The efficacy and safety of abatacept in rheumatoid arthritis

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Ther Adv Musculoskel Dis
(2010) 2(2) 89–94
DOI: 10.1177/1759720X09360429

Abstract: Despite important progress in the treatment of rheumatoid arthritis in the last decade, even in the era of tumour necrosis factor (TNF) blockade there is a need for additional therapeutic options in many patients. In recent years three therapies with a distinct mode of action became available: rituximab, an anti-B cell therapy, tocilizumab, an anti IL-6 therapy, and abatacept, a costimulation blocker. Primary efficacy results of all three therapies are comparable at 6 months, nevertheless they have distinct efficacy and safety profiles. In the current review we focus on specific aspects of efficacy and safety of abatacept: increasing clinical and X-ray improvements over time, important and stable responses over several years, timing of response, improvements in patient-centered outcomes, and also long-term safety and easy administration with low rates of perfusion reactions. Currently, head to head comparisons between biologics are still lacking and registry data of drugs with a mode of action different to TNF blockade are still rare. In the meantime detailed analysis of all trials with a drug such as abatacept provides important information for the practicing rheumatologist.

Keywords: abatacept, costimulation blockade, efficacy, rheumatoid arthritis, safety

Introduction

Rheumatoid arthritis (RA) is a destructive inflammatory disease affecting up to 1% of the population, mainly women. Within the last decade, thanks to new insights in the pathophysiology of RA and the development of targeted therapies such as tumour necrosis factor (TNF) blockers, many RA patients previously refractory to treatment can be offered new options for disease control and improvement in quality of life. In more recent years several other drugs with a different mode of action became available. Costimulation blockade provides a rational strategy to treat RA [Malmström *et al.* 2005] and the first costimulation blocker abatacept is one of the drugs that helps to fulfil the persistent needs for RA treatment in daily practice [Westhovens and Verschueren, 2008]. Abatacept is a soluble, fully human, recombinant fusion protein that selectively modulates the CD80/CD86: CD28 costimulatory signal needed for full T-cell activation and thus prevents the production of cytokines and downstream immune responses in RA.

The first report on abatacept—in monotherapy—in RA [Moreland *et al.* 2002] showed a classical dose–response curve only for American College of Rheumatology response criteria 20 (ACR20) improvements and not ACR50 or -70, probably because of the short trial duration. Since then, several papers have appeared in the literature demonstrating the potential of this drug in methotrexate (MTX) [and other disease-modifying antirheumatic drug (DMARD)] -refractory RA [Schiff *et al.* 2008; Weinblatt *et al.* 2006; Kremer *et al.* 2006, 2003], in anti-TNF refractory RA [Schiff *et al.* 2009b; Genovese *et al.* 2005] as well as in DMARD-naïve early RA patients [Westhovens *et al.* 2009f]. An overview of the studies is provided in Table 1. Many individuals participating in these trials entered long-term extension studies [Schiff *et al.* 2009a; Westhovens *et al.* 2009a, 2009b, 2009c, 2008; Genant *et al.* 2008; Kremer *et al.* 2008] and a consistent feature seems to be the relatively high retention rates of patients in long-term follow up on the drug. In this review we will discuss potential reasons for this long-term attrition on abatacept as there are increasing clinical and X-ray improvements over time, important and stable responses over years, sufficiently rapid responses, important improvements in patient-centered outcomes but also long term safety and easy administration with low rates of perfusion reactions.

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Table 1. Overview of the clinical development program of abatacept.

Study name (reference)	Year	Trial duration	RA disease duration	Study type/population studied/primary outcome (PO)
Phase IIa (Moreland *et al.* 2002)	2002	3 months	3.3 years	Aba monotherapy *versus* placebo Anti-TNF naïve population PO: ACR20 at 3 months
Phase IIb (Kremer *et al.* 2003)	2003	6 months	9.2 years	Aba + MTX *versus* MTX + placebo Anti-TNF naïve/MTX refractory PO: ACR20 at 6 months
ATTAIN (Genovese *et al.* 2005)	2005	6 months	11.9 years	Aba + DMARD *versus* DMARD + placebo Anti-TNF refractory population PO: ACR20 at 6 months
AIM (Kremer *et al.* 2006)	2006	12 months	8.6 years	Aba + MTX *versus* MTX + placebo Anti-TNF naïve population/MTX refractory PO: ACR20 at 6 months/HAQ (Health Assessment Questionnaire) and X-rays at 1 year
ASSURE (Weinblatt *et al.* 2006)	2006	12 months	9.7 years	Aba + DMARD (biologic + non-biologic) *versus* placebo + DMARD (biologic + nonbiologic) PO: adverse events within 12 months
(Weinblatt *et al.* 2007)	2007	12 months	12.9 years	Aba + etanercept *versus* etanercept + placebo Etanercept refractory population PO: ACR20 at 6 months
ARRIVE (Schiff *et al.* 2009b)	2008	6 months	8.1 years	Aba + DMARDs or Aba monotherapy comparing direct *versus* delayed switch Anti-TNF refractory population PO: adverse events at 6 months
ATTEST (Schiff *et al.* 2008)	2008	6 months	8.6 years	Aba + MTX *versus* placebo + MTX *versus* infliximab + MTX MTX-refractory population PO: DAS 28 reduction at 6 months
AGREE (Westhovens *et al.* 2009e)	2009	2 years	6.5 months	Aba + MTX *versus* MTX + placebo DMARD-naïve patients PO: DAS 28 remission +X-rays(erosions) at 1 year

Aba, abatacept; ACR20, American College of Rheumatology response criteria 20; DAS, disease activity score; DMARD, disease-modifying anti-rheumatic drug; MTX: methotrexate; PO, primary outcome; TNF, tumor necrosis factor alfa.

Increasing clinical and X-ray improvements over time

The most robust data demonstrating increasing clinical and X-ray improvements over time with abatacept treatment come from the 1-year placebo controlled AIM (Abatacept in Inadequate responders to Methotrexate) trial [Kremer *et al.* 2006]. In an intention-to-treat (ITT) analysis, the ACR50 and -70 responses increased from 6 months to year 1 from 39.9% to 48.3% and from 19.8% to 28.8% respectively, while the placebo responses did not change between 6 and 12 months, and this despite the fact that only a few patients added a DMARD between month 6 and 12 in the abatacept-treated group compared to the placebo group. Also patients in the abatacept-treated group could decrease their steroid dose a bit between month 6 and 12, while the placebo-treated patients tended to increase their steroid dose.

Posthoc analyses in completers in the long-term follow up report of the phase 2B trial [Westhovens *et al.* 2009c] showed low disease activity scores (DAS) increasing from 48.2% to 58.5% from years 1–5.

In the ATTAIN (Abatacept Trial in Treatment of Anti-TNF INadequate responders) trial extension [Westhovens *et al.* 2008], ACR20, -50 and -70 responses increased up to 81.8%, 53.6% and 25.7% response respectively at year 3 in a completers analysis. Also in the 5-year AIM follow up the same patterns were seen, which is not to be underestimated given the high attrition on drug over time in all these trials.

X-ray data in a MTX-refractory population in the AIM trial demonstrated greater reduction in progression of structural damage at year 2 compared to year 1 in a modified ITT analysis [Genant *et al.* 2008]. The mean change in Genant-modified Sharp scores was reduced from 1.07 units in year 1 to 0.46 units in year 2. Also more patients had no progression in the X-ray score (total score of 0) at year 2 (66%) *versus* year 1 (56%). In the 24-month early RA

AGREE (Abatacept study to Gauge Remission and joint damage progression in methotrexate-naïve patients with Early Erosive RA) trial [Bathon *et al.* 2009; Westhovens *et al.* 2009e] a more important reduction of X-ray progression was seen in year 2 compared to year 1 (total Genant-modified Sharp score 0.18 *versus* 0.66; $p < 0.0001$).

Important and stable responses over time

The early RA abatacept AGREE trial was one of the first to aim for remission as a primary outcome. Remission rate increased in patients treated also in year 2 from 46.1% at year 1 to 55.2% of patients at the end of year 2 [Westhovens *et al.* 2009f]. Evaluation at a more individual patient level showed that 81% of patients in remission at year 1 were still in remission at year 2. This stability of response over time was also true for X-ray evolution, with 91.1% of year-1 nonprogressors remaining nonprogressors in year 2; this with about 95% of patients entering year 2 also completing the second year of this trial.

The level of clinical response in abatacept trials was comparable with other biologicals and was in the range of 60/40/20% for ACR 20/50/70 respectively in a MTX-insufficient responder population and in the range of 50/30/10 in a TNF-refractory population. Evaluation of persistence of response over time is particularly important for long-term patient benefit. In the 5-year AIM evaluation [Westhovens *et al.* 2009a], 60.3% of patients in DAS28 remission at year 1 were still in remission at year 5 and 71.2% with a low DAS at year 1 were still in a low DAS status at year 5. Almost 72% of patients who were X-ray nonprogressors at year 1 were X-ray nonprogressors at year 5. The latter data should be seen in context; or perhaps they explain the fact that about > 70% of patients remained on treatment at year 5.

A more detailed analysis of the abatacept trials for drop-out rates revealed that only 22 (5.8%) patients stopped due to lack of efficacy during the long-term extension of the AIM trial from year 1 to year 5 [Westhovens *et al.* 2009a]. In the 2-year AGREE trial, drop-out figures for lack of efficacy in year 1 were zero in the abatacept + MTX group *versus* 8 in the MTX alone group, and only three patients dropped out in year 2 for lack of efficacy.

Speed of response

Abatacept is criticized by some for being slower than a TNF blocker in reducing disease activity, and this cannot be denied as it is probably a consequence of its mode of action. Nevertheless, a statistically significant response for ACR20 compared to placebo treated patients was seen in the TNF-refractory ATTAIN population as early as week 2 [Genovese *et al.* 2005]. In this same trial, detailed analysis of patient-centered outcomes [Westhovens *et al.* 2006] revealed a significant difference in fatigue between the abatacept treated patients and the placebo groups as early as week 4.

Given the specific pharmacokinetic profile many physicians ask themselves at which time point to stop treatment because of lack of efficacy. A recent analysis of response dynamics in the early RA AGREE trial [Westhovens *et al.* 2009d] demonstrated that of all patients achieving moderate DAS activity (>3.2, <5.1) at 6 months, 51.3% achieved DAS 28 remission (<2.6) or at least low DAS activity (>2.6, <3.2) at 12 months. From those achieving low DAS activity at 6 months, 59.4% achieved DAS remission at 12 months. In clinical practice it is probably wise to stop therapy when there is no response at 16 weeks, but when there is some improvement somewhere in line with an ACR20 response, the chance that patients will get significantly better is high.

Important improvements in patient-centered outcomes

In most of the abatacept trials there was an important focus on patient-centered outcomes. The evolution of the SF 36 physical and mental summary scores but also of the SF36 subdomains was significantly more favourable in Abatacept treated patients compared to the controls, even in the TNF-refractory population [Westhovens *et al.* 2006]. Interestingly in ATTAIN the SF36 physical component score improved in 44.6% and remained status quo in 45.8% of patients on active drug, while in the placebo arm improvement was reported in only 23.1% and 63.1% reported no change. A similar significant difference between active and placebo was found for the evolution of all SP36 subscores, except for 'role emotional'.

In the 5-year AIM evaluation [Westhovens *et al.* 2009a], 77.1% of patients having a physical component score at year 1 in the normal range (>50) stayed in this normal range up to year 5; 71.2% of patients with a mental component score in the normal range (>50) stayed in this range up to year 5.

Several specific patient-centered outcome parameters were additionally evaluated in an

explorative way during the abatacept clinical development plan. In an analysis of the AIM trial, external home help (help provided by someone other than family or friends) decreased significantly in the group treated with abatacept plus methotrexate compared to patients continuing methotrexate alone [Li *et al.* 2008]. An activity participation questionnaire assessing firstly the number of days of being unable to perform one's usual activities because of RA in the past month, and secondly a score of how often one's usual activities could be completed, was validated using data from the AIM and ATTAIN trial. Sensitivity to change as well as the ability to distinguish active treatment from placebo was demonstrated [Li *et al.* 2009]. Measures of fatigue, sleep and other patient relevant outcomes were assessed and validated during abatacept trials and although these were not primary outcome features, the results give useful insights in what can be achieved on a level of daily problems encountered by RA patients [Wells *et al.* 2008, 2007].

Long-term safety

Safety and especially long-term safety is crucial for any treatment of a chronic disease. In the early RA AGREE trial there were no differences in side effects between MTX alone and MTX + abatacept treatment the first year [Westhovens *et al.* 2009f].

In the global safety database overall frequencies of adverse events (AEs; 88.8% *versus* 85.1%), serious AEs (SAEs;14.0% *versus* 12.5%) and malignancies (1.4% *versus* 1.1%) were similar in abatacept- *versus* placebo-treated patients respectively (regardless of the potential relationship to the study therapy). Discontinuations due to SAEs were 2.8% in the abatacept group *versus* 1.6% in the placebo group. The frequency of serious infections was low overall (3.0% *versus* 1.9% in Abatacept- *versus* placebo-treated patients, respectively). Acute infusional AEs (9.8% *versus* 6.7% in the abatacept *versus* placebo groups, respectively) were mostly mild to moderate in intensity [Sibilia and Westhovens, 2007].

As some side effects might only become obvious with longer use of a drug, it is of utmost importance to continue safety evaluations over time. The observation of patients in open label extensions studies following the pivotal abatacept trials provides good quality data to judge numbers of adverse events/patient years exposure to drug and because patients are seen monthly for their perfusions, problems like recall bias are unlikely. The latest evaluation of the safety database evaluating 4150 subjects exposed to abatacept with a median exposure (range) of 26.2 (1.9–83.4) months responsible for 10,365 patient years [Smitten *et al.* 2008] revealed no particular relevant safety concerns with 2.98 serious infections/100 patient years and 2.73 hospitalizations for infections/100 patient years. There was no increase over time for infection risk. The same was true for malignancies. Opportunistic infections were rarely seen and only six cases of tuberculosis (TB) were reported, mainly coming from countries where TB is endemic. Over time also acute infusional events and newly occurring autoimmune events appear to be very rare.

Of specific interest is a close look to the ATTEST (Abatacept or infliximab *versus* placebo, a Trial for Tolerability, Efficacy and Safety in Treating rheumatoid arthritis) trial [Schiff *et al.* 2008]. By including an abatacept as well as an infliximab arm in the randomization process, in this trial a potential problem of confounding by indication could be avoided and the relative safety of both drugs in comparison to placebo could be judged. Although only powered for efficacy between abatacept and placebo and between infliximab and placebo, there was an important difference for serious adverse events, mainly infections and perfusion reactions, in favor of abatacept. Combining abatacept with another biologic is not recommended as combination therapy is associated with more side effects [Weinblatt *et al.* 2007, 2006]. In a recent meta-analysis evaluating the risk of serious infections in randomized placebo controlled trials of rituximab, abatacept and anakinra, no significant increased risk was found for abatacept and rituximab [Salliot *et al.* 2009].

Summary and future directions

Data from the extensive clinical development program of abatacept and especially the long-term follow up data of efficacy and safety provide us with a favourable 'global package' demonstrating the opportunities for this treatment in several RA populations. Potential reasons for the high attrition rates of this drug are discussed above. Being followed in a trial might induce a bias towards more long-term adherence to treatment, although specifically in a biologic naïve population some patients in long-term extensions might also have experienced a certain pressure to switch to one of the other newly available drugs. Safety data should always be judged very carefully because

most trials are not powered to evaluate infection risks and patients with more severe infection risks might have been excluded from trials. Costimulation blockade might have a specific effect in very early RA which needs further investigation; an explorative trial of 6 months monotherapy in very early RA [Emery *et al.* 2009] suggests that abatacept is able to change the course of the disease even after stopping the drug after 6-months of treatment. Cost-effectiveness of abatacept is reported to be beneficial and comparable with other biologics [Vera-Llonch *et al.* 2008a,b]. Additional data are awaited from registries evaluating this therapy in a daily practice setting, although the results might be influenced by a confounding by indication bias, since currently this drug is more often used in more refractory RA patients. A recent meta-analysis on Cochrane reviews of randomized-controlled trials of biologics for RA discusses data of indirect comparisons of efficacy and safety of all these drugs [Singh *et al.* 2009]. Ultimately head-to-head comparisons are needed to evaluate differences between biologics and because pharmaceutical companies are less interested in running such trials, academia and organizations of rheumatologists but also payers and health organizations should take their responsibilities.

Conflict of interest statement

Dr Westhovens is a consultant for BMS, Centocor, Schering Plough and Roche; he holds the UCB chair of RA care at the KU Leuven. Dr Verschueren holds the Wyeth chair in early RA at the KU Leuven.

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