

Current treatment options for psoriatic arthritis: spotlight on abatacept

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Abstract: Psoriatic arthritis (PsA) is a chronic inflammatory disease of joints, tendon sheaths, and entheses affecting patients with established skin psoriasis, or, less frequently, patients without a personal history of psoriasis with a positive familial history. Many treatment options are now available to deal with the different aspects of the disease, including traditional and biological disease-modifying antirheumatic drugs and the recently released targeted synthetic disease-modifying antirheumatic drugs. However, ~40% of patients still fail to achieve a meaningful clinical response to first-line biologic therapy advocating the development of novel medications. It is now well accepted that T-cells participate in the immunopathogenesis of several autoimmune diseases. For this reason, the potential intervention on T-cells represented an attractive therapeutic target for a long time, becoming a clinical reality with the development of abatacept. Abatacept is a biologic agent selectively targeting the T-cell costimulatory signal delivered through the CD80/86-CD28 pathway and was approved in December 2005 by the US Food and Drug Administration and in May 2007 by European Medicines Agency for the treatment of patients with rheumatoid arthritis in combination with methotrexate. Based on the relevant role of T-cells in PsA pathogenesis and following the positive results obtained in a phase III clinical trial, abatacept recently received approval for treatment of patients with PsA. In this review, we will focus on the current knowledge about the emerging role of abatacept in treatment of PsA.

Keywords: abatacept, CTLA4-Ig, T-cell, psoriatic arthritis, efficacy, safety

Introduction

Psoriatic arthritis (PsA) is a chronic inflammatory disease of joints, tendon sheaths, and entheses affecting patients with established skin psoriasis (Pso), or – less frequently – patients without a personal history of Pso exhibiting a positive familial history.¹ Musculoskeletal presentation may embrace a variety of clinical pictures including poly- or oligo-arthritis, destructive arthritis of distal interphalangeal joints, dactylitis, enthesitis, or predominantly axial disease.¹ Moreover, PsA patients are burdened by several comorbidities such as obesity, type 2 diabetes/insulin resistance, metabolic syndrome, hypertension, and hyperlipidemia,²⁻⁴ which, by synergizing with the systemic inflammatory process, lead to an overall increase in prevalence and incidence of cardiovascular diseases.⁵ The heterogeneity of PsA phenotype fostered the development of the novel concept of “psoriatic disease”⁶ to better emphasize the pleiotropic nature of this condition.

Many treatment options are now available to deal with the different aspects of the disease, including conventional synthetic and biologic disease-modifying antirheumatic drugs (DMARDs) and the recently released targeted synthetic DMARDs (tsDMARDs). However, ~40% of patients still fail to achieve a meaningful clinical

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response to first-line biologic therapy,^{7,8} advocating the development of novel medications.

It is now well accepted that T-cells participate in the immunopathogenesis of several autoimmune diseases.⁹ For this reason, potential intervention on T-cells represented an attractive therapeutic target for a long time, which became a clinical reality only following the development of abatacept. Abatacept is a biologic agent selectively targeting the T-cell costimulatory signal delivered through the CD80/86-CD28 interaction and was approved in December 2005 by the Food and Drug Administration (FDA) and in May 2007 by European Medicines Agency (EMA) for the treatment of patients with rheumatoid arthritis (RA) in combination with methotrexate (MTX).

The broad mechanism of action of this molecule raised the hypothesis that abatacept may hijack the pathophysiological mechanisms underlying many other immune-mediated diseases sharing the key role of T-cells. Encouraging data are now emerging regarding the potential usefulness of abatacept in some of them (type 1 diabetes,¹⁰ giant cell arteritis,¹¹ dermatomyositis,¹² and Sjögren's syndrome¹³), while in other diseases (systemic lupus erythematosus,¹⁴ Takayasu's arteritis,¹⁵ ulcerative colitis/Crohn's disease,¹⁶ and multiple sclerosis¹⁷) preliminary studies found no significant benefits, underlying the complex, differential interaction of profoundly diverse T-cells lineages, and between T-cells and other immune effector cells.

In this review, we will focus on the current knowledge on the emerging role of abatacept in treatment of PsA.

Current treatment options for PsA

In order to assist rheumatologists in everyday clinical practice, different international and national recommendations for the management of PsA patients have been developed to date, such as the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA)¹⁸ and the European League Against Rheumatism (EULAR)¹⁹ recommendations.

Latest EULAR recommendations for pharmacological treatment of PsA comprise 5 overarching principles and 10 recommendations concerning nonsteroidal anti-inflammatory drugs (NSAIDs), conventional synthetic DMARDs (csDMARDs), tsDMARDs, and biological DMARDs (bDMARDs) including originator or biosimilar TNF inhibitors, anti-IL-12/23, and anti-IL-17 agents. GRAPPA recommendations take in account both dermatological and musculoskeletal involvement and are organized in 6 domains (peripheral arthritis, axial disease, enthesitis, dactylitis, and skin and nail involvement) based on the predominant manifestation.

According to EULAR, MTX is the first csDMARD to be used in patients suffering from peripheral arthritis. However, sulfasalazine, leflunomide, and cyclosporine are considered only when MTX is contraindicated or has already failed. On the other hand, GRAPPA recommends MTX, sulfasalazine, or leflunomide as the first option without a definite preference.

In patients with peripheral arthritis and an inadequate response to at least 1 csDMARD, a bDMARD – usually a TNF inhibitor – should be initiated according to the EULAR recommendations. When TNF inhibitors are not appropriate, bDMARDs targeting IL-12/23 or IL-17 axis may be considered. In patients in whom bDMARDs are not appropriate, tsDMARDs – such as the phosphodiesterase 4 (PDE-4) inhibitor apremilast – may be considered. On the contrary, GRAPPA experts place TNF inhibitors, other bDMARDs, and PDE-4 inhibitors at the same level as a potential first choice in PsA patients with an inadequate response to at least 1 csDMARD.

Both GRAPPA and EULAR suggest an early use of bDMARD in patients with active enthesitis and/or dactylitis and insufficient response to NSAIDs or local glucocorticoid injections. A similar approach is reserved for patients with predominantly axial disease and insufficient response to NSAIDs.

Introduction to abatacept Physiology of T-cell costimulation

Upon generation, T-cells circulate in an anergic state waiting to become “activated” and subsequently perform their role of master players of the adaptive arm of the immune system. Complete T-cell activation requires 2 distinct receptor interactions with antigen-presenting cells (APCs) to be accomplished (Figure 1A).²⁰ The first is the encounter between the major histocompatibility complex (MHC), present on the surface of APCs and exposing an antigenic peptide, and the T-cell receptor (TCR) found on the membrane of all T-cells. The second – the so-called costimulatory signal – is mainly, but not only, mediated by the interaction between the CD80 (B7-1)/CD86 (B7-2) molecules on the membrane of APCs with the CD28 receptor expressed by T-cells.^{20,21} Other molecules, such as CD2, can deliver alternative costimulatory signals.²² CD28 is expressed constitutively on T-cells, and its engagement leads to full activation;²³ however, important differences exist between T-cell compartments, with the memory subset being less dependent on costimulation than the naïve counterpart.²⁴ To counteract an excessive activation of T-cells, an autoregulatory mechanism starts ~48 hours after activation. CTLA-4 is indeed transiently expressed

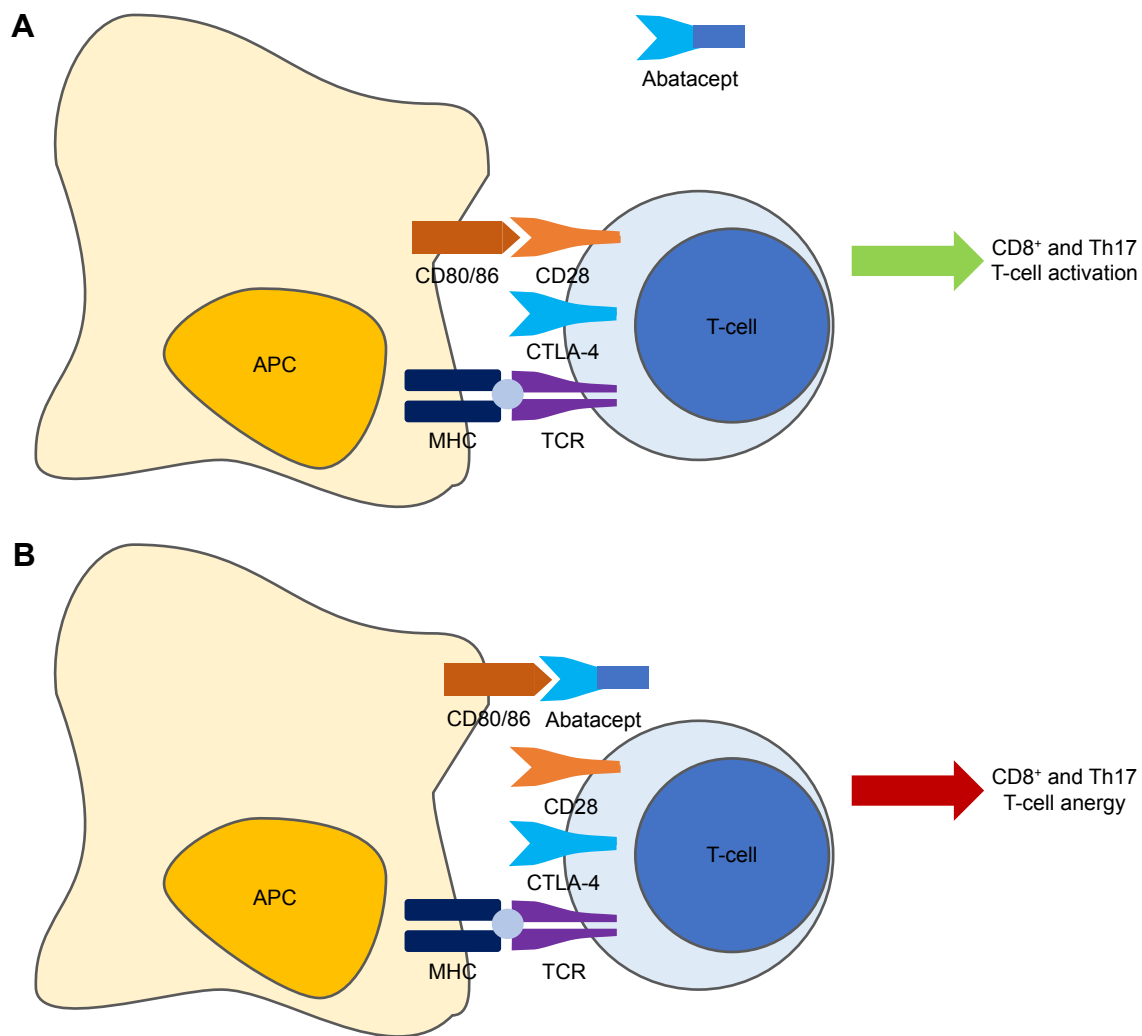


Figure 1 Mechanism of action of abatacept.

Notes: Complete T-cell activation requires 2 distinct receptor interactions with APCs to be accomplished. The first is the encounter between the MHC and the TCR found on the membrane of all T-cells. The second – the so-called costimulatory signal – is mainly, but not only, mediated by the interaction between the CD80/CD86 molecules on the membrane of APCs with the CD28 receptor expressed by T-cells. To counteract an excessive activation of T-cells, CTLA-4 is indeed transiently expressed following T-cell activation, competing with CD28 for binding to CD80/86 and delivering a signal that downregulates cellular functions thus inducing anergy of activated T-cells (**A**). Abatacept (CTLA-4-Ig) binds to CD80/86, exploiting the self-regulatory role of CTLA-4 in inducing T-cell anergy (**B**).

Abbreviations: APC, antigen-presenting cell; MHC, major histocompatibility complex; TCR, T-cell receptor.

following T-cell activation, competing with CD28 for binding to CD80/86 and delivering a signal that downregulates cellular functions, thus inducing anergy of activated T-cells.²⁵ This finely tuned mechanism clearly represented an attractive therapeutic target in T-cell-mediated diseases.

T-cells in PsA

Although the complete cascade of events leading to the development of PsA is still elusive, extensive preclinical and clinical data support the hypothesis that PsA is a T-cell-driven inflammatory disease with a predominant immunopathological role of autoreactive CD8⁺ T-cells.²⁶ First, differently from many other immune-mediated diseases in which genetic susceptibility relies on specific HLA-DR or other class II MHC genes, class I genes – notably alleles belonging to

the HLA-B and HLA-C loci – are preferentially involved in PsA.²⁷ The function of class I molecules is to present small peptides to TCR expressed by CD8⁺ T-cells. Moreover, activated CD8⁺ T-cell clones are expanded in synovial fluid^{28,29} and synovial tissue³⁰ from PsA patients. In contrast, the CD4⁺ population – as a whole – seems to play a less relevant role in this context, given the evidence that PsA and Psoriasis (Pso) develop frequently in AIDS patients despite profound CD4⁺ T-cell lymphopenia.³¹ More recently, the traditional dichotomy between Th1- and Th2-mediated diseases has been overtaken by the identification of novel T-cell subsets, namely regulatory T-cells (Treg) and T helper 17 (Th17) populations. Tregs are characterized by the expression of the transcription factor Foxp3 and act as negative regulators of immune-mediated inflammation,³² while Th17 cells

are IL-23-dependent cells characterized by the production of the proinflammatory cytokine IL-17 and participate in the pathophysiology of inflammatory diseases.³³ Globally, their balance represents the delicate razor-blade on which T-cell-mediated inflammation develops and maintains chronically.³⁴ In PsA synovial fluid, an enrichment of both CD4⁺ and CD8⁺ IL-17⁺ cells has been described; on the contrary in RA only CD4⁺ cells produce significant amount of IL-17.³⁵ Moreover, in PsA, IL-17 acts locally to enhance the production of inflammatory cytokines by synoviocytes.³⁶ The critical role of T-cells in PsO and PsA is further emphasized by the evidence that biologics directed against T-cell cytokines such as TNF (infliximab, adalimumab, golimumab, certolizumab, and etanercept), IL-12/23 (ustekinumab), and IL-17 (secukinumab) and surface costimulatory molecules (abatacept, efalizumab) demonstrated significant efficacy in treating both PsO and PsA.^{37,38}

Abatacept: pharmacodynamics and pharmacokinetics

Abatacept is a fully human glycosylated soluble fusion protein (molecular weight ~92 kDa) produced by recombinant DNA technology in mammalian CHO cells, which links the extracellular domain of human CTLA-4 to the modified Fc portion (hinge, CH2, and CH3 domains) of human immunoglobulin G1 (IgG1).³⁹ By competitively binding to CD80/86, abatacept exploits the self-regulatory role of CTLA-4 in inducing T-cell anergy (Figure 1B).

Abatacept has been originally approved for intravenous (IV) administration, but in 2011 it received the first approval by FDA for subcutaneous (SC) delivery following the demonstration of therapeutic equivalence of the two regimens.⁴⁰ Currently, the recommended IV dosage is 500 mg for individuals weighing <60 kg, 750 mg for individuals ≥60 to ≤100 kg, and 1,000 mg for those >100 kg, corresponding approximately to 10 mg/kg and administered as a 30-minute infusion at time 0, 14, and 28 days and then every 28 days.³⁹ For the SC delivery route, the approved dosage is 125 mg weekly independent of body weight.³⁹ The bioavailability of abatacept following SC administration is 78.6%.³⁹ After IV administration, the mean terminal half-life is 13.1 days, while following SC administration is 14.3 days; however, pharmacokinetic analyses indicated that the clearance of abatacept tends to increase with body weight.³⁹ Both IV⁴¹ and SC⁴² abatacept have been shown to elicit low rates of immunogenicity (~3.0% and ~3.9%, respectively) that, however, was not associated with reduced efficacy or safety.

Efficacy and safety of abatacept in RA

Several clinical trials demonstrated the efficacy of IV and SC abatacept in different populations of RA patients, including MTX naïve,^{43,44} MTX-inadequate responders,^{40,45} and in those refractory to TNF inhibitors^{46,47} with the benefits of treatment extending beyond the mere control of disease activity to the reduction of radiographic progression.⁴⁸ The safety profile has been evaluated in the long term⁴⁹ without raising major concerns, and in particular with no significant increase in the risk of serious infections⁵⁰ or malignancy.⁵¹ Furthermore, compared to other biologics, abatacept has been suggested to display a better safety profile in special populations, such as patients with chronic heart failure⁵² and demyelinating disorders.⁵³ Finally, the benefits of abatacept may affect other disease-related domains such as the risk of cardiovascular events^{52,54} by its ability to improve several well-known cardiovascular risk factors such as insulin resistance and vascular dysfunction.^{55,56}

Abatacept in PsA: current evidence

Efficacy of abatacept in PsA

Following abatacept commercialization, isolated case reports were published suggesting its potential efficacy in difficult-to-treat PsA patients.^{57–60} The efficacy and safety of abatacept in PsA patients was subsequently systematically evaluated in two randomized controlled trials (RCTs)^{61,62} ultimately leading to its approval for combination therapy in patients with PsA and inadequate response to at least one DMARD by FDA and EMA, in summer 2017.

In the first phase II, dose-ranging study by Mease et al,⁶¹ 170 patients with active PsA and inadequate response to DMARDs (including TNF inhibitors) were randomized 1:1:1 to receive IV abatacept at 3 different dosing regimens (3 mg/kg or 10 mg/kg – administered on days 1, 15, and 29 and then every 28 days – or 30 mg/kg administered on days 1 and 15, followed by 10 mg/kg every 28 days) or placebo for 6 months. The primary endpoint (American College of Rheumatology 20% improvement criteria – ACR20 – response on day 169) was achieved by 33%, 48%, and 42% of patients respectively compared to 19% of those taking placebo and resulting in a statistically significant difference for the 10 mg/kg ($p=0.006$) and 30/10 mg/kg ($p=0.022$) groups. Of note, at the 10 mg/kg dose (the one already approved for RA), the proportion of individuals achieving an ACR20 response was higher in patients who had never received TNF inhibitors compared to those who had previously received anti-TNF agents (56% vs 31%). Although the study was not adequately powered to draw firm conclusions on secondary

outcome measures, a higher number of abatacept-treated patients achieved numerically superior results on additional measures of arthritis severity (ACR50 and ACR70 response), Pso severity (target lesion 50% – TL50 – and psoriasis area severity index 50% response), physical function (proportion of patients achieving a minimal clinically important differences in Health Assessment Questionnaire Disability Index score), and quality of life (change in Short Form health survey score from baseline), with the 10 mg/kg regimen showing the overall best performance.

Following these results, a phase III RCT was conducted to confirm the efficacy and safety of abatacept in patients with active PsA,⁶² using the SC delivery route that has already shown therapeutic equivalence to IV one in RA patients.⁴⁰ For this purpose, 424 PsA patients with inadequate response to DMARDs (including TNF inhibitors) were randomized to receive SC abatacept 125 mg or placebo weekly for 24 weeks. The RCT phase was followed by an additional open-label treatment period of 28 weeks (resulting in a 52-weeks follow-up period) while patients who did not achieve $\geq 20\%$ improvement in tender/swollen joints count at week 16 were switched to open-label abatacept for 28 weeks (early escape strategy, total follow-up 44 weeks).

Abatacept treatment resulted in a significantly higher proportion of patients achieving the primary endpoint (ACR20 response) at week 24 (39.4% vs 22.3%; $p < 0.001$) with the largest treatment difference seen in anti-TNF naïve patients and in those with C-reactive protein above the upper limit of normal at baseline. Intention-to-treat analysis at week 44 showed that ACR20 response was maintained in patients treated with abatacept and improved in those who switched from placebo. Efficacy on musculoskeletal manifestations was further supported by greater improvement in disease activity score including 28 joints and disease activity in PsA scores, a higher percentage of patients achieving ACR50 and ACR70 responses, percentage of patients achieving complete resolution of enthesitis and dactylitis, and proportion of patient without radiographic progression. Finally, the proportion of patients achieving Health Assessment Questionnaire Disability Index endpoint was numerically superior (although not reaching statistical significance) while measures of skin response were only slightly numerically improved in the abatacept arm.

It is noteworthy that the ACR20 response rate at week 24 in both studies was globally lower than that observed in previous studies of agents targeting other effector molecules in PsA. However, both studies included a significant proportion

of anti-TNF exposed patients (30% and 60%, respectively) which may indicate a more treatment-refractory population. Furthermore, differently from what observed with other agents exploiting diverse mechanisms of action, abatacept demonstrated a stronger efficacy on musculoskeletal compared to skin endpoints. The reasons for this discrepancy may underlie an incomplete understanding of the divergent role of individual T-cell subsets and costimulatory pathways in orchestrating skin and synovial inflammation in psoriatic disease. Indeed, opposite to abatacept, the tight inhibition of the costimulatory signal delivered through the CD2/LFA-3 pathway by means of the fusion protein alefacept resulted in a significant improvement of skin lesions but was burdened by a decline of CD4⁺ T-cells and subsequent increase of infectious adverse events (AEs);⁶³ for this reason, the drug was voluntarily discontinued by the manufacturer in 2011. In contrast, selective targeting of the IL-23/IL-17 axis produces superior results on skin lesions without a similar level of efficacy in the joints.⁶⁴ Finally, another potential reason explaining the divergence between skin and joint endpoints may be related to the interference of abatacept with the protective function of Tregs, thus accounting for the relative superior efficacy of lower doses in treatment of cutaneous manifestations.^{65,66}

Safety of abatacept in PsA

In both studies, abatacept was generally well tolerated with no emerging safety signals with respect to what observed in RA patients.⁶⁷

In the phase II study,⁶¹ AEs were reported in ~70% of patients in each treatment arm. Seven patients developed serious adverse events (SAEs), of whom 4 were in the 30/10 mg/kg arm, 2 in the 10 mg/kg arm, and 1 in the placebo arm; only 1 SAE in the 30/10 mg/kg (osteomyelitis) and in the 10 mg/kg (gastroenteritis) arms, respectively, were attributed as drug-related. Infusion reactions were reported in 4 patients (2 in the 30/10 mg/kg arm and 2 in the 10 mg/kg arm).

Similarly, in the 24-week double-blind period of the phase III trial,⁶² the safety profile of abatacept was analogous of that observed in the placebo group, with comparable incidences of AEs (54.5% vs 53.1%) and SAEs (2.8% vs 4.3%). Only 1 serious infection (*Pneumocystis jirovecii* infection) was considered related to study drug and led to treatment discontinuation. A similar favorable safety profile was consistently maintained throughout the open-label phase, up to week 52.

Conclusion

Recent data from clinical trials demonstrated that abatacept represents a novel weapon in fighting the battle against PsA. However, many issues need still to be clarified in future studies: the potential benefits of a dosage adjustment in PsA patients with extensive skin involvement; the long-term efficacy and safety in real-life setting, the differential efficacy in different disease domains (enthesitis, dactylitis, cardiometabolic risk) and patients categories (csDMARDs naïve, bDMARDs naïve) and, finally, the comparative efficacy in direct comparison with other available molecules and the correct positioning in current treatment algorithms.

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Disclosure

The authors report no conflicts of interest in this work.

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