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Practice Guidelines for the Use of Subcutaneous Abatacept☆

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ABSTRACT

Objective: To review the clinical evidence on subcutaneous (SC) 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, practicality, effectiveness, and safety of abatacept sc and formulated recommendations after a literature review.
Results: The efficacy and safety of abatacept sc were studied in 7 clinical trials, 3 double-blind, 3 open, and one mixed, with the following endpoints: comparison against abatacept iv, impact on immunogenicity, effect of replacing iv by sc, abatacept sc in monotherapy, and non-inferiority to adalimumab. No significant differences were found between sc and iv abatacept on efficacy or safety. The development of sc abatacept has allowed a complementary study to the iv, formulation, thus making the abatacept profile better defined.
Conclusions: This is a practical document to supplement the summary of product characteristics. In summary, abatacept sc is presented as an effective and safe drug and, therefore, as an alternative to use within the broad armamentarium the rheumatologist has to treat RA. It also has the advantage of being the only biological agent that can be administered iv and sc which can facilitate its use in certain patients.

Documento práctico para el uso de abatacept subcutáneo

Palabras clave:
Abatacept
Práctica basada en pruebas
Cytotoxic T-lymphocyte antigen 4

RESUMEN

Objetivo: Revisar la evidencia clínica sobre abatacept subcutáneo (sc) 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, el modo de uso, la eficacia y la seguridad de abatacept sc y desarrolló un documento sobre el uso de este fármaco en situaciones concretas, previa revisión de la bibliografía.
Resultados: El abatacept sc sustenta su eficacia y seguridad en 7 ensayos clínicos, 3 doble ciego, 3 abiertos y uno mixto, en los que se compara la administración sc frente a la iv de abatacept, se estudia el posible impacto sobre la inmunogenicidad, el efecto de sustituir la vía iv por la sc en pacientes que previamente venían recibiendo abatacept iv, la monoterapia y la no inferioridad frente a adalimumab. No se han encontrado diferencias significativas frente a abatacept iv ni en cuanto a la eficacia ni en cuanto a la seguridad. El desarrollo de abatacept sc ha permitido un estudio complementario al del iv, con lo que el perfil del mismo queda más definido.

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Conclusiones: Se trata de un documento práctico como complemento a la información en ficha técnica. En resumen, el abatacept sc se presenta como un fármaco eficaz y seguro y, por lo tanto, como una alternativa más para utilizar entre los múltiples tratamientos con que cuenta hoy en día el reumatólogo. Además, cuenta con la ventaja de ser el único agente biológico que se puede administrar por vía iv y sc, lo cual puede facilitar su uso en determinados pacientes.

Introduction

The efficacy and safety of a biological agent are key elements when it comes to their selection for the treatment of rheumatoid arthritis (RA), but other factors also play an important role, including the route of administration. Many patients prefer the autonomy the ability to inject the drug subcutaneously (SC) provides versus having to go to a day hospital or intravenous infusion (IV) unit. A significant number of doctors prefer the SC route, considering its efficacy and safety, due to, among other factors, the fact is that it has less organizational complexities. Hence the interest in developing SC administrable formulations for drugs available for IV use still persists.

The change of the IV administration route for the SC one in the case of a protein derived drug is not a matter of simple substitution at all. SC administration poses significant differences compared to IV, both from the point of view of efficacy and safety, requiring studies and independent development. Some aspects are particularly relevant. The first is the dosage, as the SC route carries pharmacokinetic differences that result in different patterns of administration, dosages and different intervals than IV. Another key aspect is immunogenicity. Parenteral administration of proteinaceous drugs is associated, at least theoretically, with the possibility of developing antibodies against the drug (ADA). The route of administration and the dosage are factors that may influence this phenomenon, because, among other things, differences in antigen presentation[1]; in addition, the different composition of the excipients for both formulations may also contribute to differences in immunogenicity and hence the enormous importance of analyzing the immunogenicity in the process of developing an IV biologic drug for SC administration. In addition, factors such as drug temporary interruption and subsequent reintroduction, the change in the same patient from IV to SC of the use of the drug alone or association with disease modifying drugs (DMARDs), may modify the immunogenic properties of a protein product.[2] Another safety aspect that deserves special analysis is the possible occurrence of reactions at the site of SC injection.

Abatacept is a selective proteinaceous biological modulator of T cell costimulation, approved for treatment of RA. IV use has demonstrated efficacy with an adequate safety profile in different populations of patients with this disease, including patients who had never previously received methotrexate (MTX), patients with inadequate response to synthetic disease-modifying drugs (DMARDs) and anti-TNF biological.[3–5]

In addition to the IV formulation, in recent years a new way to use abatacept has been developed subcutaneously. Table 1 shows the summary of the major clinical trials. The ACQUIRE study is the main trial, with a larger number of patients, which compared, from the point of view of efficacy and safety, compared SC to IV administration of abatacept.[6] The ALLOW study specifically analyzes the possible impact on immunogenicity of the suspension and subsequent drug reintroduction.[7] The ATTUNE trial studied the effect of replacing IV abatacept administration with SC in patients who previously had been receiving IV.[8] In the ACCOMPANY trial, the effect of SC administration of abatacept in monotherapy versus combination with MTX is investigated mainly from the standpoint of immunogenicity.[9] In the AMPLE study, the efficacy and safety of two biologic drugs, abatacept and adalimumab are compared in combination with MTX.[10]

Abatacept for SC use is presented in prefilled glass syringes with 125 mg of active ingredient in 1 ml volume. The SC formula contains no maltose, unlike the IV form 11. Phase I and phase II studies have concluded that a weekly dose of 125 mg SC provides therapeutic levels of abatacept.[12]

The availability of a new formulation of abatacept for SC use expands options for the treatment of RA. The objective of this paper is to review the clinical evidence on SC abatacept and discuss potential benefits that its use may incur.

Methods

The document was based on a meeting in which the available evidence on SC abatacept was discussed and decisions about the issues that were most important for clinical practice were taken. Each panelist carried out a review of the relevant item that was assigned based on searches in PubMed, ACR and EULAR meetings and drug inserts. The final document was agreed upon by all the panelists. The level of evidence was graduated with the Oxford scale.[13]

Results

Pharmacokinetics

Several studies have shown that the trough concentration at steady state of abatacept provides optimal inhibition of T cells and thus leads to an adequate clinical response is $\geq$10 μg/ml.[14] These concentrations are achieved with the approved IV abatacept dose and in 90% of patients treated with SC abatacept.[11] To demonstrate the efficacy and safety of SC abatacept compared to the classical IV form used so far, studies in animals[15,16] and humans have been performed.[6,11,17,18] To this end, clinical trials were designed with and without an IV loading dose where the impact of the dose on clinical efficacy, pharmacokinetics and immunogenicity of abatacept SC was evaluated. In clinical trials of SC abatacept (including the essential ACQUIRE) an IV loading dose of abatacept is included on day one to rapidly achieve therapeutic concentrations and then compare whether the efficiency of the SC administration is similar to the IV administration.[6,11,17,18] In these studies, a similar profile regarding efficacy and safety for the 2 routes of administration is demonstrated, and the vast majority of patients receiving SC abatacept reach a stable concentration of abatacept in the valley $\mu \geq 10$ g/mL, with less variation between peak and trough concentration than with IV administration.[18]

Although with some reservations, due to the different study designs (ALLOW and ACCOMPANY), we can deduce that the clinical efficacy of SC abatacept, followed or not by an IV loading dose, is similar at 3 months of starting treatment, with abatacept attaining therapeutic levels at 2 weeks in the majority of patients (88%) in which no loading dose was used.[17,19] Thus, in those patients who are scheduled to start SC abatacept, it does not seem necessary to administer a loading dose (LE 2b).

Several studies have determined the level of abatacept in serum, and the presence of antiabatacept antibodies by ELISA, showing that SC abatacept is well tolerated and has a safety profile similar to IV