



Review

Anti-TNF α therapy in ankylosing spondylitis: symptom control and structural damage modification

José Luis Andreu,* Teresa Otón, Jesús Sanz

Servicio de Reumatología, Hospital Universitario Puerta de Hierro, Majadahonda, Madrid, Spain

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ABSTRACT

Anti-TNF α agents represent an outstanding advance in the symptomatic control of patients with ankylosing spondylitis presenting an inadequate response to non-steroidal anti-inflammatory drugs. Anti-TNF α antagonists have demonstrated efficacy and safety in the long-term but continuous therapy is needed for an adequate control of symptoms. After the failure to a first anti-TNF α agent, the use of a second TNF α antagonist seems to be effective and safe. Despite the fast and continuous suppression of bone inflammation, demonstrated by magnetic resonance imaging, the beneficial effect of treatment with TNF α antagonists on the radiological evolution has not been demonstrated to date in ankylosing spondylitis. It seems that insights into new therapeutic molecular targets implicated in the process of ossification are needed.

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Terapia anti-TNF α en espondilitis anquilosante: control sintomático y modificación del daño estructural

RESUMEN

Los agentes anti-TNF α han representado un notable avance en el control sintomático de los pacientes con espondilitis anquilosante y respuesta inadecuada a AINE. Los antagonistas del TNF α son eficaces y seguros a largo plazo pero es necesario su uso continuado para un adecuado control sintomático. Tras el fracaso a uno de ellos, el uso de un segundo agente anti-TNF α parece ser eficaz y seguro. Aún no se ha demostrado un efecto beneficioso del tratamiento con antagonistas del TNF α sobre la evolución radiológica en la espondilitis anquilosante, a pesar de la desaparición rápida y mantenida de la inflamación ósea, evidenciada mediante RM. Parece necesario explorar nuevas dianas moleculares implicadas en el proceso de osificación.

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Ankylosing spondylitis (AS) is a chronic inflammatory autoimmune disease characterized, from a clinical point of view, by the presence of inflammatory-type pain and stiffness in the spine. Structurally, AS presents a very pronounced tendency to ankylose the spine. Both elements, axial pain and ankylosis of the spine, entail significant impairment in the patient's functional capacity.

Symptomatic control with anti-TNF treatment in ankylosing spondylitis

Until quite recently, treatment of AS was based on the use of non-steroidal anti-inflammatory drugs (NSAID) and physical therapy. Around the middle of the 1990s, the expression of a pro-inflammatory

cytokine, TNF α , was revealed in the biopsies of sacroiliac joints of patients with AS.¹ Furthermore, toward the end of the 90s it was seen that, in patients with Crohn's disease and associated AS, treatment with infliximab (a chimeric anti-tumour necrosis factor alpha antibody indicated for fistulizing Crohn's disease) brought about a spectacular improvement of the painful symptomatology and axial stiffness. These data were the rationale underlying the clinical development of TNF α antagonists in AS.

All the TNF α antagonists currently on the market for the indication of AS with inadequate response to NSAID have proven to be very significantly superior to placebo in randomized, double blind clinical trials with a duration of 12–24 weeks, achieving ASAS20 response rates of some 60% in patients treated with the TNF α antagonist, in comparison with 20% of the patients assigned to placebo.^{2–4} A clinical trial has recently been published, with a 24-week follow-up period,

* Corresponding author.

E-mail address: jlandreu@arrakis.es (J.L. Andreu).

comparing the efficacy and safety of golimumab, a humanized anti-TNF α IgG₁ monoclonal antibody, in patients with AS, which also showed a ASAS20 response in approximately 60% of patients.⁵ Moreover, anti-TNF α agents are not only capable of improving combined disease activity indices, but have also shown their ability to improve self-reported patient outcomes using different questionnaires exploring health-related quality of life, such as the SF-36 or EuroQol-5D.⁶

In a chronic disease such as AS, it is essential to know whether the treatment agents maintain their safety and efficacy over the medium and long term. In this regard, several studies have confirmed that TNF α antagonists maintain their safety and efficacy for years in patients with AS. In fact, more than 60% of the patients who participated in the randomized, double blind, placebo-controlled clinical trials maintain ASAS40 response with infliximab over the course of a 5-year, open-label, follow-up period.⁷ On the other hand, during a 192-week, open-label follow-up period, approximately 60% of the patients treated with etanercept maintained a ASAS40 response.⁸ In the case of adalimumab, results have been published on the open-label, 2-year follow-up of patients from the ATLAS Study, a double blind, randomized, placebo-controlled trial, revealing a ASAS40 response in close to 60% of the patients after 104 weeks of follow-up.⁹ Furthermore, there have been recent reports that most patients with AS continue to present an appropriate response to treatment following seven years of treatment with infliximab, achieving an 83% ASAS20 response rate, without any safety issues or loss of efficacy.¹⁰

The long-term efficacy and safety of TNF α antagonists in AS are also apparent in the data extracted from the BIOBADASER registry of biological agents.¹¹ Experience in standard clinical care reveals that treatment retention with TNF α antagonists is close to 75% at 4 years, a figure clearly superior to the 60% found in patients with rheumatoid arthritis (RA), confirming the clinical impression that response to anti-TNF agents is superior in AS than in RA,¹¹ and also that adverse effects forcing suspension of treatment are less common.

An issue that is extremely relevant in clinical practice in patients with AS in whom the disease is controlled for prolonged periods of time is whether therapy with TNF α antagonists can be suspended. Two studies have attempted to answer this question. In the first of them, Baraliakos et al¹² evaluated 42 individuals with AS controlled with infliximab for at least 3 years. After suspending infliximab, data was recorded with respect to the clinical response, as well as time until the following relapse, defined as a BASDAI score of 4 or more. The mean time to relapse was 17.5 weeks. In fact, only 12 weeks after interrupting treatment with infliximab, one fourth of the patients had already relapsed; 90% had done so at 36 weeks and, at one year of follow-up, 97% of the patients had relapsed. The authors looked at whether there might be some clinical characteristic at the time of withdrawal that determined earlier relapse. A trend toward earlier relapse was seen in the patients who were not in remission ($P=.059$). Both a BASDAI score of more than 3 ($P=.039$), as well as C-reactive protein >6 mg/L ($P=.009$) showed a significant association with earlier relapse. Fortunately, all the patients responded satisfactorily to the re-introduction of infliximab.¹³ The response to the interruption of etanercept in patients with satisfactory control is very similar. Brandt et al¹⁴ conducted an observational study, with a 54-week follow-up period, in 26 patients with AS from a randomized clinical trial. They discontinued etanercept treatment and determined the time until relapse, considering relapse to be a BASDAI score greater than 4. They also observed that at 36 weeks, all the patients had relapsed but that, luckily, the re-introduction of etanercept was accompanied by a rapid response in all individuals.

Likewise, the question as to whether or not it is possible to prevent the re-appearance of axial symptoms in patients with

TNF α antagonist therapy on demand. Breban et al¹⁵ carried out a randomized clinical trial, with a one-year follow-up period, in patients with active AS, defined by a BASDAI score of 3 or higher and at least one of the following three conditions: high C-reactive protein levels, sacroiliac MRI showing an activity signal or positive Doppler signal at the entheses. They randomly assigned 124 patients to receive 5 mg/kg of infliximab every 6 weeks and compared them to 123 patients assigned to infliximab (in monotherapy or associated with methotrexate) only after symptoms had re-appeared. The primary endpoint was the proportion of patients who achieved a ASAS20 response at the one-year time point. A significantly greater percentage of patients treated with infliximab using a fixed schedule of administration attained a ASAS20 response, 75% vs 46% of the group treated with infliximab on demand plus methotrexate or 40% in the group treated with infliximab without methotrexate.

Some AS patients do not respond adequately to the first anti-TNF α agent tried or develop side effects that lead to withdrawal of the treatment. *A priori*, it might appear that in these patients, attempting a second agent aimed at the same treatment target would make no sense whatsoever, although, on the other hand, it has been well documented that in RA it is not uncommon to achieve adequate response to a second TNF α antagonist after withdrawal of the first one. The data available regarding changing anti-TNF α agents in patients with AS are as yet quite scant. Conti et al¹⁶ reported a series of 6 patients with AS in whom infliximab was substituted by etanercept due to inefficacy or adverse effects of the former. They saw that close to 80% of the patients responded favourably to etanercept, attaining a reduction of at least 50% on the BASDAI score. Along the same lines, Delaunay et al. have published another small series¹⁷ of 7 patients with AS and 6 patients with undifferentiated spondyloarthritis in whom infliximab had to be suspended due to inadequate response (9 patients) or because of the appearance of adverse effects (4 patients). The patients were treated with etanercept and after 10 months of follow-up, the authors observed that 9 of the 13 patients presented an adequate response to etanercept, with a BASDAI score of less than 4 and without any relevant toxicity. Finally, Coates et al, using a registry of 113 patients with AS treated with anti-TNF agents at Professor Emery's Rheumatology Department at Leeds, between 1999 and 2006, identified only 9 patients who discontinued treatment with the first anti-TNF agent due to toxicity and 15, owing to inefficacy. Of these 24 patients, 15 received a second anti-TNF agent and, once again, an excellent response was seen, given that 14 of the 15 patients (93%) responded adequately to treatment with the second TNF α antagonist, reaching a BASDAI score of less than 4.¹⁸

Anti-TNF α agents can also be of use in the pre-radiological stages of AS, as proven in an interesting controlled, randomized trial, in patients with inflammatory lumbar pain, HLA-B27 positive, and inflammatory findings in the MRI study of the sacroiliac joints.¹⁹ These patients, with a clinical diagnosis of AS but failing to meet the New York classification criteria because they did not present radiological sacroiliitis, were randomized to receive infliximab or placebo, with a follow-up of 12 weeks. Fifty-five per cent (55%) of the patients treated with infliximab achieved an ASAS70 response, versus 12% of the group that received placebo ($P=.009$). On the other hand, it appears that treatment with anti-TNF α agents in these pre-radiological stages of AS is unable to abort the pathogenic process definitively since, once the anti-TNF α agent is discontinued, symptoms re-appear in most patients.²⁰ Fortunately, treatment with adalimumab in these individuals is efficacious again when re-introduced after the re-appearance of symptoms.²⁰

In short, the experience in recent years has shown us how the use of TNF α antagonists in patients with AS and inadequate response to full doses of NSAID provides excellent symptomatic control of the illness, improves our patients' quality of life, and improves functional

indices of the disease, maintaining their treatment effect over the course of years, with an outstanding safety profile.

Modification of structural damage with anti-TNF treatment in ankylosing spondylitis

As in RA, sustained control over time of the inflammatory activity of the illness would be expected to translate into a modification of the radiological progression of AS, avoiding its natural tendency to form syndesmophytes and ankylosis. Halting the structural progression is of the utmost importance, given that patients' functional capacity appears to be directly related not only to the inflammatory activity present but also, indirectly, to the accumulated radiological structural damage. Landewé et al. have recently published an electronic version of a study in which physical function in AS is proven to be independently determined by both the activity of the disease as well as by the radiological lesion of the spine.²¹ The investigators used baseline data and data after 2 years of follow-up of the OASIS cohort, made up of patients with AS followed prospectively and without treatment with biological agents. In these patients, physical function was evaluated as a dependent variable by means of the Dougados Functional Index and the BASFI score, whereas inflammatory activity was determined by means of the BASDAI score (self-perceived clinical inflammatory activity), red blood cell sedimentation rate, and levels of C-reactive protein. Structural damage was quantified using the modified *Stoke Ankylosing Spondylitis Spine Score* (SASSS-m). In the multivariate analysis, the BASFI variable was seen to depend on both the BASDAI score ($P<.001$) as well as SASSS-m ($P<.001$). The Dougados Functional Index was also independently associated with the BASDAI score ($P<.001$) and the SASSS-m ($P<.001$). Although a trend toward association was seen between the Dougados Functional Index and red blood cell sedimentation rate, the association failed to achieve statistical significance ($P=.065$).

MRI is an extraordinarily informative imaging technique in AS. It enables identification of acute inflammatory lesions on the vertebral bodies (Romanus lesion, Anderson lesion) and on the inter-apophyseal joints, both on STIR sequences and post-gadolinium T1 sequences.²² Likewise, MRI is useful in identifying chronic lesions with fatty replacement in T1 sequences without gadolinium. In contrast, MRI is not the best technique for identifying syndesmophytes, since compact bone is not properly visualized by means of any MRI sequence. During the core TNF α antagonist development trials in AS, MRI were performed of the spine before and after treatment, revealing a clear reduction of inflammatory oedema after treatment, both at the individual level, as well as the pooled appraisal of the indices of activity on the MRI.²³ Baraliakos et al²⁴ used MRI to evaluate AS patients' spines before and after treatment with etanercept. Forty (40) patients were admitted and randomized to receive either etanercept or placebo. MRI of the lower thoracic spine and the lumbar spine were taken prior to treatment and at 12, 24, and 48 weeks of treatment with etanercept or placebo. After 24 weeks of controlled study, the patients originally assigned to the placebo group were allowed to switch over to etanercept. Treatment with etanercept was able to achieve a dramatic decrease in the active inflammatory signals present on the baseline MRI. At the group level, at week 12, the patients treated with etanercept exhibited a 53% decrease on their bone oedema score versus a 12% increase in the placebo group. At 24 weeks, the etanercept-treated group had reduced the inflammatory signal by 72% as compared to 4% in the placebo group. At week 48, the group that had initially been assigned to placebo and that started receiving etanercept at week 24 presented a 40% reduction in the inflammatory signal.

What is more, treatment with infliximab has been proven to be capable of reducing inflammation of the vertebral bodies, as assessed by means of MRI, over a 2-year treatment period. Sieper

et al²⁵ studied 20 patients with AS (11 of whom were treated with placebo and 9 with infliximab). At 12 weeks of follow-up, the patients in the placebo group switched over to infliximab. An MRI was performed in all patients at baseline, at 3 months, and again at 2 years. Whereas treatment with placebo was incapable of eliminating the inflammatory signals on the STIR sequences and on the post-gadolinium T1 sequences, infliximab was efficacious in reducing the bone oedema signal. At the group level, at 12 weeks, patients who were treated with infliximab had a 48% reduction on their MRI indices of inflammatory activity versus a mere 9% in the group that received placebo. The STIR sequences at 2 years, revealed a 70% decrease in patients treated with infliximab.

In line with the current paradigm of the physiopathogenesis of AS, inflammation of the subchondral bone is followed by reparative processes with fibrosis and the appearance of osteoblast lineage cells that produce bone apposition and syndesmophytes formation, the typical structural lesion of AS. Therefore, it follows that the acute inflammatory lesions seen on the STIR sequences and post-gadolinium T1 sequences on the MRI appear in the future radiologically evident syndesmophytes. Baraliakos et al²⁶ studied the MRI and simple X-rays of 39 patients with AS treated with anti-TNF α agents in an attempt to correlate the oedema seen on the baseline MRI with the appearance of syndesmophytes in the X-ray performed 2 years later. They analyzed a total of 922 vertebral margins in the cervical and lumbar spine. There were structural changes on the baseline X-rays in 71% of the patients and in 16% of the margins analyzed. Two years later, 26 new syndesmophytes had formed in 2.9% of all the margins analyzed. Of these new syndesmophytes, 62% were located at points where there had been inflammation on the baseline MRI. In fact, in both the STIR sequences and the post-gadolinium T1 sequences, the presence of oedema on the baseline MRI was significantly associated with the development of syndesmophytes on the X-ray performed 2 years later and close to 6% of the vertebral margins with oedema on the STIR sequences developed syndesmophytes versus only 2% of the margins without oedema on the baseline MRI, a statistically significant difference ($P=.006$).

Three works have researched the radiological evolution of structural damage in patients with AS treated with anti-TNF α agents (Table). In the first one, Baraliakos et al²⁷ studied 33 patients with AS treated with infliximab over the course of 3 years, performing X-rays at baseline, at 2 years and again at 4 years. Despite the excellent symptomatic control achieved with infliximab, radiological progression was detected in 30% of the patients. Those individuals who already had structural lesions on the baseline X-rays were the ones who presented the greatest radiological progression. The authors then compared these patients with the subjects from the OASIS cohort not treated with TNF α antagonists, observing a mean increase of 4.4 units of the SASSS-m in the OASIS cohort versus a mere 1.6 units in the cohort treated with infliximab, suggesting a relative halt of radiological progression. In contrast, van der Heijde et al²⁸ were unable to demonstrate differences with respect to the OASIS cohort in the 279 patients who participated in the ASSERT study and who were treated with infliximab for 72 or 96 weeks. The third study assessed the patients who participated in a core developmental clinical trial of etanercept in AS.²⁹ They compared 257 patients treated with etanercept for 96 or 72 week with the individuals from the OASIS cohort and, again, no statistically significant differences could be found in the radiological evolution of the 2 groups of patients.

The explanation for this disparity between the sustained control of inflammatory activity and the lack of modification of the evolution of the structural lesion might be due to the fact that in AS, after inflammation of the subchondral bone, which typically fluctuates, erosive bone destruction takes place in which repair phenomena occur with fibrous tissue and fibroblasts, followed by

Table
Descriptive studies regarding safety and efficacy of the change between anti-TNF α agents in ankylosing spondylitis

Authors	Number of patients	First anti-TNF α	Cause of discontinuation of first anti-TNF α	Second anti-TNF α	Efficacy	Safety
Conti et al ¹⁴	6	Infliximab	Lack of efficacy: 3 cases Reactions to infusion: 3 cases	Etanercept	Adequate response (BASDAI score <4) in 5 of 6 cases	No adverse events
Delaunay et al ¹⁵	7	Infliximab	Lack of efficacy: 6 cases Reactions to infusion: 1 case	Etanercept	Adequate response (BASDAI score <4) in 3 of 7 cases	No adverse events
Coates et al ¹⁶	15	Infliximab	Primary inefficacy: 7 cases Secondary inefficacy: 2 cases Adverse effects: 2 cases Preference for self-injectable: 4 cases	Etanercept: 6 cases Adalimumab: 1 case Not specified: 8 cases	Adequate response (Reduction >50% in BASDAI score) in 14 of 15 cases	Allergic reaction to adalimumab: 1 case

the appearance of osteoblasts and neo-osteogenesis that gives rise to syndesmophytes. The pro-inflammatory cytokine TNF α produces bone resorption by inducing the expression of Dickkopf-1, which leads to suppression of the Wnt signalling pathway, essential to the communication of signalling for osteoblastogenesis and neoosteogenesis,³⁰ and to enhanced expression of the receptor activator of nuclear factor B ligand, which is a potent stimulator of bone resorption by binding to the RANK on the surface of the osteoclast. When Dickkopf-1 is inhibited, Wnt signalling induces the formation of new bone and the expression of osteoprotegerin, which blocks the bone resorption mediated by the receptor activator of nuclear factor B ligand. Therefore, inflammation should disappear prior to new bone apposition. It is therefore reasonable to think that anti-TNF α agents not only inhibit the formation of new bone, but that they stimulate it, by inhibiting the resorptive effect mediated by the TNF α . In fact, this action has been demonstrated in a murine model of ankylosis.³¹ Figure presents a summary of the pathogenic phenomena probably intervening in AS. In a first stage, subchondral bone becomes inflamed and an intense infiltration by CD3⁺ CD8⁺ T lymphocytes, osteoclasts, and neoangiogenesis is seen. In this initial stage, the treatment targets would be TNF α , interleukin-6, T lymphocytes, macrophages, and CD68⁺ osteoclasts, and the humoral factors involved in angiogenesis, such as vascular endothelial growth factor. In a second stage, repair phenomena would take place, with the appearance of fibroblasts and fibrosis; during this stage, the main molecular target would be *transforming growth factor*- β . In a third phase, bone apposition would occur with the appearance of osteoblasts in the repair focus. In this final stage, the biological targets would be bone matrix proteins and the pro-osteoblastogenic Wnt pathway.

In addition to these biological targets, it is wise to remember that the continuous use of NSAID compared to their use on demand depending on symptomatology, has demonstrated reduction of radiological damage assessed by means of the SASSS-m at 2 years in a randomized clinical trial.³² The mechanism by which NSAID might delay ankylosis in AS is unknown, but it appears unlikely that it is due to better control of the inflammatory phase in comparison with anti-TNF α agents. On the other hand, cyclooxygenase-2 is known to play a relevant role in bone formation, since COX-2 knock-out mice display decreased bone callus after fracture.³³ Furthermore, NSAID are known to be capable of reducing the risk of heterotopic bone formation by up to 65% following hip replacement surgery.^{34,35} Perhaps, as in Edgar Allan Poe's *The Purloined Letter*, the solution to the mystery is in full sight, but, precisely because it is so obvious, it goes unnoticed and, in this regard, it would be very interesting to carry out a randomized, double blind, placebo-controlled clinical

	Inflammation	Fibrosis	Osteogenesis
Image characteristics			
Histological findings	Mononuclear inflammatory infiltrate CD68+ Macrophages CD68+ Osteoclasts Angiogenesis	Fibroblasts Reparative fibrous tissue Angiogenesis	Osteoblasts Bone apposition
Potential treatment targets	TNF α IL-6 Co-stimulation molecules	TNF β	PMO Wnt pathway

Figure. Correlation between the findings on the imaging studies, anatomical/pathological characteristics, and potential treatment targets in the various evolutionary phases of the core lesion in AS. In an initial inflammatory phase, characterized by bright lesions on the STIR sequences and post-gadolinium T1 sequences, there is an intense infiltrate of the subchondral bone by osteoclast CD3⁺/CD8⁺ T lymphocytes and neoangiogenesis. In this first stage, treatment targets would be TNF α , interleukin-6, T lymphocytes, macrophages, and CD68⁺ osteoclasts, and the humoral factors involved in angiogenesis, such as vascular endothelial growth factor. In a second stage of fibrosis, characterized in the T1 sequences as grey areas, reparative fibrosis is produced, with the presence of fibroblasts; in this stage, the main molecular target would be transforming growth factor- α . In a third stage, bone apposition would take place with the appearance of osteoblasts in the reparative focus. In this final stage, the biological targets would be the bone matrix proteins and the pro-osteoblastogenic Wnt pathway.

trial in which the use of a TNF α antagonist could be combined with a continuously used NSAID.

Conclusions

Anti-TNF α agents have revolutionized drug treatment in AS patients. They are efficacious and safe over the medium and long term, but they must be used continuously if appropriate symptomatic control is to be achieved, with pain and stiffness re-appearing after they have been discontinued. Despite the paucity of data available, the information we do have suggests that following failure to respond to one anti-TNF α , treatment with a second anti-TNF α is both efficacious and safe.

Despite the excellent sustained symptomatic control, a beneficial effect of treatment with TNF α antagonists on the radiological

evolution of AS has yet to be demonstrated, even though there is rapid, sustained disappearance of bone inflammation, as demonstrated by MRI studies. The use of anti-TNF α agents in earlier stages of AS would probably make it possible to control not only the inflammation, but also the formation of syndesmophytes. Perhaps the study of new molecular targets involved in the pathogenic phases of fibrous tissue and bone apposition in AS opens up new avenues of treatment, although measures as simple as the continuous use of an NSAID during the reparative stage might mean the end of the osteogenesis that leads to the development of syndesmophytes.

Conflict of interest

The authors state that there is no conflict of interests.

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