The Journal of Rheumatology 2021;xx:xxxx
doi:10.3899/jrheum.210455
First Release September 15 2021

The Journal of Rheumatology

Letter

Abatacept as Adjunctive Therapy in Refractory Polymyalgia Rheumatica

To the Editor:

Glucocorticoids (GCs) are the mainstay of treatment for patients with polymyalgia rheumatica (PMR).[1] Despite their efficacy, GCs are associated with well-known adverse events and a substantial proportion of patients with PMR do not respond adequately, or are refractory, to initial GC treatment. GC-sparing agents in PMR are limited to methotrexate (MTX).[1] More recently, favorable results were reported with tocilizumab (TCZ), an interleukin (IL)-6 receptor blocking agent, in patients with steroid-dependent/resistant PMR.[2,3] The results of a randomized clinical trial of abatacept (ABA) suggested that this agent could be an adjunctive therapy in patients with giant cell arteritis (GCA).[4] In this study, we aimed to evaluate the efficacy of ABA in patients with isolated PMR and who had GC-refractory disease.

According to the French Regulatory Authority for clinical studies, prospective and retrospective studies consisting of observational analyses only do not need to obtain approval from ethics committees. The cases reported in this paper and this study design received no statement of opposition from the local ethics committee. As this study is a case series, written informed consent was not required due to its retrospective design.

A call for observations of all cases of patients with PMR who received at least 1 injection (intravenously or subcutaneously) of ABA was sent to the members of a specialized French rheumatism and inflammation network (Club Rhumatismes et Inflammation: www.cri-net.com; including rheumatologists and specialists in internal medicine). Patients had to satisfy the European Alliance of Associations for Rheumatology (EULAR)/American College of Rheumatology criteria for PMR[5] and have isolated PMR, without symptoms or clinical signs of GCA. Over a 12-month period (from January 2019 to January 2020), 4 cases were identified: 2 men and 2 women (Table 1). The median (range) disease duration was 19 (7–48) months and the median duration of GC treatment before starting ABA was 42 (10–72) months. All patients required GC at a daily dose of 14 (10–20) mg. Before ABA administration, they had all received MTX treatment (17.5 [10–25] mg/week); 2 patients had been treated by an IL-6 receptor inhibitor without improvement. One patient had a contraindication to TCZ (previous history of diverticulitis), whereas the second did not accept this drug for fear of side effects. ABA treatment duration ranged from 3 to 18 months. Two patients (patients 3 and 4) responded to the treatment with a progressive decline in PMR activity score (patient 4), and/or tapering of GC dosage over a 12-month follow-up period (patients 3 and 4). However, for these 2 patients, prednisone was not completely ceased (Table 1). There was no improvement in the other 2 patients. C-reactive protein levels decreased for 1 responder. Safety was excellent without any adverse events for all the patients. ABA was still maintained after 12 months for 1 responder, whereas it was discontinued in the second patient due to progressive improvement. Among the nonresponders, 1 patient was switched to TCZ and the second still received high GC dosage.

We observed that ABA may improve disease activity and may have a steroid-sparing effect in certain patients with PMR. MTX is strongly recommended by the EULAR group as a steroid-sparing drug, especially in patients with high risk of relapse.[1] However, this conventional synthetic disease-modifying antirheumatic drug is generally associated with moderate response and overall, the reported benefits are usually small. There are numerous reports of the benefit of IL-6 blockade in PMR using TCZ. However, results stem from limited series of patients[2,3] or an open-label clinical trial.[6] In addition, TCZ is not currently approved in PMR, and results of a randomized clinical trial are still pending.[7] It is now established that Th17 lymphocytes are implicated in the pathogenesis of PMR and GCA.[8] Together with experimental data, it is thought that PMR and GCA are antigen-driven diseases in which not only activated T lymphocytes but also macrophages and dendritic cells play a critical role. This led to the initiation of a randomized trial evaluating ABA, a costimulatory inhibitor, in patients with GCA.[4] The results of that trial showed that in patients with GCA who achieved remission under GC and ABA, the maintenance of ABA, on top of standardized prednisone taper, significantly reduced the risk of relapse compared to patients randomized to receive placebo and GC. All in all, ABA would appear to have therapeutic potential in PMR that warrants further investigation. The results in our series are mixed, with an improvement in disease activity in 2 patients, and drug failure for the 2 others. Based on these findings, ABA may be considered as a potential adjunctive therapy in selected or difficult cases of PMR. It may also be considered as an alternative to an IL-6 blocking agent, especially when this drug class has failed or is contraindicated. A clinical trial is currently ongoing in patients with early-onset PMR, aiming to evaluate the ability of ABA alone to improve PMR and its capacity to provide a steroid-sparing effect after this induction treatment.[9]

Eric Toussirot[1], MD, PhD
Martin Michaud[2], MD
Daniel Wendling[3], MD, PhD
Valérie Devauchelle[4], MD, PhD
[1]INSERM CIC-1431 Centre Investigation Clinique, Fédération Hospitalo-Universitaire INCREASE, and Rhumatologie, CHU de Besançon, and Département de Thérapeutique, and INSERM UMR1098 Relations Hôte Greffon Tumeurs, ingénierie cellulaire et génique, Université de Bourgogne Franche-Comté, Besançon;
[2]Médecine Interne, Hôpital Joseph Ducuing, Toulouse;
[3]Rhumatologie, CHU de Besançon, Besançon;

Table 1. Clinical features, therapies, and outcomes of patients with isolated PMR treated by ABA.

Patient	Age, yrs/sex	GC Therapy Duration Before Initiating ABA, months	Previous csDMARD Before ABA	Previous bDMARD Before ABA	ABA Treatment	PMR-AS				CRP, mg/L				GC Dosage, mg		ABA Duration, months
						M0	M3	M6	M12	M0	M3	M6	M12	M0	At Last ABA Administration	
1	50/F	24	MTX	Sarilumab (3 months)	125 mg SC/QW	20	20	21	NA	5	8.6	8.4	NA	20	80	6 ABA stopped
2	59/M	10	MTX	–	125 mg SC/QW	31.1	30.5	NA	NA	21	25	NA	NA	12	6	3 ABA stopped
3	66/F	60	MTX	–	750 mg IV/QM	10.7	8.3	5	13	37.2	22.7	22	22	10	3	18 ABA ongoing
4	68/M	72	MTX	TCZ (6 months)	125 mg SC/QW	22	17.2	12	12	1.2	3.3	3.5	3	16	5	18 ABA stopped

ABA: abatacept; AS: activity score; bDMARD: biologic disease-modifying antirheumatic drug; CRP: C-reactive protein; csDMARD: conventional synthetic disease-modifying antirheumatic drug; GC: glucocorticoids; IV: intravenous; M: month; MTX: methotrexate; NA: not available; PMR: polymyalgia rheumatica; QM: once a month; QW: once a week; SC: subcutaneously; TCZ: tocilizumab.

[4]Rhumatologie, CHU de Brest, and INSERM 1227 LBAI Université de Bretagne Occidentale, Centre de Référence des Maladies Auto-Immunes Rares de l'Adulte, Brest, France.

The authors declare no conflicts of interest relevant to this article.

Address correspondence to Prof. E. Toussirot, INSERM CIC-1431 Centre d'Investigation Clinique, CHU de Besançon, 25000 Besançon, France. Email: etoussirot@chu-besancon.fr.

REFERENCES

1. Dejaco C, Singh YP, Perel P, Hutchings A, Camellino D, Mackie S, et al. 2015 Recommendations for the management of polymyalgia rheumatica: a European League Against Rheumatism/American College of Rheumatology collaborative initiative. Ann Rheum Dis 2015;74:1799-807.
2. Toussirot É, Martin A, Soubrier M, Redeker S, Régent A. Rapid and sustained response to tocilizumab in patients with polymyalgia rheumatica resistant or intolerant to glucocorticoids: a multicenter open-label study. J Rheumatol 2016;43:249-50.
3. Lally L, Forbess L, Hatzis C, Spiera R. Brief report: a prospective open-label phase IIa trial of tocilizumab in the treatment of polymyalgia rheumatica. Arthritis Rheumatol 2016;68:2550-4.
4. Langford CA, Cuthbertson D, Ytterberg SR, Khalidi N, Monach PA, Carette S, et al; Vasculitis Clinical Research Consortium. A randomized, double-blind trial of abatacept (CTLA-4Ig) for the treatment of giant cell arteritis. Arthritis Rheumatol 2017; 69:837-45.
5. Dasgupta B, Cimmino MA, Maradit-Kremers H, Schmidt WA, Schirmer M, Salvarani C, et al. 2012 provisional classification criteria for polymyalgia rheumatica: a European League Against Rheumatism/American College of Rheumatology collaborative initiative. Ann Rheum Dis 2012;71:484-92.
6. Devauchelle-Pensec V, Berthelot JM, Cornec D, Renaudineau Y, Marhadour T, Jousse-Joulin S, et al. Efficacy of first-line tocilizumab therapy in early polymyalgia rheumatica: a prospective longitudinal study. Ann Rheum Dis 2016;75:1506-10.
7. ClinicalTrials.gov. U.S. National Library of Medicine. Safety and efficacy of tocilizumab versus placebo in polymyalgia rheumatic with glucocorticoid dependence. SEMAPHORE. Identifier NCT02908217. [Internet. Accessed July 16, 2021.] Available from: https://clinicaltrials.gov/ct2/show/NCT02908217
8. Samson M, Audia S, Fraszczak J, Trad M, Ornetti P, Lakomy D, et al. Th1 and Th17 lymphocytes expressing CD161 are implicated in giant cell arteritis and polymyalgia rheumatic pathogenesis. Arthritis Rheum 2012;64:3788-98.
9. ClinicalTrials.gov. U.S. National Library of Medicine. Abatacept in early onset polymyalgia rheumatica. ALORS Study. Identifier NCT03632187. [Internet. Accessed July 16, 2021.] Available from: https://clinicaltrials.gov/ct2/show/NCT03632187