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Abatacept for the treatment of systemic lupus erythematosus

Victor R. Pimentel-Quiroz*, Manuel F. Ugarte-Gil†,‡ and Graciela S. Alarcón†

*Rheumatology Department, Hospital Guillermo Almenara Irigoyen, EsSalud, Lima, Peru; †School of Medicine, Universidad Científica del Sur, Lima, Peru; ‡Division of Clinical Immunology and Rheumatology, School of Medicine, The University of Alabama at Birmingham, Birmingham, AL, USA

ABSTRACT

Introduction: Due to improvements in our understanding of the pathogenesis of systemic lupus erythematosus (SLE), several target drugs have been and are being developed. One of the possible targets in SLE is co-stimulation between antigen-presenting cells and T cells. Abatacept is a co-stimulation moderator approved for the treatment of several autoimmune diseases. There is an unmet need for drugs with a better efficacy and safety profile when treating patients with SLE.

Areas covered: In this review, the authors discuss the mechanism of action of abatacept including its role in the immune system and glomerul, and relevant information about its clinical efficacy and safety. Possible explanations for the failure of previous randomized clinical trials are also discussed.

Expert opinion: Abatacept has demonstrated efficacy in other autoimmune diseases, but in SLE, randomized clinical trials have failed to achieve their primary outcome. Despite these disappointing results and based on its mechanism of action, abatacept seems to have a role in lupus nephritis and arthritis. This should be corroborated with new trials which hopefully will overcome the design pitfalls of the ones conducted to date.

1. Introduction

Systemic lupus erythematosus (SLE) is a severe and potentially life-threatening multisystem autoimmune disease with a prevalence that ranges between 7.4/100,000 in Caucasians from the USA and 159.4/100,000 in African descendants from the United Kingdom; the great majority of those affected is women in their childbearing years. Yet, despite the fact that the prevalence data from Asia are somewhere in between these two figures (for 100,000 inhabitants), the majority of patients with lupus worldwide are Asians. The disease is characterized by the presence of autoreactive cells and aberrant antibody responses to multiple self-antigens; its course and prognosis is characterized by remissions and flares.

Although significant strides have been made in the management of SLE over the last several decades, mortality rates remain high with current treatment modalities; furthermore, treatments currently used for SLE have many undesirable adverse effects that impact on patients’ health and quality of life. Dependence on glucocorticoids as well as inefficacy and/or toxicity of immunosuppressive agents used for severe disease manifestations represent considerable challenges in the treatment of SLE.

In terms of the pathophysiology of SLE, as we understand it to date, there are prominent immune system alterations involving B cells, T cells, and cells of the monocytic lineage resulting in a significant increased number of autoantibody producing cells. The activation of B cells and T cells requires their stimulation by specific antigens. Professional antigen presenting cells (APCs) including B cells process these antigens into peptides which are then presented to the T cells through their surface human leukocyte antigen (HLA) molecules. The activated T cells in turn stimulate the B cells to produce autoantibodies; the interaction of B cells and T cells requires of accessory molecules such as those of the CD40/CD40L and CD80–CD86/CD28 pathways. Loss of self-tolerance contributes significantly to the development and persistence of autoreactive T and B cells after their maturation and has been the subject of intense research interest. An improved understanding of SLE pathogenesis may allow the identification of new therapeutic targets. Among the currently available compounds, abatacept, a T-cell co-stimulation modulator, may have a therapeutic role in SLE.

Abatacept was initially approved for the treatment of moderately and severely active rheumatoid arthritis (RA) refractory to conventional disease modifying antirheumatic drugs or an antitumor necrosis factor (TNF) compound. Subsequently, it was also approved for the treatment of polyarticular idiopathic juvenile arthritis. This biological agent has not yet been approved for the treatment of SLE, but there are several clinical trials with promising results, which may provide a new opportunity for SLE patients.

2. Overview of the market

According to the European League Against Rheumatism (EULAR)”s recommendations, the treatment of SLE patients without major-organ involvement should include glucocorticoids, antimalarials, and nonsteroid anti-inflammatory drugs; immunosuppressive drugs should be added in severe and refractory cases. Major organs involved include the central...
Box 1. Drug Summary

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Abatacept</th>
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<tbody>
<tr>
<td>Phase</td>
<td>III</td>
</tr>
<tr>
<td>Indication</td>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td>Pharmacology description</td>
<td>T-cell inhibitor</td>
</tr>
<tr>
<td>Route of administration</td>
<td>IV or SC</td>
</tr>
<tr>
<td>Pivotal trial(s)</td>
<td>NCT00119678, NCT00430677, NCT00774852</td>
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</table>

3. Introduction of the product

Abatacept, a CTLA-4 agonist, modulates T cells co-stimulation, by interrupting the interaction of CD80/CD86 with CD28. It was initially approved for the treatment of RA in which it has been shown that in combination with methotrexate (MTX) is effective in MTX naïve RA patients compared to MTX alone; it has also been shown to be effective in patients with inadequate response to MTX [17] or to anti-TNF therapy.[18]

Based on the mechanism of action of abatacept, Daikh et al. studied a murine model of lupus nephritis using CTLA4ig. On their first publication, these authors showed long-lasting inhibition of autoantibody production and a diminished occurrence of renal disease when CTLA4ig combined with anti-gp39 was administrated to NZB/NZW F1 (B/W) mice [19] compared to CTLA4ig alone; subsequently, they showed that, in B/W mice with advanced nephritis, treatment with CYC and CTLA4ig was more effective than either agent alone in reducing their renal disease manifestations and prolonging their survival.[20]

4. Chemistry

Abatacept is a first generation homodimeric fusion protein [21] produced by fermentation of an ovary cell line from a genetically engineered Chinese hamster.[5] The fusion protein gene contains the coding sequence for the CTLA – 4 domain of rat cytotoxic T lymphocyte antigen-4 (CTLA-4), and the IgG1 domain of mouse immunoglobulin (human recombinant IL-1 receptor antagonist) or sifalimumab (interferon alpha inhibition), and finally, inhibition of T-cell activation as abatacept (fusion protein of CTLA-4 and the Fc portion of human IgG1). Currently, the only biological drug approved worldwide is belimumab, a fully humanized IgG1 monoclonal antibody that inhibits BlyS activity.[16] The only other biological therapy commonly used off label for severe disease manifestations is rituximab.[15]

5. Pharmacodynamics

As already noted, CTLA-4 as well as abatacept have higher affinity for CD80/CD86 in APCs than CD28 which results in an inhibitory signal to the T cells and their dependent immune responses (Figure 1).[8] The antibody response is blocked about 95% in over 80% of subjects treated with abatacept in doses higher than 8 mg/kg.[22] Serum abatacept concentrations of 10–50 μg/ml are necessary to obtain maximal clinical efficacy according to in vitro studies.[22]

The ability of abatacept to inhibit T-cell proliferation and cytokine production (TNF-α, IL-2, 4, 5, 6, 17, and IFN-γ) has been well-documented.[5] Furthermore, abatacept also inhibits T follicular helper cell formation and induces CD4+CD25 + naïve T cells to convert into CD4+CD25+ T regulatory cells.[24]

There are also other cells that may express CD80 including podocytes as has been shown in patients with many glomerular diseases, lupus nephritis included. In these patients the administration of abatacept is followed by a decreased in proteinuria [25] which results from the inactivation of the migration of podocytes promoted by β1 integrin which in turn is induced by CD80.[26] In a clinical trial, the efficacy and safety of 52 – week treatment with IV abatacept compared with placebo in patients with SLE and active classes III or IV lupus nephritis was evaluated; although there were no differences among treatment arms in terms of the trial’s main end-point, time to confirmed complete response, abatacept showed evidence of biologic activity (greater improvements in

nervous system (primary neuropsychiatric lupus) and the kidneys (lupus nephritis).[9] The treatment of neurological involvement in SLE, including seizures, peripheral/cranial neuropathy, optic neuritis, transverse myelitis, brainstem disease, or coma requires a regimen of intravenous (IV) methylprednisolone followed by IV monthly cyclophosphamide (CYC).[9,10] In lupus nephritis, the treatment consists of induction therapy followed by a longer period of maintenance therapy.[9,11] The American College of Rheumatology (ACR) and the EULAR recommend mycophenolate mofetil (MMF 2–3 g daily) or CYC along with glucocorticoids as induction therapy.[9] There are two regimens of IV CYC: low dose CYC (500 mg IV once every 2 weeks for a total of six doses) followed by maintenance therapy with daily oral azathioprine (AZA) or daily oral MMF (called Euro-Lupus Nephritis Trial regimen [12]) and high dose CYC (500–1000 mg/m² IV once a month for six doses [13,14]), followed by maintenance treatment with MMF or AZA (usually referred as the NIH regimen, for the National Institutes of Health where it was developed). A study comparing the two regimens in a mainly Caucasian population showed similar rates of lupus nephritis flares, end-stage renal disease, and doubling of serum creatinine.[12]

Despite currently available treatments, the mortality rates in SLE remain higher than in the general population; furthermore, these therapies have many undesirable adverse effects that impact on the patients’ health and their quality of life.[2,3] Dependence on glucocorticoids and inefficacy and/or toxicity of immunosuppressive agents used for severe disease manifestations represent considerable challenges in the treatment of these patients.[4] Therefore, new compounds with a better efficacy toxicity profile are highly desirable.

Biological therapies against specific molecular targets that play a role in lupus pathogenesis have been developed,[15] among them, B-cell targeted treatments as rituximab (anti-CD20) or epratuzumab (anti-CD22), BLYS targeted therapy as belimumab, cytokine blockade targeted treatment as anakinra (human recombinant IL-1 receptor antagonist) or sifalimumab (interferon alpha inhibition), and finally, inhibition of T-cell activation as abatacept (fusion protein of CTLA-4 and the Fc portion of human IgG1). Currently, the only biological drug approved worldwide is belimumab, a fully humanized IgG1 monoclonal antibody that inhibits BLYS activity.[16] The only other biological therapy commonly used off label for severe disease manifestations is rituximab.[15]
6. Pharmacokinetics

Abatacept is administered IV or subcutaneous (SC) at a dose of approximately 10 mg/kg on days 1, 15, 29 and every 4 weeks thereafter. After multiple IV infusions, the maximum serum concentration (C_{max}) and the area under the curve rise as the dose is increased from 2 mg/kg to 10 mg/kg. At 10 mg/kg a steady-state serum concentration is achieved in 60 days with a mean trough level of 24 μg/ml. Peak serum concentration is about 295 μg/ml, the volume of distribution 0.07 l/kg, and the terminal half-life 13.1 days.[5,22] Systemic exposure to abatacept increases as a function of the dose; regardless of the route of administration, accumulation has been demonstrated.[22,23] The bioavailability of abatacept following its SC administration relative to its IV administration is 78.6% and its mean pharmacokinetic parameters are comparable between both forms of administration.[28] The clearance of abatacept is higher with increasing body weight, but it is not affected by age and sex. Regarding drug–drug interactions, clinical data do not suggest any interactions with the concomitant treatment with other antirheumatic agents. Furthermore, concomitant antirheumatic drugs do not influence the clearance of abatacept.[5,22]

7. Overview of clinical trials

7.1 Non-Life Threatening SLE

The first randomized clinical trial (RCT) of abatacept in SLE included patients with active arthritis, discoid lesions, or serositis (pleuritis or pericarditis). For this trial, disease activity was assessed with the British Isles Lupus Activity Group (BILAG). The dose of abatacept used was of approximately 10 mg/kg, with loading doses in weeks 0, 2, and 4 followed by abatacept administered every 4 weeks. Abatacept was added over the background therapy which consisted of prednisone or equivalent (not higher than 30 mg/day), antimalarials and/or immunosuppressive drugs (including AZA, MTX, or MMF) as well as therapies aimed at controlling proteinuria. The primary outcome of this RCT was the proportion of patients with new flares (defined as a BILAG A or B). Abatacept was not superior to placebo in achieving the primary or secondary outcomes of this trial. However, in a post-hoc analysis, abatacept was superior to placebo in preventing severe articular flares, and also, in preventing flares defined as physician global assessment of whether a patient did or did not present symptoms of acute SLE flare. Furthermore, in the subgroup of patients on a low dose of prednisone (≤7.5 mg/day), the proportion of patients who did not develop a new flare was higher in the abatacept than in the control group. In addition, abatacept was superior to placebo in increasing the physical component of the short form 36 and in improving fatigue and sleep disturbances.[29]
7.2 Nephritis Trials

In the ACCESS trial, abatacept was added to the background therapy, which consisted of IV CYC 500 mg every 2 weeks for six doses, followed by AZA 2 mg/kg/day and prednisone at a dose of 60 mg/day for 2 weeks which was tapered to 10 mg/day over the subsequent 10 weeks. Patients with classes III or IV lupus nephritis with or without features of class V and with a urinary protein-to-creatinine ratio > 1.0 were included. The dose of abatacept was approximately 10 mg/kg, with a loading dose on weeks 0, 2, and 4, followed by abatacept administered every 4 weeks thereafter. Abatacept did not improve the patients’ outcome at either 24 or 52 weeks. Complete response was defined as a urinary protein-to-creatinine ratio < 0.5, serum creatinine level ≤ 1.2 mg/dl or ≤125% of baseline and adherence to the tapering of prednisone to 10 mg/day by week 12. Complete response was obtained in 33% of patients from the abatacept group and in 31% of patients from the control group; partial or complete responses were 59% in both groups.[30]

Another lupus nephritis RCT included the addition of abatacept to the background therapy, which consisted of a regimen of MMF (dose between 2 and 3 g/day) and prednisone at a dose of 30–60 mg/day for 4 weeks followed by tapering to 10 mg/day over the subsequent 11 weeks; however, this tapering was not mandatory. In this study, two doses of abatacept were given; the low dose group received around 10 mg/kg with a loading dose on weeks 0, 2, and 4, and the same dose every 4 weeks thereafter and the high dose group received 30 mg/kg for four doses (weeks 0, 2, 4, and 8) and 10 mg/kg every 4 weeks subsequently.[27] Patients in this RCT had active class III or IV lupus nephritis with or without features of class V; patients with only chronic lesions were excluded. To enter this trial, patients had to have an active urinary sediment and urinary protein-to-creatinine ratio ≥ 0.44. A complete response was defined as an estimated glomerular filtration rate ≥90% of its baseline level (if it was normal) or of its 6-month pre-flare value (if it was abnormal at baseline), a urinary protein-to-creatinine ratio < 0.26 and inactive urinary sediment for at least two consecutive visits. Abatacept failed to reach the primary end-point of the trial, complete remission; however, several criticisms to this study have been raised mainly because of the definition of remission used. For example, the goal for proteinuria was stricter than the one used in the ACCESS trial, or in the rituximab trial for lupus nephritis (Lupus Nephritis Assessment with Rituximab [LUNAR]) [31] or on the MMF’s Aspreva Lupus Management Study (ALMS) trial [32]; in these three trials, the goal was a urine protein/creatinine ratio of less than 0.50. Furthermore, using the definitions of remission of these trials, abatacept would have been associated with a higher probability of remission and it seemed to be even better in patients with nephrotic proteinuria.[33]

According to the definition of complete response from the ACCESS trial, it would have occurred in 33.3% of patients on the high dose of abatacept group, in 36.4% of those on the low dose and in 19.0% of patients in the control group. If instead the definition of complete response from the LUNAR trial is used, the response rates would have been 24.2%, 22.2%, and 6.0% for the high and low doses of abatacept and the control group, respectively. If the definition of complete response from the ALMS trial would have been used, the response rates for the three groups would have been 28.3%, 25.3%, and 13.0%, respectively.[33] Finally if instead, the ACR definition of remission would have been used, a goal for proteinuria of less than 0.20 g/g and an estimated glomerular filtration rate within 25% of baseline or screening value,[34] patients with nephrotic proteinuria on the high dose of abatacept’s arm achieved remission more frequently than controls; in contrast, neither high nor low dose of abatacept were associated with remission in patients with non-nephrotic proteinuria.[33]

8. Safety and tolerability

In three RCT in SLE patients, the percentage of adverse events (AEs) was similar in the abatacept and the placebo groups; these data are depicted in Table 1.[27,29,30] In the first RCT, Merrill et al. reported, however, that severe (S) AEs, occurred more commonly among the abatacept-treated groups than in the control-treated group (19.8% vs. 6.8%); treatment-related SAEs occurred also more frequently among the abatacept-than the control-treated groups (5.8% vs. 3.4%).[29] In the ACCESS trial, SAEs occurred with similar frequency among the abatacept- and the control-treated groups (28.8% and 29.4%, respectively) as they were the proportion of patients who died in each treatment group (1.5% for the placebo group and 0.0% for the abatacept group).[30] In the RCT reported by Furie et al., SAEs were similar among three groups (high dose, low dose, and placebo); in fact, deaths occurred at higher frequency among the placebo (7.0%) than the high dose (5.1%) and the low dose groups (2.0%); pneumonia was the most common serious infection, but its incidence was similar among the three groups. Herpes zoster infection occurred more frequently among the high (3.0%) and low (6.1%) dose groups than in the placebo group (0.0%) but gastroenteritis did occur more frequently among the high dose (5.1%) than the low dose (1.0) and placebo-treated groups (2.0%). Discontinuation due to SAEs was more common in the high (14.1%) and low dose (12.1%) groups than in the placebo group (7.0%). Finally, peri-infusional AEs were marginally more common among the high dose group (23.2%) than the low dose (18.2%) and placebo groups (17.0%). The incidence of acute infusional events was 4% in the abatacept groups in the RCT reported by Furie et al.[27]

In RA with over 12,000 patient years of experience, pneumonia, UTI, and cellulitis have been the most frequently reported infections whereas non-melanoma skin cancer, lung cancer, and lymphoma have been the most frequently reported neoplasms; however, the overall frequency of cancer has not been higher than expected in the general population. Autoimmune events such as vasculitis and psoriasis, and rarely SLE and multiple sclerosis have also been reported.[35,36]

9. Conclusions

Co-stimulatory blockade seems to be a promissory therapeutic target. Despite the disappointing results of abatacept RCTs, a new and more efficient definition of outcomes on SLE RCTs
Table 1. Adverse events reported in SLE trials of abatacept.

<table>
<thead>
<tr>
<th></th>
<th>Non-nephritis trial</th>
<th>Nephritis trials</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Standard of care plus abatacept or placebo [29]</td>
<td>Cyclophosphamide plus abatacept or placebo [30]</td>
</tr>
<tr>
<td></td>
<td>Abatacept (n = 121)</td>
<td>Control (n = 59)</td>
</tr>
<tr>
<td>AE (%)</td>
<td>90.9</td>
<td>91.5</td>
</tr>
<tr>
<td>Treatment-related AE</td>
<td>48.8</td>
<td>47.5</td>
</tr>
<tr>
<td>SAE (%)</td>
<td>19.8</td>
<td>6.8</td>
</tr>
<tr>
<td>Death (%)</td>
<td>0.8</td>
<td>0.0</td>
</tr>
<tr>
<td>Infections (%)</td>
<td>47.1</td>
<td>47.0</td>
</tr>
<tr>
<td>URI</td>
<td>20.7</td>
<td>15.3</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>2.5</td>
<td>11.9</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>11.6</td>
<td>6.8</td>
</tr>
<tr>
<td>UTI</td>
<td>10.7</td>
<td>8.5</td>
</tr>
<tr>
<td>Serious infections (%)</td>
<td>2.5</td>
<td>1.7</td>
</tr>
<tr>
<td>Pneumonia (%)</td>
<td>4.0</td>
<td>4.0</td>
</tr>
<tr>
<td>Herpes zoster (%)</td>
<td>3.0</td>
<td>6.1</td>
</tr>
<tr>
<td>Gastroenteritis (%)</td>
<td>5.1</td>
<td>1.0</td>
</tr>
<tr>
<td>UTI (%)</td>
<td>0.0</td>
<td>2.0</td>
</tr>
<tr>
<td>Malignancy (%)</td>
<td>0.8</td>
<td>0.0</td>
</tr>
</tbody>
</table>

SLE: Systemic lupus erythematosus; AE: adverse event; SAE: serious adverse event; URI: upper respiratory tract infection; UTI: urinary tract infection. *Infection-related grade 3 or higher AEs.
could provide information about its usefulness in the treatment of SLE.

The safety profile of abatacept in SLE and RA suggest abatacept could be considered an option in refractory cases.

10. Expert opinion

Even though three abatacept’s SLE trials have failed to achieve their primary outcomes; based on the mechanism of action of this compound, effects over the immune system in general, and the renal podocytes in particular, there is still some possible role for its use for the treatment of lupus nephritis. Furthermore, abatacept has been used in five patients with focal and segmental glomerulosclerosis after plasmapheresis with partial or complete remission for a follow-up of at least 10 months.[26] But, this has not been a uniform finding since other cases without response to abatacept therapy have also been reported.[37]

Further evidence in support of the role of abatacept for the treatment of kidney involvement is the successful use of belatacept (another CTLA-4 agonist), in patients receiving renal allografts. In this setting, belatacept has been associated with less chronic kidney scarring and a better kidney function compared with calcineurin inhibitors albeit no difference in preventing acute rejection, graft loss, and death has been reported.[38]

Based on this information and the post-hoc analyses of the lupus nephritis trial of MMF and abatacept,[33] a new RCT using abatacept and MMF has been started [39]; this new RCT could define the usefulness of abatacept on lupus nephritis. The RCTs of lupus nephritis conducted so far could have failed for a number of reasons. First, the definition of remission may have been too stringent; in fact, when alternative definitions were used, the combination of abatacept and MMF seems to be effective. Second, the protocols allowed the intake of a moderate dose of prednisone which may have prevented observing the benefits of the combined regimen. In future trials achieving an adequate prednisone tapering should be considered a secondary end-point. Finally, the combination of abatacept and CYC does not seem to be a good option, as there is no evidence of its clinical efficacy in terms of the many variables examined (proteinuria, normalization of complement levels negativization of anti-dsDNA antibody titers, and improvements in BILAG and health-related quality of life scores).

In addition, in non-renal disease activity, abatacept has been effective on preventing articular flares and also on improving the patients’ quality of life, their fatigue and their sleep problems [29]; these results suggest that abatacept could be effective for some SLE manifestations. Furthermore, in patients receiving a low dose of prednisone (≤7.5 mg/day), abatacept has been effective in preventing new flares; so, the use of prednisone at higher doses may be a possible explanation for the failure of this RCT. Furthermore, as previously reported a dose of prednisone higher than 7.5 mg/day is not safe in SLE patients,[40] so one of the end-points of a RCT should be achieving a dose of prednisone at or below that threshold. It seems possible that this abatacept could be effective in this subpopulation of patients. Another RCT, using abatacept 125 mg/week SC for articular involvement among SLE patients will be started soon.

Declaration of interest

MF Ugarte-Gil is a secondary investigator in Bristol-Myers Squibb trials. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

References

- = of interest, ↔ = of considerable interest


- Epidemiological data are specified.


- ↔ The need and importance of new therapies for SLE is emphasized.


- ↔ The role of abatacept in systemic lupus erythematosus is described.


14. Boumpas DT, Austin HA 3rd, Vaughn EM, et al. Controlled trial of pulse methylprednisolone versus two regimens of pulse...

**New therapies in SLE are very well specified.**

• Murine models in SLE are specified.

• Pharmacological features of abatacept are amply described.

**The clinical trial of abatacept and MMF in patients with lupus nephritis is described.**

• The randomized clinical trial of abatacept in non-life-threatening manifestations.

• The randomized clinical trial of abatacept and CYC in lupus nephritis is described.

• The efficacy of abatacept and MMF using alternative outcomes is presented.