# Infliximab in Psoriatic Arthritis

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***ABSTRACT.*** Tumor necrosis factor-α (TNF-α) plays a central role in the pathogenesis of psoriasis and psoriatic arthritis (PsA). Recently, 2 expert committees provided evidence-based recommendations for the treatment of PsA. Anti-TNF-α drugs are indicated in all forms of PsA resistant to traditional therapeutic approaches. Anti-TNF-α infliximab (IFX) is an immunoglobulin G-1 antibody that binds to soluble and cell membrane-bound TNF-α with its inactivation. Confirming previous open-label studies, 2 randomized, placebo-controlled clinical trials, IMPACT and IMPACT2, have provided evidence of the efficacy and safety of IFX in the treatment of PsA as evaluated by American College of Rheumatology (ACR)20, ACR50, and ACR70 response rates. At Week 16, a significant proportion of 51 IFX-treated patients achieved ACR20, ACR50, and ACR70 responses compared to the 51 patients of the placebo arm in the IMPACT trial. In the IMPACT2 study, 58% of the IFX-treated patients and 11% of placebo patients achieved an ACR20 response ($p < 0.001$), and 41% and 27% of patients in the IFX group were ACR50 and ACR70 responders, compared with 4% and 2% of placebo patients, respectively. Of note, a significant inhibition of radiographic disease progression was observed in the IFX-treated group. In both trials, psoriasis improvement was recorded in more than 80% of patients receiving IFX, with a significant difference compared to placebo group. IFX was well tolerated, with no difference compared to placebo in terms of adverse events. The extension phase of these studies showed the sustained efficacy and safety of the drug. (J Rheumatol 2012;39 Suppl 89:71–3; doi:10.3899/jrheum.120249)

*Key Indexing Terms:*
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Psoriatic arthritis (PsA) has long been considered a benign disease, but several followup studies have demonstrated an aggressive course, with development of joint erosions and deformities in up to 70% of the cases[1].

Tumor necrosis factor-α (TNF-α) plays a key pathogenic role both in psoriasis and PsA. Increased levels of TNF-α have been observed in serum, skin, synovial fluid, and synovial tissue from affected patients[2,3,4,5]. The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis[6] recommends anti-TNF-α agents for all patients with peripheral PsA that has resisted traditional disease-modifying antirheumatic drugs (DMARD), in those with PsA spondylitis failing to respond to nonsteroidal antiinflammatory drugs (NSAID), and in patients with dactylitis and enthesitis that does not improve with NSAID and local corticosteroid injections. These recommendations have been confirmed by a committee of Italian experts[7].

The anti-TNF-α agent infliximab (IFX) is an immunoglobulin G-1 antibody composed by a variable region of a murine antibody grafted to the constant region of human antibody. It binds to soluble and cell membrane-bound TNF-α with high affinity, halting the interaction between TNF-α and its receptor[8]. The drug is administered by intravenous infusion at the dose of 3-5 mg/kg at weeks 0, 2, 6, and every 8 weeks thereafter. If needed, the infusion intervals may be shortened to 6 weeks. IFX has been licensed for the treatment of DMARD-resistant PsA in combination with methotrexate (MTX) or alone in MTX-intolerant patients at the dose of 5 mg/kg.

Apart from case reports and open studies suggesting the effectiveness of IFX in active PsA[9], 2 randomized placebo-controlled trials have provided evidence of the efficacy of IFX in the treatment of PsA[10,11].

In the first, the IMPACT trial[10], 102 patients (mean age at arthritis diagnosis 34.4 years; mean arthritis duration 11.0 years; mean psoriasis duration 18.8 years) were randomized to receive IFX 5 mg/kg or placebo (1:1 randomization) for a 16-week period followed by a 52-week extension phase in which all patients received IFX with maintenance of the original blinding. Patients were included if they had active peripheral PsA as expressed by arthritis of at least 5 joints, elevated acute-phase reactants, and failure of at least 1 DMARD. Concomitant medications were prosecuted at stable doses in 69/102 (68%) patients. Efficacy was evaluated by using the American College of Rheumatology (ACR)20, ACR50, and ACR70 response criteria[12]. At Week 16, 65.4% of patients treated with IFX were ACR20 responders com-

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pared with only 9.6% of placebo patients. Further, 46.2% and 28.8% of patients of active treatment arm were ACR50 and ACR70 responders, respectively, compared with none of the placebo patients. Also, a significant reduction of dactylitis and enthesitis sites scores was recorded in the IFX-treated group compared to the placebo group. These percentages of responders were maintained at Week 50. The radiographic analysis at Week 50 demonstrated the inhibition of disease progression induced by IFX therapy. A significant improvement of psoriasis was observed in the IFX group, with an 86% average reduction of the Psoriasis Area and Severity Index (PASI)[13] compared to an average increase of 12% in the placebo group.

In the IMPACT 2 study[11], 200 patients with active PsA and inadequate response to at least 1 DMARD were randomized to receive IFX 5 mg/kg or placebo for 24 weeks. At Week 24, patients of the placebo arm crossed over to receive IFX 5 mg/kg through Week 54, while patients initially randomized to active treatment continued to receive IFX at the same dose. The demographic and clinical characteristics at baseline were similar between the 2 treatment arms. The primary endpoint was the clinical response at weeks 14 and 24, evaluated by the ACR response criteria and PsA response criteria (PsARC)[14]. At Week 14, 58% of IFX-treated patients and 11% of placebo patients achieved an ACR20 response ($p < 0.001$), and at Week 24, 41% and 27% of patients in the IFX group were ACR50 and ACR70 responders, compared with 4% and 2% of placebo patients, respectively. The PsARC score at Week 14 improved in 77% of the IFX arm compared to 27% of the placebo arm ($p < 0.001$). The improvement in joint symptoms was sustained throughout 54 weeks. At Week 24, radiographs of the hands and feet showed significantly less progression of structural damage in IFX-treated patients compared with those taking placebo (mean change from baseline in modified van der Heijde–Sharp score, –0.70 and 0.82, respectively), and 84.3% of the total patient population had no radiographic progression after IFX treatment at Week 54. Moreover, dactylitis and enthesitis counts dropped significantly in IFX-treated patients compared to the placebo group ($p < 0.001$ and $p < 0.002$, respectively). Additionally, IFX therapy improved the psoriatic skin symptoms: 64% of the IFX-treated patients achieved an improvement in PASI score of 75% compared with 2% of the patients taking placebo ($p < 0.001$).

In both trials IFX was well tolerated with no significant difference between active treatment and placebo arms regarding adverse events (AE) including serious AE, infections, tuberculosis, congestive heart failure, demyelinating or new autoimmune disorders, malignancies, and infusion reactions. Five patients receiving IFX had marked increase of transaminases, with return to normal after drug discontinuation. Newly positive antinuclear antibodies (defined by titer > 1/160) were detected in 9.9% of patients in the IFX group compared with 2.6% in the placebo group, with no patient developing a lupus-like condition.

The 2-year extension phase of the IMPACT study confirmed the sustained efficacy of IFX on PsA symptoms and radiographic disease progression[15].

The recently published open-label, randomized RESPOND trial[16] has confirmed the efficacy of IFX in severe polyarticular PsA. This study compared the efficacy and safety of infliximab 5 mg/kg plus MTX with MTX alone in 115 MTX-naive subjects who had an inadequate response to steroids and DMARD therapy. At Week 16, 86.3%, 72.5%, and 49% of patients receiving combined IFX + MTX were ACR20, ACR50, and ACR70 responders, respectively, compared to 66.7%, 39.6, and 18.8% of those treated with MTX alone ($p = 0.021$, 0.0009, and 0.0015, respectively), with a significantly higher remission rate on the 28-joint Disease Activity Score.

The clinical trials demonstrated that IFX is an effective and safe therapy for PsA and psoriatic skin disease, with inhibition of radiographic disease progression and long-lasting efficacy.

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