treatment with a TNF-α inhibitor may increase the risk of malignancy in patients with psoriasis.[44] In a study by Dommasch et al, no statistically significant increased risk of cancer was seen with short-term use of a TNF-α inhibitor.[27] The EXPRESS II trial reported 12 malignancies in 12 patients in the infliximab group, comprising nine cases of basal cell carcinoma and one case each of squamous cell carcinoma, breast carcinoma, and salpingeal adenocarcinoma. All patients with skin carcinoma had a history of exposure to either narrow-band ultraviolet B or psoralen plus ultraviolet A, or both.[14] Shear et al reported two patients with basal cell carcinoma and one patient each with adenocarcinoma, malignant peritoneal neoplasm, and penile carcinoma.[45]

Since there may be an increased, although low, risk of malignancy in patients treated with TNF-α antagonists, patients with psoriasis should be assessed properly before and during treatment with TNF-α inhibitors. TNF-α antagonists should be prescribed cautiously in patients with a history of carcinoma, particularly if diagnosed and treated <5 years previously and where the baseline risk of skin cancer is increased (eg, previously treated non-melanoma skin cancer).[32]

Hepatic effects

The use of TNF-α antagonists can cause liver function test abnormalities, which are usually transient and asymptomatic. Hepatitis has been seen in patients treated with infliximab with additional risk factors such as viral hepatitis, alcohol intake, and concomitant use of hepatotoxic drugs.[42] In a study by Reich et al, asymptomatic marked increases in alanine aminotransferase and aspartate aminotransferase were seen in 6% and 2% of patients, respectively, during treatment with infliximab, but no other abnormalities indicative of liver function impairment (eg, abnormal bilirubin levels) were seen.[21] Cases of infliximab-induced hepatitis during treatment of psoriasis have also been reported.[42]

According to the Japanese Dermatological Association, liver function tests should be performed before the initiation of treatment, after 1 and 3 months of treatment, and then every 6 months.[46] Treatment is possible when the aminotransferase values are <3× upper limit of normal (ULN), treatment should be administered cautiously if values are 3–5×ULN, and treatment should be stopped if values are >5× ULN.[8] Anti-TNF-α therapy may lead to the reactivation of hepatitis B virus (HBV) in patients who are chronic carriers of this virus.[8] Thus, proper screening of patients for HBV markers before starting anti-TNF therapy is essential.

Hematological changes

Certain hematological adverse events, including thrombocytopenia, neutropenia, and hypercoagulability, have been encountered, although rarely, with the use of TNF-α antagonists. Uncommon but life-threatening aplastic anemia and pancytopenia have also been reported with TNF-α antagonist therapy.[47] In the RESTORE2 study, hematological conditions were reported in three patients in the continuous group (increased eosinophil count, and leucopenia [two patients]) and four patients in the intermittent group (increased eosinophil count, decreased lymphocyte count, increased lymphocyte count, increased neutrophil count [two patients], and neutropenia).[13] Decreased lymphocyte levels and abnormally low neutrophil counts were reported in the PSUNRISE study with the use of infliximab.[48] As hematological abnormalities have been reported in various studies, it is wise to carry out a complete blood count before initiation and during treatment

with TNF-α antagonists, which may further help in reducing the hematological adverse events.

Neurological disorders

Several neurological disorders have been associated with TNF-α antagonists, including alterations of peripheral nerves, multiple sclerosis (MS), optic neuritis, and acute transverse myelitis.[49] As an association is seen between TNF-α antagonists and demyelinating diseases, American Academy of Dermatology guidelines do not recommend the use of TNF-α inhibitors in patients with MS or other demyelinating diseases or in patients with a history of MS in their first-degree relatives.[1]

Cardiac effects

The association of TNF-α inhibitors with cardiac complications is somewhat controversial. In a 2017 meta-analysis by Rungapiromnan et al, it was found that there was no statistically significant difference in the risk of major cardiovascular events (MACEs) in patients with plaque psoriasis exposed to biologic therapies used at the licensed doses compared to placebo.[50] The PSOLAR study concluded that treatment with biologics did not have an impact on the risk of MACEs in patients with moderate-to-severe psoriasis.[51]

American Academy of Dermatology guidelines recommend that patients with New York Heart Association class III or IV congestive heart failure (CHF) avoid all use of TNF inhibitors, and that patients with class I or II CHF undergo echocardiogram testing; if the ejection fraction of these patients is <50%, then TNF inhibitor treatment should potentially be avoided.[1]

Worsening of psoriasis

TNF-α antagonists have been associated with the new onset of psoriasis or worsening of psoriasis with their use in various indications including psoriasis, both in adults and in the pediatric population.[52,53] Shmidt et al reported 56 patients who had new-onset or worsening of psoriasis which occurred after a mean duration of 17.1 months of treatment with TNF-α antagonists.[53] Mössner et al reported five cases of chronic plaque-type psoriasis who developed palmoplantar pustulosis during or after discontinuation of infliximab therapy.[52] Sherlock et al reported new-onset psoriasis in 10.5% (18/172) of pediatric patients and worsening of psoriasis in one child treated with infliximab for Crohn's disease, and three patients had to discontinue treatment owing to this complication.[54] Wollina et al reported 120 patients who developed psoriasis or psoriasiform rash during treatment with a TNF-α antagonist, of whom 63 of them were on infliximab. In 74 patients, psoriasis was newly diagnosed, while in 25, there was exacerbation or aggravation of pre-existing psoriasis.[55]

Pregnancy and lactation

Infliximab is an FDA pregnancy category B drug, so it is not recommended during pregnancy or breast-feeding. Because of the long half-life of the product, reliable contraception is required in women of child-bearing potential until 6 months after the last infusion.[8]

Loss of response

LOR with long-term infliximab therapy in some patients has been a major problem in many clinical studies. LOR to infliximab has been a major reason for the discontinuation of the drug. The exact reason for LOR not fully known, but it is thought that the formation of ATIs may play a role.[56] Maintenance of the clinical response is associated with the attainment of stable infliximab serum concentrations and ATI status, although the presence of ATIs does not preclude a clinical response to infliximab.[14,21] In ATI-positive patients, infliximab was rapidly eliminated from the serum, resulting in low serum infliximab concentrations.[48,56,57] In a study by Takahashi et al, the minimum trough level of infliximab in good responders was 0.92 μg/mL, while in another study, by Bito et al, a trough level of 0 μg/mL was seen in good responders, indicating a period of temporary absence of infliximab just before the next injection.[58,59] There are some studies showing the LOR owing to the presence of ATIs and low serum infliximab concentrations. Balsa et al demonstrated that a significantly lower proportion of patients receiving concomitant disease-modifying anti-rheumatic drugs developed anti-drug antibodies compared with those receiving biologic monotherapy in rheumatoid arthritis and spondyloarthritis.[60]

In a study by Kui et al, ATIs were detected in 25% of patients treated with infliximab. The PASI scores were significantly higher in the antibody-positive patients than in antibody-negative patients. The presence of ATIs was related to the decrease in the serum infliximab concentration and also to the increase in plasma TNF-α concentration.[61] A pilot study investigating the anti-infliximab antibody status and it relationship to clinical response in psoriatic patients showed that the ATI-

positive patients experienced new lesion development or an increase in erythema and induration in previous lesions, which led to increased PASI scores. In ATI-negative patients, with 5.9±3.2 (mean±SD) of infliximab infusions the PASI scores fell from a mean of 20.4±8.3 to 5.3±2.4, while there was a fall in PASI scores from a mean of 23.3±11 to 10±4.9 with 9±5.2 infliximab infusions in ATI-positive patients.[56] In a study by Reich et al, in patients who maintained the PASI 75 response throughout week 50 the median pre-infusion infliximab concentration was above 1.0 μg/mL at week 30 and thereafter, while it was less than 1.0 μg/mL in patients who lost the response by week 50. ATI status also had an effect on the maintenance of the response attained at week 10. For patients who attained a PASI 75 response at week 10, 39% of the patients who were positive for ATIs maintained this response throughout week 50 compared to 81% and 96% of patients who were antibody negative and inconclusive, respectively.[21]

Torii and Nakagawa demonstrated that the PASI 75 response rate was increased with the increment in serum infliximab concentrations. At week 62 of infliximab infusion, 95.7% of patients with a serum infliximab concentration of 1 to <10 μg/mL had a PASI 75 response compared to 60.0% and 71.4% of the patients with serum infliximab concentrations of <0.1 μg/mL and 0.1 to <1 μg/mL, respectively. ATIs developed in 20% of the patients. At 8 weeks post-infusion, the serum infliximab concentration was decreased to <0.1 μg/mL in ATI-positive patients but it remained above that in ATI-negative and inconclusive patients.[57] In a 1-year prospective study by Bito et al, patients with ATIs showed a decrease in the clinical response. There was a significant difference in the improvement in PASI scores at weeks 12 and 48 between patients with a high titer of ATIs and those with no ATIs.[58] The median serum trough level of infliximab was higher in the PASI 90% response (PASI 90) responders than in PASI 90 non-responders. PASI 90 responders had a median trough concentration of ≥2 μg/mL throughout the assessment period, while PASI 90 non-responders had levels of 1 μg/mL at week 30 and thereafter and <0.1 μg/mL at week 46 onwards.[62]

Biosimilar to infliximab

A biosimilar, as defined by the European Medicines Agency (EMA), is a biological medicine that is developed to be similar to the existing biological medicine (reference medicine).[63] Although infliximab is highly effective, its use is often limited by financial constraints. The availability of less expensive treatment could increase both the initiation and maintenance of treatment for patients with chronic inflammatory diseases. Remsima® is a biosimilar of infliximab which was the first biosimilar approved by the EMA, in September 2013, and is less expensive than the originator. Studies have shown that there are no differences in safety, immunogenicity, and pharmacokinetics between infliximab and Remsima, and the transition from infliximab to Remsima does not lead to disease worsening.[64–66] Physiochemical characterization studies demonstrated the identical pharmacokinetic and pharmacodynamic profiles of Remsima and the infliximab originator. This study revealed that primary as well as higher order structures were identical between the infliximab biosimilar and the originator. It also showed that the monomer and aggregate contents, and the glycan types and distribution, were similar between the biosimilar and the originator.[67]

A single-center retrospective cohort study showed that patients were satisfied in the transition process from infliximab to Remsima and supposed that there is no difference between them.[68] In contrast, an unblinded, retrospective study showed a worse effect after switching from infliximab to Remsima, with patients showing increased adverse events, from 6.7% to 22.2%, and a decline in quality of life. The rate of upper respiratory tract infections when using a biosimilar was significantly greater than for infliximab.[69] The NOR-SWITCH trial showed that switching from Remicade® to CT-P13 was not inferior to continued treatment with Remicade. In this study, patient who were on stable treatment with Remicade in a hospital setting for at least 6 months were randomized in a 1:1 ratio to receive either Remicade or CT-P13 with an unchanged dosing regimen.[64]

Some studies on the use of infliximab biosimilar in psoriasis have shown that patients on infliximab can be switched to Remsima, and it can also be prescribed to infliximab-naïve patients. The studies by Dapavo et al and Gisondi et al, conducted in patients with psoriasis, showed that the patients on infliximab originator could be switched to Remsima without much change in the clinical response or additional adverse events. These studies also demonstrated that infliximab biosimilar is effective in infliximab-naïve patients, with the improvement in PASI score being in line with the infliximab originator.[70,71]

Switching to the biosimilar is relevant to patients on stable treatment with an originator drug in terms of cost savings. With biosimilars of infliximab becoming increasingly available, rigorous and normative research studies into biosimilar infliximab in the clinic are necessary.

Measures to address LOR

The lack of adherence to treatment is a problem for both healthcare providers and patients. As loss of efficacy to the drug has been one of the significant reasons for discontinuation to infliximab therapy, combatting this is likely to lead to long-term durability of infliximab therapy. However, the exact reasons for LOR and methods to identify patients at risk of LOR are not yet known. In addition, a study suggests that gender, prednisone intake (>5 mg/day), and inflammatory indices can be predictive factors for discontinuation of anti-TNF-α treatment.[72] Some studies have suggested an association between ANA and anti-dsDNA titers and LOR. Pink et al suggested that the development of ANA and anti-dsDNA antibodies upon anti-TNF treatment may act as a marker for forthcoming treatment failure.[73] Another study, by Hoffmann et al, reported that infliximab-antibody-positive patients and patients with LOR had significantly higher pretreatment ANA and anti-dsDNA titers compared to infliximab-antibody-negative and responsive patients, respectively.[74] Intermittent infusion may be more immunogenic than continuous infusion. International experts recommend decreasing the infusion interval (to every 6 weeks) or increasing the dose of infliximab when there is LOR.[75]

In the SPREAD study, a phase III, multicenter, single-arm, 40-week trial in Japanese patients with psoriasis, an increase in the dose of infliximab was effective and well tolerated in patients with LOR to standard-dose therapy. This study included patients with psoriasis showing LOR to standard infliximab treatment (5 mg/kg every 8 weeks). Before increasing the dose, a standard infliximab dose was given to the patients with plaque psoriasis and psoriatic arthritis to confirm that the efficacy was not transient. The dose was escalated to 10 mg/kg in patients who failed to achieve a PASI 50% response (PASI 50) after 8 weeks of additional treatment with the standard dose. The efficacy and safety were evaluated until week 40. PASI 75 response ranged from 40% to 64% after week 24 and was 44% at week 40. Dose escalation led to an increase in the serum infliximab concentration, which correlated with the clinical response. The dose escalation was more effective in patients with a detectable infliximab level (≥0.1 μg/mL) than in those without a detectable infliximab level at the initiation of dose escalation.[24] Increasing the infusion frequency before increasing the dose of infliximab may also increase the possibility of maintaining the clinical response.

In a retrospective cohort study, patients with moderate-to-severe psoriasis with or without psoriatic arthritis, who experienced LOR, received an infliximab dose escalation in the form of either increased infusion frequency or increased dose. Out of 93 patients included in this study, 62 patients required dose escalation. The 44 patients who increased the infusion frequency before increasing the dose remained on infliximab therapy longer than the patients who increased the dose before increasing the infusion frequency.[76]

Reinduction may lead to the response being regained in psoriasis patients who relapse during long-term maintenance treatment with infliximab. In a retrospective analysis, reinduction was carried out in 22 patients who had experienced a relapse of psoriasis (loss of <50% of the PASI improvement previously observed at week 10). The mean period of relapse was 13 months after the first induction. Twenty out of 22 patients attained PASI 50 response at week 10, with nine of them attaining a PASI 75 response after the first reinduction. During an average follow-up period of 13 months, nine patients had maintained the clinical improvement with infusion every 8 weeks, with 11 patients requiring further reinduction. Eight patients showed a stable recovery from psoriasis after the second reinduction.[77]

Concomitant use of MTX with infliximab has been shown to reduce ATI formation in other diseases,[25] and a decrease in ATI formation may aid in increasing the efficacy of infliximab. A combination of infliximab with MTX has been used in rheumatological conditions and psoriatic arthritis but its use in chronic plaque psoriasis has not been well investigated.[8] However, some studies on psoriasis suggest that combining MTX with infliximab may increase the efficacy of the drug. Adisen et al demonstrated that combining MTX with infliximab led to a negative ATI status and achieved a sustained clinical efficacy in previously ATI-positive patients.[56] Another study confirmed that combining MTX with infliximab could significantly improve the maintenance of clinical efficacy. In this study, patients on concurrent use of MTX required infliximab dose escalation after a mean±SD of 29.4±5.6 months, compared to 17.4±2.4 months in patients who were not on concurrent MTX.[76] In a retrospective study by Dalaker and Bonesronning, long-term therapy with infliximab combined with MTX was effective and tolerated for moderate-to-severe psoriasis. After 1 year of concomitant MTX and infliximab therapy, 80%, 60%, and 33.3% of the patients had PASI 50, 75, and 90 responses, respectively.[78]

Conclusion

Infliximab is an effective and safe treatment option for moderate-to-severe psoriasis. Lack of adherence to the treatment, mostly due to LOR and adverse events (infusion reaction), is the major drawback with infliximab therapy. The exact reason for LOR is unknown, but the development of ATIs is thought to play an important role. However, the presence of ATIs does not preclude the clinical response. ATIs are also thought to play a role in infusion reactions. Decreasing the infusion interval, increasing the dose, and reinduction have been shown to re-establish the response. Concomitant use of MTX can reduce the immunogenicity of infliximab, thus enhancing the efficacy and reducing infusion reactions, but its use in psoriasis is not well investigated. Proper screening of patients before the initiation of infliximab therapy and during the therapy, both clinically and with laboratory reports, is essential to decrease the incidence of adverse events. Whether lengthening the time interval between injections of infliximab in patients who reach minimal disease activity is safe and effective remains unknown and needs further study. Infliximab biosimilars could be a good choice to decrease the financial burden on patients, and thus further study regarding infliximab biosimilars in psoriasis would be of great help.

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Author contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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