Mod Rheumatol (2007) 17:174–177
DOI 10.1007/s10165-006-0561-8

CASE REPORT

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Therapeutic efficacy and safety profile of infliximab in active systemic lupus erythematosus

Received: October 25, 2006 / Accepted: December 26, 2006

Abstract Since levels of the proinflammatory cytokine tumor necrosis factor alpha (TNFα) are significantly increased in systemic lupus erythematosus (SLE) and may be involved in the disease pathogenesis, we report on the safety and efficacy of infliximab, a chimeric monoclonal antibody directed against TNFα, given to a patient with difficult-to-treat active nonrenal SLE. This patient, who failed to remit with full doses of glucocorticoids, hydroxychloroquine, methotrexate, and azathioprine, went into sustained remission with the addition of infliximab infusions. Glucocorticoids could be tapered off completely.

Key words Infliximab · Systemic lupus erythematosus · Tumor necrosis factor alpha · Tumor necrosis factor alpha blocker

Introduction

Presently, long-term administration of glucocorticoids continues to be the sheet anchor for control of disease activity in systemic lupus erythematosus (SLE).[1] The side effects and toxicities of glucocorticoids are well known, and furthermore, they are only partially successful in controlling lupus activity.[1] Therefore, new treatments for SLE are urgently needed. Because disease activity in SLE correlates well with increased serum levels and activity of the cytokine tumor necrosis factor alpha (TNFα),[2,3] we report on the safety and efficacy of infliximab, a chimeric monoclonal antibody directed against TNFα, given to a patient with active nonrenal SLE.

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Case report

This 25-year-old unmarried Kuwaiti woman, with a history of SLE in her mother, had disease onset in 1995 with vague ill-health and nonspecific myalgias and arthralgias. She was evaluated and kept under regular follow-up but did not show any abnormal clinical or serological findings. Four years later, in 1999, while the myalgias and arthralgias continued, she was found to have positive antinuclear antibody (ANA) in a titer of 1:2560 with a mixed homogeneous and speckled pattern, high levels of anti-dsDNA antibodies (>400 IU/ml), low levels of serum complement C3 (0.4 g/l) and C4 (0.08 g/l), and positive anti-SmB, anti-SmD, and anti-RNP-A antibodies. Anticardiolipin antibodies and anti-β2GPI were absent. Urine examination did not show protein, cells, or casts. At that point she was commenced on hydroxychloroquine (HCQ) 400 mg every night, with which her nonspecific symptoms gradually came under fairly good control.

From 2003 she started to have significant diffuse alopecia, Raynaud's phenomenon, and increasingly severe nonerosive symmetrical polyarthritis. At this stage methotrexate and glucocorticoids were added. Subsequently, from April 2004 she presented on multiple occasions with significant disabling nonerosive RF-negative polyarthritis, pleurisy, pericardial effusion, and Raynaud's phenomenon associated with active SLE serology. The patient did not fulfill ACR criteria for rheumatoid arthritis. From 2004 to 2005 she required four admissions to hospital for severe pleurisy and polyarthritis and had to be given methylprednisolone pulse therapy (500 mg in 500 ml 5% dextrose infused over 2 h for three consecutive days) and stepped-up dose of prednisolone 90 mg per day (body weight 110 kg) each time, in addition to methotrexate and HCQ. Nevertheless, the patient continued to have lupus flares each time the dose of glucocorticoids was tapered down to 50–60 mg/day. Even when methotrexate was substituted by azathioprine 200 mg/day as a steroid-sparing agent, the patient failed to remit. Adversely, she developed Cushingoid features, hypertension, and spinal osteopenia (T score –1.9)

Table 1. Evaluation at baseline and at 6 months of infliximab therapy

Clinical features	Baseline	6 months
	Malar rash, alopecia, Raynaud's phenomenon, myalgias, arthralgias, polyarthritis, pleurisy, pericardial effusion	–
CBC		
WBC (10^9/l)	4.7	5.7
Hb (g/l)	9.5	12.0
Plt (10^9/l)	607	397
ESR (mm/h)	97	30
RFT		
BUN (mmol/l)	5.7	4.8
Crea (μmol/l)	65	62
Albumin (g/l)	34	31
LFT	Normal	Normal
Urinanalysis		
WBC (/mm3)	–	–
RBC (/mm3)	–	–
Cast	–	–
Protein (g/l)	0.1	0.1
Immunology		
C3 (g/l)	0.4	1.02
C4 (g/l)	0.08	0.149
ANA	1:2560 homogenous and speckled	1:2560 homogenous
Ds-DNA (IU/ml)	>400	23
ENA	Anti-SmB, anti-SmD, anti-RNP-A	Anti-SmB, anti-SmD, anti-RNP-A
ACL Ab	Negative	Negative
Anti-B2GP1 Ab	Negative	Negative
CRP	1.64	0.6
TNF-α level	NA	NA
TNF-r level	NA	NA
SLEDAI	14	1
SF36	88	98
Patient's global assessment of disease activity (0–5)[a]	4	2
VAS for fatigue	70	30
SLICC/ACR-DI	1	1

CBC, complete blood count; WBC, white blood cells; ESR, erythrocyte sedimentation rate; RFT, renal function tests; BUN, blood urea nitrogen; LFT, liver function tests; RBC, red blood cells; ANA, antinuclear antibody; ENA, extractable nuclear antibodies; ACL Ab, anticardiolipin antibodies; CRP, C-reactive protein; SLEDAI, systemic lupus erythematosus disease activity index; SF36, short form 36; VAS, visual analogue scale; SLICC/ACR-DI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Disease Damage Index; NA, not available

[a] Assessment of her disease activity by the patient on a score of 0 to 5. 0 being no disease activity, 5 being severe disease activity

as a result of glucocorticoid therapy, and her obesity worsened.

At this stage, she was recruited into an open label study on the safety and efficacy of infliximab in patients with active lupus. This study was approved by the Vice President of Research Administration of the Kuwait University and by the Ethical Committee of the Kuwait University Faculty of Medicine. Informed consent was obtained from the patient and she was commenced in May 2005 on a protocol of 400 mg (3 mg/kg body weight) infliximab infusions at 0, 2, 6, 14, and 22 weeks. The treatment she was already receiving was initially continued.

One month after starting infliximab, the patient reported a sense of well-being and was totally symptom-free. Lupus serology showed marked improvement (anti-dsDNA 23 IU/ml, C3 1.11 g/l, and C4 0.16 g/l). Health status measures (SF-36 and VAS-fatigue) and disease activity measures (patient's global assessment of disease activity and SLEDAI) showed marked improvement: at baseline, the patient had lower scores in SF-36 subclasses for all dimensions of health and significantly higher scores for VAS-fatigue, patient's global assessment of disease activity, and SLEDAI (scores 88, 70, 4 and 14, respectively). At 6 months, significant improvement in all the measures was noticed indicating better health and a state of remission (scores 98, 30, 2 and 1, respectively). The SLEDAI improved by 13 points. The organ damage score SLICC/ACR-DI at baseline and follow-up remained unchanged at 1 (Table 1). Meanwhile glucocorticoids were tapered and then completely stopped in September 2005. Azathioprine was also stopped and only HCQ 400 mg/day was continued. The patient continues to do well only at 1 year after her last infliximab infusion.

Discussion

Permanent end-organ damage occurs in SLE in direct proportion to the level and duration of uncontrolled disease activity.[4] Presently, glucocorticoids are the sheet anchor of therapy for control of disease activity in SLE but have serious long-term toxicities including dyslipidemia, premature atherosclerosis, coronary artery disease, and osteoporosis. Infliximab, a potent blocker of the proinflammatory cyto-

kine TNFα, should be potentially effective in controlling SLE activity since TNFα is significantly increased in SLE and may be involved in its disease pathogenesis.[2,3,5,6] Furthermore, there is good correlation between the high levels of TNFα and the clinical and serological parameters of SLE disease activity.[3,7]. Serum levels of TNFα and of the p55 and p75 type 1 and 2 TNFα receptors are valuable markers of disease activity in patients with SLE,[8] and the serum levels of these is significantly higher in patients with active than inactive disease.[8–10] Chloroquine therapy has been shown to significantly lower elevated TNFα levels in SLE patients.[11] Furthermore, TNFα is implicated in the pathogenesis of proliferative lupus nephritis and may cause apoptosis in this setting by triggering TNF receptor types 1 and 2 in the kidney.[12] Membrane TNFα, a precursor form of soluble TNFα, exerts proinflammatory functions in a cell-to-cell contact manner, and is induced upon activation on the surface of CD4+ and CD8+ T cells. Very recently it has been shown that in patients with SLE, the percentage of membrane TNFα-bearing CD8+ T cells is significantly higher compared with those of healthy controls or patients with rheumatoid arthritis, and these cells may be involved in the increased apoptosis and the generation of autoantigens.[13] In a study of genes involved in the apoptosis of PBMC in SLE patients, it was found that genes for TNF and the TNF-receptor family were drastically upregulated 60- and 19-fold higher than in healthy controls, respectively. Moreover, the degree of apoptosis correlated with the level of TNFα in plasma, suggesting that the TNF family plays a role in the induction of apoptosis in SLE. In the presence of etanercept, a TNFα blocker, active SLE plasma reduced the level of apoptosis to 26 %.[14]

These data suggest a central role for the TNF system in the pathophysiology of SLE, and present an attractive rationale for using TNF blockade in SLE. Therefore, we decided to study the safety and efficacy of infliximab in active SLE. The present patient with active nonrenal lupus and severe polyarthritis who failed to remit with full doses of glucocorticoids, methotrexate, azathioprine, and hydroxychloroquine, went into sustained remission with the addition of infliximab. We were able to taper off glucocorticoids completely in this young lady who had developed Cushingoid features, spinal osteopenia, and hypertension as a result of glucocorticoid therapy. Also, we were able to discontinue azathioprine and methotrexate.

Notwithstanding the therapeutic potential of TNFα blockade in SLE, researchers have so far shied away from this modality for several reasons, primarily the concern regarding the ability of infliximab to induce the production of autoantibodies and even a lupus-like syndrome in patients with rheumatoid arthritis (RA). A recent study noted that 76% of patients receiving infliximab developed new autoantibodies with the most common new autoantibody being ANA in 45%, followed by anti-DNA in 33%, anti-smooth muscle in 31%, and anti-ribonucleoprotein in 29%.[15] However, no patient developed clinical signs of a new connective tissue disease. This may be explained by the fact that infliximab induces anti-dsDNA antibodies predominantly of IgM class, whereas anti-dsDNA antibodies of only IgG class are pathogenic.[16] An editorial published in *Arthritis & Rheumatism* in 2000 said: "While rheumatologists who are using TNFα blockers to treat RA may breathe a sigh of relief, they should also pause and take a deep breath before considering the use of this revolutionary therapy in SLE. Without a controlled clinical trial, ideas about the safety and efficacy of TNFα blockers will be mired in uncertainty and speculation. Hopefully, such a trial will be conducted soon."[17] A recent pilot study of six patients with moderately active SLE administered infliximab showed that it resulted in clinical improvement of the disease without any adverse events.[18] Of the 6 patients, 4 had nephritis and 3, like our patient, had arthritis refractory to other therapies. All 3 patients with joint involvement experienced remission of arthritis, as in our patient, relapsing 8–11 weeks after the last infliximab infusion. In the 4 patients with lupus nephritis, proteinuria decreased significantly within 1 week after initiation of therapy and was diminished by 60% or more within 8 weeks, remaining at low levels until the end of the observation period (at least several months). Our case report also indicates that anti-TNFα alpha therapy may constitute an interesting candidate approach for treating SLE inflammatory organ disease, but large clinical trials will be required to answer whether TNFα blockade fulfills this hope with an acceptable safety profile. The question of whether the pro-inflammatory properties or the pro-apoptotic properties of TNFα (or both) are neutralized by infliximab in the setting of SLE also needs to be answered by further studies.

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