Original Articles

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) con 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 mejoría 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

ellos 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.

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 Group[3,4] 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 criteria[5-7] 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,[9] 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.[10-16]

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 blinding of the assignation, 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).

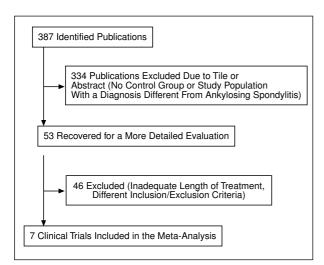The general estimation of the relative risk (RR=3.89; 95% CI, 2.73-5.53) indicated a significant effect of treatment

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

with anti-TNFα drugs. Of patients with treatment 48.4% (221/457) reached a BASDAI50 response versus 12.3% (29/236) of the patients in the control group and the NNT was 3 (95% CI, 2-6) patients.

Three studies were used to perform the metaanalysis with the ASAS50 criteria (Figure 4). Time until evaluation of treatment was 6 weeks for the Brandt study and 12 weeks for the Braun and Calin studies.

The general estimation for relative risk (RR=5.17; 95% CI, 2.68-9.94) indicated a significant effect of treatment with anti-TNFα drugs. Of the patients with treatment 49.5% (46/93) reached an ASAS50 response versus 9.6% (9/94) of patients in the control group; with a NNT of 3 (95% CI, 2-7) patients.

The meta-analysis was done with 4 studies in which the inclusion/exclusion criteria or partial remission was employed (Figure 5). The response was evaluated at 6 weeks in the study by Brandt and at 24 weeks in the studies by Davis, Heijde 2005, and Heijde 2006. The general estimation of relative risk (RR=4.95; 95% CI, 2.82-8.70) indicated a significant effect of treatment with anti-TNFα drugs.

Of patients with treatment 20.5% (115/561) reached an ASAS partial remission response versus 4.1% (14/340) of patients in the control group, and a NNT of 8 patients (95% CI, 4-19).

Table 2 expresses the documented adverse events in the studies that were the object of analysis, and Figure 6 shows the result of the meta-analysis of the severe adverse events (SAE), with the proportion of patients developing SAEs being larger in the 2 groups, 3.94% (26/660) in the group that received treatment versus 2.30% (10/434) in the control group (RR=1.71; 95% CI, 0.86-3.38). In addition, no significant differences were detected among the proportion of patients with an upper airway infection (the most common adverse event), 20.6% (84/408) in the

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

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

*NSAIDs indicates non-steroidal anti-inflammatory drugs; ASAS, Asessment in Ankylosing Spondylitis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; sc, subcutaneous; iv, intravenous; TNF, tumor necrosis factor.
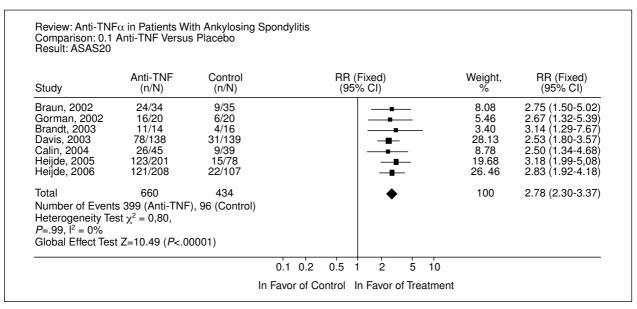
Review: Anti-TNFα in Patients With Ankylosing Spondylitis
Comparison: 0.1 Anti-TNF Versus Placebo
Result: ASAS20

Study	Anti-TNF (n/N)	Control (n/N)	RR (Fixed) (95% CI)	Weight, %	RR (Fixed) (95% CI)
Braun, 2002	24/34	9/35		8.08	2.75 (1.50-5.02)
Gorman, 2002	16/20	6/20		5.46	2.67 (1.32-5.39)
Brandt, 2003	11/14	4/16		3.40	3.14 (1.29-7.67)
Davis, 2003	78/138	31/139		28.13	2.53 (1.80-3.57)
Calin, 2004	26/45	9/39		8.78	2.50 (1.34-4.68)
Heijde, 2005	123/201	15/78		19.68	3.18 (1.99-5.08)
Heijde, 2006	121/208	22/107		26.46	2.83 (1.92-4.18)
Total	660	434		100	2.78 (2.30-3.37)

Number of Events 399 (Anti-TNF), 96 (Control)
Heterogeneity Test $\chi^2 = 0,80$,
$P=.99$, $I^2 = 0\%$
Global Effect Test Z=10.49 ($P<.00001$)

0.1 0.2 0.5 1 2 5 10

In Favor of Control   In Favor of Treatment

Figure 2. *Meta-analysis with the ASAS20 criteria in patients with ankylosing spondylitis randomized to receive inhibitors of tumor necrosis factor alpha (anti-TNFα) or placebo. 95% CI indicates 95% security confidence interval; RR (fixed), fixed effects model relative risk.*

Review: Anti-TNFα in Patients With Ankylosing Spondylitis
Comparison: 0.1 Anti-TNF Versus Placebo
Result: BASDAI50

Study	Anti-TNF (n/N)	Control (n/N)	RR (Fixed) (95% CI)	Weight, %	RR (Fixed) (95% CI)
Braun, 2002	18/34	9/35		7.81	6.18 (2.00-19.07)
Brandt, 2003	8/14	1/16		2.46	9.14 (1.30-64.34)
Heijde, 2005	101/201	8/78		30.44	4.90 (2.51-9.58)
Heijde, 2006	94/208	17/107		59.29	2.84 (1.79-4.51)
Total	457	236		100	3.89 (2.73-5.53)

Number of Events 221 (anti-TNF), 29 (Control)
Heterogeneity Test $\chi^2=3.61$,
$P=.31$, $I^2 = 16.8\%$
Global Effect Test Z=7.52 ($P<.00001$)

0.01   0.1   1   10   100

In Favor of Control   In Favor of Treatment

Figura 3. *Meta-analysis with the BASDAI50 criteria in patients with ankylosing spondylitis randomized to receive inhibitors of tumor necrosis factor alpha (anti-TNFα) or placebo. 95% CI indicates 95% security confidence interval; RR (fixed), fixed effects model relative risk.*
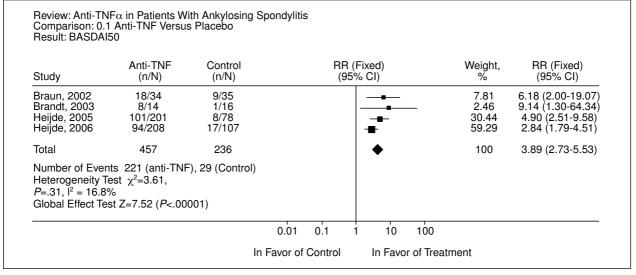
group receiving anti-TNFα therapy versus 22.1% (63/285) in the placebo group (RR=1.07; 95% CI, 0.81-1.41) (Figure 7).

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.

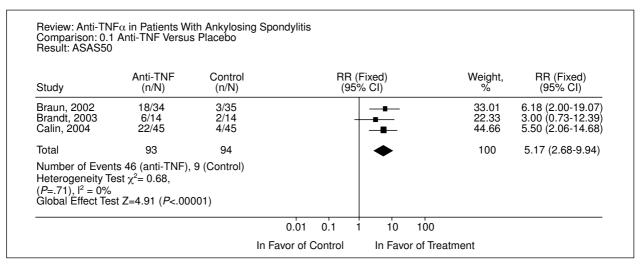2. Time of evaluation of the outcome measures: in the 7 studies that were finally selected for the use of at least

Review: Anti-TNFα in Patients With Ankylosing Spondylitis
Comparison: 0.1 Anti-TNF Versus Placebo
Result: ASAS50

Study	Anti-TNF (n/N)	Control (n/N)	RR (Fixed) (95% CI)	Weight, %	RR (Fixed) (95% CI)
Braun, 2002	18/34	3/35		33.01	6.18 (2.00-19.07)
Brandt, 2003	6/14	2/14		22.33	3.00 (0.73-12.39)
Calin, 2004	22/45	4/45		44.66	5.50 (2.06-14.68)
Total	93	94		100	5.17 (2.68-9.94)

Number of Events 46 (anti-TNF), 9 (Control)
Heterogeneity Test χ^2= 0.68,
(P=.71), I^2 = 0%
Global Effect Test Z=4.91 (P<.00001)

0.01 0.1 1 10 100

In Favor of Control — In Favor of Treatment

Figure 4. *Meta-analysis with the ASAS50 criteria in patients with ankylosing spondylitis randomized to receive inhibitors of tumor necrosis factor alpha (anti-TNFα) or placebo. 95% CI indicates 95% security confidence interval; RR (fixed), fixed effects model relative risk.*
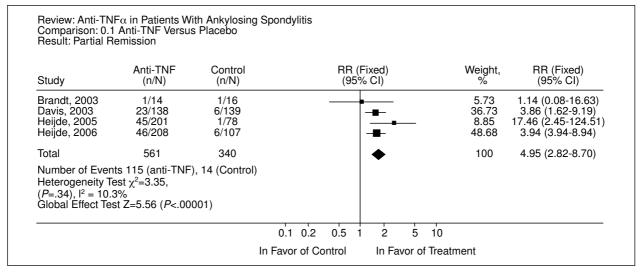
Review: Anti-TNFα in Patients With Ankylosing Spondylitis
Comparison: 0.1 Anti-TNF Versus Placebo
Result: Partial Remission

Study	Anti-TNF (n/N)	Control (n/N)	RR (Fixed) (95% CI)	Weight, %	RR (Fixed) (95% CI)
Brandt, 2003	1/14	1/16		5.73	1.14 (0.08-16.63)
Davis, 2003	23/138	6/139		36.73	3.86 (1.62-9.19)
Heijde, 2005	45/201	1/78		8.85	17.46 (2.45-124.51)
Heijde, 2006	46/208	6/107		48.68	3.94 (3.94-8.94)
Total	561	340		100	4.95 (2.82-8.70)

Number of Events 115 (anti-TNF), 14 (Control)
Heterogeneity Test χ^2=3.35,
(P=.34), I^2 = 10.3%
Global Effect Test Z=5.56 (P<.00001)

0.1 0.2 0.5 1 2 5 10

In Favor of Control — In Favor of Treatment

Figure 5. *Meta-analysis with the partial remission criteria in patients with ankylosing spondylitis randomized to receive inhibitors of tumor necrosis factor alpha (anti-TNFα) or placebo. 95% CI indicates 95% security confidence interval; RR (fixed), fixed effects model relative risk.*

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, cloroquine, and gold salts, both in the treatment group as in the placebo group.

TABLE 2. Serious Adverse Events (SEA)

Study	Anti-TNF, Patients With SAE/Total (n)	Type	Removed From Trial	Placebo, Patients With SAE/ Total (n)	Type	Removed From Trial
Braun, 2002	Infliximab, 3/34	Systemic tuberculosis	Yes	0/35		
		High fever (enlarged lymph nodes and pulmonary lesions)	Yes			
		Transient leukopenia	Yes			
Gorman, 2002	Etanercept, 0/20			0/20		
Brandt, 2003	Etanercept, 0/14			0/16		
Davis, 2003	Etanercept, 9/138	Adenopathy	No	5/139	Thoracic pain	No
		Staphilococcus cellulitis after spider bite	No		Viral infection	No
		Wound infection after cat bite	No		2 accidents	No
		Bone fracture after fall	No		Suicide attempt	Yes
		Fever associated to the site of infection	Yes			
		Signs of ulcerative colitis	Yes			
		Intestinal obstruction due to adhesion	Yes			
		Two bone fractures after trauma	Yes			
Calin, 2004	Etanercept, 1/45	Post-angioplasty myocardial infarction	No	0/39		
Heijde, 2005	Infliximab, 7/201	Vertigo	No	2/78	Pain and arthralgia	No
	Cholecystitis		No			
	Arthritis		No			
	Leukocytosis and pneumonia		No			
	Inguinal hernia		No			
	Hemiparesis		No			
	Abdominal pain, back pain, fever, and ganglioneuroma					
Heijde, 2006	Adalimumab, 6/208	Head wound		3/107	Pancreatitis	No
		Thoracic pain	No		Appendicitis	No
		Hypersensitivity to adalimumab	Yes		Hypersensitivity	Yes
		Patellar fracture	No			
		Non-cardiac thoracic pain	No			
		Increase in liver enzimes	No			

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 Ia level of evidence (Systematic review of randomized clinical trials, with homogeneity).[22] Their efficacy is substantial and proven in the short term, between 6 and 24 weeks. NNT to obtain a favorable response
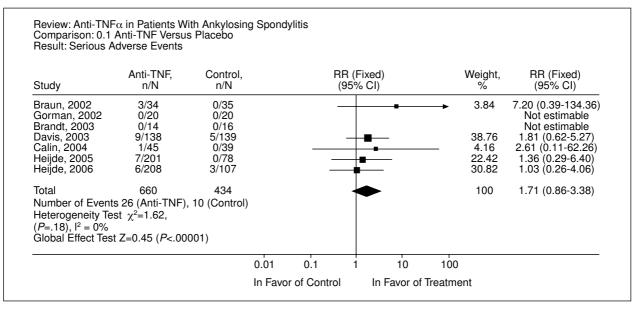
Figura 6. *Meta-analysis with the serious adverse events criteria in patients with ankylosing spondylitis randomized to receive inhibitors of tumor necrosis factor alpha (anti-TNFα) or placebo. 95% CI indicates 95% security confidence interval; RR (fixed), fixed effects model relative risk.*
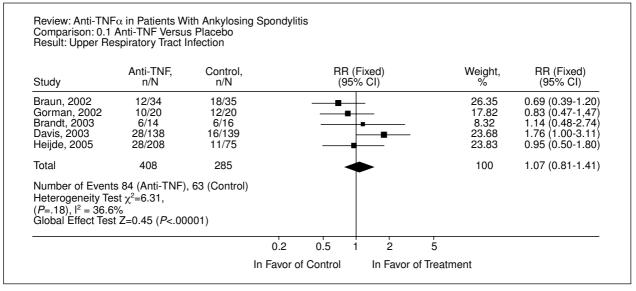

Figura 7. *Meta-analysis with the upper respiratory tract infection criteria in patients with ankylosing spondylitis randomized to receive inhibitors of tumor necrosis factor alpha (anti-TNFα) or placebo. 95% CI indicates 95% security confidence interval; RR (fixed), fixed effects model relative risk.*

(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),[22] 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.

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