Original Articles

Indication for Anti-TNF-alpha Treatment in Patients With Ankylosing Spondylitis in Spain

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Objectives: To know the perception of Spanish rheumatologists of the profile of the patients with ankylosing spondyloarthritis, candidates for biological therapy treatment. To determine what proportion of patients with ankylosing spondylitis is considered a candidate for this therapy and to know up to what point this decision agrees with the recommendations of the ASAS working group on anti-TNF therapies and with the consensus of the SER.

Method: Rheumatologists from 19 Spanish centers who are experts in treating patients with AS and in the use of anti-TNF drugs participated in this study but they were not aware of the recommendations of the ASAS group and of the SER (unpublished until this work).

Results: One hundred and eighty five patients were included in the study. Spanish rheumatologists indicated that they would start therapy with anti-TNF drugs altogether in 37.8% of the patients. The candidates had the highest values of disease activity, of acute-phase reactants, the worst spinal mobility, worst function, most hip damage, and highest sick leave prevalence. Out of the total of the patients considered as candidates for treatment with biological therapies by their rheumatologists, 45.7% did not comply with the ASAS recommendations with respect to prior treatments with NSAIDs and BASDAI and 48.6% did not comply with the SER criteria; 29.1% of the patients who did not comply with the ASAS criteria (NSAIDs-BASDAI) were considered to be candidates for treatment with anti-TNF drugs; 29.6% of the patients who did not comply with the SER criteria were also considered to be candidates. The most important criterion was the clinical activity of the disease.

Conclusions: The agreement between the criteria applied by the Spanish rheumatologist and proposed by ASAS working group and the SER consensus is low. Axial affectation, activity, and severity in their disease were the criteria used but frequently by the Spanish rheumatologist to indicate biological therapy in patients with AS.

Key words: Ankylosing spondylitis. Biologics therapies. Anti-TNF-alpha.

Indicación de terapia anti-TNF alfa en pacientes con espondilitis anquilosante en España

Objetivos: Conocer el perfil que el reumatólogo español percibe del paciente con espondilitis anquilosante (EA) que es candidato a terapia biológica. Determinar qué proporción de pacientes con EA son candidatos a recibir este tratamiento y saber hasta qué punto esta decisión concuerda con las recomendaciones del grupo de trabajo Assessment in Ankylosing Spondylitis (ASAS working group) y de la Sociedad Española de Reumatología (SER) sobre el uso de terapias anti-TNF (factor de necrosis tumoral).

Método: Reumatólogos de 19 centros hospitalarios españoles, expertos en tratar a pacientes con EA y en el uso de fármacos anti-TNFα pero que desconocían las recomendaciones del grupo ASAS y de la SER (inéditas hasta este trabajo), tuvieron que evaluar a 10 pacientes con EA, de forma consecutiva, y decidir si cada uno de ellos comenzaría un tratamiento con fármacos anti-TNFα, según sus propios criterios.

Resultados: De 185 pacientes incluidos en el estudio, al 37,8% se clasificó como candidatos a anti-TNFα. Comparados con el resto del grupo, los candidatos tenían mayor grado de actividad inflamatoria, concentraciones más elevadas de velocidad de sedimentación globular (VSG) y proteína C reactiva (PCR), menor movilidad

espinal, BASFI (Bath Ankylosing Spondylitis Functional Index) más elevado, afectación de la cadera con mayor frecuencia y alta prevalencia de baja por enfermedad. El 45,7% de los pacientes candidatos a tratamiento biológico no cumplían las recomendaciones de ASAS y el 48,6% los de la SER para el uso de anti-TNFα. Los reumatólogos españoles consideraron como candidatos para el tratamiento con anti-TNFα al 29,1 y el 29,6% de los pacientes que no cumplían los criterios de ASAS y la SER, respectivamente. El criterio más importante fue la actividad clínica de la enfermedad.
Conclusiones: La concordancia entre los criterios aplicados por los reumatólogos españoles y los propuestos por ASAS y SER es baja. Afectación axial, actividad y severidad de la enfermedad fueron los criterios usados más frecuentemente por los reumatólogos españoles para indicar terapia biológica en pacientes con EA.

Palabras clave: Espondiloartritis anquilosante. Terapia biológica. Anti-TNFα.

Introduction

The results of the international study on starting TNF-blocking agents in ankylosing spondylitis (ISSAS)[1] have been recently published, in which Spain participated as one of the countries in which the study was carried out. The results and conclusions of the general work seem interesting to know the Spanish participation (which differs in several aspects from other participating countries) and reflects the thinking of some of our rheumatologists regarding the start of treatment with anti-TNFα in patients with ankylosing spondylitis (SA).

Non-steroidal anti-inflammatory drugs (NSAID), education, exercise, and other modalities of physiotherapy are considered the main tenet of the treatment of patients with SA.[2,3] Disease modifying drugs (DMARD) are considered a second step, though there is no clear evidence of their efficacy with respect to axial manifestations.[4,5] The introduction of biologic therapy has radically changed the treatment options in SA. Etanercept,[6] infliximab,[7] and adalimumab[8] seem to be very effective in improving the signs and symptoms of such a disease and are well tolerated.

Due to the high cost of these drugs and the fact that there is still a great gap in the knowledge of the advantages and disadvantages in their long term use, and it would be interesting to know in which patients it would be appropriate to apply these treatments.

The ASAS (assessment in ankylosing spondylitis) working group has developed a series of recommendations for the treatment with anti-TNFα in SA,[9] with a very recent update.[10] The Spanish Society of Rheumatology (SER) on its part has published its own consensus on the use of biologic therapy in patients with spondyloarthritidies.[11] Both sets of recommendations differ discreetly because ASAS requires a BASDAI ≥4 for the start of treatment and the opinion of an expert, while SER requires BASDAI ≥4 and at least 1 of the following: *a)* general evaluation of the disease by the patient (VAS >4); *b)* inflammatory lower back pain (VAS >4); and *c)* elevated C-reactive protein (CRP) and/or the erythrocyte sedimentation rate (ESR). Both sets of recommendations were written after a systematic literature review and expert consensus meetings.[12] But before these recommendations (ASAS and SER) were published and/or distributed, an evaluation among the community of rheumatology specialists was carried out to find out what type of patients with SA should be treated with anti-TNFα. A sample of rheumatologists from several countries in Europe, Canada, Mexico, and Australia (ISSAS) was chosen.[1]

The main objective of the ISSAS study was to paint a picture of the type of patient with SA that the rheumatologist in each of these countries considered was a candidate for the application of anti-TNFα agents. For that end, an attempt to link this decision to the demographic characteristics, the job situation and the disease activity, and severity of the patients was made. This study also attempted to find the proportion and characteristics of patients with SA who were candidates and if the recommendations of ASAS and SER, which were not published when the ISSAS study was done, were followed.

Methodology

Rheumatologists

In the European study, members of the ASAS group were invited to function as coordinators in their respective countries. Ten countries in all accepted voluntarily to participate. The methodological design was similar in all of the participating countries.[1] In Spain, the study coordinator (who had participated in the European study) invited rheumatologists who had previously shown interest in the field of spondyloarthropathies, to participate, due to their scientific production or because they belonged to the Spanish interest group in spondyloarthritis (GRESSER); afterward, he selected from among the interested 20 expert researchers in the treatment of SA and with ample experience in the use of anti-TNFα therapies (Spanish ISASS group).

In Spain, patients were selected and evaluated the same as in the other countries,[1] using instruments selected by the ASAS group,[13,14] as well as others which are commonly employed, such as the BASDAI[15] (bath ankylosing spondylitis disease activity index), next to the information on disease severity, previous concomitant treatments, and job status.

Then, questionnaires of each patient were reviewed and data was introduced in a database created for that end using the SPSS v.11 software package.

Statistical Analysis

Patients were divided into 2 groups in relation to whether or not they were candidates to biologic therapy according to the election criteria of their rheumatologist. First, a descriptive analysis was done (calculating arithmetic means and typical deviations for quantitative variables and frequencies for qualitative variables) for the whole group and whether or not they were candidates for such a treatment. The unvaried analysis was done using the Mann-Whitney U test and the χ^2 test, according to the performed contrast.

The odds ratio (OR) was for the risk factors considered to start anti-TNFα treatment were considered in order to prove if the "candidates" adjusted to the ASAS group and the SER recommendations in an independent manner. The patient profile was defined using BASDAI and failure to treatment with NSAIDs.

All of the contrasts were bilateral and a P value less than .05 was considered significant.

Results

The Spanish rheumatologists included 185 patients with SA, 167 (90.3%) had axial involvement and 18 (9.7%), peripheral disease. The candidates to receive anti-TNFα were 37.8% of the patients included. The decision was mainly based on the following criteria: clinical disease activity (82.2%), severity of the disease (50%), an increase in acute phase reactants (32.4%), and lack of control with current treatment (30.8%). On the contrary, with a reduced frequency, the decision was based on criteria such as: rapid radiographic progression (11.9%), comorbidity (9.7%), concomitant infections (5.9%), history of tuberculosis (5.9%), disease activity as seen by magnetic resonance imaging (5.9%), high risk of adverse events (5.4%), or a perception of non-compliance with therapy by the rheumatologist (2.7%).

The baseline and demographic characteristics of the patients are shown in Table 1, as well as the variables that are related to the state of the disease. Patients who were considered by rheumatologists as candidates for anti-TNFα therapy had a higher degree of disease activity,

higher concentrations of acute phase reactants, worse spinal mobility, worse functionality, a larger affection of the hips, and there was a larger percentage of patients who were on job leave than those who were not considered as candidates (Table 1).

The distribution of the groups according to BASDAI was represented using a cumulative probability; in Figure it can be seen that even though the candidates had a mean BASDAI which was higher than those that were not considered as candidates, 43.9% of the latter had BASDAI levels higher than 4. On the contrary, 30% of the patients considered as candidates had a BASDAI lower than 4. The minimum and maximum values observed in both groups were similar.

The ASAS group recommendations did not comply 45.7% of the patients considered as candidates for anti-TNFα treatment by their rheumatologist (Table 2); on the other hand, of the total of patients that complied with the ASAS group recommendations, 30.4% were considered as candidates for biologic therapy.

With respect to the SER recommendations, these percentages were 48.6 and 27.8%, respectively. The OR was similar to that calculated according to the ASAS and SER criteria independently (Table 2). The OR of the patients who were candidates and complied with both ASAS criteria was not superior to that of the ones who only complied with a single criterion (BASDAI, ≥4 or 2 or more NSAIDs) (Table 3).

Discussion

The results of this study show differences in the appraisal of use (utility) of anti-TNFα therapy for patients with SA between the Spanish rheumatologists and the SER and ASAS recommendations. The data of this subanalysis of the Spanish population are very similar to international rheumatologists, in general, with regard to the ASAS recommendations. The criteria most commonly taken into account by Spanish rheumatologists do not differ from those of rheumatologists from other countries when it comes to the indications for biologic therapy in patients with SA.

This study shows that almost 40% of patients with SA seen in the clinic of Spanish rheumatologists would be candidates for treatment with anti-TNFα agents according to their own criteria; this study also shows that in general, patients who are candidates have a larger degree of disease activity and severity than patients who are not candidates. One of the objectives of this study was to determine what type of patient with SA is a candidate for treatment with an anti-TNFα agent before the ASAS consensus criteria for biologic therapy was established.[9] The most important criteria are BASDAI ≥4 and the use of 2 or more NSAID, along with the opinion of an expert panel who take into account clinical, laboratory, and imaging data related to

TABLE 1. Demographic Characteristics of the Patients Included in the Study[a]

	Total (n=185)	Anti-TNF Treatment		P[b]
		Candidate	Not Candidate	
Baseline and demographic characteristics				
Males, %	78.9	75.7	80.9	.400
Age, mean (SD), y	47.4 (12.4)	46.9 (10.4)	47.6 (13.6)	.800
Time since onset of disease, mean (SD), y	19.5 (11.9)	6.6 (8.6)	6.5 (8.1)	.655
Paying job, %	63	65.7	61.7	.590
Job loss due to illness, %	38.9	51.4	30.3	.006
Chronic inflammatory intestinal disease, %	5.9	7.1	5.2	.590
Hip disease, %	28.6	41.4	20.9	.003
Previous treatment with methotrexate, %	14.1	20.0	10.4	.070
Previous treatment with sulphasalazine, %	29.7	25.7	14.8	.070
Disease activity and function				
BASDAI, mean (SD)	4.4 (2.4)	5.2 (2.3)	3.9 (2.3)	.000
BASFI. mean (SD)	3.8 (2.7)	4.6 (2.7)	3.4 (2.7)	.004
BASG, mean (SD)	5.0 (2.3)	5.8 (2.4)	4.5 (2.2)	.000
Nocturnal pain, mean (SD), cm	3.8 (3.0)	4.6 (3.1)	3.3 (2.8)	.006
VAS patient, mean (SD), cm	4.7 (2.6)	5.7 (2.7)	4.0 (2.4)	.000
ESR elevation, %	47.5	41.4 (29.5)	16.51 (15.3)	.000
CRP elevation, %	53.1	25.3 (32.5)	8.02 (8.4)	.010
Chest expansion, mean (SD), cm	3.4 (1.8)	3.0 (1.6)	3.6 (2.0)	.040
Cervical rotation, mean (SD), degrees	50.3 (26.9)	49.4 (26.2)	50.8 (27.5)	.729
Lateral flexion, mean (SD), cm	42.8 (19.2)	45.3 (18.6)	41.3 (19.5)	.083
Intermaleolar distance, mean (SD), cm	86.1 (27.1)	82.3 (22.1)	88.5 (29.7)	.043
Occiput-wall distance, mean (SD), cm	6.3 (9.9)	5.7 (8.9)	6.7 (10.5)	.491
Modified Schober distance, mean (SD), cm	13.2 (2.3)	13.3 (2.3)	13.1 (2.2)	.660
Swollen joints, mean (SD), n	0.9 (2.1)	1.5 (2.6)	0.5 (1.5)	.000
Positive enthesis, mean (SD), n	3.0 (4.5)	4.0 (4.9)	2.4 (4.1)	.002

[a]BASDAI indicates bath ankylosing spondylitis disease activity index; BASFI, bath ankylosing spondylitis functional index; BASG, bath ankylosing spondylitis global assessment of disease activity; SD, statistical deviation; CRP, C-reactive protein; TNF, tumor necrosis factor; ESR, erythrocyte sedimentation rate.
[b]Statistical significance based on the Mann-Whitney U test or in χ^2.

the disease. In this study, the Spanish rheumatologists start biologic therapy based fundamentally on axial affection, disease activity, and severity, the values of BASDAI, acute phase reactants, and functional limitation. One of the main criteria for starting anti-TNFα therapy is a score larger that 4 on the BASDAI on a range from 0 to 10. This cut-point is sufficiently robust to classify patients with SA according to their functional state and quality of life.[16] In our study, 70% of patients classified by the rheumatologists as candidates had BASDAI scores higher than 4 and 56.1% of those that were not candidates

had scores inferior to 4. However, other domains considered as important by the experts, such as the values of acute phase proteins or previous failure with NSAIDs, moderately influenced the decision of the rheumatologists. Even though the evidence that anti-TNF therapy halts radiographic progression is still not consistent, rheumatologists do seem to consider the criteria of rapid radiographic progression as decisive when recommending the therapy.[17] There is also no firm evidence to consider that other variables such as CRP, ESR, or activity detected through magnetic resonance imaging, are more important
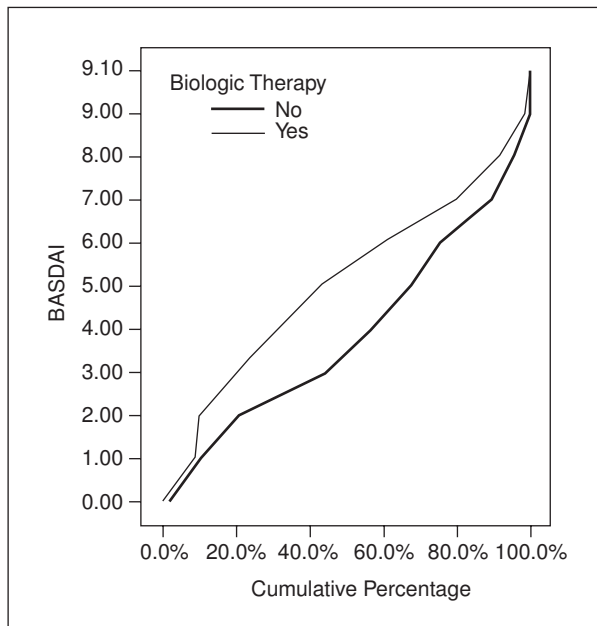
Figure. *Cumulative percentage with respect to BASDAI in relation to the decision of the rheumatologist.*

than the values of BASDAI for the decision to start biologic therapy.

Use of NSAIDs does not seen to really influence the decision of Spanish rheumatologists because the OR is very similar for patients who comply with a single ASAS criterion and for those that comply with both. We also observed in this study that the OR is similar with the ASAS or SER criteria.

The difference between the opinion of the rheumatologists, in their clinical practice, and the recommendations from experts, are not new and can be seen in different fields of medicine and does not invalidate the recommendations, but it must be considered an important element when reviewing consensus and recommendations.

Spanish ISSAS Group

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TABLE 2. Use of Biologic Therapy. Comparison Between Expert Opinion and ASAS and SER Recommendations[a]

	Anti-TNF Indications			P^d
	Candidates[b] (n=70), n (%)	Not Candidates[c] (n=112), n (%)	Odds Ratio (95% CI)	
Comply with ASAS recommendations	38 (54.3)	34 (30.4)		
Do not comply with ASAS recommendations	32 (45.7)	78 (69.6)	2.72 (1.47-5.06)	.001
Comply with SER recommendations	36 (51.4)	32 (27.8)		
Do not comply with SER recommendations	34 (48.6)	83 (72.2)	2.75 (1.48-5.11)	.001

[a]ASAS indicates assessment in ankylosing spondylitis; CI, confidence interval; SER, Spanish Society of Rheumatology; TNF, tumor necrosis factor.
[b]Candidates indicates patients who merit anti-TNF treatment according to expert opinion.
[c]Not candidates indicates patients who do not merit anti-TNF according to the experts.

TABLE 3. Evaluation of the Different Components of the ASAS Recommendations Among Patients Considered as Candidates to Treatment and Not Candidates According to the Experts[a]

	Anti-TNF Indication			P^c
	Candidates[b]	Not Candidates[b]	Odds Ratio (95% CI)	
BASDAI ≥4	49 (70.0%)/(49.5%)	50 (43.9%)/(51.5%)		
BASDAI <4	21 (30.0%)/(24.71%)	64 (56.1%)/(75.29%)	2.99 (1.59-5.61)	.001
NSAID ≥2	56 (80.0%)/(17.53%)	65 (58.0%)/(82.47%)		
NSAID <2	14 (20.0%)/(66.7%)	47 (42.0%)/(33.3%)	2.89 (1.44-5.80)	.002
BASDAI ≥4 and NSAID ≥2	38 (54.3%)/(52.78%)	34 (30.4%)/(47.22%)	2.72 (1.47-5.06)	.001

[a]NSAID indicates non-steroidal anti-inflammatory drugs; BASDAI, bath ankylosing spondylitis disease activity index; CI, confidence interval; TNF, tumor necrosis factor.
[b]Numbers express quantity of patients (percentage with respect to the total candidates and not candidates)/(percentage with respect to the total line).
[c]Statistical significance based on the χ^2 test.

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