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Original article

Infliximab treatment in Psoriatic Arthritis: our experience

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Abstract. The aim of this work was to give clinical practice recommendations on the use of tumour necrosis factor blocking agents in psoriatic arthritis, underlining the pathogenetic mechanism of this condition and its articular and dermatologic manifestations. We retrace the stages leading to the therapeutic indications of biological agents that are presently used in the treatment of psoriatic arthritis: Entanercept, Adalimumab, Infliximab. We also report our personal experience describing an emblematic case of a patient with psoriatic arthritis in which a decisive regression of joint/skin involvement was obtained with Infliximab treatment. (www.actabiomedica.it)

Key words: Psoriatic arthritis, cutaneous psoriasis, TNF-α, TNF-α blocking agents, Infliximab

Psoriatic arthritis is a chronic, debilitating condition that is characterized by the presence of psoriasis, inflammation of the joints and vertebral column, and enthesitis. It is also defined as a seronegative spondylopathy which is usually progressive and debilitating (1, 2). Around 40% of the patients present progressive and destructive arthritis (3). Various studies have demonstrated that the frequency of psoriatic arthritis varies from 5 to 42% in patients with psoriasis (4-6). This condition usually appears in subjects around the ages of 40 and 50. Patients usually show stiffness, swelling and pain of the joints and surrounding tissues, especially in the fingers and toes. The majority of the patients have poliarthitis, others have asymmetrical oligoarthritis, but these forms may vary during the course of the disease (7). The spine and sacroiliac joints are affected in 20-40% of the cases while the isolated form is present in approximately 3% of patients (1, 3, 8). Enthesitis, periostial reaction, and dactylitis are associated with psoriatic arthritis. Extra-articular and extra-dermatologic manifestations include iritis, conjunctivitis, and mucosal membrane lesions. 90% of the patients also show alterations of the nails (pitting of fingers and toes) (1, 2, 7). Both psoriasis and psoriatic arthritis significantly reduce the quality of life and the presence of arthritis in a psoriatic patient drastically contributes to the decline in the quality of life (9, 10).

Recent studies have shown the progressive nature of the condition in the majority of patients that were studied in a two-year period (11, 12).

This condition is associated with an increased mortality rate that is due to cardiovascular disease (13).

Family history is common in psoriatic arthritis and there is no sex difference in incidence. Population studies have identified different genetic HLA associations with psoriatic arthritis, such as HLA-B7 and HLA-B27 (14-18).

The dermatologic and articular manifestations are characterized by chronic inflammation. T lymphocytes seem to play a key role in guiding this process in both the skin and joints; an altered response of keratinocytes to the production of INF-γ by T lymphocytes and the beneficial effect of therapies aimed at T lymphocytes are based on the clonal characteristics of skin and synovial infiltrations of T lymphocytes that are antigen-specific (19-30). The synovia is infiltrated by a variety of inflammatory cells

and shows an increased expression of adhesion molecules (ICAM-1, VCAM-1), angiogenetic mediators (vWF, VEGF), matrix metalloproteinases (MMP1 and 3), and pro-inflammatory cytokines (TNF-alpha, IL-1) (30-35).

Similarly to what happens in rheumatoid arthritis, macrophages infiltrate the synovia and produce large amounts of pro-inflammatory cytokines, such as TNF-α, which are also abundant in the psoriatic scales. It appears that this cytokines plays an important role in the pathological process (35).

In patients with psoriatic arthritis, TNF promotes osteoclastogenesis while its inhibition attenuates this process, providing protection against joint destruction (36-38).

Based on these evidences, many studies have demonstrated the beneficial effects that derive from the inhibition of TNF-α in psoriasis and psoriatic arthritis. These benefits are associated with a significant reduction of T lymphocytes and macrophages in the synovia and skin (39).

In conclusion, TNF-α plays a key role in the psoriatic inflammation of the synovia and in the damage of the joints. Inhibiting its effects with the use of TNF blocking agents reduces the migration of cells to the inflammation site and diminishes the clinical signs of arthritis, articular destruction, and dermatologic manifestations.

Therapeutic strategies

The traditional approach in the treatment of psoriatic arthritis is based on the use of non steroidal anti-inflammatory drugs (NSAIDs), a controlled use of corticosteroids, and a precocious introduction of disease-modifying antirheumatic drugs (DMARD).

The most utilized DMARDs include sulphasalazine, methotrexate, cyclosporine A, and more recently, leflunomide. In general, clinical studies have been carried out on a small number of patients and have revealed only a moderate efficacy of these drugs (40). In particular, studies using methotrexate recruited only a few patients and further studies are therefore needed. Nevertheless, methotrexate remains the DMARD of choice for many physicians (41).

The first observations of elevated levels of TNF in the synovia and synovial liquid in patients affected by psoriatic arthritis, recent understandings of an immunological mechanism in the condition, and new biotechnologies led the way for the introduction of biological agents in the treatment of psoriatic arthritis. These drugs were already used in the treatment of chronic inflammatory and autoimmune pathologies (42-47).

In the era of biological agents, in which the need for newer and better pharmacological approaches in patients with psoriatic arthritis seems clear, DMARDs still play an important role in the treatment. Further controlled studies on DMARDs, including association trials, are necessary.

The results of clinical studies and post-marketing surveillances show that in patients with psoriatic arthritis, biological agents are better tolerated than DMARDs (48,49). TNF-α blocking agents are associated with side effects (administration reactions, worsening of bacterial infections), but these effects are usually rare and controllable (48-50). Overall, biological agents are safer and better tolerated than traditional DMARDs and their greater efficacy should always be taken into consideration when confronting risks/benefits.

TNF-α is not the only biological target in the treatment of psoriatic arthritis and various other molecules have been studied as therapeutic targets in this condition. Alefacept, a co-stimulator signal blocking agent, has been shown to be effective and studies on this drug are presently underway (51, 52). Other targets have been developed for other cytokines, such as IL-6, IL-2, and IL-15. The development of a biological therapy aimed at the different components of the inflammatory process in psoriatic arthritis represents an important progress in the treatment of this disease (53).

Presently, three biological agents have been approved by the FDA and EMEA for the treatment of psoriatic arthritis: Etanercept, Adalimumab, Infliximab.

Etanercept: This is a dimeric fusion protein that is composed of an extra cellular portion, containing the ligand site, of the human TNF receptor 75 Kda, which is connected to the Fc portion of the human IgG1.

This molecule can bind to both TNF-α and TNF-β making their interaction with the TNF cell receptor impossible (54).

Its efficacy in the treatment of psoriatic arthritis has been demonstrated by various studies. The first study conducted was a double-blinded trial with placebo that recruited 60 patients, lasted 12 weeks, and consisted in the administration of 25 mg of Entanercept in the treated group (55). The first endpoint considered was the activity of arthritis which was assessed using a composed index, the Ps ACR; according to this index an improvement in 87% of the treated patients compared to 23% in the placebo group was shown. The second endpoint considered was the achievement of an overall improvement of 20% according to the ACR criteria (ACR20). 73% of the patients treated with etanercept, compared to 13% of the patients that were given the placebo, reached this objective.

Concerning psoriasis, the objective was the achievement of PASI 75; in patients with dermatologic manifestations (≥3% of body area involvement), 26% of patients treated with etanercept reached PASI 75, compared to 0% of patients receiving the placebo.

A fase III clinical trial conducted on 205 patients confirmed these results, demonstrating that ACR 20, 50, 70 was reached respectively in 59%, 38%, and 11% of the treated patients compared to 15%, 4%, and 0% in patients receiving the placebo at the 12th week. This result was maintained at the 24th week (56).

Other results that emerged from studies on Etanercept consisted in a significant increase in HAQ scores in treated patients, the possibility of reducing or suspending the use of methotrexate, and a prolonged tolerability of the therapy (56,57). Even the radiographic progression of the condition showed a variation in the Sharp index score of −0.03 in the treated patients compared to a variation of +1.00 in those receiving the placebo (56).

Adalimumab: This is a monoclonal antibody IgG 1k that is specific for the TNF-α (58,59). Its efficacy in the treatment of psoriatic arthritis has been tested in the ADEPT study (2005, Adalimumab Effectiveness in PsA trial); 151 patients received Adalimumab and 162 patients received the placebo. At the 24th week, the ACR 20, 50 and 70 was reached by 57%, 39%, and 23% of the patients receiving the drug compared to 15%, 6%, and 1% of those receiving the placebo. The PASI 50, 75, and 90 was 75%, 59%, and 42% of patients receiving Adalimumab compared to 12%, 1% and 0% of patients receiving the placebo. The study also demonstrated its effectiveness in inhibiting the radiographic progression of the disease (60).

Infliximab: This is a monoclonal chimeric antibody comprised of a variable human region (75% of the molecule) and a variable murine region (25% of the molecule). This molecule has a high binding affinity for TNF-α (but not for TNF-β) making the cytokine incapable of binding to its receptors when it is in its soluble form and when it is bound to the cell membrane. Infliximab is capable of provoking the complement mediated rupture of cells with TNF on their membrane (61,62).

The use of Infliximab has been approved in the treatment of moderately or severly active rheumatoid arthritis, rheumatoid spondylitis, psoriatic arthritis, and in moderately or severely active crohn's disease.

Infliximab has also been shown to be effective in the treatment of other inflammatory diseases such as sarcoidosis and Wegener's granuloma. Since this drug is given intravenously every 4-8 weeks, its concentration varies with peaks that determine the rupture of cells that produce or express TNF while the low levels between injections maintain the suppression of TNF and prevent the reheightening of the disease (45). Initially, open-label studies showed a significant improvement in the signs and symptoms of inflammation of the articular and dermatologic manifestations associated with a significant reduction of VES and PCR levels (63-65). These paved the way for the IMPACT study (66) (Infliximab Multinational Psoriatic Arthritis Controlled Trial) which randomly recruited 104 patients in a 16 week double-blinded study followed by a 50 week single-blinded study. The results to the ACR20, 50, 70 at the 16th week were respectively 69%, 49%, 29% in the treated patients compared to 8%, 0%, 0% in patients receiving the placebo. At the 50th week these results were confirmed by an ACR20, 50, 70 that was 72%, 54%, 35% in the patients treated with infliximab.

A second study (IMPACT2) was later conducted (67). In this study 200 patients randomly received either infliximab or the placebo for 24 weeks. The ACR20, 50 and 70 at the 24th week were reached by 54%, 41%, 27% of the patients that were treated with infliximab compared to 11%, 4%, 2% of those receiving the placebo. PASI75 was reached by 60% of the group treated with infliximab and by 1% of the group receiving the placebo.

The radiographic progression of the disease was valued through two studies (68, 69). The first study utilized the Sharp method that was modified for psoriatic arthritis. At the 24th week this method showed a variation of -0.7±2.53 in patients treated with infliximab compared to a variation of +0.82±2.62 in patients receiving the placebo. At the 50th week, the study showed a halt in the radiographic progression in both patients that had received infliximab during all 50 weeks and in those who had been treated from the 16th to the 50th week. The second study analyzed the radiographic progression of the disease in 72 patients. Patients were initially randomized into a double-blinded study and received infliximab or the placebo for 14 weeks, subsequently all patients blindly received infliximab up until the 50th week. It emerged that, at the 50th week, patients in both the placebo/infliximab group and patients in the infliximab/infliximab group did not show a worsening in the modified vdH-S total score.

Treatment with Infliximab is usually well tolerated. The most common side effects of this drug include headaches, upper respiratory tract infections, and administration reactions (48). A prolonged use has been associated with the production of anti-infliximab antibodies, which is the reason for which methotrxate is associated to the therapy. These antibodies can reduce the efficacy of infliximab with time, making an increase in its dose necessary (70,71). Rare cases of demyelinating pathologies, lupus-like conditions, and opportunistic infections including tuberculosis have been described in patients in treatment with infliximab (72).

Our experience

We treated 11 patients (7 male, 4 female), diagnosed with psoriatic arthritis, with an infusion of 5 mg/kg of infliximab at week 0, 2, and 6 and then every 8 weeks, following the classic scheme (66).

In this article we discuss an emblematic case of a patient treated with infliximab that showed improvement of his arthritis and dermatologic manifestations.

The patient was a 61 year old male affected by psoriatic arthritis since 1979: the psoriasis appeared in 1975 (diffuse manifestations localized on his chest, back, upper and lower limbs) then followed by the appearance of the classic symptoms of arthritis (sausage fingers, involvement of distal interphalangeal and metacarpophalangeal joints, nail alterations, involvement of the left knee).

Initial treatment included 10 mg of methotrexate given intramuscularly once a week, NSAIDs, and low doses of steroids which obtained a discrete resolution of symptoms. Inflammation indexes were reduced (VES from 45 to 28 1h; PCR from 3,18 to 1,28 (NV <0,5)) while functional and pathological indexes were the following: AIMS 2 from 40,12 to 38,15; SF 36 from 610,5 to 628,5; HAQ from 9,0 to 8,0; DAS from 3,60 to 3,70.

Scarce improvement in dermatological manifestations was obtained.

Given the persistence of pain the dose of methotrexate was increased to 15 mg/week obtaining poor results: VES 30 1h; PCR 1,45 mg/dl; AIMS 2 practically unmodified (from 38,15 to 33,38); SF 36 practically unmodified (from 628,5 to 631,5); HAQ practically unmodified (from 8,0 to 7,0); DAS practically unmodified (from 3,70 to 3,84).

At this point, we decided to add Infliximab 400 mg to the therapy following the classic scheme (73). Good remission of the clinical articular symptoms associated with a regression of the dermatological psoriatic manifestations was obtained.

Inflammation index and disease parameter trends during the four injections of Infliximab are shown in Table 1.

The photographs show the dermatological manifestations at baseline, after 2 week, after 6 weeks, and 14 weeks from the first injection (Figure 1).

At the 5th injection, clinical, laboratory and dermatological conditions remained unvaried.

Table 1

Time	VES 1 h	PCR mg/dl	AIMS 2	SF 36	HAQ_	DAS
0	32	1,45	33,38	631,5	7,0	3,84
week 2	13	0,42	27,25	698,5	3,0	1,68
week 6	10	0,28	25,75	678,0	1,0	0,83
week 14	8	0,11	22,25	686,5	1,0	0,90

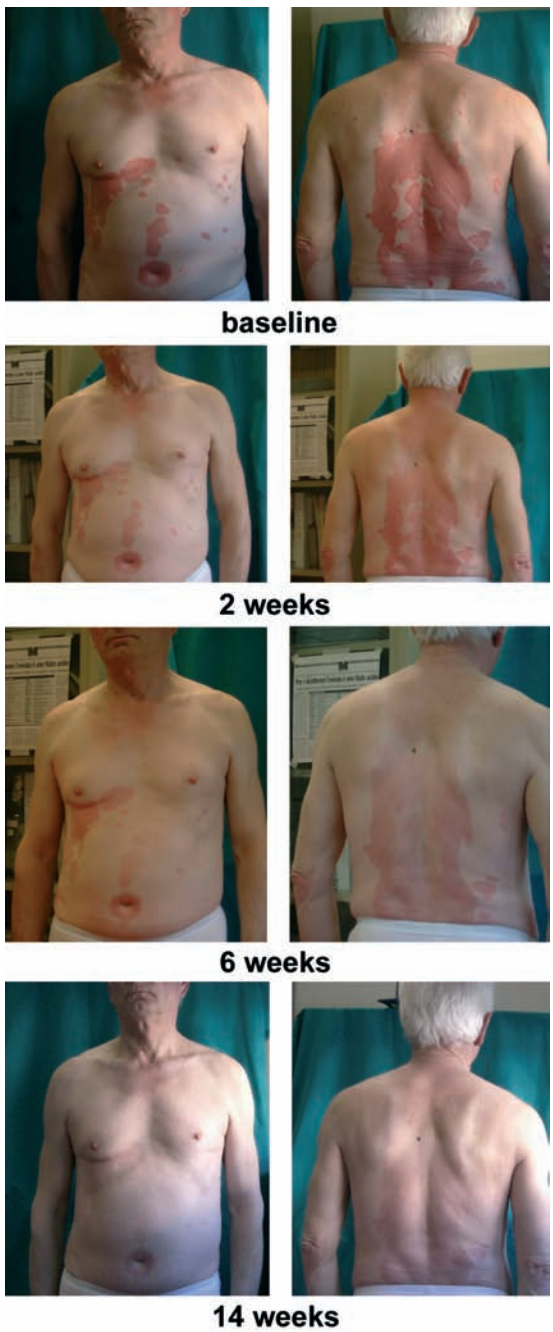

Figure 1. Dermatological manifestations at baseline, after 2 week, after 6 weeks, and 14 weeks from the first injection

Conclusions

Our experience, even with a limited case number, confirms the findings in literature on the validity of treatment with Infliximab in psoriatic arthritis.

We wanted to report this case which seems emblematic in demonstrating the beneficial effects of injections of Infliximab on dermatological manifestations, already documented in literature (63-67).

It is interesting to note the decisive improvement after the first injections of infliximab in articular and particularly in dermatological manifestations. This improvement was maintained after 5 months from the first injection.

At this point is crucial to understand how long this improvement is maintained and how long the therapy must be continued; this is the object of many discussions in literature (74, 75).

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