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Treatment of Severe Psoriasis with Infliximab: Report of Two Cases

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SUMMARY Infliximab is an anti-tumor necrosis factor-α monoclonal antibody shown to be effective in the treatment of moderate-to-severe psoriasis and psoriatic arthritis. We report on the first two patients in Croatia in which the efficacy of infliximab therapy was monitored and evaluated primarily on the basis of cutaneous manifestations of psoriasis. Both patients had severe, treatment-resistant chronic plaque psoriasis and psoriatic arthritis and were on methotrexate therapy before the initiation and throughout the course of infliximab treatment. Infliximab was administered intravenously at a dose of 4 or 5 mg/kg at week 0, 2, 6 and every 8 weeks thereafter. Disease severity was measured before each infusion by means of Psoriasis Area and Severity Index (PASI) score. A remarkable clinical response was achieved in both patients with a 50% or greater improvement in baseline PASI at week 2 after therapy initiation and a 90% or greater improvement at week 6 in one patient and at week 14 in the other. Both patients also reported a significant decline in their arthritis symptoms shortly after the introduction of infliximab. The concomitant use of infliximab and methotrexate in these two patients resulted in rapid and sustained remission of psoriasis with no major adverse effects detected.

KEY WORDS: psoriasis, psoriatic arthritis, infliximab

INTRODUCTION

Psoriasis is a chronic, immune-mediated, inflammatory disease with predominantly skin and joint manifestations that can significantly affect the patients' quality of life (1-3). A subset of patients with severe psoriasis remain poorly responsive to conventional therapies with narrow-band UVB and PUVA phototherapy, oral retinoids and immunosuppressive drugs such as methotrexate and cyclosporine. According to the immune basis of psoriasis, biologic agents including T cell inhibi-

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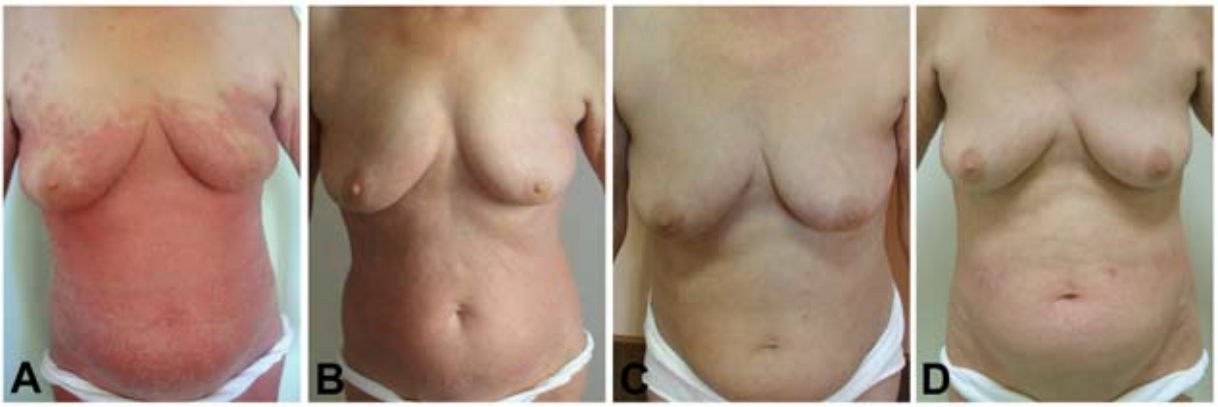

Figure 1. Patient 1: front view of the trunk at baseline (A), after 2 weeks (B), 14 weeks (C) and 30 weeks (D) of treatment with infliximab (5 mg/kg).

tors and tumor necrosis factor (TNF)-α inhibitors have recently emerged as a new line of therapy for this disease (1,2). Many of these agents have been widely approved by the regulatory agencies for the treatment of moderate-to-severe psoriasis and psoriatic arthritis. In Croatia, the use of biologic agents in the management of psoriasis is still restricted to patients with severe psoriatic arthritis resistant to disease-modifying antirheumatic drugs such as methotrexate. We report on the first two patients in our country treated and monitored for the efficacy of infliximab therapy at a dermatology-venereology clinic, based primarily on the severity of cutaneous manifestations of psoriasis.

Infliximab (Remicade®), a TNF-α inhibitor, was administered intravenously over a period of 2.5 hours at weeks 0, 2, and 6 and every 8 weeks thereafter according to the protocol for psoriasis and psoriatic arthritis (4-6). Before therapy initiation, *QuantiFERON*-TB Gold and chest x-ray tests were performed in both patients to exclude latent tuberculosis, one of the absolute contraindications for the use of TNF-α inhibitors (1). Before each infusion, complete blood cell count, platelet count, basic biochemistry tests with liver enzymes, urinalysis, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels were obtained. Patients were premedicated with dexamethasone to minimize the possibility for the occurrence of infusion reactions, and were monitored for another 2 hours after infusion. Disease severity was evaluated before each infusion by means of Psoriasis Area and Severity Index (PASI) score.

CASE REPORTS

Case 1

A 64-year-old woman with a 20-year history of chronic plaque psoriasis had in the past received systemic therapy with acitretin, methotrexate as well as courses of PUVA and narrow-band UVB phototherapy, which all resulted in poor control of the disease. In the last 4 years, she developed symptoms of symmetric peripheral polyarthritis, seronegative for rheumatoid factor, when non-steroidal anti-inflammatory drugs and occasional low dose steroids were introduced in therapy. Before the first infusion of infliximab, the patient had a PASI score of 28.2, pain and limitation of motion in knees, ankles and shoulders as well as painful swelling of distal interphalangeal joints. CRP level was increased to 50.3 mg/dL. She was on concurrent therapy with methotrexate (12.5 mg weekly dose with folate supplementation), ibuprofen and topical steroids. After the introduction of infliximab (5 mg/kg), the patient's PASI score decreased to 14 by week 2 (Fig. 1A, B) and to 11.6 by week 6. It was accompanied by considerable relief of joint pains and a decline in CRP level (14.4 and 4.6 mg/dL, respectively). On day 5 of the first infusion, the patient became febrile up to 38 ˚C. Antibiotic treatment was prescribed for a presumed urinary tract infection and the patient turned afebrile within the next 4 days, so the second infusion of infliximab was not delayed. Fourteen weeks from the initiation of treatment, after having received 3 infusions of infliximab, the patient's skin manifestations improved by 90% from baseline, with a PASI score of 2.7 (Fig.1C). Unexpectedly, the patient complained of aggravation of joint symptoms characterized by pain in shoulders and knees that started 2 weeks prior to the scheduled fourth infusion. This relapse of arthritis was accompanied by elevation in the ESR and CRP values (56 mm/h and 36.3 mg/dL, respectively), but responded well to subsequent therapy. Up to now, the patient has received 6 doses of infliximab and her skin remained minimally affected by psoriatic lesions for

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30 weeks of the initiation of treatment (Fig. 1D). Her articular symptoms were also reduced significantly, although she occasionally complained of pain in the involved joints. Treatment with infliximab was well tolerated without any serious side effects detected.

Case 2

A 27-year-old man with a 12-year history of chronic plaque psoriasis and psoriatic arthritis had frequent exacerbations of psoriasis involving more than 50% of total body surface area and was refractory to previous treatments with PUVA and narrow-band UVB phototherapy, acitretin and methotrexate. At the time of infliximab introduction, the patient was on therapy with narrow-band UVB, methotrexate (12.5 mg weekly dose with folate supplementation) and diclofenac for his joint symptoms. The patient's baseline PASI score was 50.9 with involvement of more than 90% of total body surface area, he had generalized lymphadenopathy and difficulty in walking due to symmetric polyarthritis and spondylitis. Both the skin and joint manifestations of the disease responded dramatically to the first infusion of infliximab (4 mg/kg). The patient experienced an instantaneous relief of his joint pains within the first 24 hours and had no need for treatment with diclofenac thereafter. His PASI score dropped to 24.8 by week 2 (Fig. 2A, B). The rapid clinical response to the infliximab treatment was further characterized by remarkable reduction in ESR (from 74 to 20 mm/h) and CRP values (from 40.0 to 0.4 mg/dL). By week 6 of the initiation of treatment, an impressive, 95% improvement with a PASI score of 2.7 was achieved (Fig. 2C). ESR reduced to 8 mm/h and CRP remained low at 0.4 mg/dL. The beneficial effects of treatment were maintained by week 14, with complete clearance of psoriatic lesions (Fig. 2D). Throughout the period of the first 4 infusions of infliximab, the patient did not experience any infusion reaction or adverse effect of the treatment.

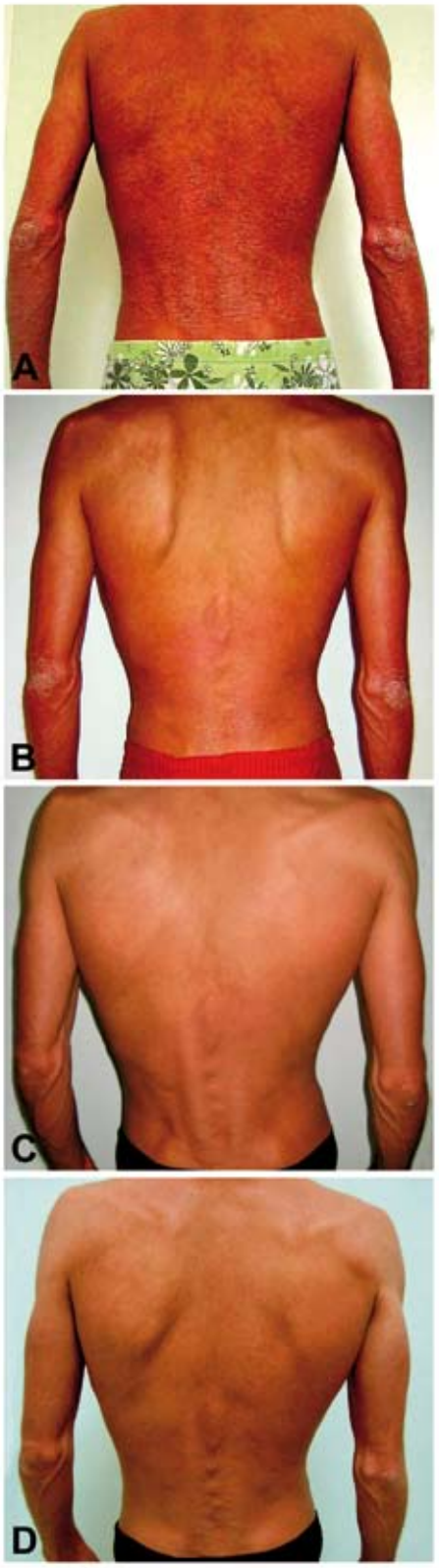

Figure 2. Patient 2: back view of the trunk and arms at baseline (A), after 2 weeks (B), 6 weeks (C) and 14 weeks (D) of treatment with infliximab (4 mg/kg).

DISCUSSION

According to the current concepts of pathogenesis, psoriasis is a T lymphocyte mediated autoimmune disease (2). Recently developed biologic therapies approved for the management of moderate-to-severe psoriasis specifically target T cells or inflammatory mediators. TNF-α is one of the central cytokines involved in the molecular pathways of inflammation in psoriasis and its levels correlate with disease severity (2,7,8). Infliximab is a chimeric human-mouse monoclonal antibody that binds

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both to the soluble and the membrane-bound TNF-α, neutralizing its biologic activity (1,4). The efficacy of infliximab in the management of moderate-to-severe chronic plaque psoriasis has already been established in clinical trials (5,6,9,10). More recent studies report on the efficacy and safety of infliximab in severe, treatment-resistant disease, or in combination with other immunosuppressant agents (11-14).

In our initial experience, based on the cases presented in this report, the concomitant use of infliximab and methotrexate can result in rapid and impressive improvement even in patients with severe, treatment-resistant psoriasis. The remarkable clinical response observed in our patients is comparable with short-term response demonstrated by clinical trials (6,11-13). In a phase III trial of infliximab, at week 10 of infliximab monotherapy for moderate-to-severe psoriasis, 80% of patients achieved at least a 75% improvement from baseline PASI score (PASI 75), and 57% of patients achieved at least a 90% improvement (PASI 90) (6). In a study that included patients on concomitant therapy with infliximab and methotrexate for severe recalcitrant psoriasis, slightly lower PASI 75 and PASI 90 rates at week 14 (68% and 52% of patients, respectively) have been reported (13). Both of our patients achieved 50% improvement in PASI score already by week 2, and PASI 90 was reached by week 6 and 14, respectively. A striking clinical response was observed in Patient 2, treated with a lower dose of infliximab (4 mg/kg), who reached practically complete remission of the disease with a 95% improvement in PASI already by week 6. The partial recurrence of joint symptoms in Patient 1 was probably a sign of different levels of infliximab efficacy achieved in joints and skin, implying differences in tissue-specific regulation of inflammatory response.

During the infliximab maintenance therapy, loss of efficacy may occur due to the formation of neutralizing antibodies to infliximab (ATI). The development of ATI is also associated with an increased risk of infusion reactions. However, it has been shown that low-dose methotrexate or other immunosuppressive treatment used concurrently with infliximab helps maintain clinical efficacy (15), while steroid premedication reduces the titer of ATI (15,16). Our patients were concomitantly treated with methotrexate (12.5 mg/kg weekly) and premedicated with dexamethasone before each infusion of infliximab. The beneficial effects of infliximab therapy were sustained in both patients throughout the period of treatment (for 30 weeks in Patient 1 and for 14 weeks in Patient 2), and no infusion reaction was detected. Although infliximab was generally well tolerated, our patients have been continuously monitored, according to recommendations available (1,4,17). Interestingly, there are a growing number of reports regarding the induction or exacerbation of psoriasis in patients with rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and Crohn's disease receiving TNF-α inhibitor therapy. This paradoxical side effect usually responds to conventional psoriasis treatment and does not necessarily require therapy cessation (18,19).

The new biologic agents have significantly increased therapeutic choices for the management of moderate-to-severe psoriasis. Apart from infliximab, clinical efficacy in the treatment of psoriasis has been shown for two additional antagonists of TNF-α, adalimumab (Humira®) and etanercept (Enbrel®), as well as for the T cell inhibitors efalizumab (Raptiva®) and alefacept (Amevive®) (1). Our experience is an example of great therapeutic advance achieved in patients with severe, previously treatment-resistant psoriasis. In Croatia, due to the substantial costs of such treatment modalities, severe psoriasis remains a therapeutic challenge. The use of biologic agents has thus far been restricted to patients with psoriatic arthritis that have responded inadequately to methotrexate, like the ones presented in this report.

Note added in proof: Since submission of this report, both of the presented patients have been treated with infliximab for a total period of 78 and 62 weeks, respectively. In Patient 1, we recently observed a gradual loss of clinical efficacy as her PASI score increased to 12.3 (56% improvement from baseline) before twelfth infusion. Therefore, we decided to shorten the interval between future infusions to every 6 weeks, or eventually consider discontinuation of therapy with this biologic agent. Patient 2 remained completely free of skin lesions, has received 10 infusions thus far and had none adverse effect of the treatment.

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