Switching from Intravenous to Subcutaneous Formulation of Abatacept: A Single-center Italian Experience on Efficacy and Safety

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ABSTRACT. ***Objective.*** Subcutaneous (SC) abatacept (ABA) is comparable to intravenous (IV) formulation in terms of efficacy and safety profile. Our work analyzed the switch to SC formulation from IV administration in patients with rheumatoid arthritis.

Methods. Fifty-one patients treated with SC ABA were included. Clinical data were obtained from clinical charts.

Results. Fourteen patients relapsed and needed to return to the IV administration. Neither clinical and laboratory features nor the previous therapies were identified as risk factors for SC formulation inefficacy. Disease activity decreased after the return to IV infusions.

Conclusion. SC ABA showed a risk of relapse in 27% of cases. The reinsertion of the IV administration quickly reinstated disease control. (J Rheumatol First Release Dec 15 2014; doi:10.3899/jrheum.141042)

Key Indexing Terms:

RHEUMATOID ARTHRITIS | THERAPY | ABATACEPT
SUBCUTANEOUS FORMULATION | EFFICACY | SAFETY

Abatacept (ABA) is a selective T cell costimulation modulator indicated for the treatment of moderately to severely active rheumatoid arthritis (RA) in adults. In Italy, the drug has been available since 2008 as an intravenous (IV) formulation, administered once a month in a weight-tiered dosing regimen. Its efficacy and safety have been largely demonstrated in a wide range of patient populations, with and without the association of disease-modifying antirheumatic drugs (DMARD)[1,2,3].

Since August 2013, in Italy, ABA has also been available in a subcutaneous (SC) formulation, consisting of a fixed dose of 125 mg of the drug, administered once weekly.

Six clinical trials have been performed with patients treated with the SC formulation (phase II dose-finding study, ACQUIRE[4], ALLOW[5], ACCOMPANY[6], ATTUNE[7], and AMPLE[8]) and they all seemed to demonstrate an efficacy and a safety profile comparable to that obtained with the classic IV administration[9,10,11]. In particular, it has been demonstrated that the fixed dose of the drug achieved a serum concentration comparable to that reached with the weight-tiered IV regimen, eliciting therapeutic concentrations in > 90% of the patients.

Only the ATTUNE study[7] analyzed the switch from longterm IV to SC ABA in detail, and it showed no problems in terms of efficacy, safety, and immunogenicity. In the study, mean disease activity and physical function scores achieved during longterm IV administration were maintained with the SC treatment.

The aim of our work was to confirm the results of the ATTUNE study[7] in a real-world setting and to compare them with the clinical response of a series of patients with RA who were previously treated with monthly IV infusions and then converted to the SC formulation of ABA.

MATERIALS AND METHODS

In our study, we included 51 patients with RA[12] previously treated with monthly IV infusions of ABA and then converted to the SC formulation of the drug from October 2013 to February 2014. The selection of patients for the switch was based on their subjective preference for the means of administration, and were divided into 2 groups, depending on their need to return to the IV formulation at the appearance of a disease flare. A disease flare was defined as a worsening in disease activity as shown by an increase in the Disease Activity Score at 28 joints (DAS28).

The main clinical and serological features of the 2 groups were compared using the chi-square, the Student t test, or the Mann-Whitney U test when appropriate.

RESULTS

Fifty-one patients, representing 51% of all cases previously receiving IV ABA therapy in our unit, were included in our study: 11 men (21.6%) and 40 women (88.4%).

No patient received the IV "loading dose". Thirty-seven patients (72.5%) took oral steroid (mean dose in prednisone equivalents of 19.2 mg/week, SD 16.1). No significant difference was observed between the dosage taken by the group of patients who relapsed and those who maintained the SC formulation (20.7 vs 18.31 mg/week, p = 0.53).

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Thirty-nine patients (76.5%) received methotrexate (in 7 cases in association with hydroxychloroquine) while 3 patients received other DMARD (1 cyclosporine, 1 leflunomide, and 1 sulfasalazine). Five patients (9.8%) received no immunosuppressive therapy: 1 experienced an arthritic flare and returned to IV infusions while 4 maintained the SC formulation. No patient changed or modified DMARD therapy in the 6 months prior to the introduction of the SC formulation or during the treatment.

Fourteen patients (27.5%) needed to return to IV administration after a mean of 11 injections (range 4–30): 13 patients experienced a disease reactivation (mean DAS28 3.96 vs 2.19, $p = 0.002$), while 1 discontinued the SC formulation because of related adverse effects (headache and nausea). Thirty-seven patients (72.5%) continued the SC administration to date with a good disease control and no adverse reactions.

The main features compared between the 2 groups of patients are summarized in Table 1. The ABA dosage administered, evaluated in mg/kg/month, was significantly lower with the SC formulation than with the IV infusion ($p < 0.001$) both in the group of patients who maintained the SC formulation (mean 7.96 vs 9.57 mg/kg/mo) and in those who returned to IV infusions (mean 7.39 vs 9.39 mg/kg/mo).

No significant differences were observed between the dosage assumed by patients who relapsed and those who continued the new formulation ($p = 0.49$).

In patients who experienced an arthritis flare, disease activity decreased after returning to the IV administration of the drug (mean DAS28 3.96 vs 2.57, $p = 0.007$), after a mean of 37.5 days (SD 13.6). No cutaneous reactions in the site of injection or severe adverse effects (SAE) were registered.

DISCUSSION

ABA is a drug widely used in RA, and the commercialization of the SC formulation, which occurred in Italy in August 2013, was welcomed by both medical staff and patients as a comfortable delivery system that freed patients from visiting the hospital for monthly infusions.

The main difference between the 2 formulations is the cumulative dosage administered monthly, which was previously weight-tiered and has become fixed with the SC injections.

The doubts expressed about a possible underdosing and a consequent inefficacy in patients weighing > 60 kg (previously receiving 750 mg/month, and with the SC formulation, only 500 mg/month) seemed dispelled by both the phase II dose-finding trial (NCT00254293), which demonstrated equal efficacy in all the subgroups of dosage tested (75–200 mg/week), and the ACQUIRE study[4], which confirmed the non-inferiority of the 2 formulations despite the different dosage.

The switch from the IV formulation to the SC formulation had been analyzed in detail, considering safety, efficacy, and immunogenicity, by the ATTUNE study[7], which showed that all the analyzed variables were satisfactory.

Currently, no data regarding the efficacy and safety of the new formulation in clinical practice are available because the drug has been on the market for little more than a year.

In our experience, the transition to the SC formulation

Table 1. Comparison between the clinical and serological features of patients who did and did not return to IV administration of ABA after the switch to SC administration. Values are n (%) unless otherwise specified. None of the p values were significant.

Analyzed Features	Patients Who Maintained the SC Formulation, n = 37 (72.5%)	Patients Who Returned to IV Infusions, n = 14 (27.5%)
Mean age, yrs (SD)	59.6 (14.2)	53.8 (11.3)
Positivity for RF	34/37 (91.9)*	12/13 (92.3)*
Positivity for ACPA	21/29 (72.4)*	10/13 (76.9)*
Mean disease duration, mos (SD)	136.3 (116.5)	132.8 (95.4)
Previous IV therapy duration, mos (SD)	21.4 (18.5)	16.6 (17.4)
BMI, mean (SD)	24.6 (4.7)	25.8 (5.1)
Smokers	4 (10.8)	3 (21.4)
DMARD in association	33 (89.2)	10 (71.4)
Previous use of biological agents	25 (65.8)	8 (72.7)
No. different biological agents used in the past, mean (SD)	1.6 (1.6)	1.9 (2.2)
ABA as first biological agent	12 (32.4)	4 (28.6)
Remission of the disease at SC therapy start, DAS28 < 2.6	29 (78.4)	8 (57.1)
DAS28 at SC therapy start, mean (SD)	2 (0.96)	2.19 (0.98)

* Percentage based on available data. IV: intravenous; ABA: abatacept; SC: subcutaneous; RF: rheumatoid factor; ACPA: anticitrullinated protein antibodies; BMI: body mass index; DMARD: disease-modifying antirheumatic drug; DAS28: Disease Activity Score at 28 joints.

was welcomed by more than half of the patients treated with ABA in our unit, but in about one-third of the cases it was necessary to return to the IV administration because of the onset of an arthritic flare.

The analysis of the main factors related to an articular recurrence after the beginning of the SC injections, first of all the patient body mass index, did not reveal clear risk factors predictive for a switch failure.

It must be emphasized that with the SC formulation, patients received significantly less drug pro-kg/month compared with the IV infusion. This was true for those who showed no problem with the change of formulation and experienced no disease flares as well as for those who did.

In most cases, both patient groups changed the means of administration while the underlying disease was not active. The group that relapsed showed a slightly lower, albeit nonsignificant, percentage of remission.

Nevertheless, a higher percentage of our patients experienced a lack of efficacy of the SC administration compared to that reported in previous studies[4,7]. One of the reasons could be the different number of subjects receiving ABA in combination with DMARD (84%), especially in nonresponders to the SC administration (71%), in our study compared to the ACQUIRE trial (99.6%)[13]. Nonetheless, comparable clinical and functional improvements were shown for SC ABA with concomitant methotrexate versus SC ABA monotherapy in the ACCOMPANY study[6].

All patients except 1, who required a change of biological agent, showed a quick return to clinical remission after 1 to 2 IV infusions, demonstrating that an eventual failure of the SC formulation does not compromise the efficacy of the ABA therapy itself, which provided good disease control once reintroduced through the traditional means of administration.

This consideration can reassure the clinician who decides to propose the formulation change. To date, no risk factors have been identified that may help in pre-selection of patients who will benefit from the SC formulation and exclusion of candidates for whom the switch would not work.

Data about the safety of SC ABA shown in clinical trials have been confirmed in real-world settings.

Only 1 patient preferred to return to the IV administration because of the onset of minor side effects, attributable to the SC formulation. No SAE or cutaneous manifestations of note were recorded at the injection site.

The new formulation of ABA is a step forward in the care of patients with RA, who are increasingly young and professionally active. The SC formulation ensures them a considerable therapeutic independence while maintaining a high safety profile.

In a preliminary analysis, the efficacy did not seem exactly comparable to that guaranteed by the IV formulation of the drug, at least in some patients. Such consideration should not limit physicians in proposing to their patients the new SC formulation. If an arthritis flare manifests, the reinsertion of the traditional IV administration seems to quickly reinstate disease control in almost all cases.

However, ours is only a small case series and does not allow for definitive conclusions. Further research with a greater number of patients will be helpful in confirming this trend and to better understand the phenomenon.

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