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BRIEF REPORT

Fast recovery with etanercept in patients affected by polymyalgia rheumatica and decompensated diabetes: a case-series study

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Abstract We enrolled nine consecutive patients affected by newly diagnosed polymyalgia rheumatica and decompensated diabetes mellitus. All patients were treated with etanercept (25 mg twice weekly) and prednisone and were followed up to 1 year. At the sixth-month follow-up, etanercept and prednisone were withdrawn. Patients were seen at regular intervals (days 0, 30, 60, 90, 150, 180) and the following variables determined: erythrocytes sedimentation rate, C-reactive protein, fasting serum glucose, pain measured by visual analog scale, and the Health Assessment Questionnaire. Our results indicate that etanercept might have some steroid-sparing effects, but controlled investigations are needed to support etanercept use in clinical practice for this kind of patients.

Keywords Biological therapy · Decompensated diabetes mellitus · Etanercept · Polymyalgia rheumatica · Steroid therapy

Introduction

Polymyalgia rheumatica (PMR) is a common rheumatic disorder in the elderly population (0.1% to 0.5% over 50 years and 2% over 60 years) [1, 2]. PMR often presents a 'challenge' because of (a) lack of definitive diagnostic criteria, (b) large number of differential diagnoses, (c) atypical clinical features, and (d) lack of conformity in therapeutic regimes [3, 4]. The mainstay of therapy is oral steroids: prednisone at 15- to 25-mg dosage. Many authors report as median starting dosage of prednisone 20 mg/day [5–7]. Oral steroids usually suppress inflammation dramatically. Notwithstanding, up to 60% relapse during steroid tapering and some studies indicate steroid treatment can only rarely be discontinued before 2 years with an administering time ranging from 18 to 36 months [7, 8]. This long-term treatment brings about obvious side effects, particularly osteoporosis, hypertension, hyperglycemia, and cataracts, and supports the need for improved therapeutic options, mainly in patients at high risk for steroid-related toxicity [8].

For a long time, rheumatologists have sought a drug to control PMR-sparing prednisone. Methotrexate was their main hope. However, research studies on methotrexate steroid-sparing effects in PMR and giant cell arteritis have been frustratingly inconclusive. Moreover, clinical trials report controversial data [9–11] and, in our experience, methotrexate steroid-sparing effects are limited, sometimes inconclusive, and often need too much time to show clinical relevant effects. Recently, a multicenter trial has pointed out that adding infliximab to prednisone for newly diagnosed PMR patients is not useful and could sometimes be harmful [12]. For all these reasons, in our experience, we prefer to use etanercept when we are compelled by clinical constraints such as decompensated diabetes mellitus by steroid therapy. We report "all or none" case series [13] of nine consecutive patients with PMR and decompensated diabetes mellitus successfully treated with etanercept and followed up until 1 year.

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Materials and methods

Nine consecutive patients referred to our out-patient clinic were included. PMR was diagnosed according to Chuang et al. [4] criteria. Inclusion criteria were: age older than 50 years; erythrocytes sedimentation rate (ESR) ≥40 mm/h; aching and stiffness at shoulder, hip girdle, or both for more than 1 month; and no signs or symptoms of other musculoskeletal or connective tissue conditions (elevated levels of serum creatine kinase and polyarthritis included).

All recruited patients have suffered from diabetes mellitus for at least 15 years. They were undergoing oral hypoglycaemic agents and no one had been taking insulin therapy during the last 6 months before inclusion in this study. All patients had good metabolic control (fasting serum glucose <140 mg/dl; HBA1c <7%) at the moment of PMR diagnosis and had started prednisone at 15- to 20-mg daily dosage basing on clinical and laboratory features. All patients had decompensated diabetes mellitus (fasting blood glucose >450 mg/dl) at the first outpatient control visit (after about 30 days), which is the baseline time of this case-series study. All underwent chest X-ray, echocardiography, and intradermal injection of purified protein derivatives five tuberculin units (PPD). All the patients were without clinical or subclinical heart failure, PPD reaction greater than 5 mm, and with chest X-ray active lesions. Hence, all the patients were treated with etanercept 25 mg twice a week. Subjects were taught to inject short-acting insulin before each meal and intermediate-acting insulin at bedtime. Insulin was started at a dose of 5 U of regular insulin before meals and 10–15 U NPH at 10:00 P.M. The insulin dose was increased by two to five additional units at each injection time everyday to ameliorate metabolic control. All the patients discontinued insulin therapy when fasting serum glucose levels were below 200 mg/dl.

Moreover, daily doses of prednisone were abruptly reduced and afterwards tapered in 2.5 mg steps basing on clinical and laboratory features.

Patients were seen at regular intervals (days 0, 30, 60, 90, 150, 180), and the following variables were collected at all visits: ESR (mm/h), C-reactive protein (CRP, mg/l), fasting blood glucose (mg/dl), aching at shoulder and/or hip girdle (measured by visual analog scale, VAS). The Health Assessment Questionnaire (HAQ) was performed at baseline and a 180-day visit to evaluate patient functional status [14]. Laboratory tests were performed according to local standards and quality control regulations.

We requested permission of our ethical committee for etanercept use in this kind of patients (indication not approved by healthcare authorities in Italy). Patient consent was also acquired.

No statistical analysis was performed because all the patients had remission, all the studied variable values improved in a significant way, and no control group was used for comparisons.

Results

Eight patients withdrew insulin therapy within 4 weeks. Only one patient (woman, 79 years old) needed both insulin therapy for 10 weeks and a daily dosage of regular insulin more than 24 IU.

Etanercept was withdrawn at 6-month follow-up, and at the same control visit, all patients were asked to withdraw prednisone after 30 days. All the patients have been regularly followed up after the end of the aforementioned tight monitoring. No patient needed to restart prednisone therapy. Table 1 shows biochemical variables and prednisone daily dosage as median (min–max) at each control visit through the 6-month follow-up period. Data are shown as median (min–max). Average values were computed for age and body mass index (BMI). Eight patients were women, the mean age was 76.7 years (74–81), mean BMI was 28.1 kg/m^2 (25.4–30.5), and did not significantly change during the follow-up period. Figures 1, 2, and 3 show ESR, CRP, and VAS single patient trends. All the patients are still having complete remission after 1-year follow-up, and variable values were virtually the same at the sixth-month control visit.

Table 1 Laboratory variables and steroid daily dosage trend during the 6-month etanercept trial

Follow-up time	VAS score	ESR (mm/h)	CRP (mg/dl)	HbA1c (%)	Fasting blood glucose (mg/dl)	Prednisone daily dosage (mg)
Baseline	9 (8–10)	84 (77–90)	4.8 (3.7–7.0)	8.4 (7.6–10.1)	501 (300–690)	10 (7.5–10.0)
30 days	7 (6–8)	65 (40–80)	3.0 (2.0–4.0)	7.9 (7.1–8.9)	258 (145–320)	7.5 (5–10)
60 days	5 (4–6)	50 (32–60)	1.5 (1.0–3.0)	7.4 (6.7–8.2)	200 (128–308)	5 (5–7.5)
90 days	3 (2–4)	30 (22–44)	1.0 (0–1.5)	6.8 (6.4–7.3)	140 (120–160)	5 (2.5–5)
150 days	2 (1–3)	21 (20–30)	0.6 (0.0–1.0)	6.4 (6.0–6.7)	110 (100–130)	2.5 (2.5–5)
180 days	1 (0–2)	20 (12–25)	0.1 (0.0–0.6)	6.0 (5.8–6.3)	120 (100–140)	–

Data are shown as median (min–max)
VAS visual analog scale for the evaluation of shoulder and/or hip girdle pain, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein

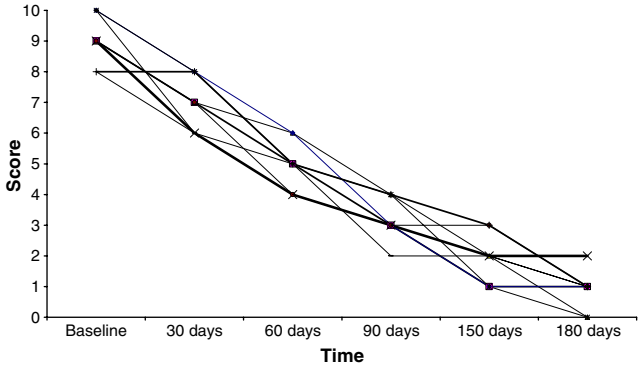

Fig. 1 VAS score trend of each patient during the 6-month etanercept trial (VAS score concerns visual analog scale for the evaluation of shoulder and/or hip girdle pain)

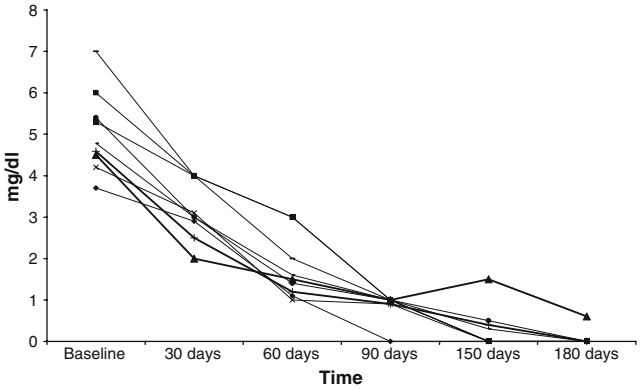

Fig. 3 C-reactive protein trend of each patient during the 6-month etanercept trial

Discussion

To control disease, sparing prednisone is a mainstay for avoiding side effects in patients with PMR. In the past, methotrexate was a main hope. However, research studies on methotrexate steroid-sparing effects in PMR and giant cell arteritis have been frustratingly inconclusive [9–11]. On the other hand, in our knowledge, few data exist about infliximab as sparing agent in this kind of patients. One study of four patients dealt with the use of biologic agents (infliximab–antitumor necrosis factor-alpha antibody) in refractory PMR [15]. In this study, Salvarani et al. pointed out both a potential efficacy of infliximab infusion in three patients treated and cortisone-sparing effect (prednisone dosage was reduced to 5 mg/day). In 6 months of follow-up study, Migliore et al. [16] also evidenced that infliximab could be useful in the treatment of PMR patients with diabetes mellitus not only for steroid sparing purposes but also as first-line therapy in the presence of severe comorbidity, such as diabetes mellitus or osteoporosis. Other recent studies [17, 18] have shown that infliximab therapy is efficacious on insulin resistance in patients with rheumatoid arthritis. Moreover, Yazdani-Biuki et al. [19] reported a case of diabetes relapse after interruption of chronic administration of infliximab.

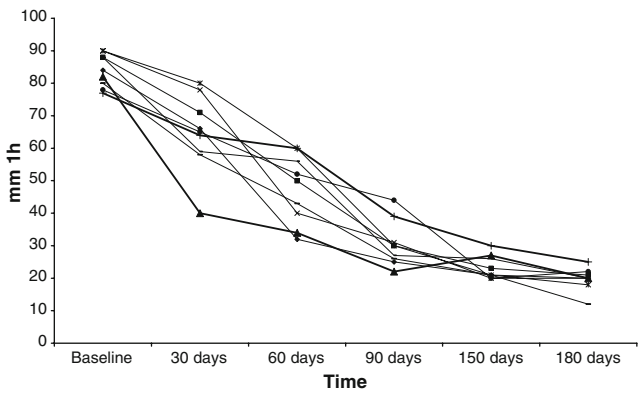

Fig. 2 Erythrocyte sedimentation rate trend of each patient during the 6-month etanercept trial

Some literature data might explain and support the use of anti TNF-alpha therapy in dysmetabolic patients. A very interesting preclinical study about possible pathophysiological mechanisms [20] showed that expression of extracellular-superoxide dismutase (EC-SOD), but not other SOD isozymes, in smooth muscle and fibroblast cells were suppressed by TNF-alpha. EC-SOD is the major SOD isozyme in blood vessel walls, normal cartilage, and synovial fluid and may be important for the antioxidant capability of these tissues. In previous studies, EC-SOD gene-transferred mice exhibited significant suppression of clinical symptoms of type II collagen-induced arthritis [21], and plasma EC-SOD levels in type 2 diabetic patients resulted negatively, which is related to indices of insulin resistance [22]. Therefore, it could be speculated that decline in TNF-alpha activity with an anti-TNF agent might result in the liberation of EC-SOD from the suppressed state of gene expression. This could reveal a potential usefulness of anti-TNF agents on some TNF-alpha-related pathological conditions such as arthritis or other rheumatologic diseases, but it could be useful in other conditions such as those related to insulin resistance.

In our study, nine patients with PMR and decompensated diabetes mellitus were treated with etanercept, another biological agent anti TNF-alpha. In patients affected by diabetes mellitus and PMR, sparing prednisone could be very important. Indeed, this complicates rheumatologist's decision making. For this reason, we treated our patients with etanercept basing on both its good patient compliance and previously encouraging results using infliximab. Moreover, Bernstein et al. [23] suggested etanercept usefulness in patients with insulin resistance, and etanercept therapy usually allows monitoring patients on an outpatient basis.

Our results show that all the patients had complete remission of disease activity after a therapy trial of 6-month up to 1-year follow-up. During etanercept and concomitant prednisone therapy, we observed reduction of fasting blood glucose levels, improvement of clinical and laboratory variables, rapid tapering of prednisone (withdrawn in all the patients after the 6-month tight monitoring), and no relapses during the further 6-month follow-up after therapy discontinuation.

Etanercept therapy seems to allow a sparing use of prednisone. In fact, daily dosage was started at 15–20 mg and rapidly tapered. We also registered a significant reduction of HAQ score that confirms the optimal clinical result from the patient quality-of-life point of view.

Conclusions

Our study is the first one supporting effective etanercept treatment of PMR in patients with decompensated diabetes mellitus. Our study was not a controlled one, but we report "all or none" case series of nine consecutive cases with complete remission until 1 year follow-up. But the main limit of our study was the lack of a control group, so no strong conclusion could be drawn. However, our study strongly supports the hypothesis that etanercept therapy might be effective and safe as first-line treatment in this kind of patients.

Moreover, further investigations using a blinded controlled study design are needed before introducing in clinical practice etanercept use as first-line treatment in PMR patients with decompensated diabetes mellitus.

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Disclosures None.

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