

The Changing Face of Spondyloarthropathies Under TNF α Blockade

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Abstract: *Objectives:* Tumor necrosis factor alpha (TNF- α) therapy has been implicated in the development of autoimmune diseases. Our aim was to describe three patients with spondyloarthropathies who responded to infliximab, a chimeric monoclonal antibody specific for TNF- α , but developed new symptoms of spondyloarthropathies. In parallel, a review of the literature on psoriasis induced by TNF- α blockers was undertaken.

Results: The first patient had been suffering from ankylosing spondylitis (AS) for more than 12 years. Infliximab induced a remission of AS, but he developed overt Crohn's disease two years after starting treatment. The second patient had AS for more than 20 years. Infliximab had an excellent effect on his AS, but he developed palmo-plantar psoriasis a few months after initiating therapy with the drug. The third patient, whose long-term and severe psoriasis had responded to infliximab developed peripheral arthritis. A review of the literature revealed 63 cases of psoriasis induced by TNF- α blockers (33 on Infliximab, 16 on Etanercept and 14 on Adalimumab). The underlying diseases were variable, including all the spectrum of conditions for which TNF- α blockers are indicated. Patients developed psoriasis after a mean duration of treatment of 11 months. Interestingly, a substantial proportion of patients continued treatment with TNF α blockers, the psoriasis improving in a majority of cases under topical treatment only.

Conclusion: While Infliximab may change the course of spondyloarthropathy, depressing the original symptoms it may uncover other occult aspects of these diseases.

Keywords: Infliximab, spondyloarthropathy, crohn, psoriasis, anti-TNF α .

INTRODUCTION

Tumor necrosis factor alpha (TNF- α) is an inflammatory cytokine that has been implicated in a variety of rheumatic and inflammatory diseases [1]. Infliximab, a chimeric monoclonal antibody specific for TNF-alpha, has been approved for the treatment of rheumatoid arthritis, Crohn's disease, ankylosing spondylitis, psoriasis and psoriatic arthritis [1]. In addition to dramatically changing the prognosis of these diseases, the use of infliximab has been associated with the development of a variety of autoimmune diseases such as systemic lupus erythematosus (SLE), vasculitis as well as psoriasis [2, 3].

Spondyloarthropathies are a family of related diseases which share striking points of similarity, such as negative tests for rheumatoid factor, absence of subcutaneous rheumatoid nodules, peripheral inflammatory arthritis, radiological sacroiliitis, tendency to familial aggregation, and – notably – a spectrum of overlapping features shared between the individual entities of this group [4]. As such, patients with one manifestation of spondyloarthropathy may develop features of other spondyloarthropathies. We report three cases of patients who suffered from spondyloarthropathy related diseases who responded to treatment with infliximab but developed new manifestations of spondyloarthropathies in

spite of responding well to therapy, suggesting that TNF- α blockade had stimulated overt manifestation of occult features of their disease.

METHODS

The three cases are reported with special emphasis on the clinical history and appearance of new symptoms with respect to the use of Infliximab. A Medline database search using the terms “psoriasis infliximab etanercept adalimumab crohn arthritis” between January 1985 and august 2007 was performed.

CASES

The 3 case reports are summarized in Table 1.

CASE REPORT 1

The patient, a 33-year-old man, was diagnosed as ankylosing spondylitis in 1995. There was no personal or familial history of psoriasis, inflammatory bowel disease or reactive arthropathy. He had failed several non-steroidal anti-inflammatory drugs (NSAIDs) and sulphasalazine due to lack of efficacy or side effects. He was commenced on low dose infliximab (3mg/kg) in June 2005 and experienced an impressive improvement in his complaints. The pretreatment BASDAI score of 7 dropped to 3 and C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) levels normalized. On February 2007, 2 weeks after the last infusion of infliximab and while he was free of the musculoskeletal complaints, he developed abdominal pain and bloody diarrhea. A colonoscopy performed a few days later revealed

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Table 1. Characteristics of the 3 Patients Reported

| | Age/Gender | Disease | Adverse Event | Time to Adverse Event | Outcome |
|--------|------------|-----------|---------------|-----------------------|--|
| Case 1 | 33/M | AS | Crohn's | 22 months | Resolution with mesalazine, Infliximab continued |
| Case 2 | 46/M | AS | Psoriasis | 5 months | Resolution after switching to etanercept |
| Case 3 | 46/F | Psoriasis | Arthritis | 7 months | Resolution after switching to etanercept |

macroscopic and histological findings typical of Crohn's disease. In retrospective he denied any past symptoms of IBD. The patient was treated with Mesalazine with resolution of his symptoms. He subsequently continued treatment with Infliximab at a dosage of 5 mg/kg.

CASE REPORT 2

A 46-year-old man diagnosed as having ankylosing spondylitis in 1985. He ultimately developed stiffness of the entire spine, kyphosis of the thoracic spine and ankylosis of the cervical spine, but never experienced any extra-skeletal manifestation of the condition. Despite the advanced anatomical status of the primary disease, activity was evident based on severe inflammatory back pain, the constant need for NSAIDs and increased ESR and CRP levels. In 2006, infliximab was prescribed. After the second infusion, he reported a significant improvement in back pain and morning stiffness, accompanied by a decrease in ESR and CRP levels. Five months after starting this treatment, however, he developed a symmetric erythematous eruption of his palms and soles (Fig. 1) mandating cessation of treatment. Infliximab was exchanged with etanercept resulting in rapid resolution of the rash and excellent effect on symptoms of ankylosing spondylitis.



Fig. (1). Plantar psoriasis in patient 2, after treatment with infliximab.

CASE REPORT 3

A 46-year-old woman, having psoriasis more than 20 years. The condition became progressively severe, and involved more than 70% of the body most of the time. She had failed topical treatments, methotrexate, cyclosporine, neotigazone and psoralen ultraviolet A (PUVA). Despite the severity of the psoriasis, she never had musculoskeletal complaints. In 2006, she was started on 5 mg/kg infliximab, with

resolution of more than 75% of the psoriatic lesions. Three weeks after the sixth infusion, she developed arthritis of the small joints of the hands, shoulders and knees, without enthesitis or dactylitis. The laboratory tests revealed an increased ESR and a positive antinuclear factor with normal anti-dsDNA. She nevertheless continued treatment with infliximab, and experienced a significant improvement in both skin and musculoskeletal signs, lasting for 3 weeks after each infusion. Treatment with Infliximab was subsequently stopped and switched to Etanercept.

LITERATURE REVIEW

A Medline database search of relevant publications in the English literature between January 1985 and August 2007 did not reveal reports of Crohn's disease or psoriatic arthritis following infliximab. However, more than 80 cases of psoriasis in patients treated with TNF- α blockers have been described [2, 3, 5-30]. Table 2 summarizes the clinical characteristics of these patients. 33 patients were on Infliximab, 16 on Etanercept and 14 on Adalimumab. The underlying diseases were variable, including the whole spectrum of conditions for which TNF α blockers are indicated. Patients developed psoriasis after a mean duration of treatment of 11 months. Table 2 reports the outcome of these patients. Interestingly, a substantial proportion of patients continued treatment with TNF α blockers, the psoriasis improving in a majority of cases under topical treatment only; implicating that cessation of therapy is not always indicated.

DISCUSSION

Our 3 described patients underwent an impressive resolution of the original symptoms which warranted the administration of infliximab, but each went on to develop new spondyloarthropathic features while under this TNF- α therapy. All 3 patients had a protracted disease before being starting infliximab, without a hint for their eventual post-infliximab additional symptoms, which make it much more likely that their de novo symptoms are related to the effect of the medication.

Several lines of evidence pointing to the immunomodulatory effects of TNF- α blockades have been accumulating with the increasing use and longer follow-up of treatment with TNF- α antagonists. Testimony of autoimmunity triggered by TNF- α blockers includes 92 reported cases of lupus, 113 patients with vasculitis and 24 cases of interstitial lung diseases [2]. The ability of TNF- α to induce autoantibodies in a large proportion of patients was established in several studies [31-33].

Our cases represent untoward immunomodulation triggered by infliximab that had brought about the desired therapeutic effects on the existing disease symptoms for which it had been prescribed. The first case was a patient with long-

Table 2. Clinical and Demographic Characteristics of Patients Who Developed Psoriasis Under Treatment with TNF α Blocker

| | |
|---|---|
| Gender | 57 Females, 33 Males, 3 UK |
| Mean Age; Range | 45;13-78 |
| Underlying disease | 44 RA, 2 JRA,9 Crohn, 1 UC, 17 AS (+4 Crohn), 2 Behcet, 1 PsA,1 eosinophilic fasciitis, 1 uveitis |
| Concomitant drugs | None 6, Methotrexate 22 Prednisone 8, Salazopyrine 5, Leflunomide 8, Azathioprine 3 |
| Infliximab | 47 |
| Etanercept | 17 |
| Adalimumab | 16 |
| Family history of psoriasis | 3 |
| Mean duration of treatment until psoriasis; SD | 11 \pm 12 Infliximab: 9 \pm 10 Etanercept: 7 \pm 7 Adalimumab: 16 \pm 19 |
| Characteristics of psoriasis | 39 PPP, 38 Psoriasis vulgaris, 4 UK |

PPP - Pustular Palmoplantar Psoriasis, UK - Unknown.

standing ankylosing spondylitis who acutely developed Crohn's disease. Endoscopic studies in patients with ankylosing spondylitis have demonstrated the presence of intestinal inflammation in up to 60% of them, particularly in those with active peripheral joint disease [34]. One prospective follow-up of patients with juvenile onset disease who initially presented with peripheral rather than axial joint disease also showed that intestinal inflammation increases the likelihood of progression to axial disease [35]. Our patient was probably predisposed to develop inflammatory bowel disease, but the fact that it developed with the introduction of infliximab, by itself indicated for Crohn's disease, despite highly satisfactory control of his ankylosing spondylitis, strongly suggests a triggering effect of the drug. Interestingly, etanercept, a soluble receptor of TNF- α has been implicated in the onset of 6 cases of Crohn's disease [36-39] -3 of them in patients with ankylosing spondylitis [39]. The second case was a patient with very long-standing ankylosing spondylitis who developed palmo plantar psoriasis shortly after beginning a course of infliximab. There have been several reports in the medical literature of new-onset psoriasis or worsening of pre-existing skin diseases in patients treated with TNF- α inhibitors for psoriatic arthritis, rheumatoid arthritis, ankylosing spondylitis and inflammatory bowel disease. Interestingly, infliximab is efficacious in treating skin psoriasis. A great proportion of the patients described in the literature presented with palmo-plantar psoriasis, although all forms of psoriasis were described [2, 3, 5-30]. It has been suggested that palmo plantar psoriasis may be induced by an abnormal expression of TNF- α in the eccrine palmar sweat gland and duct [40]. Although TNF- α is a well-documented contributor to the psoriatic skin lesion, another important pathway for triggering common human

autoimmune disease involves plasmacytoid dendritic cell precursors and type 1 interferon (INF) production. TNF- α regulates INF- α production and neutralization of endogenous TNF- α may promote INF- α production by plasmacytoid dendritic cells inducing psoriatic plaques [41]. Our third case was a woman with long-standing psoriasis who developed peripheral arthritis during treatment with infliximab. The differential diagnosis of this case includes infliximab-induced lupus and psoriatic arthritis. The fact that the arthritis subsequently responded to the infusion of infliximab and that the anti-dsDNA result was negative support the likelihood of the seronegative arthritis having been triggered by infliximab.

Another plausible explanation for the undesired evolution of our three cases may involve the effect of TNF- α antagonists on the risks of infection. TNF- α blockers have been implicated in the reactivation of a variety of infectious diseases, including mainly intracellular pathogens, such as Mycobacterium tuberculosis and others [42]. Immune activation by bacteria was shown to have a crucial role in the development of the disease in both reactive arthritis (ReA) and in the HLA-B27 transgenic rats model [43]. There is evidence that this is related to an abnormal persistence of intracellular pathogens, at least in ReA [31]. Recent studies indicate that other subtypes of SpA may also have an impairment of certain aspects of the innate immune defense, particularly with regard to the expression of scavenger receptors [44, 45]. However, whereas SpA has traditionally been associated with urogenital infection with chlamydia or gastrointestinal infections with Gram-negative pathogens, such as salmonella, shigella, campylobacter, and yersinia [46], treatment with anti-TNF- α blockers may affect the intestinal flora by inducing a change in the predominant manifestation of spondyloarthropathies.

Table 3. Outcome of Patients Who Developed Psoriasis After Treatment with TNF α Blocker

| TNF Blocker | Outcome |
|-------------------------|---|
| Infliximab (33 cases) | |
| Continued | 22; 17 improved, 4 progressed, 2 UK |
| Discontinued | 20; 18 improved, 0 progress, 2 UK |
| Switched to another TNF | 10; recurrence in 5 |
| Unknown | 4 |
| Etanercept (16 cases) | |
| Continued | 9; 8 improved, 1 persisted |
| Discontinued | 4; 4 improved |
| Switched to another TNF | 2, recurrence in 1 |
| Unknown | 4 UK |
| Adalimumab | |
| Continued | 6; 3 improved, 1 progressed, 1 UK |
| Discontinued | 9; 8 improved, 1 progressed |
| Switched to another TNF | 3 switthed to another TNF, 1 recurrence |
| Unknown | 1 UK |

In conclusion, in addition to the well-known autoimmune effects of anti-TNF- α therapy, our cases suggest the possibil-

ity of other and untoward alterations of the course of spondyloarthropathies as a result of this treatment. In our patients, the trade-off was successful depression of one aspect of the disease at the expense of triggering a none less undesirable though occult facet of the spondyloarthropathic repertoire in an apparently predisposed patient.

ACKNOWLEDGEMENT

Esther Eshkol is thanked for editorial assistance.

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Received: February 26, 2008

Revised: March 25, 2008

Accepted: May 8, 2008

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