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Treatment of Refractory Polymyalgia Rheumatica with Infliximab: a Pilot Study

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ABSTRACT. ***Objective.*** To investigate whether infliximab has a steroid-sparing effect in the treatment of patients with polymyalgia rheumatica (PMR) who are resistant to corticosteroid (CS) therapy and have had CS-related side effects.

Methods. In a pilot study, infliximab 3 mg/kg was administered at weeks 0, 2, and 6 in 4 patients with relapsing PMR who were not able to reduce their prednisone dose below 7.5-12.5 mg/day and who had experienced multiple vertebral fractures. The patients were regularly monitored for clinical signs/symptoms and erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and interleukin-6 (IL-6) during the one-year followup period.

Results. Two patients had a complete response to infliximab with clinical remission 2 weeks after the first infusion. At this time ESR and IL-6 values were normal and the patients were able to suspend prednisone. Normal ESR, CRP, and IL-6 levels persisted after the suspension of infliximab and prednisone during the followup period, paralleling the clinical remission. The third patient had a complete and persistent clinical remission 2 weeks after the first infusion, although IL-6 levels remained elevated during the followup period despite the normalization of ESR values. These 3 patients were symptom-free with normal ESR and CRP at the end of 1-year of followup. The fourth patient had continuous clinical activity associated with persistently elevated acute phase reactants, although IL-6 levels measured during followup were lower compared to baseline values and the patient was able to reduce prednisone dosage to 5 mg/day.

Conclusion. Our encouraging results suggest that a controlled study may assess the efficacy of infliximab as CS-sparing drug in PMR. (J Rheumatol 2003;30:760–3)

Key Indexing Terms:
INFLIXIMAB POLYMYALGIA RHEUMATICA RELAPSING DISEASE

Corticosteroids (CS) are the drug of choice to treat polymyalgia rheumatica (PMR). In absence of giant cell arteritis (GCA), an initial dose of 10 to 20 mg/day of prednisone or equivalent is adequate in most cases of PMR[1]. A treatment course of 1-2 years is often required. However, in about 30 to 50% of the patients, disease exacerbations occur and a prolonged course of CS treatment for several years is necessary[2-5]. CS-related adverse events are frequently observed during treatment course. A longterm population-based followup study found that 65% of PMR patients developed at least one adverse event[6]. CS-related side effects were mainly related to cumulative steroid dose, female gender, and age at diagnosis. To date, there have been conflicting results on the efficacy of CS-sparing drugs in PMR, in particular methotrexate (MTX). Furthermore, there is no evidence that cytotoxic agents may be possible alternatives to CS[7].

Infliximab, a chimeric monoclonal anti-tumor necrosis factor (TNF)-α antibody, has been demonstrated to be effective and safe in the treatment of rheumatoid arthritis (RA) and ankylosing spondylitis (AS)[8,9]. Recently, a pilot study done by our group reported the efficacy of infliximab in patients with CS resistant GCA, a condition strictly related to PMR[10].

However, no data have been published to evaluate the efficacy of TNF-α blockade in PMR. In this pilot study we used infliximab to treat 4 patients with longstanding PMR that had remained active despite CS treatment.

MATERIALS AND METHODS

Patients. Four women with longstanding PMR who were followed at the rheumatological units of Prato and Reggio Emilia Hospitals, Italy made up the study group. At diagnosis, all 4 patients satisfied the criteria defined by Healey for PMR[11]. These patients were regularly followed for a median of 49 months (range: 48 to 52), receiving a starting prednisone dose of 20 mg/day. When symptoms had remitted for one month, the dosage was reduced to 15 mg/day. Small decrements of 5 mg to 2.5 mg every 2 weeks were successively scheduled until the minimal maintenance dose was

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reached. All 4 patients had relapsed every time the CS dose was reduced to 7.5-12.5 mg/day and all had experienced multiple vertebral fractures.

Treatment protocol. Once the local ethics committee approval and a written informed consent had been obtained, the 4 patients were scheduled to receive 3 intravenous infusions of infliximab 3 mg/kg at weeks 0, 2, and 6, which is the current administration schedule for patients with RA[8]. The drug was infused over a 2-h period. The dosage of prednisone was reduced and prednisone was administered during the first 2 weeks at a dosage of 5 mg/day. The steroid was withdrawn if clinical remission occurred after the second infusion of infliximab. PMR was considered active in presence of a relapse characterized by typical proximal musculoskeletal symptoms and morning stiffness ≥ 1 h associated with elevated erythrocyte sedimentation rate (ESR) (Westergren; normal value ≤ 30 mm/h) and/or C-reactive protein (CRP) (nephelometry; normal value: ≤ 0.5 mg/dl).

Patients were evaluated for the variables of disease activity at baseline (T0: at the time of first infusion), 2 weeks after the first infusion (T1: at the time of the second infusion), 4 weeks after the second infusion (T2: at the time of the third infusion), 4 weeks after the third infusion (T3), monthly until the sixth month after the first infusion (T4), then every 2 months until the end of the one-year followup period (T5). Side effects were evaluated at each visit. During the infusion and for one hour afterwards, blood pressure, pulse, and temperature were measured every 30 min. Moreover, at every visit, ESR, CRP, serum interleukin-6 (IL-6) levels, complete blood count, and liver and kidney function tests were examined. Serum IL-6 concentrations were evaluated by immunoassay using a commercial enzyme-linked immunosorbent assay (ELISA) kit (R&D Systems, Minneapolis, MN, USA), according to the manufacturer's instructions. The sensitivity of the test is typically less than 0.70 pg/ml. IL-6 serum levels were also measured in 43 controls matched for age and sex with PMR patients[4]. Normal IL-6 levels were considered as < 4 pg/ml (normal mean + 3 SD). Patients were considered responders if all clinical and laboratory variables of disease activity remitted after the second infusion of infliximab. The same variables were used during the followup period. All 4 patients had active disease before starting the treatment with infliximab.

CASE REPORTS

Patient 1. A 63-year-old woman developed gradual onset of aching and morning stiffness in the shoulder and hip girdles. At the same time she also felt tired, became anorexic with a weight loss of 3 kg, and her ESR was 90 mm/h. A diagnosis of PMR was made. Prednisone 20 mg/day was started with resolution of joint pain within 48 h after treatment. The prednisone dosage was gradually decreased, although it was not possible to reduce it below 10 mg/day because of relapses. Two years later she developed multiple lumbar vertebral fractures. Two months later she also experienced a dorsal vertebral fracture. MTX 10 mg/week in association with CS at a stable dose of 12.5 mg/day was started without efficacy. Two years after this, while she was in therapy with MTX 10 mg/wk and prednisone at 12.5 mg/day, the disease relapsed.

Patient 2. A 67-year-old-female developed aching and stiffness in the neck, torso, and shoulders. ESR was 82 mm/h. Prednisone 20 mg/day was started and her symptoms resolved within 72 h. Four months later, when the prednisone dosage was lowered to 7.5 mg/day, she noted marked aching and morning stiffness in shoulders and hips. ESR was 44 mm/h. Prednisone was increased to 15 mg/day with remission of symptoms. During the followup period the patient had relapses every time the prednisone dosage was reduced below 7.5 mg/day and developed multiple lumbar vertebral fractures. Four years later, while she was taking prednisone 7.5 mg/day, she relapsed again.

Patient 3. A 64-year-old woman developed aching and morning stiffness in the neck, shoulders and hips, as well as fatigue, anorexia, low grade fever and weight loss of 4 kg. ESR was 100 mm/h. Prednisone 20 mg/day was begun, and her symptoms resolved within 48 h. Prednisone was gradually reduced to 10 mg/day. Six weeks later the proximal aching and stiffness recurred. ESR was 52 mm/h. Prednisone dosage was increased to 17.5 mg/day with complete clinical remission and normalization of ESR. During the followup, when the dosage of prednisone was reduced to 10 mg/day, symptoms relapsed again. Chloroquine, MTX, and azathioprine were thus added to CS at different times but with no efficacy. Three years after diagnosis the patient developed multiple dorsal vertebral fractures. One year after this, clinical manifestations of PMR recurred while she was given prednisone 12.5 mg/day.

Patient 4. A 69-year-old female was referred for a 3-month history of musculoskeletal discomfort and stiffness in the neck, shoulder and pelvic girdles. ESR was 76 mm/h. The symptoms remitted within 3 days after the start of prednisone treatment with 20 mg/day. During the followup she had multiple relapses when the prednisone dose was tapered to 10 mg/day. MTX 10 mg/wk was associated without efficacy. Two years later the patient experienced multiple dorsal vertebral fractures. Two years after this, when prednisone dose was reduced to 10 mg/day, the patient had a relapse.

RESULTS

Table 1 shows the clinical and laboratory data of the 4 patients before and after infliximab treatment. Two patients had a complete response to therapy with clinical and humoral remission 2 weeks after the first infusion (patients 2 and 3). The third patient (patient 4) had sustained clinical remission 2 weeks after the first infusion, although IL-6 levels remained elevated during the followup period despite the normalization of ESR values. These 3 patients were symptom-free with normal ESR and CRP at the end of one-year followup. The fourth patient (patient 1) had continuous clinical activity. Although acute phase reactants remained elevated for the entire followup period, IL-6 levels were lower compared to baseline values and the steroid dose was reduced by one-half. Infliximab was well tolerated without any side effects by all 4 patients.

DISCUSSION

Our pilot study of 4 patients with steroid resistant PMR shows that infliximab could be useful as a steroid-sparing agent in this disease.

Three of our 4 patients who had been treated for 4 years with a dose of prednisone ranging from 7.5 to 12.5 mg/day were able to suspend the treatment. These patients had experienced severe steroid-related side effects such as multiple osteoporotic vertebral fractures. Morbidity in PMR is mainly related to major steroid-related complications, the most common being fractures. One study showed that 65% of the PMR patients treated with CS developed at least one adverse event[6]. The risk of osteoporotic fractures was 2 to 5 times higher among patients with PMR than among similarly aged individuals from the same population. Increasing age at diagnosis, cumulative dose of prednisone of at least 1800 mg, and female sex independently increased the risk of fractures.

MTX has been proposed as a CS-sparing drug in PMR, but the data are conflicting[7]. In the only double-blind, placebo-controlled study no CS-sparing effect of MTX in a dosage of 7.5 mg/week was found[12].

TNF-α, which is released by macrophages and activated

Table 1. Infliximab therapy in 4 patients with longstanding PMR.

	T0 Baseline (at time of 1st infusion)	T1 2 Wks After 1st Infusion (at time of the 2nd infusion)	T2 4 Wks After 2nd Infusion (at time of 3rd infusion)	T3 4 Wks After 3rd Infusion	T4 6 Mos After 1st Infusion	T5 State of the Patient At 1-yr Followup
Patient 1.						
Symptoms/signs	Yes	No	Yes	No	Yes	Yes
ESR (mm/h)	87	51	67	47	54	53
CRP (mg/dl)	1.3	0.7	1.1	0.5	1.6	0.7
IL-6 (pg/ml)	49.5	4.2	7.2	2.5	6.3	-
Prednisone dose (mg/d)	12.5	5	0	5	5	5
Patient 2.						
Symptoms/signs	Yes	No	No	No	No	No
ESR (mm/h)	46	16	18	30	13	14
CRP (mg/dl)	1.1	0.3	0.3	0.5	0.3	0.3
IL-6 (pg/ml)	25.5	1.1	2.0	3.5	3.2	-
Prednisone dose (mg/d)	7.5	5	0	0	0	0
Patient 3.						
Symptoms/signs	Yes	No	No	No	No	No
ESR (mm/h)	38	16	11	14	15	12
CRP (mg/dl)	3.6	0.9	0.4	0.4	0.3	0.3
IL-6 (pg/ml)	61.2	1.8	1.7	2.3	2.7	-
Prednisone dose (mg/d)	12.5	5	0	0	0	0
Patient 4.						
Symptoms/signs	Yes	No	No	No	No	No
ESR (mm/h)	46	20	10	25	20	22
CRP (mg/dl)	4.1	0.7	0.4	1.0	0.8	0.4
IL-6 (pg/ml)	48.1	9.8	3.2	15.7	9.1	-
Prednisone dose (mg/d)	10	5	0	0	0	0

T-lymphocytes, plays a major role in inflammatory response. Circulating TNF-α concentrations in most of the studies of PMR and/or GCA were similar to those of controls[13,14]. However, detectable plasma TNF-α does not represent the concentration of cytokine locally produced at the site of inflammation. A strong association of PMR/GCA with TNF-α2 microsatellite polymorphism has been reported[15].

The use of anti-TNF-α agents in our PMR patients was also justified on the basis of the successful treatment of other inflammatory arthropathies such as RA and AS[8,9]. These agents seem to be very effective in AS, although there are conflicting data about the circulating levels of TNF-α and its polymorphisms in this condition. Furthermore, a recent pilot study from our group showed the efficacy of infliximab as steroid sparing in a condition closely related to PMR such as GCA[10].

The potent antiinflammatory effect of infliximab in PMR was demonstrated by the reduction of the levels of acute phase reactants 2 weeks after the start of the infliximab therapy. In particular, the rapid reduction in CRP was accompanied by marked changes in IL-6 circulating levels. The reduction in IL-6 levels is of particular interest, as this cytokine is considered the most sensitive marker of disease activity in PMR/GCA. PMR/GCA recurrences are associated with increased plasma IL-6 levels, and the persistence of elevated IL-6 levels despite ESR normalization characterized PMR patients with continued active disease who required higher and more prolonged CS doses[13,16,17].

IL-6 levels decreased to normal 2 weeks after the first infusion in 2 (patients 2 and 3) of our 3 patients who had complete response to therapy. Interestingly in these patients the normal IL-6 levels persisted after the suspension of infliximab and prednisone, paralleling the clinical remission. The third patient (patient 4) had a complete and sustained clinical remission 2 weeks after the first infusion, although elevated levels of IL-6 persisted in the followup period, despite the normalization of ESR and the discontinuation of prednisone. The fourth patient (patient 1) had continuous clinical activity associated with persistently elevated acute phase reactants, although IL-6 levels measured during the followup were lower compared to baseline values and the patient was able to reduce prednisone dosage to 5 mg/day. The efficacy of TNF-α blockade in down-regulating the production of IL-6 has been observed in *in vitro* studies with RA cell synovial culture systems[18].

The limited number of patients included in this study and the open label design did not allow us to draw definitive conclusions from our findings. Our encouraging results suggest that a controlled study may assess the efficacy of infliximab as CS-sparing drug in PMR. Of particular interest

is the sustained down-regulation in the production of IL-6, which represents the main inducer molecule of the systemic acute phase reaction in PMR.

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