

TNF-alpha blockade induce clinical remission in patients affected by polymyalgia rheumatica associated to diabetes mellitus and/or osteoporosis: a seven cases report

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Abstract. – Polymyalgia rheumatica (PMR) is a chronic inflammatory condition of the elderly, characterized by aching and morning stiffness in the cervical region, shoulders and pelvic girdles. A steroid treatment course of 6-24 months is often required, but, due to important side effects, it is troublesome if the PMR patient is also affected by diabetes mellitus (DM) and/or osteoporosis. Aim of our study is to test anti-TNF alpha treatment as a steroid sparing tool in PMR patients affected by DM or osteoporosis. In particular, we hypothesise that TNF alpha blockade can be useful not only in remission maintaining, but also in the induction of clinical remission without corticosteroids in this kind of patients.

In a six months follow up, patients had clinical improvement, confirmed by physical medical examination, and a statistically significant reduction in ESR and CRP mean values. Anti-TNF alpha treatment was well tolerated by all patients.

These preliminary data suggest that Infliximab can be useful in the treatment of PMR patients, not only for steroid sparing purposes, but also as first line therapy in PMR patients with severe comorbidity, such as diabetes mellitus or osteoporosis.

Key Words:

Polymyalgia reumatica, Diabetes mellitus, Osteoporosis, Infliximab, TNF alpha blockade, Corticosteroid treatment.

tions that affect people of middle age and older and frequently occur together. Many authors consider them as different phases of the same disease. PMR and GCA have a polygenetic origin, influenced by multiple environmental factors.

PMR is an inflammatory disorder characterized by aching and morning stiffness in the cervical region, shoulders and pelvic girdles. Annual incidence of PMR ranges from 12.5 cases per 100,000 in Italy through 52,5 cases per 100,000 in USA^{1,2}.

The incidence of PMR and GCA increases after the age of 50 years and peaks between 70 and 80 years of age. Being the patient an elderly subject, he will frequently have co-morbidities, such as diabetes mellitus (DM) or osteoporosis. Either such diseases are preexisting, and may be complicated by long term steroid treatment, or they are induced by PMR treatment. Although no literature data exist, reporting diabetes and osteoporosis prevalence in PMR patients, we can hypothesize it is relevant; DM type II prevalence ranges, in Italy, 6% to 11%, and increases with increasing age. The Center for Disease Control and Prevention (CDC) estimates that 17 million United States people, corresponding to 6.2% of the population, are affected by diabetes, and 20.1% of over-65 population³; moreover, it is well known that in U.S. population, 14,8% of subjects in their fifties have vertebral, hip or radial osteoporosis, while 70% of people in their eighties have vertebral, hip or radial osteoporosis⁴.

Concise Communications

Polymyalgia rheumatica (PMR) and giant-cell arteritis (GCA) are closely related condi-

PMR was first described in 1888⁵, but current diagnostic criteria were formulated only in 1982 by Chuang et al⁶, and revised in 1984 by Healy⁷. In 1990, the American College of Rheumatology stated the current criteria for the classification of GCA⁸.

Corticosteroids are the drug of choice to treat PMR and GCA. An initial dose of 10 to 20 mg of prednisone or its equivalent per day is adequate in most cases of PMR. The response to corticosteroids is rapid, with the resolution of many symptoms within the first few days of therapy. A corticosteroid treatment course of one to two years is often required. However, about 30% to 50% of the patients have spontaneous exacerbations of disease, especially during the first two years, that are independent of the corticosteroid regimen^{10,11}.

Corticosteroid induced toxicity¹²⁻¹⁵ has led to efforts aimed to identify alternative or adjunctive treatments¹⁸⁻²².

Anti-TNF-alpha treatment was suggested by some as a like steroid sparing therapy in refractory PMR patients^{25,26}.

We hypothesised that TNF-alpha blockade can be useful not only as steroid sparing drug in remission maintaining, but also in the induction of clinical remission without corticosteroids in a higher risk subset of PMR patients, affected by severe osteoporosis or diabetes mellitus.

We report our experience with seven female outpatients affected by PMR with diabetes mellitus or and osteoporosis, treated with Infliximab.

Materials and Methods

Demographic and clinical features of the patients are reported in Table I. Seven patients were enrolled, five affected by PMR and diabetes mellitus, two affected by PMR and osteoporosis complicated by vertebral fractures. All the patients were female, mean age 72 years (range 68-84); PMR diagnosis was stated in our divisional ambulatory, meeting ACR criteria⁷. Out of the diabetes mellitus patients, four were on oral antidiabetic agents, one on insulin treatment. Mean time from DM diagnosis was 13 years. Patients affected by osteoporosis were newly diagnosed through WHO criteria, were complicated by vertebral fractures and were not under osteoporosis treatment. None of the seven patient had ever been administered steroids since the first PMR diagnosis.

All patients were screened for tuberculosis infection; they were taken a chest radiogram and underwent skin Mantoux reaction; also, hepatitis B and C virus markers were checked, along with urine infections. After all such screenings proved negative, patients were administered four infliximab infusions, at the dose of 3 mg/kg, performed respectively at time 0, after 15 days and at weeks 6 and 14 following the first infusion. Methotrexate was then introduced (7,5-10 mg per week, oral or intramuscular administration) for maintaining remission. Erythrocyte sedimentation ratio (ESR), C-reactive protein (CRP), glycaemia and haemoglobin A_{1c} ratio were evaluated at weeks 0,6 and 14. Mean follow up was of eight months (range 7-9 months).

Table I. Demographic and clinical features of the patients.

Patient	Age	BMI	Years from diagnosis diabetes	Sex	Diabetes mellitus	Insulin	Oral hypoglycaemic agents	Osteoporotic fractures	Months of follow-up
1	70	24	15	F	Type 1	Yes	No	No	9
2	73	26	12	F	Type 2	No	Yes	No	8
3	71	24	12	F	Type 2	No	Yes	Yes	8
4	65	25	15	F	Type 2	No	Yes	No	9
5	73	24	11	F	Type 2	No	Yes	No	7
6	84	17	-	F	No	No	No	Yes	8
7	68	18	-	F	No	No	No	Yes	8
Media	72		11.4						8.14

Table II. Mean reduction of ESR and CRP after six and fourteen weeks of infliximab treatment.

Patient	ESR			CRP mg/dl		
	Baseline	6 th week	14 th week	Baseline	6 th week	14 th week
1	83	13	27	3.7	0.59	0.5
2	61	21	3	16	0.24	0.31
3	55	41	22	5.2	0.7	0.26
4	35	23	35	1.3	0.1	0.1
5	49	49	57	1.7	2.5	4.1
6	89	31	30	26.3	2.6	2.4
7	60	34	40	26	11.8	11.2
Media	61.875	33.5	34.5	12.7	3.3	7.16667

$p < 0.05$

Results

A remission of clinical symptoms was observed in all patients. Data also show normalization in serological parameters ESR and CRP following infliximab in five of seven patients; two patients had no amelioration in ESR and CRP titers, despite a net improvement in overall symptoms. In particular, one of such patients had at week 6 an episode of diverticulitis. Mean reductions in ESR e CRP values were statistically significant when compared to baseline values, at weeks 6 and 14 ($p < 0.05$, paired t-test for the comparison of means between paired data) (Table II).

None of the five patients with diabetes mellitus had an increase of haemoglobin A_{1c} ratio or glycaemia, nor needed a modification of their diabetes therapy scheme. Results

show an improvement in glycaemic levels at weeks 6 and 14, although the difference does not reach statistical significance (p 0.08 and p 0.12) (Table III).

After a mean 8 months follow-up, clinical symptoms and serological features are still under control with weekly administration of low dose Methotrexate. None of the seven patients ever needed steroid therapy during the follow-up period.

Discussion

PMR is an inflammatory disorder characterized by muscular aches and mobility impairment of neck, shoulders and pelvic girdle. A corticosteroid treatment course of one to

Table III. Mean reduction of glycaemia and Hb_{A1c} after six and fourteen weeks of infliximab treatment.

Glycaemia mg/dl			Hb _{A1c} %		
Baseline	6 th week	14 th week	Baseline	6 th week	14 th week
366	128	206	9.5	8.4	7.2
66	31	94	5.7	5.3	4.5
108	118	98	7.1	5.7	5.9
151	120	127	9.5	8.0	8.1
177	99	126	9.5	6.8	7.1
173.6	99.2	130.2	8.26	6.84	6.56

$p < 0.05$

two years is invariably needed, thus treated patients are at high risk of steroid-dependent complications. First of all, many patients have their hypothalamic-pituitary-adrenal axis suppressed by the long term treatment; an abrupt discontinuation of corticosteroid treatment may easily lead to a life-threatening adrenal insufficiency. On the other hand, patients treated with low steroid doses must receive a higher dose when they are affected by an infection, or in the case that they plan to undergo surgery or other increased physiologic stresses. Patients with PMR have an increased risk for serious complications caused by corticosteroids because of age and co-morbidity. Osteoporosis, increased susceptibility to infection, impaired wound healing, glycaemia and blood pressure instability, cataracts, glaucoma and psychiatric disorders are among the complications that may cause serious problems in these patients¹².

Some authors reported that at least one complication occurs in 65% of PMR patients treated solely with corticosteroids, and in 80% of PMR patients treated with both steroids and NSAIDs¹³.

The risk of diabetes mellitus onset and osteoporotic fractures is two to five times higher for PMR patients than it is in healthy subjects of matching age¹⁴, and the risk may be directly dependent of the cumulative steroid dose¹³. Steroid related damages in this kind of patients may be very severe, despite prevention of fractures by Calcium and Vitamin D supplementation and bisphosphonates¹⁵. Epidemiological studies show that the elderly is the category with the most prevalent prescriptions for corticosteroids, patients affected by RA and PMR/GCA are prescribed the highest dosages, and for the longest duration¹².

The toxicity of corticosteroids compels to try and find alternative or adjunctive treatments. Unfortunately, no other treatment has been found to even approach the efficacy of corticosteroids¹⁷. Concomitant therapy with corticosteroids and dapsone, azathioprine, cyclosporine A, idrossicloroquine, cyclophosphamide or gold salts has not been found to reduce corticosteroid toxicity^{18,19}.

Some authors have used Methotrexate as corticosteroid sparing drug in PMR patients with conflicting results²⁰⁻²². Others have considered anti-TNF-alpha treatment with infliximab in both GCA and PMR.

As regards GCA, Cantini et al.²³ reported their experience with three infusions of Infliximab, 3 mg/kg, for the treatment of four patients with longstanding or refractory active giant cell arteritis. Three of such patients have been followed up for 18 months, and remained symptoms-free, with normal ESR and CRP²⁴.

A recent pilot study, performed by Salvarani et al., suggested that TNF-alpha blockade may exert a steroid-sparing effect in patients with long-standing and steroid-resistant polymyalgia rheumatica. Thus, the Authors propose to reserve TNF-alpha blockade to patients with partial response to corticosteroids treatment or requiring high CS dose, to reach clinical improvement^{25,26}.

Since CS-related side effects may be deleterious in patients suffering from diabetes mellitus and osteoporosis, we hypothesised that infliximab, an anti-TNF-alpha agent, might be beneficial in patients affected by PMR associated with diabetes mellitus and/or osteoporotic fractures. We have indeed previously reported successful induction of clinical remission induced by infliximab in three patients of the kind²⁷. The objective of this study was to investigate whether infliximab could induce clinical remission of PMR symptoms and spare diabetic and/or osteoporotic CS-related complications in a cohort of PMR patients with associated diabetes and/or osteoporosis.

Although seven patients represent a very poor population to draw reliable results, and definitive conclusions, we suggest that anti-TNF-alpha agents can have a positive effect on the hypothalamus-pituitary-adrenal axis (HPA axis), reducing negative effects of inflammatory cytokines on the axis. This reduction would improve HPA responsiveness to chronic stress, resetting endogen cortisol levels to normal²⁸.

All patients referred a clinical improvement, confirmed by physical medical examination; even though a statistically significant reduction in ESR and CRP values was observed comparing baseline with final mean values, only five out of seven patients showed a reduction in ESR and CRP at weeks 6, persisting at week 14. To account for this partial serological response we can summon genetic factors determining susceptibility to treatments: it is well known that a proportion of

PMR patients may not respond to steroids and, on the other hand, literature data exist regarding rheumatoid arthritis patients who are refractory to TNF-alpha blockade. In the same way, the two patients who failed to reach serological remission might have genome-determined resistance to infliximab, or else a peculiar pattern of cytokine disorder causing their unresponse²⁹. Anti-TNF-alpha treatment was well tolerated by all patients. There were no systemic reactions nor infectious complications during follow-up. Development of ANA was not detected.

No patient showed increasing glycaemic level or hemoglobin A_{1c} ratio (Table II), confirming what was observed elsewhere by Di Rocco et al³⁰. At ninth month of follow-up no patient needed CS treatment.

Our preliminar data suggest that Infliximab can be useful in the treatment of PMR patients, not only as steroid sparing tool, but also as first line therapy in PMR patients with severe comorbidity, such as diabetes mellitus or osteoporosis complicated by vertebral fractures. Steroid treatment in this kind of patients is to be avoided whenever possible, due to its severe side-effects on glycaemia, bone mineral density and bone fracture incidence, which endows this treatment of very scarce cost-effectiveness. Patients should be informed about potential benefits and risks of corticosteroid therapy and physicians have to consider alternative treatments.

The limited number of patients do not allow to draw definitive conclusions from our findings; controlled studies with a greater number of patients and prolonged follow-up are needed.

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