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Review

# Modulating the co-stimulatory signal for T cell activation in rheumatoid arthritis: Could it be the first step of the treatment?

Roberto Caporali [a,*], Serena Bugatti [a], Lorenzo Cavagna [a], Marco Antivalle [b], Piercarlo Sarzi-Puttini [b]

[a] Division of Rheumatology, University of Pavia, IRCCS Policlinico S. Matteo Foundation, Pavia, Italy
[b] Rheumatology Unit, L. Sacco University Hospital, Milan, Italy

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ABSTRACT

Advances in our understanding of the key mediators of chronic inflammation and tissue damage in rheumatoid arthritis (RA) have fostered the development of targeted therapies and greatly expanded the available treatment options. Abatacept, a soluble human fusion protein that selectively modulates the co-stimulatory signal required for full T-cell activation, is approved for the treatment of moderate to severe RA in the United States, Canada, and the European Union. This review summarises the data on efficacy (disease activity, quality of life, prevention of structural damage) and safety from randomised clinical trials of abatacept plus methotrexate in patients with: i) active RA and an inadequate response to methotrexate who are naïve to biological disease-modifying anti-rheumatic drugs; and ii) methotrexate-naïve early RA with poor prognostic factors. Novel imaging outcomes and biological changes induced by abatacept treatment are also briefly reviewed. Optimal use of abatacept as a first-line biological therapy is discussed in light of the current recommendations and guidelines.



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## 1. Introduction

Recent years have witnessed enormous progress in the treatment of rheumatoid arthritis (RA). Early institution of disease-modifying anti-rheumatic drug (DMARD) therapy soon after disease onset, use of DMARDs in combination and pursuit of a predefined target, ideally remission, have allowed better disease control both clinically and in the prevention of structural damage [1,2]. Conventional DMARDs are the mainstay of RA treatment, with methotrexate (MTX) being the anchor drug [3]. However, a significant proportion of patients does not respond adequately to such treatment [4]. Patients with inadequate responses to conventional DMARDs can benefit from biological agents that target various elements involved in the immune-pathologic cascade of RA. The tumor necrosis factor (TNF) inhibitors were the first of the biological drugs to be accessible in RA [5]. Along with the increasing understanding of the complex network of cellular and humoral interactions of the disease, therapeutic options have further expanded to strategies alternative to cytokine

* Corresponding author at: UOC Reumatologia, IRCCS Policlinico S. Matteo, 27100 Pavia, Italy.
*E-mail address:* caporali@smatteo.pv.it (R. Caporali).

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inhibition. Effective approaches include depleting circulating CD20+ B lymphocytes using a monoclonal anti-CD20 antibody (rituximab) [6] and modulating the co-stimulatory signal for T cell activation using a cytotoxic T-lymphocyte antigen 4 (CTLA-4) fusion protein (abatacept) [7]. Here we review studies of abatacept in biologic-naïve patients with active RA despite treatment with MTX and summarise current recommendations covering indications for use of abatacept as a first-line biological. Data supporting the use of abatacept before conventional DMARDs in early RA are also reviewed.

## 2. Rationale for T cell targeting and mode of action of abatacept

Several observations over the years have supported a critical role for T cells in RA. The presence of CD4+ T cells in the synovium of patients with RA [8] and the strong association between RA susceptibility and HLA-DRB1 alleles on major histocompatibility complex (MHC) class II [9] is a reflection of T cell participation to distinct aspects of disease pathogenesis. Studies in murine models of RA have shed further light on the ability of CD4+ T cells to initiate, maintain, or control the disease via diverse mechanisms [10]. Once activated, T cells orchestrate downstream responses from other resident and infiltrating immune cells, including synovial fibroblasts, macrophages and B cells [11,12]. In addition, activated T cells produce the receptor activator of nuclear factor-κB ligand (RANKL) [13] that, in turn, induces osteoclastic bone resorption.

In contrast to the beneficial effect of B cell depletion in RA, direct targeting of CD4+ T cells with monoclonal antibodies soon appeared accompanied by significant adverse effects and mortality [14]. Nonetheless, the improved knowledge of the co-stimulation regulatory mechanisms has offered modulation of T cell function as an alternative strategy. Full activation of resting T cells requires not only recognition of cognate antigens (presented in the context of the MHC) by the T-cell receptor (TCR), but also a co-stimulatory signal delivered through the engagement of CD28 with CD80/86 on the surface of professional antigen-presenting cells (APCs) [15]. If a T cell receives only signals by TCR stimulation, in the absence of co-stimulation, the T cell becomes anergic or undergoes apoptotic cell death. CTLA-4 is a second, high-affinity receptor for both CD80 and CD86, which outcompetes CD28 binding and terminates T cell activation by providing negative signals [16]. Abatacept was developed to mimic the action of CTLA-4. Abatacept is a fully human soluble fusion protein, incorporating the extracellular domain of human CTLA-4 linked to the modified fragment crystallisable portion of human immunoglobulin G1. Abatacept is administered by intravenous infusion at a dose of around 10 mg/kg every 4 weeks (based on three weight bands), following loading doses at 0, 2 and 4 weeks. Subcutaneous abatacept administered at a fixed dose of 125 mg/week has been recently shown to be equally effective and safe to intravenous abatacept [17].

## 3. Clinical trials evaluating the efficacy of abatacept in patients with active rheumatoid arthritis despite methotrexate therapy

Abatacept in combination with MTX in biologic-naïve patients with active RA and an inadequate response to MTX has been assessed in three multicenter, randomised, double-blind, placebo-controlled, 12-month trials: one Phase IIb dose-finding study (n = 339) [18]; the Phase III Abatacept in Inadequate Responders to Methotrexate (AIM; n = 652) trial [19]; and Abatacept or Infliximab Versus Placebo, a Trial for Tolerability, Efficacy, and Safety in Treating RA (ATTEST; n = 431) [20].

The Phase IIb trial evaluated the safety and efficacy of abatacept [2 mg/kg (n = 105) or 10 mg/kg (n = 115)] plus MTX compared with placebo plus MTX (n = 119) [18]. Patients had active disease defined by ≥10 swollen and ≥12 tender joints and a C-reactive protein (CRP) level >1 mg/dl. The primary endpoint was the American College of Rheumatology criteria (ACR) 20% response at 12 months. Secondary end-points were ACR50 and ACR70 responses. Patients completing the double-blind period were eligible to enter an open-label long-term extension (LTE), in which all received a fixed dose of abatacept at 10 mg/kg. Results from the LTE have been published up to 5 years [21].

The Phase III AIM trial included a similar population of patients with active RA despite MTX therapy [19]. Mean disease duration was approximately 8.5 years. Patients were randomly assigned to receive either a fixed dose of abatacept (n = 433) or placebo (n = 219). Co-primary end-points were ACR20 response at 6 months, clinically significant improvement in physical function and joint damage progression (as assessed by the Genant-modified Sharp score) at 1 year. After completing the 12-month double-blind period, patients were eligible to enter the open-label extension phase. Clinical and radiographic results at years 2 and 3 have been recently published [22–24].

The ATTEST trial, although not powered to detect significant differences between abatacept and infliximab, provided information on the relative efficacy and safety profiles of the two biologics vs placebo [20]. Patients with active RA (mean disease duration approximately 8 years) and an inadequate response to MTX were randomly assigned to receive abatacept (approved dose, n = 156), infliximab (3 mg/week, n = 165) or placebo (n = 110), with background MTX. At month 6, the patients in the placebo group were reallocated to abatacept, and the infliximab and abatacept groups continued to year 1 (with blinding maintained). The primary endpoint was reduction in 28-joint Disease Activity Score (DAS28)-erythrocyte sedimentation rate (ESR) at 6 months for abatacept vs placebo. Secondary endpoints included mean reduction in DAS28-ESR with infliximab vs placebo at 6 months, mean reduction in DAS28-ESR with abatacept vs infliximab at 6 months and 1 year, European League Against Rheumatism (EULAR) responses, low disease activity status (LDAS) (DAS28-ESR ≤ 3.2), DAS28-ESR remission (DAS28-ESR < 2.6), ACR20, 50 and 70 responses, Health Assessment Questionnaire Disability Index (HAQ-DI) response rates, and mean changes in the physical and mental component summary of the Short Form-36 (SF-36). Patients completing the 1-year double-blind period were eligible to receive abatacept at 10 mg/kg in the open-label LTE, and efficacy at year 2 has been recently reported [25].

### 3.1. Clinical efficacy

In the Phase IIb dose-finding study, a significantly greater percentage of patients treated with abatacept at 10 mg/kg met the ACR20 improvement criteria at year 1 compared to that of the placebo recipients (62.6% vs 36.1%, p < 0.001) [18]. ACR50 and ACR70 responses, the percentage of patients achieving DAS28 remission as well as improvements in physical function were also statistically significant [18]. The 2 mg/kg dose was considered suboptimal and was not pursued in Phase III. Of the patients who entered the LTE, 59.4% remained on treatment at year 5, with 11.0% discontinuing due to lack of efficacy [21]. Improvements observed at year 1 were maintained over 5 years, as assessed by ACR20, 50 and 70 responses [21]. Furthermore, LDAS and DAS28 remission were reported in 58.5% and 45.3% of the patients at year 5, respectively. Reductions in functional disability were also maintained.

Clinical results from the AIM trial were consistent with those ones from the Phase IIb study. More patients in the abatacept group than in the placebo group achieved ACR20 response at month 6 (67.9% vs 39.7%, p < 0.001). ACR response rates improved further between 6 and 12 months in the abatacept group, with ACR20, 50 and 70 responses being achieved by 73.1%, 48.3% and 28.8% of abatacept recipients, respectively [19]. Disease activity assessed using DAS28-CRP at 6 and 12 months was reduced to a greater extent in the abatacept arm than in the placebo arm. At year 1, LDAS and DAS28 remission were reached by 42.5% and 23.8% of the abatacept group respectively, compared with 9.9% and 1.9% of the placebo recipients [19]. 83% of