Meta-Analysis of Efficacy of Anti-TNF Alpha Therapy in Ankylosing Spondylitis Patients

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Introduction: Tumor necrosis factor (TNF) plays an important role in the pathology of ankylosing spondylitis (AS). Therefore, anti-TNF antibody based therapies could hopefully be a treatment in AS patients without response to current drugs, mainly non-steroidal anti-inflammatory drugs (NSAIDs).

Objective: To assess the evidence from clinical trials on the efficacy of anti-TNF alpha for the treatment of AS by performing a meta-analysis to derive estimates of responses occurring in randomized trials employing anti-TNF therapy.

Methods: A systematic literature search of EMBASE, PubMed, Cochrane Library, and electronic abstract databases of the annual scientific meetings of both the European League Against Rheumatism and the American College of Rheumatology was conducted through August 2006. To be selected, the studies had to fulfill all of the followings conditions: a) randomized controlled trial comparing one therapy anti-TNF alpha (infliximab, etanercept, or adalimumab) versus placebo. Used between 6 and 24 weeks in patients with AS; b) diagnosis based on the New York modified criteria for AS; and c) the primary end point had to be the proportion of patients with a 20% improvement response according to the criteria of the Assessment in Ankylosing Spondylitis (ASAS) International Working Group (ASAS20 responders).

Results: Seven trials met our inclusion criteria and were selected for meta-analysis and were considered of high methodological quality with a total of 1094 patients, 660 patients in treatment group and 434 patients in control/placebo group. In anti-TNF alpha treatment group, the ASAS20 response rate improvement was 60.4% and 22.1% in placebo group at 6-24 weeks period. The relative risk was 2.78 (95% CI, 2.3-3.4), favorable to treatment group. The number needed to treat was 3 (95% CI, 2-4).

Conclusions: There is evidence of an increased relative benefit of improved clinical outcomes in patients with AS, treated with anti-TNF antibody therapy with 2 assessment criteria ASAS20 at short term (6 to 24 weeks) treatment periods; with an evidence level I and recommendation level A.

Key words: Systematic review. Meta-analysis. Anti-TNF. Ankylosing spondylitis.

Metaanálisis de la eficacia del tratamiento con anti-TNF alfa en pacientes con espondilitis anquilosante

Introducción: El factor de necrosis tumoral (TNF) desempeña un papel importante en la espondilitis anquilosante (EA). Los tratamientos con anti-TNFα han demostrado ser útiles en el tratamiento de los pacientes con EA que no responden adecuadamente o no toleran los antiinflamatorios no esteroideos (AINE).

Objetivo: Evaluar, mediante una revisión sistemática y metaanálisis, la evidencia de la eficacia del tratamiento con anti-TNFα en pacientes con EA.

Métodos: Se realizó una búsqueda bibliográfica en EMBASE, PubMed, Cochrane Library y bases de datos electrónicas de resúmenes de los congresos científicos del European League Against Rheumatism y del American College of Rheumatology. Dicha búsqueda finalizó en agosto de 2006. Los estudios seleccionados debían cumplir las siguientes condiciones: a) ensayos controlados con asignación aleatoria que compararan un tratamiento anti-TNFα (infliximab, etanercept o adalimumab) versus placebo. Utilizados entre 6 y 24 semanas en pacientes con EA; b) diagnóstico de EA basado en los criterios de Nueva York modificados; y c) variable de desenlace principal definida como la proporción de pacientes con una mejora de al menos el 20% según los criterios de respuesta del grupo internacional para la valoración de la EA (ASAS20).

Resultados: Siete estudios cumplieron los criterios de inclusión y se los seleccionó para el metaanálisis. Todos
els tenían una alta calidad metodológica con un total de 1,094 pacientes, 660 pacientes en el grupo de tratamiento y 434 pacientes en el grupo control-placebo. En el grupo de tratamiento con anti-TNFα, la respuesta ASAS20 fue del 60,4% y el 22,1% en el grupo placebo en un período de 6-24 semanas. El riesgo relativo fue 2,78 favorable al grupo de tratamiento, con un intervalo de confianza (IC) del 95% de seguridad de 2,3-3,4. El número necesario de pacientes a tratar fue 3 (IC del 95%, 2-4).

**Conclusiones:** Los tratamientos con anti-TNFα son eficaces en los pacientes con EA, con un nivel de evidencia I y recomendaciones de nivel A. Su eficacia es sustancial y demostrable a corto plazo, entre 6 y 24 semanas.

**Palabras clave:** Revisión sistemática. Metaanálisis. Anti-TNF. Espondilitis anquilosante.

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**Introduction**

Ankylosing Spondylitis (SA) is the prototype of the inflammatory diseases of the locomotor apparatus that affects axial skeleton, grouped as Spondyloarthropathies (SpA). It is characterized by progressing through inflammatory lapses that preferentially affect sacroiliac joints and the tip of the column, with a tendency to fibrosis, and frequently to later ankylosis. Peripheral joints, enthesis, and other, extra-articular tissue are affected on numerous occasions.1,2

In contrast with other rheumatic diseases, the evaluation of activity in patients with SA is especially difficult, especially in axial forms, by the scarcity of objective clinical signs and the low sensibility of the biologic markers; therefore, the Assessment in Ankylosing Spondylitis (ASAS) Working Group3–5 has proposed a system of criteria that quantify most of the relevant clinical characteristics of the disease. On the other hand, evaluation of therapeutic response in SA is a concept that is currently being developed and that until recently had not published its first consensus criteria6–7 for the follow up of the disease. Disease activity is evaluated through the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI),8 that compounds the results from visual analog scales (VAS) on fatigue, axial pain, peripheral joint affection, enthesitis, and morning stiffness as well as its duration.

The most frequently employed outcome measures in medical literature are based on this index: BASDAI50 (a reduction of at least 50% with respect to baseline) and ASAS20. An ASAS20 response is defined when a patient presents a relative improvement of at least 20%, and an absolute one, of at least 1 unit (on a scale of 0 to 10) in 3 of the following 4 domains: a) global evaluation of the disease by the patient measured through VAS from 0 to 10; b) evaluation of the pain by the patient through VAS on a scale of 0 to 10; c) evaluation of the physical function through the Bath Ankylosing Spondylitis Function Index (BASFI) on a scale of 0 to 10; and d) evaluation of inflammation (0, absent; 10, very intense) measured through the last 2 items of the BASDAI; apart from not worsening in the remaining domain, defined as deterioration ≥20% and a net worsening of at least 1 unit on a scale of 1 to 10.

The introduction of inhibitors of tumor necrosis factor alpha (anti-TNFα) in the treatment of patients with SA is a decisive and determining step, especially in patients affected by severe forms or those resistant to common treatments, basically non-steroidal anti-inflammatory drugs (NSAIDs) and, in some cases, disease modifying antirheumatic drugs (DMARDs), such as sulphasalazine and methotrexate.

The prognosis of these patients is truly somber, because the disease leads to a terrible quality of life and incapacity, apart from complications and deformities that arise during the course of the disease. After medical treatment failure, the only option left to patients as a therapeutic alternative was corrective or substitutive surgery.

Since approximately a decade ago, interesting experiences with anti-TNF drugs in other disease such as rheumatoid arthritis have been published. After that, results from the first SpA clinical trials were published (SA mainly), showing an excellent response to anti-TNFα treatment in these diseases. The impact has been such that they are leading to a redefinition of the concepts, such as outcome measures, adequate follow-up techniques, resistance criteria, etc.

It is therefore necessary to unify criteria that facilitate therapeutic decision-making with the object of optimizing the use of anti-TNFα in patients with SA. Though the existing medical literature on the topic is acceptable, it is rather complex to present an eagle-eyed view due to the disparity in the outcome measures employed in the different studies, the type of anti-TNFα drugs, the differences in follow-up times, clinical entities studied (axial or peripheral forms…).

Due to this great heterogeneity, it is complicated to contrast the results published on the efficacy of different SA therapies, complicated even more as a consequence of the diversity in the forms of clinical presentation of the disease itself (axial or peripheral, extraarticular manifestations, etc). With the meta-analysis of the selected results with concrete and homogeneous criteria, a great measure of the heterogeneity of the results that today exist can be solved.

Recommendations for the treatment of SA have recently been published,8 contemplating the entire available therapeutic spectrum, with special attention to anti-TNFα of which there are several studies that demonstrate treatment efficacy in the treatment of AS.9–16
The objective of this study is to adequately define what each 1 of these anti-TNFα therapies to the treatment of SA. Therefore, the methods of evidence-based medicine in the systematic review and metaanalysis are shown as the most methodologically adequate instruments to this end.17-21

Methods

Data Source and Search Strategy

A search was carried out in EMBASE, PubMed, and the Cochrane Library, up to August 2006, using the terms: ankylosing spondylitis; infliximab; adalimumab; etanercept, randomized controlled trial; random allocation; multicenter studies; clinical trials, phase II; clinical trials, phase III; and clinical trials, phase IV.
To locate clinical trials that have not yet been published, electronic databases of the scientific meetings of the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) from 1996 to the present.
The evaluation of inclusion or exclusion criteria for the studies and the selection of outcome variables were done independently by 2 researchers. Disagreements were solved through consensus.

Study Selection and Outcome Variables

Randomized clinical trials of the 3 anti-TNF drugs with currently published studies: infliximab, etanercept, and adalimumab, in patients diagnosed with SA according to the modified New York criteria. Participants in the trial had to have been randomized to receive treatment with an anti-TNF drug or a placebo for at least 6 weeks.
The main outcome variables of the studies were: ASAS20 and BASDAI50. As secondary variables ASAS50 (50%, and 2 units of improvement in 3 of the 4 domains of the ASAS20 criteria, without worsening in the remaining domain) and partial remission (a value inferior to 2 units in the 4 previous domains) were used.
Primary data sources were the publications of the identified trials. To avoid bias, 2 independent reviewers evaluated the following methodological characteristics of the most important studies: randomization, hiding, and binding of the assignment, intention to treat analysis, follow-up loss, and outcome variables. Disagreements were solved by consensus.

Statistical Analysis

The combination of the results of the studies, that is, the global estimation of effect, was carried out through measuring relative risk (RR) of the response in the group with active treatment in relation to the placebo group and its corresponding 95% security confidence interval (CI).
In the absence of significant heterogeneity of the studies (Q test as proposed by DerSimonian and Laird) the results were combined using the fixed effect model; the size of the study and its own variance (intra-study variability) were the only determinants of its weigh in the metaanalysis.
The solidity and firmness of the global effect estimation was carried out through a sensibility analysis.
The number of patients needed to treat (NNT) was calculated to provide a more practical measure. Meta-analysis was done with the Epidat 3.0 and Review Manager 4.2 software.

Results

Of the 387 potentially relevant publications in our initial search, 334 were excluded because they were not designed as randomized and controlled clinical trials, the control group was missing or the study population had other diagnosis apart from SA.
A total of 53 studies were evaluated in detail, of which 46 were excluded because the duration of treatment was inadequate, there were differences in the inclusion/exclusion criteria among the treatment groups or they had no control group (Figure 1).
Seven clinical trials were included in the meta-analysis (Table 1). In all of them, the assignation of treatment was random and both the patients and the observer were blinded. In regard to the use of concomitant drugs, the included studies presented some heterogeneity. All included patients with a high degree of heterogeneity, in spite of traditional treatment with NSAIDs. A total 1094 patients with SA were randomized to receive treatment with anti-TNF or placebo.
The 7 studies were used to do the metanalysis when the outcome measure was the ASAS20 criteria (Figure 2). Time until the evaluation of the response was different in each study; 6 weeks for the study by Brandt, 12 for the studies of Braun and Calin, 16 for the Gorman study, 24 weeks in the studies by Davis and Heijde (2005), and 12 and 24 weeks in the study by Heijde (2006). The general appraisal of the relative risk (RR=2.78; 95% CI, 2.30-3.37) indicated a significant effect of anti-TNFα drug therapy. 60.4% (399/660) of patients with treatment reached an ASAS20 response versus 22.1% (96/434) of controls. NNT was 3 (95% CI, 2-4) patients.
When the result variable was the BASDAI50 (Figure 3), 4 studies were used for the meta-analysis. Time to response evaluation was 6 weeks for the study by Brandt, 12 weeks for the one by Braun and Heijde (2006), and 24 for the one by Heijde (2005).
The general estimation of the relative risk (RR=3.89; 95% CI, 2.73-5.53) indicated a significant effect of treatment
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387 Identified Publications
334 Publications Excluded Due to Title or Abstract (No Control Group or Study Population With a Diagnosis Different From Ankylosing Spondylitis)
53 Recovered for a More Detailed Evaluation
46 Excluded (Inadequate Length of Treatment, Different Inclusion/Exclusion Criteria)
7 Clinical Trials Included in the Meta-Analysis

Figure 1. Flow diagram showing the studies identified in the systematic review.

Table 1. Characteristics of the Randomized and Controlled Clinical Trials Included in the Meta-Analysis*

<table>
<thead>
<tr>
<th>Study</th>
<th>Publication</th>
<th>Outcome Measures</th>
<th>Total Patients, No.</th>
<th>Patients With Anti-TNF</th>
<th>Patients With Placebo, No.</th>
<th>Duration, Weeks</th>
<th>Doses Anti-TNF</th>
<th>Control</th>
<th>Concomitant Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Braun, 2002</td>
<td>Lancet, 2002</td>
<td>BASDAI, ASAS20</td>
<td>69</td>
<td>34</td>
<td>35</td>
<td>12</td>
<td>Infliximab 5 mg/kg (iv), 0, 2, and 6 weeks</td>
<td>Placebo (iv), 0, 2, and 6 weeks</td>
<td>NSAIDs with no dose increase</td>
</tr>
<tr>
<td>Gorman, 2002</td>
<td>NEJM, 2002</td>
<td>ASAS20</td>
<td>40</td>
<td>20</td>
<td>20</td>
<td>16</td>
<td>Etanercept 25 mg (sc), 2 times/week</td>
<td>Placebo (sc), 2 times/week</td>
<td>NSAIDs, oral steroids, gold salts, methotrexate, sulphasalazine</td>
</tr>
<tr>
<td>Brandt, 2003</td>
<td>Arthritis &amp; Rheum, 2003</td>
<td>BASDAI, ASAS20</td>
<td>30</td>
<td>14</td>
<td>16</td>
<td>6</td>
<td>Etanercept 25 mg (sc), 2 times/week</td>
<td>Placebo (sc), 2 times/week</td>
<td>NSAIDs with no dose increase</td>
</tr>
<tr>
<td>Davis, 2003</td>
<td>Arthritis &amp; Rheum, 2003</td>
<td>ASAS20</td>
<td>277</td>
<td>138</td>
<td>139</td>
<td>24</td>
<td>Etanercept 25 mg (sc), 2 times/week</td>
<td>Placebo (sc), 2 times/week</td>
<td>NSAIDs, steroids, methotrexate, sulphasalazine, chloroquine</td>
</tr>
<tr>
<td>Calin, 2004</td>
<td>Ann Rheum Dis, 2004</td>
<td>ASAS20</td>
<td>84</td>
<td>45</td>
<td>39</td>
<td>12</td>
<td>Etanercept 25 mg (sc), 2 times/week</td>
<td>Placebo (sc), 2 times/week</td>
<td>NSAIDs, steroids, methotrexate, sulphasalazine, chloroquine</td>
</tr>
<tr>
<td>Heijde, 2005</td>
<td>Arthritis &amp; Rheum, 2005</td>
<td>ASAS20</td>
<td>279</td>
<td>201</td>
<td>78</td>
<td>24</td>
<td>Infliximab 5 mg/kg (iv), 0, 2, and 6 weeks</td>
<td>Placebo (iv), 0, 2, and 6 weeks</td>
<td>NSAIDs without dose increase</td>
</tr>
<tr>
<td>Heijde, 2006</td>
<td>Arthritis &amp; Rheum, 2006</td>
<td>ASAS20, BASDAI50</td>
<td>315</td>
<td>208</td>
<td>107</td>
<td>12-24</td>
<td>Adalimumab 40 mg (sc), every 2 weeks</td>
<td>Placebo (sc), every 2 weeks</td>
<td>AINE, steroids, methotrexate, sulphasalazine, chloroquine, leflunomide</td>
</tr>
</tbody>
</table>

*NSAIDs indicates non-steroidal anti-inflammatory drugs; ASAS, Assessment in Ankylosing Spondylitis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; sc, subcutaneous; iv, intravenous; TNF, tumor necrosis factor.
group receiving anti-TNFα therapy versus 22.1% (63/285) in the placebo group (RR=1.07; 95% CI, 0.81-1.41) (Figure 7).

Discussion

The main difficulties and limitations found in the realization of the metaanalysis were:

1. Diversity of the outcome measures: the ASAS20 and BASDAI50 determinations, in conclusion, were the outcome measures chosen for the evaluation of the efficacy of anti-TNFα therapy in patients with SA. Following several consensus, they represent the best and most used measures to evaluate the response obtained with drugs in clinical trials and clinical practice.

2. Time of evaluation of the outcome measures: in the 7 studies that were finally selected for the use of at least
1 of the 2 established outcome measures (ASAS20 or BASDAI50), these were evaluated in different periods in the available publications. To avoid a possible bias produced by disagreement in the time of the evaluation period, unifying the result of the outcome measures in the period between 6 and 24 weeks was attempted, which was considered “short-term.” Therefore, the results of the meta-analysis were done with the outcome measures of the different short-term studies (6-24 weeks) of the start of treatment.

3. Drugs concomitant to the treatment (anti-TNFα): in some of the studies selected for the metaanalysis, the use of concomitant drugs was allowed. However, in other studies their use was not allowed. Allowed concomitant drugs in some studies could be 1 of 3 types: NSAIDs, glucocorticosteroids, and DMARDs. In the case of NSAIDs as concomitant drugs, these would not represent bias because their use was allowed in all of the studies selected for metaanalysis. On the contrary, the same does not occur with steroids and DMARDs, because some of the studies allowed the use of 1 or several: methotrexate, sulphasalazine, chloroquine, and gold salts, both in the treatment group as in the placebo group.
TABLE 2. Serious Adverse Events (SEA)

<table>
<thead>
<tr>
<th>Study</th>
<th>Anti-TNF, Patients With SAE/Total (n)</th>
<th>Type</th>
<th>Removed From Trial</th>
<th>Placebo, Patients With SAE/Total (n)</th>
<th>Type</th>
<th>Removed From Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Braun, 2002</td>
<td>Infliximab, 3/34</td>
<td>Systemic tuberculosis</td>
<td>Yes</td>
<td>0/35</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>High fever (enlarged lymph nodes and pulmonary lesions)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Transient leukopenia</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Gorman, 2002</td>
<td>Etanercept, 0/20</td>
<td></td>
<td></td>
<td>0/20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brandt, 2003</td>
<td>Etanercept, 0/14</td>
<td></td>
<td></td>
<td>0/16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Davis, 2003</td>
<td>Etanercept, 9/138</td>
<td>Adenopathy</td>
<td>No</td>
<td>5/139</td>
<td>Thoracic pain</td>
<td>No</td>
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<td>Staphylococcus cellulitis</td>
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<td></td>
<td>Viral infection</td>
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<tr>
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<td>after spider bite</td>
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<td></td>
<td></td>
<td>Wound infection</td>
<td>No</td>
<td>2 accidents</td>
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<td>after cat bite</td>
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<td>Bone fracture after fall</td>
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<td>Suicide attempt</td>
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<tr>
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<td>Fever associated to the site of infection</td>
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<td>Signs of ulcerative colitis</td>
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<td>Intestinal obstruction due to adhesion</td>
<td>Yes</td>
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<tr>
<td></td>
<td></td>
<td>Two bone fractures</td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td>after trauma</td>
<td>Yes</td>
<td></td>
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<tr>
<td>Calin, 2004</td>
<td>Etanercept, 1/45</td>
<td>Post-angioplasty myocardial infarction</td>
<td>No</td>
<td>0/39</td>
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<td>No</td>
<td>2/78</td>
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<td>Inguinal hernia</td>
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<tr>
<td></td>
<td>Abdominal pain, back pain, fever, and ganglioneuroma</td>
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<td>Heijde, 2006</td>
<td>Adalimumab, 6/208</td>
<td>Head wound</td>
<td>No</td>
<td>3/107</td>
<td>Pancreatitis</td>
<td>No</td>
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<td></td>
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<td>Thoracic pain</td>
<td>Yes</td>
<td></td>
<td>Appendicitis</td>
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<tr>
<td></td>
<td></td>
<td>to adalimumab</td>
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<td></td>
<td>Hypersensitivity</td>
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<td></td>
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<td>Non-cardiac thoracic pain</td>
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<td></td>
<td></td>
<td>Increase in liver enzymes</td>
<td>No</td>
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</table>

4. Different anti-TNFα drugs: infliximab, adalimumab, and etanercept, though belonging to the same therapeutic group because of their capacity to inhibit the action of TNFα, have 2 different mechanisms. Infliximab and adalimumab are monoclonal antibodies that bind TNFα both in a soluble form and adhered to the cell membrane, and have the capacity to induce lysis of these cells. Their administration route is intravenous. Etanercept is a fusion protein constituted by a soluble human type II receptor obtained by genetic recombination, joined to the constant fraction of a human IgG, which confers it with stability and a longer half-life. It is capable of inhibiting the action of TNFα and lymphotoxin by binding to them and avoiding their action on cell receptors. It is administered subcutaneously.

In summary, treatments with anti-TNFα are efficacious in SA with a level of evidence (Systematic review of randomized clinical trials, with homogeneity). Their efficacy is substantial and proven in the short term, between 6 and 24 weeks. NNT to obtain a favorable response...
(evaluated with the ASAS20 or BASDAI50 criteria) with anti-TNFα therapy in the short term is 3; therefore, the magnitude of their effect is considerable. Anti-TNFα must be considered in order to treat patients with severe axial symptoms and elevated markers of activity who do not respond in an adequate way to treatment with NSAIDs. Our systematic review and metaanalysis demonstrates a favorable response of patients with SA treated with anti-TNFα drugs.

With regard to the adverse events observed in the clinical trials that were included, the metaanalysis has not detected any significant differences among both groups; however, it is important to state that the studies were short-term and that differences, if any, will be detected in longer term studies.
The current degree of evidence for SA treatment with anti-TNFα, according to clinical response, with ASAS20 or BASDAI50 criteria is Ib (randomized clinical trial with a narrow confidence interval), because it derives from controlled randomized trials. After performing the metaanalysis with the results of the previously selected studies a higher level of evidence can be established (Ia); therefore, the efficacy of anti-TNFα drugs, in the treatment of S, is completely established.

References