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Original Article

Abatacept Use in Rheumatoid Arthritis: Evidence Review and Recommendations☆

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ABSTRACT

Objective: To review the clinical evidence on abatacept and to formulate recommendations in order to clear up points related to its use in rheumatology.
Method: An expert panel of rheumatologists objectively summarized the evidence on the mechanism of action, practicalities, effectiveness and safety of abatacept, and formulated recommendations following a literature review. The level of evidence and degree of recommendation was established.
Results: The document presents 21 statements focused on evidence or recommendations on abatacept (14 evidence summaries and 9 recommendations). The level of evidence was 2b or higher according to the Oxford Centre for Evidence-Based Medicine scale on 14 occasions. The degree of the recommendation was A in two recommendations, C in one, and D in the rest. It was considered important to make recommendations on aspects with lower levels of evidence.
Conclusions: This is a practical document to supplement the summary of product characteristics.
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El uso de abatacept en artritis reumatoide: revisión de la evidencia y recomendaciones

Palabras clave:
Abatacept
Práctica basada en evidencias
CTLA-4-Ig

RESUMEN

Objetivo: Revisar la evidencia clínica sobre abatacept y emitir recomendaciones con objeto de aclarar su uso en Reumatología.
Método: Un panel de expertos reumatólogos resumió de forma objetiva las pruebas existentes sobre el mecanismo de acción, modo de uso, eficacia y seguridad de abatacept y emitió recomendaciones de uso en situaciones concretas, previa revisión de la bibliografía. Se estableció el nivel de evidencia de las pruebas y el grado de apoyo de dichos datos a las recomendaciones emitidas.
Resultados: El documento presenta 21 enunciados resumen de la evidencia encontrada o recomendaciones sobre abatacept (14 enunciados y 9 recomendaciones). El nivel de evidencia es superior a 2b según la escala de Oxford del Centro de Medicina Basada en la Evidencia en 14 ocasiones. El grado de apoyo de las recomendaciones es A en 2 recomendaciones, C en una y D en el resto. Se consideró importante realizar recomendaciones precisamente en los aspectos con menor grado de evidencia.
Conclusiones: Se trata de un documento práctico como complemento a la información en ficha técnica.
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Introduction

Since the advent of biological agents, clinicians have accumulated a large amount of relevant information quickly. This has made it difficult to disentangle the differences between the various biological agents: 5 TNF inhibitors, anakinra, rituximab, abatacept and tocilizumab. This has led to a series of simplistic conclusions such as that "all biological agents are equal" or that "everyone would have a similar safety and tolerability profile'. The absence of direct comparative studies has also helped, although there are meta-analysis based clinical trials that have provided some light on these differences.[1–4]

Abatacept is a parenterally administered drug characterized by a different mechanism of action than other biological agents. It is a fusion protein consisting of the extracellular domain of CTLA-4 expressed on the T cell and a modified Fc fragment of human immunoglobulin IgG1. This protein modulates costimulation when the antigen presenting cell interacts with the T lymphocyte.

The indications for abatacept are restricted to rheumatoid arthritis (RA) and polyarticular juvenile idiopathic arthritis (JIA). It is currently approved for patients with inadequate response to previous treatment with one or more disease modifying drugs (DMARDs) or TNF inhibitor (at least one in the case of JIA).[5]

The objective of this document is to provide the clinician with a review of the evidence of this biological agent, focusing especially on the most relevant aspects of its efficacy in RA and existing data to date on safety. The document presents 21 statements focused on evidence or recommendations, whose mission is to try to resolve any questions that might arise with its use.

Methods

The head of the project (EMM) selected 7 rheumatologists; all were experts in RA. All have extensive experience in the use of biologic therapies, as well as being authors of scientific articles on the subject. Besides these features, the panelists were chosen based on their geographical distribution, which tried to be as close as possible due to their small number. There were two meetings, the first on May 20, 2011 and a second one on November 14, 2011. At the first meeting, issues were agreed upon, as well as the scope and format the document should have, and tasks were distributed. All experts conducted a non-systematic review of the scientific literature and were responsible for drafting the document. In addition, 3 reviewers (LL, LR and LC) from the previous group were incorporated into the project from the beginning, conducted systematic reviews of questions that the panelists considered as disputable and that were not included in the Cochrane meta-search for abatacept.[6] During the last meeting, consensus statements were drafted summarizing late evidence and its clinical applicability. The level of evidence (LE) and degree of recommendation (DR) were established by one reviewer (LC), based on the Oxford Centre for Evidence-Based Medicine[7] scale. When the DR could not be used because of lack of a recommendation, it was labeled "not applicable" (NA).

Results

A tabular summary of the evidence and recommendations is shown in Table 1 together with the appropriate level of evidence and degree of recommendation. Below is a description of the various aspects of abatacept.

Mechanism of Action

Abatacept is the first therapeutic agent approved for treatment of RA that acts by selectively blocking the activation of T cells by disrupting coestimulatory[8] signals. The T cell plays a key role in the pathogenesis of RA.[9,10] In a simplified form, T cell activation requires 2 signals by key antigen presenting cells.[11] The first is that of antigen presented in the context of the major histocompatibility complex system, recognized by the T cell receptor. The second signal is provided by costimulatory molecules such as CD80 and CD86, binding to CD28 on the T cell. This binding to CD28 leads to T cell proliferation and production of cytokines.[8,12] CTLA-4 is expressed physiologically on the surface of activated T cells and its basic task is facilitating CD28 binding to CD80/CD86, and thus suppressing T cell activation.[12,13] Abatacept is a fusion protein consisting of the extracellular domain of human CTLA-4 linked to an Fc fragment of human IgG1 that selectively inhibits the second signal, blocking the binding of CD80/CD86 to CD28 (Fig. 1).

Several in vitro and in vivo models have shown that selective abatacept induced blockade of costimulation is accompanied by a regulation of the function of CD4+T cells, a reduction of proinflammatory cytokines, autoantibodies and metalloproteinases and a increased function of regulatory T cells.[14–19] Although data on the mechanism of action in RA patients are limited, it is known that abatacept reduces the inflammatory component of rheumatoid synovium and the expression of genes involved in bone destruction.[18] In addition, CTLA-4 has an antiresorptive effect, binding directly to the precursors of osteoclasts and inhibiting their differentiation.[12,20]

The Fc fragment of abatacept is designed with several mutations that inactivate it. Thus, abatacept does not bind to low affinity receptors CD16 and CD32 and does so suboptimally to high affinity receptor CD64.[21] Because of this, abatacept is not accompanied by antibody-dependent cellular or complement cytotoxicity.

Particular Mode of Administration and Evidence/Recommendation 1. Abatacept is Administered as an Intravenous Infusion of Short Duration and Has a Low Incidence of Infusion Reactions (LE: 1b, DR: NO)

Abatacept is administered as a short intravenous infusion at a dose of approximately 10 mg/kg. After the first infusion, abatacept is administered at 2 and 4 weeks and then every 4 weeks.[5] Details on dosage, route of administration, and precautions to take before and during the administration are shown in Table 2. Intravenous administration of abatacept has the characteristic that is administered in 30 min and rarely requires the use of premedication since infusion reactions are infrequent.[6,22,23] In general, the dose and administration intervals of abatacept are often kept constant over time.[24]

Although abatacept is expected to be approved for subcutaneous administration within the next few months,[25,26] at present in Europe it is only available for intravenous administration. Subcutaneous administration offers patients the convenience of being home administered. In any case, the patient's preferences with respect to the route of administration must be explored. It is reported that 50% of patients prefer the intravenous to subcutaneous administration due to the calming effect of the presence of medical personnel and security of hospital treatment, the distaste for self-administration and frequency of administration, generally more spaced intervals than with subcutaneous.[27]

There is a substudy of the AGREE trial in which patients who achieved remission at 2 years (ESR DAS28<2.6) were randomized in a double-blind fashion to receive abatacept at doses of 10 mg/kg

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