Effects of Abatacept on T-Lymphocyte Sub-populations and Immunoglobulins in Patients Affected by Rheumatoid Arthritis

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ABSTRACT: **Background:** Abatacept acts as a co-stimulation modulator preventing activation of T cells. Although it is approved for the treatment of rheumatoid arthritis (RA), its effects on adaptive immune response have not been fully elucidated.

Objectives: To observe in a cohort study, based on a clinical practice setting, the variation of peripheral blood T cells, immunoglobulin levels, and autoantibodies in the serum of RA patients during abatacept therapy.

Methods: Our study comprised 48 RA patients treated with abatacept. All clinical data were collected at baseline and after 3 months of treatment. Clinical and laboratory tests included erythrocyte sedimentation rate, C-reactive protein, 28-joint disease activity score, RF, anti-citrullinated protein antibody, total immunoglobulins, immunoglobulin A (IgA), immunoglobulin G (IgG), immunoglobulin M (IgM), and lymphocyte sub-population.

Results: Total immunoglobulin serum levels significantly decreased after 3 months of treatment and correlated positively with disease activity both at baseline and after 3 months of abatacept treatment. A reduction of serum IgM, IgG, IgA and RF was also demonstrated. The absolute number and percentage of cytotoxic (CD8+) T cells significantly decreased after 3 months of abatacept treatment, in particular the percentage of cytotoxic (CD8+) T cells significantly decreased only in patients responding to the treatment.

Conclusions: Our results highlight a different role of abatacept in the modulation of the adaptive immune response in RA by the reduction of polyclonal B-cell activation and cytotoxic T cells.

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KEY WORDS: biological disease modifying antirheumatic drug (DMARD), T cells, rheumatoid arthritis (RA), abatacept, cytotoxic T-lymphocyte-associated protein 4 (CTLA-4)

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by synovitis and bone damage in the presence of autoantibodies, which can result in loss of function and reduction of quality of life as well as an increase in morbidity and mortality [1,2]. A dysregulation of the innate and adaptive immune system, under the influence of several genes [3,4], results in an inflammatory process targeted by conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs), steroids, and biological agents [5,6]. One of the biological agents is abatacept, a fully human, recombinant, soluble fusion protein comprising the extracellular domain of human cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and a fragment of the Fc portion of human IgG1 [7]. Abatacept is an effective treatment for patients after failure of an anti-tumor necrosis factor (TNF) agent [8]. Abatacept acts as a co-stimulation modulator blocking interaction between CD80/CD86 on antigen presenting cells (APCs) and CD28 on T cells. CD28 is mainly expressed by CD4+ T cells and by more than 50% of CD8+ T cells [9]. Therefore, abatacept may prevent activation of both CD4+ and CD8+ T cells [10]. Although the role of abatacept on CD4+ T cells has been largely investigated by both in vivo and in vitro studies with murine models of arthritis [11], only scant evidence shows the inhibition of CD8+ T cells [12]. A study of 71 patients showed that patients who smoke and have a lower proportion of terminally differentiated effector memory CD8+ T cells at baseline were more likely to discontinue abatacept therapy, mainly because of inefficacy [13].

B cells may act as APCs expressing CD80/CD86 and, in the context of the T-B crosstalk, produce immunoglobulins and autoantibodies [10]. Therefore, abatacept prevents activation of T cells and leads to impaired B-cell activation [10]. However, little evidence is available on the effect of abatacept on immunoglobulins and autoantibodies in RA [14].

The aim of this study was to analyze the variations of peripheral blood T cells, immunoglobulin levels, and autoantibodies in a cohort of RA patients during abatacept therapy.

PATIENTS AND METHODS

In our cohort study we enrolled RA patients who started abatacept therapy at the Rheumatology, Allergology and Clinical Immunology Clinic, University of Rome Tor Vergata, Rome, Italy (November 2010–December 2016). Inclusion criteria were:

RA diagnosis according to the 2010 European League Against Rheumatism (EULAR) / American College of Rheumatology (ACR) revised criteria [15], age ≥ 18 years old, high or moderate disease activity based on 28-joint disease activity score (DAS28; four variables, erythrocyte sedimentation rate [ESR]-based) [16], failure of treatment with at least one csDMARD and/or a biological DMARD. Exclusion criteria were: recent infection (< 3 months), HIV infection, history of cancer, major organ dysfunction or pregnancy. Patients were treated with abatacept 10mg/kg administered intravenously at 2 and 4 weeks after the first infusion and every 4 weeks thereafter. Concomitant csDMARDs and steroids were permitted according to guidelines and clinical efficacy and tolerance. Clinical data were collected at baseline (T0) and after 3 months of treatment (T3). A disease duration < 12 months was defined as early arthritis, while RA disease duration ≥ 12 months was defined as established arthritis [17]. Laboratory assays included: ESR (normal value < 20 mm/h), C-reactive protein (CRP; normal value < 3 mg/L, using nephelometric methods), RF (normal value < 20 IU/L), anti-citrullinated protein antibody (ACPA) (normal value < 20 IU/L), lymphocytes subpopulations, serum proteins electrophoresis, immunoglobulins IgA, IgG and IgM (mg/dl). Electrophoresis of serum proteins was executed trough capillary method. RF-IgG, IgA, IgG and IgM were quantified by nephelometry using Immage 800® (Beckman Coulter, Fullerton, CA, USA) according to the manufacturer's guidelines. ACPA were quantified by second generation commercial enzyme-linked immunosorbent assay (ELISA) kit (QUANTA Lite® CCP IgG, Medical Technology Promedt Consulting, St. Ingbert, Germany). Patients were considered seropositive when they showed a positivity for either RF or ACPA. Immunophenotypic analysis of lymphocytes subpopulations CD3+CD45+, CD3+CD4+CD45+ T cells, CD3+CD8+CD45+ T cells, CD19+CD45+ B cells was performed as previously described [18]. Disease activity and response to treatment were measured by DAS28. A score < 2.6 was considered as remission, > 2.6 and < 3.2 was considered as low disease activity (LDA), > 3.2 and < 5.1 was considered moderate disease activity (MDA), and > 5.1 was considered high disease activity (HDA) [16]. EULAR response criteria were used to classify patients as responders and non-responders [19]. Written informed consent was obtained from patients according to the Declaration of Helsinki (updated 2008) and the study was approved by the scientific ethics committee of the University of Tor Vergata, Rome, Italy.

STATISTICAL ANALYSIS

All data were stored on a server and statistical analyses were performed using GraphPad Prism for Windows, version 6 (GraphPad Software, La Jolla, CA, USA). To test normality of data sets, the D'Agostino-Pearson normality test was used. Normal variables were expressed as mean ± standard deviation. The Wilcoxon and Mann–Whitney tests were used to analyze differences between paired and non-paired data groups, respectively. Fisher's exact test was used to analyze contingency of categorical variables. Pearson's correlation test was used to assess correlations between variables. All statistical tests were two-sided, and $P < 0.05$ was considered significant.

RESULTS

A total of 48 patients were enrolled in this study. RF and ACPA were present in 60.4% (29/48) and 68.7% (33/48) of patients, respectively. DAS28 at baseline was 6.29 ± 1.41 and 83% (40/48) of patients had already failed treatment with at least one biological agent; 70.8% (34/48) of patients received an additional therapy with a csDMARD. Demographic and clinical characteristics of the population at baseline are summarized in Table 1. Changes in clinimetric and laboratory findings are described in Table 2. DAS28 decreased to 3.5 ± 1.45 ($P < 0.0001$) after 3 months of treatment, and the 66% (32/48) of patients gained a good or moderate response. After 3 months of treatment the percentage of CD3+CD8+CD45+ T cells decreased from 26.8% to 17.9% ($P = 0.01$) [Figure 1A] as well as the absolute number of CD3+CD8+CD45+ T cells ($P = 0.03$) [Figure 1B]. Figure

Table 1. Demographic and clinical characteristics of the study population

Patients (n)	48
Gender	40 F, 8 M
Age (years)	62 ± 13
Disease duration (months)	147 ± 115
Early arthritis % (n)	17 (8)
DAS28	6.19 ± 1.41
RF % (n)	60.4 (29)
ACPA % (n)	68.75 (33)
ESR (mm/h)	48 ± 27
CRP (mg/L)	14.4 ± 22.16
csDMARDs % (n)	70.8 (34)
Methotrexate % (n)	43.7 (21)
Leflunomide % (n)	14.5 (7)
Salazopyrin % (n)	6.2 (3)
Prednisone 7.5 mg/die % (n)	33.3 (16)
First bDMARD % (n)	17 (8)
Second bDMARD % (n)	19 (9)
Third bDMARD % (n)	44 (21)
Fourth bDMARD % (n)	19 (9)
Fifth bDMARD % (n)	2 (1)

Data are expressed as mean ± standard deviation unless specified otherwise
DAS28 = 28-joints disease activity score, RF = rheumatoid factor, ACPA - anti-citrullinated peptide antibody, ESR = erythrocyte sedimentation rate, CRP = C-reactive protein, csDMARDs = conventional synthetic disease-modifying antirheumatic drugs, bDMARD = biological disease-modifying antirheumatic drug

Table 2. Modifications of clinimetric and laboratory findings in the study population

Variable	T0	T3	*P* value
DAS28	6.29 ± 1.41	3.5 ± 1.45	‹ 0.0001*
CRP (mg/L)	14.4 ± 22.17	12.74 ± 22.49	0.32
ESR (mm/h)	49 ± 27	38 ± 23	0.0042*
ACPA (IU/dl)	157 ± 160	188 ± 170	0.7
IgG (mg/dl)	1056 ± 378	1034 ± 317	0.02*
IgM (mg/dl)	107 ± 59	95 ± 53	0.009*
IgA (mg/dl)	263 ± 146	198 ± 81	0.008*
CD3+CD45+ (%)	79.34 ± 7	77 ± 7	0.99
CD3+CD45+ (cells/ml)	1619 ± 759	1063 ± 284	0.95
CD3+CD4+CD45+ (%)	52.3 ± 12	57.4 ± 12	0.3
CD3+CD4+CD45+ (cells/ml)	1052 ± 593	1181 ± 872	0.54
CD19+CD45+ (%)	8.6 ± 6	9.3 ± 7	0.74
CD19+CD45+ (cells/ml)	174 ± 149	191 ± 165	0.73
CD3+CD8+CD45+ (%)	26.8 ± 12.6	17.9 ± 7	0.01*
CD3+CD8+CD45+ (cells/ml)	537 ± 319	359 ± 286	0.03*

Data are expressed as mean ± standard deviation (SD)

DAS28 = 28-joints disease activity score, CRP = C reactive protein, RF = rheumatoid factor, ESR = erythrocyte sedimentation rate, ACPA = anti-citrullinated peptide antibody, IgG = immunoglobulin G, IgM = immunoglobulin M, IgA = immunoglobulin A.

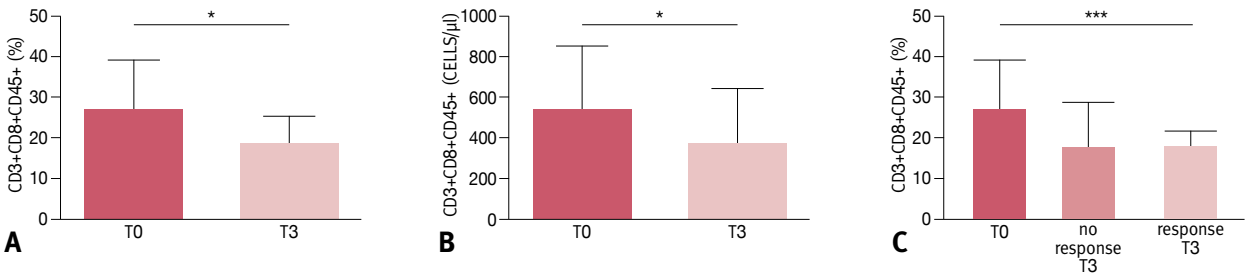
*P ‹ 0.05

1C shows that the percentage of CD3+CD8+CD45+ T cells decreased significantly only in responders patients compared with no-responders (P = 0.005). The percentage and the absolute number of CD3+CD4+CD45+ T cells and CD19+CD45+ B cells did not show any significant variation after the treatment [Table 2]. Immunoglobulin levels measured by serum protein electrophoresis decreased after 3 months compared to baseline (P = 0.01) [Figure 2A]. Moreover, the level of immunoglobulins correlated positively with the DAS28 score both at the baseline (P = 0.03, R = 0.4) [Figure 2B] and after 3 months (P = 0.01, R = 0.6). Levels of IgG, IgA and IgM decreased after 3 months of treatment (P = 0.02, P = 0.008, and P = 0.009, respectively) [Figure 2C-E]. Likewise, RF titer decreased after 3 months of treatment (P = 0.007) [Figure 2F]. ACPA did not show any significant variation [Table 2].

DISCUSSION

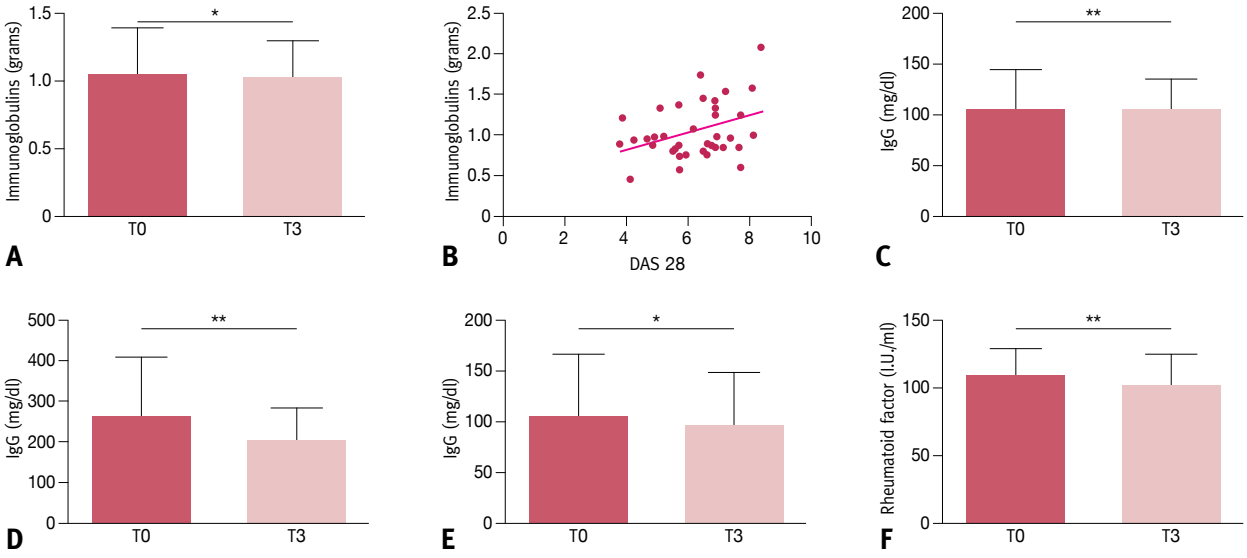
Abatacept is an effective treatment for RA, both for its efficacy and safety as a first line treatment and after the failure of other biological DMARDs [20]. In our study we demonstrated that serum immunoglobulin levels significantly decrease after 3 months of abatacept treatment and they also have a direct correlation with disease activity assessed through DAS28. This finding was confirmed by the reduction of every singular subset of immunoglobulins IgG, IgM and IgA, as well as of RF-IgG after 3 months. Similar results regarding immunoglobulin behavior were observed in another small study on 30 RA patients treated with abatacept. In particular, Scarsi et al. [21] observed a reduction of both immunoglobulins and RF at 6 and 12 months of abatacept therapy and a positive correlation between RF-IgM levels and disease activity. We were not able to demonstrate variations in ACPA levels, possibly because of the shorter time of observation and the relatively small number of ACPA-positive patients who responded to the treatment. Indeed, most of the enrolled patients were refractory to several biological DMARDs and displayed a high disease activity at baseline. Moreover, previous studies on synovial tissue from RA patients treated with abatacept found inhibition of B-cell proliferation and down regulation of the expression of B-cell markers [22,23]. Overall, these results could be explained considering the effects of abatacept in the cross-talk between T and B cells. Abatacept decreases T cell activation, including T helper cells [10]. Therefore, B cells might receive less co-stimulation by T helper cells resulting in less antibody production [10]. Future studies should investigate in depth the potential role of immunoglobulins to act as a biomarker of response to treatment.

Figure 1. Peripheral blood CD8+ T cells during abatacept treatment
[A] Reduction of the percentage of CD3+CD8+CD45+ cells after 3 months of treatment **[B]** Reduction of the absolute number of CD3+CD8+CD45+ cells after 3 months of treatment **[C]** Reduction of the percentage of CD3+CD8+CD45+ cells in patients with good-moderate European League Against Rheumatism (EULAR) response after 3 months of treatment. Statistical analyses were performed using Wilcoxon's signed-rank test



*P ‹ 0.05, ***P ‹ 0.001

Figure 2. Variations of serum immunoglobulins during abatacept treatment
[A] Reduction of serum total immunoglobulin levels after 3 months of treatment **[B]** Positive correlation between serum total immunoglobulin levels and DAS28 at baseline **[C]** Reduction of serum IgG levels after 3 months of treatment **[D]** Reduction of serum IgA levels after 3 months of treatment **[E]** Reduction of serum IgM levels after 3 months of treatment **[F]** Reduction of RF-IgG levels after 3 months of treatment



Statistical analyses were performed using Wilcoxon's signed-rank test (A, C, D, E, F) and Pearson's correlation test (B)
IgG = immunoglobulin G, IgM = immunoglobulin M, IgA = immunoglobulin A, DAS28 = 28-joints disease activity score
*$P < 0.05$, **$P < 0.01$

Among all the biochemical parameters observed, CD8+ T cells showed a significant decrease in percentage as well as in absolute number. Abatacept is a potent inhibitor of CD28 mediated T cell co-stimulation. The CD28 blockade results in increased cell death, energy induction, and blockade of cell differentiation [24]. Therefore we can hypothesize that the observed reduction of CD8+ T cells was due to the mechanism of abatacept displayed above. Moreover, the reduction of the percentage of CD8+ T cells was evident in responder patients rather than in no-responders. A similar result was observed in another small study on 20 RA patients where decreasing levels of CD8+ T cells in patients treated with abatacept also correlated with responsiveness to treatment [25]. This finding is in agreement with previous data from literature showing that a lower proportion of CD8+ T cell at baseline was associated with the discontinuation of abatacept therapy because of inefficacy [13]. Indeed, it has been shown that low numbers of CD28- T cells (and consequently high levels of CD28+T cells) at baseline also correlated with higher likelihood of achieving clinical remission compared with higher numbers of baseline CD28- T cells [13].

This study consists of several limitations: low number of enrolled patients, analysis of the cell populations relies on basic cell surface markers that should be further improved by using specific immunophenotyping and activity assays.

CONCLUSIONS

In conclusion our study highlights a different role of abatacept in the modulation of the adaptive immune response by the reduction of polyclonal B cell activation and cytotoxic T cells.

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Capsule

Mycophenolate mofetil versus placebo for systemic sclerosis-related interstitial lung disease: an analysis of scleroderma lung studies I and II

To compare mycophenolate mofetil (MMF) with placebo for the treatment of systemic sclerosis (SSc)-related interstitial lung disease (ILD), Volkman and colleagues conducted a study, which included participants enrolled in the placebo arm of Scleroderma Lung Study (SLS) I and the MMF arm of SLS II. SLS I randomized participants to receive either oral cyclophosphamide or placebo for 1 year, while SLS II randomized participants to receive either MMF for 2 years or oral cyclophosphamide for 1 year followed by 1 year of placebo. Eligibility criteria for SLS I and SLS II were nearly identical. The primary outcome was percent of predicted forced vital capacity (FVC). Key secondary outcomes included percent of predicted diffusing capacity for carbon monoxide (DL_{CO}), the modified Rodnan skin thickness score (MRSS), and dyspnea. Joint models were created to evaluate the treatment effect on the course of these outcomes over 2 years. At baseline, the MMF-treated group in SLS II (n = 69) and the placebo-treated group in SLS I (n = 79) had similar numbers of men and women and similar disease duration, SSc subtype, extent of skin disease, and percent of predicted FVC. MMF-treated patients in SLS II were slightly older (mean ± standard deviation [SD] age 52.6 ± 9.7 years vs, 48.1 ± 12.4 years, $P = 0.0152$) and had higher percent of predicted DL_{CO} (mean ± SD 54.0 ± 11.1 vs. 46.2 ± 13.3, $P = 0.0002$) than placebo-treated patients in SLS I. After adjustment for baseline disease severity, treatment with MMF in comparison with placebo was associated with improved percent of predicted FVC ($P < 0.0001$), percent predicted DL_{CO} ($P < 0.0001$), MRSS ($P < 0.0001$), and dyspnea ($P = 0.0112$) over 2 years. Although there are inherent limitations in comparing participants from different trials, treatment with MMF was associated with improvements in physiologic outcomes and dyspnea compared with placebo, even after accounting for baseline disease severity. These results further substantiate the use of MMF for the treatment of SSc-related ILD.

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Eitan Israeli

"Once you bring life into the world, you must protect it. We must protect it by changing the world"

Elie Wiesel (1928–2016), Romanian-born American Jewish writer, professor, political activist, Nobel Laureate and Holocaust survivor. He was the author of 57 books written mostly in French and English