An agent-to-agent real life comparison study of tocilizumab *versus* abatacept in giant cell arteritis

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ABSTRACT

Objective. *The present study aimed at evaluating the efficacy of abatacept (ABA) compared to tocilizumab (TCZ), assumed as a gold standard biologic treatment in the management of patients with giant cell arteritis (GCA).*

Methods. *Thirty-three biospy-proven GCA consecutive patients were prospectively collected. Odd patients (from 1 to 33) were assigned to TCZ, given either intravenously (IV 8 mg/kg/month), #8 cases, or subcutaneously (SC 162 mg/week) #9, based on patient's preference. ABA was administered subcutaneously at the dose of 125 mg/week in 16 even patients (from 2 to 32). Biological therapies were prescribed in addition to oral prednisone.*

Results. *A single biologic agent was administered in 28 patients out of 33 (85%) (8 TCZ IV, 9 TCZ SC and 16 ABA). Five patients (15%) needed a therapeutic switch (one patient from TCZ to ABA, and 4 patients from ABA to TCZ). Among the TCZ IV group, all patients experienced a response (57% complete response and 43% partial response). Among the TCZ SC group, 7 experienced a clinical response (complete in 67% and partial in 16%). Among the ABA group, 10 patients (62%) achieved either complete (5 patients) or partial (5) response, respectively.*

After 12 months of therapy, 100% of patients in TCZ groups, both IV and SC, and 7 (43%) of ABA group were receiving doses of oral prednisone not exceeding 7.5 mg/day as maintenance.

Conclusion. *Both TCZ and ABA can be proposed as an effective therapeutic option in GCA with relevant inflammatory symptoms. ABA can be considered in the patient with absolute or relative or contraindications to TCZ.*

Introduction

Giant cell arteritis (GCA) belongs to a group of immune-mediated diseases affecting vessels of large size. It is considered a rare disease, but among the primary systemic vasculitis is the most prevalent (1, 2), and is characterised by high morbidity and mortality. In 1932, Horton *et al*. described the picture of a patient suffering from blindness, necrosis of the tongue, and mandibular claudication that they referred to a new clinical entity (3), the characteristic vessel wall infiltration by T lymphocytes and macrophages, with giant cells. It is histologically characterised by intimal hyperplasia, granulomatous lesions, and the disruption of of the elastic fibres (4). GCA mainly affects people over 50 years. The prevalence is greater in Scandinavia and North American than in South Europe, and black people are only occasionally affected. Geographical differences and occasional family clustering suggest a role for either environmental or infectious or genetic factors (2). A genetic predisposition in subjects with the HLA-DRB1*04 allele is recognised (5).

The histologic changes of GCA are especially relevant in temporal artery, a traditional milestone of diagnosis. However, there is a marked heterogeneity in histopathology findings in biopsy samples from different patients. Only half of the positive biopsies show multinucleated giant cells associated with granulomatous infiltrates, including CD41 T-cells and macrophages detected at the intima-media junction. In the other cases, the histopatology findings are characterised by lympho-mononuclear-infiltrates with panarteritis features, occasionally including granulocytes in the absencee of giant cells. A minority of the cases present with periadventitial vessels and/or vasa vasorum inflammation (6). Of special clinical importance, arterial wall thickening with partial or complete occlusion of the lumen (with ischaemic sequaele) can lead to anterior ischaemic optic neuropathy (7).

Therapy has rapidly progressed in these years, achieving prolonged survival and, occasionally, definitive healings. Therapy of CGA has been centered on the use of glucocorticoids (GCs) (8) with immunosuppressive agents, *e.g.* methotrexate (MTX), considered as GCs-sparing therapy or in cases of refractory/resistant cases. Nevertheless, results in terms of efficacy have not been well established (8). While numerous biologic agents have been proposed over the last decades to control GCA, the recombinant humanised anti-IL-6 receptor antibody, tocilizumab (TCZ), is the sole avaialbe biologic agent currently approved for this indication. It proved to be effective in improving clinical manifestations, having a GCs-sparing effect and reducing the rate of relapses both in clinical trials and in real-life studies (9-11).

Some data suggest a possible role for abatacept (ABA), a fusion protein composed of the Fc region of the immunoglobulin IgG1 and the extracellular domain of CTLA-4. Some data showed that inappropriate activation, development, and overexpression of antigen-presenting adventitial dendritic cells (11) are involved in the early stages of the pathogenis of GCA. These cells create an ideal environment for microbial pathogens via the action of toll-like receptors (TLRs). Due to their vessel-specifcity, TLR profiles might justify the typical vessel involment charaterising GCA (12).

In order to activate T cell, the antigen-presenting cell must present two signals: the MHC complexed with the antigen, and the co-signaling of CD80 or CD86 molecule. Binding the CD80 and CD86 molecule, ABA inihibits the second signal. In randomised controlled trials (RCT), ABA proved to be significantly more effective compared to placebo for the management of GCA. In the *intent-to-treat analysis* of the 41 patients randomised to receive ABA (20 patients) or placebo (20 patients) the relapse-free survival at 12 months was higher for ABA than placebo, and the median duration of remission significantly prolonged (13).

The present study aimed at evaluating the efficacy of ABA compared to TCZ, assumed as a gold standard biologic treatment.

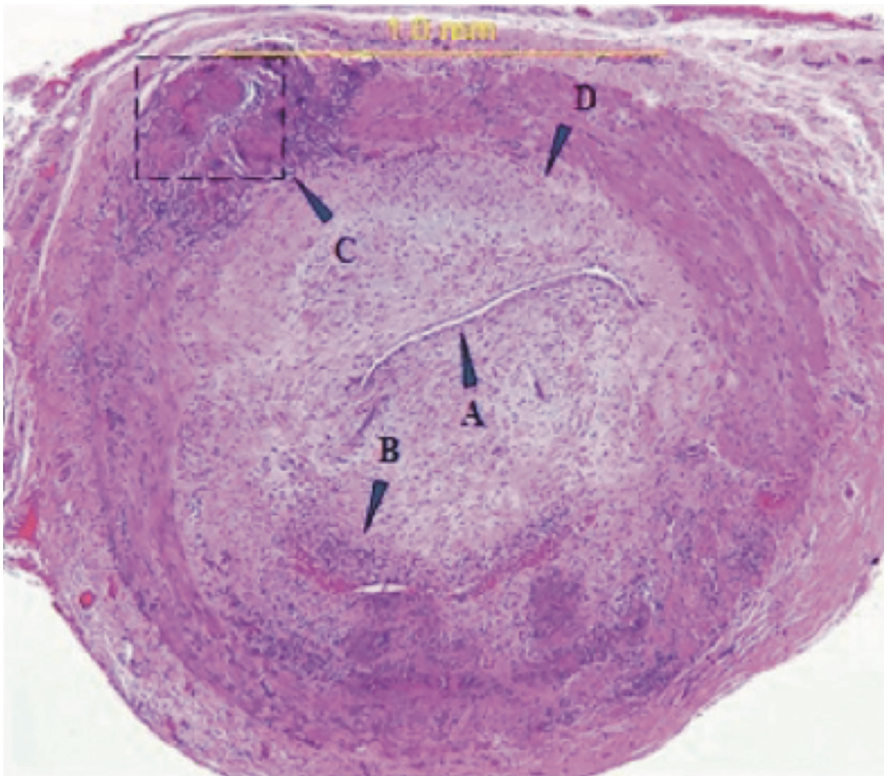

Fig. 1. Simplifying histological findings in temporal artery biopsy from one patient involved in the study. **A**: vessel lumen; **B**: lymphocyte and monocyte infiltrates; **C**: granulomatous lesion; **D**: intimal hyperplasia.

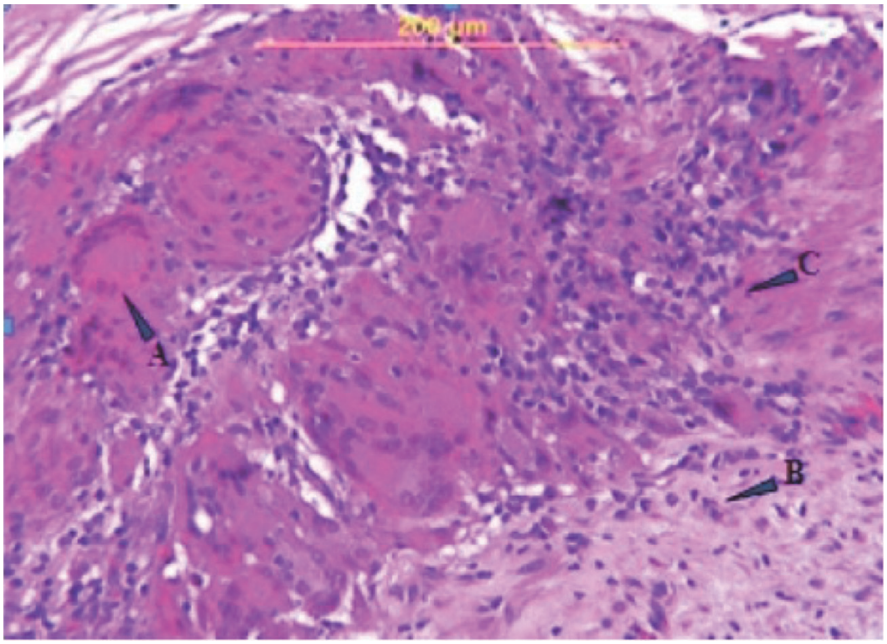

Fig. 2. Magnification of the granulomatous lesion. A: giant cell; B: eosinophils; C: lymphocyte and monocyte infiltration.

Methods

Data from 33 GCA consecutive patients recruited at the San Giovanni Bosco Hub Hospital in Turin (north-west Italy) between 2016 and 2018 were prospectively collected. Diagnosis was based on clinical and histological ground, each patient having a temporal artery biopsy-proven diagnosis (Figs.

1 and 2). Odd patients (from 1 to 33) were assigned to TCZ, given either intravenously (IV) (8 mg/kg/month), #8 cases, or subcutaneously (SC) (162 mg/week), #9, based on the patient's preference. ABA was administered SC at the dose of 125 mg/week in 16 even patients (from 2 to 32). Biological therapies were prescribed in addition to oral prednisone 50 mg/day for 2 weeks (tapered to 20 mg/day by the end of the 3rd month and then slowly tapered until discontinuation within 6 months). In patients who were receiving mycophenolate mofetil (MMF) or MTX (Table I), biological agents were started after conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) discontinuation.

Table I summarises the patients' main characteristics.

Complete response to treatment after 12 months of therapy was defined, based on clinical (disappearance of symptoms), imaging (ultrasound reversal of abnormalities) and serological [normalisation of erythrocyte sedimentation rate (ESR) and C reactive protein (CRP)] ground. Partial response was defined as a substantial amelioration of clinical manifestations and serological parameters with persistent ultrasound abnormalities at one-year.

Efficacy and safety outcomes were assessed every three months or in case of clinical changes.

Eleven out of 16 cases treated wit ABA could be examined for the presence of CD80 staining.

Statistical analysis

For the comparison of variables at baseline and follow-up, Student's t-test was used for normally distributed parameters and the non-parametric Mann-Whitney test for non-normally distributed parameters. For these analyses, the SPSS (IBM Corporation, NY, USA) software was used. $p<0.05$ was considered statistically significant.

Table I. Characteristics of GCA patients included in the study.

	Total number of patients (33)	%
Demographic characteristics		
Female/male	21/12	
Age (years) (mean, SD)	73.6 ± 8.7	
Clinical characteristics at the onset of GCA		
Fever (n)	12	36.4
Fatigue (n)	18	54.5
Headache (n)	28	84.8
Scalp tenderness (n)	8	24.2
Jaw claudication (n)	15	45.4
Vision loss (n)	16	48.5
Polymyalgia rheumatica (n)	11	33.3
Diagnosis		
Biopsy-proven	27/32	84.4
Positron emission tomography positivity	12/29	41.4
Eco-colour-Doppler positivity	30/31	97.0
GC therapy		
Previous methylprednisolone pulses (n)	7	21.2
Oral prednisone (n)	33	100.0
Dose of oral prednisone (mg/day) (mean, SD)	49.7 ± 15.1	
Previous immunosuppressive therapies		
Methotrexate (n)	11	33.3
mean dose (mg/week) (mean, SD)	15.6 ± 1.7	
Mycophenolate (n)	11	33.3
mean dose (mg/day) (mean, SD)	2.2 ± 0.4	

Table II. Dose of GCs at baseline, 6 months, and 12 months as well as the number of switches due to lack of efficacy.

	TCZ=17	ABA=16	*p*
Mean GCs dose at baseline	50 mg/day	50 mg/day	NS
Mean GCs dose at 6 months	0 mg/day	2.5 mg/day (min 0-max 10)	NS
N° of patients on PDN >7.5 mg/day	0	4	0.0445
Mean GCs dose at 12 months	0.8 mg/day	5.6 mg/day (min 0-max 10)	NS
N° of patients on PDN >7.5 mg/day	0	9	0.0003
N° of switch for lack of efficacy	0	4	0.0445

TCZ: tocilizumab; ABA: abatacept; GCs: glucocorticoids; PDN: prednisone.

Results

This prospective study included 33 GCA patients [mean age 74 (range 85-57), females 63%, mean follow-up from GCA diagnosis 44.4±33.5 months)].

A single biologic agent was administered in 28 patients out of 33 (85%) (8 TCZ IV, 9 TCZ SC, and 16 ABA). Five patients (15%) needed a therapeutic switch (one patient from TCZ to ABA for referred general malaise the day after the drug administration, and 4 patients from ABA to TCZ for lack of efficacy).

No difference was observed in terms of baseline disease symptoms, vessel involvement, sex, age, comorbidities when comparing the TCZ and ABA groups.

In 17 patients, biological treatment (8 TCZ and 9 with ABA) was started because of a disease relapse despite ongoing therapy.

Among the TCZ IV group, all patients experienced a response (57% complete response and 43% partial response). Among the TCZ SC group, 7 experienced a clinical response (complete in 67% and partial in 16%). Among the ABA group, 10 patients (62%) achieved either complete (5 patients) or partial (5 patients) response, respectively.

After 12 months of therapy, 100% of patients in TCZ groups, both IV and SC, and 7 (43%) of ABA group were receiving doses of oral prednisone not exceeding 7.5 mg/day as maintenance (Table II). A significant reduction in inflammatory parameters (CRP and ESR)

was observed after 12 months of therapy with TCZ: TCZ IV group: mean baseline CRP (mg/dl) 3.9±2.3, mean CRP after 12 months of therapy 0.3±0.2 (p<0.01); mean baseline ESR (mm/h) 58.1± 25.6, mean ESR after 12 months 9.5±4.2 (p<0.01); TCZ SC group: mean baseline CRP 4.5±3.8, mean CRP after 12 months 0.2±0.2 (p<0.01); mean baseline ESR 51.9±27, mean ESR after 12 months 6.5±6, p<0.01].

With regard to ABA, mean baseline ESR and CRP were 57.8±35.8 and 3.8±3.1, respectively, and 8.7±7.1 and 0.3±0.2 at 12 months (p<0.01 for both parameters).

Of the 11 cases treated with ABA that could be examined for CD80 staining, 10 were positive. Three of them showed complete remission, 5 had partial remission and 2 were non-responders. The negative case had a complete response. One out of the 5 remaining cases who could not be analysed for CD80 staining had a complete remission.

When compared to standard GCs regimen (8), in patients treated with TCZ, we estimated a median steroid-sparing effect of 30 mg daily in the first month and an overall steroid-sparing effect of 15 mg daily when assessed in 12 months.

No significant difference in outcomes was observed when comparing relapsing patients with newly diagnosed CGA. No significant side effect related to biological administration was recorded.

Discussion

GCA is considered the most prevalent vasculitis in elderly people, especially in western countries. It is characterised by severe mortality and morbility, including permanent visual loss.

The therapy for GCA has been centered on GCs. While the use of GCs has been associated to an excellent rate of response, yet relapses are frequent when GCs are tapered and their prolonged use is associated to metabolic and infective complications (14), paving the way for the search of alternative options for the management of GCA. Among the conventional immunosuppressant agents, MTX has been the most commonly reported, especially in cases of refractory GCA, albeit with only modest results.

The positive results of RCTs showing the efficacy of TCZ in both newly diagnosed and in relapsing cases of GCA (9-11) led to the approval of its use for the management of GCA. Results for RCTs were mirrored by those coming from real-life experience, further supporting the inclusion of TCZ in the therapeutic harmamentarium for the management of GCA, especially in refractory cases. ABA was proven to be more effective than placebo in treating GCA patients (13).

This is the first study that has compared the effectiveness of these two biologic agents in treating GCA.

In our experience, both TCZ and ABA (though at a lesser extent) showed significant sparing effects on steroid dose, and proved to limit the risk of disease re-exacerbation. Compared to ABA, TCZ showed to be more effective both in inducing a clinical response and sparing steroids.

CD80 staining revealed to be almost invariably positive in biopsies of temporal artery. A positive staining cannot be used as a predictor of clinical response to ABA. A negative staining does not affect response to ABA.

However, we acknowledge that our study is limited by the lack of randomisation and the relatively small sample size. Larger randomised trials are needed to address this topic in a definite way. Similarly, some degree of heterogeneity in previous treatment exists when referring to the use of steroids.

Both TCZ and ABA can be proposed as an effective therapeutic option in cases of GCA with relevant inflammatory symptoms.

Although significant, in this study the effect of ABA seemed to be moderate and arose concerns about its position as a first- or second-line therapeutic approach.

While further studies are still needed for including ABA in the standard treatment of severe cases of GCA, a putative role can be envisaged in the patients with absolute or relative or contraindications to TCZ, such as those with diverticulitis, hepatopathies, and hypercolesterolaemia.

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