



Original article

Consensus Statement of the Spanish Society of Rheumatology on the management of biologic therapies in Spondyloarthritis except for Psoriatic Arthritis

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ABSTRACT

Objective: Due to the amount and variability in quality regarding the use of biologic therapy (BT) in patients with spondyloarthritis (SpA), except for psoriatic arthritis (PsA) patients, the Spanish Society of Rheumatology has promoted the generation of recommendations based on the best evidence available. These recommendations should be a reference for rheumatologists and those involved in the treatment of patients with spondyloarthritis (SpA), except for psoriatic arthritis (PsA), who are using, or about to use BT. **Methods:** Recommendations were developed following a nominal group methodology and based on systematic reviews. The level of evidence and grade of recommendation were classified according to the model proposed by the Center for Evidence Based Medicine at Oxford. The level of agreement was established through Delphi technique.

Results: We have produced recommendations on the use of BT currently available for SpA (but not PsA) in our country. These recommendations include disease assessment, treatment objectives, therapeutic scheme and switching.

Conclusions: We present an update on the SER recommendations for the use of BT in patients with SpA, except for PsA.

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Documento SER de consenso sobre el uso de terapias biológicas en la espondilitis anquilosante y otras espondiloartritis, excepto la artritis psoriásica

RESUMEN

Palabras clave:

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Objetivo: Dada la gran cantidad de información sobre las terapias biológicas (TB) en las espondiloartritis (EspA), excepto la artritis psoriásica (APs), y la variabilidad en cuanto a su calidad, desde la Sociedad Española de Reumatología (SER) se ha impulsado la generación de recomendaciones basadas en la mejor evidencia posible. Estas deben servir de referencia para reumatólogos e implicados en el tratamiento de estos pacientes.

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Espondiloartritis

Métodos: Las recomendaciones se emitieron siguiendo la metodología de grupos nominales. El nivel de evidencia y el grado de recomendación se clasificaron según el modelo del Center for Evidence Based Medicine de Oxford y el grado de acuerdo se extrajo por técnica Delphi.

Resultados: Se realizan recomendaciones sobre el uso de las TB para el tratamiento de las EspA (excepto la APs). Incluyen la evaluación de la enfermedad, objetivos del tratamiento, esquema terapéutico y cambios en éste.

Conclusiones: Se presentan las actualizaciones a las recomendaciones SER para el uso de TB en pacientes con EsA, excepto la APs.

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Introduction

This document is part of the second update of the consensus from the Spanish Society of Rheumatology (SER) on the use of biological therapies (BT) in spondyloarthritis (SpA). The recommendations offered are intended as a reference to assist in therapeutic decision making for rheumatologists and for those professionals from various levels of healthcare or managers who are involved in the treatment of SpA.

Both the high cost of these drugs and the limited information available on their long-term safety force a rational use of these drugs. It is therefore necessary to integrate their use into a global therapeutic strategy for the disease. Although the recommendations are based especially on the evidence available for ankylosing spondylitis (AS), the paradigm of SpA (for which BT use is approved in Spain), these recommendations can serve for the rest of SpA diseases, taking into account the characteristics of each patient.

In contrast with earlier documents, psoriatic arthritis (PsA) has not been included in this one, and its consensus is published as a separate document. The panel has considered that the evidence and current trends in the literature support this differentiation. We should also add that all the evidence and recommendations on BT monitoring will be presented in a forthcoming consensus document.

The term SpA refers to a heterogeneous group of diseases with defined diagnostic criteria, such as AS,¹ reactive arthritis,² PsA,³ spondylitis associated with inflammatory bowel disease (IBD) (which includes Crohn's disease and ulcerative colitis) and a subgroup of juvenile chronic arthritis. However, it also encompasses patients with clinical features of SpA (according to the criteria of the European Spondyloarthropathy Study Group [ESSG]⁴ or those of Amor⁵) who do not meet the criteria for a defined SpA. Traditionally, they have been classified and named as undifferentiated SpA (USpA).

The problem with patients with USpA is that clinically they can be affected as significantly as with defined SpA⁶ and the fact of being "undifferentiated" may have an impact at the therapeutic level. A clear example is that of many patients with chronic inflammatory back pain without radiographic evidence of sacroiliitis, for whom years may pass before it is detected.⁷

Based on the above, the ASAS group (Assessment in Ankylosing Spondylitis International Society) has developed and validated criteria for classifying patients at the early stage (such as those with chronic low back pain initiated before 45 years of age⁸ without radiographic sacroiliitis) that can be used in clinical trials and in daily practice. This has generated two sets of criteria, some for axial SpA⁹ and others for peripheral SpA¹⁰ (Table 1, Table 2).

Consequently, it has been proposed to consider all patients with predominantly axial SpA (with or without peripheral involvement, although this would be less relevant clinically) as axial SpA, regardless of whether they have definite radiographic sacroiliitis or not, and to refer to patients without radiographic sacroiliitis as non-radiographic axial SpA.¹¹ Likewise, cases would be considered as peripheral SpA when the peripheral involvement is the sole or clinically dominant entity.

These criteria highlight the inclusion of the concept of active sacroiliitis (acute), according to the images obtained in magnetic resonance imaging (MRI), as one of the imaging parameters. The

Table 1

ASAS (Ankylosing Spondylitis Assessment Study) Group classification criteria for axial SpA^a

Criteria for the classification of axial SpA in patients with lumbar pain >3 months evolution and age of onset <45 years	
A. Clinical criteria	
1.	Inflammatory low back pain ^b
2.	Peripheral arthritis (present or past active synovitis diagnosed by a physician)
3.	Enthesitis (enthesitis in heel: presence or history of spontaneous pain or numbness upon exploration in the insertion of the Achilles tendon or plantar fascia in the calcaneus)
4.	Dactylitis (presence or history of dactylitis diagnosed by a physician)
5.	Good response to NSAIDs (clear improvement or disappearance of lumbar pain 24–48 h after the administration of maximum doses of an NSAID)
6.	Family history (presence in first- or second-degree relative of any of: AS, psoriasis, uveitis, ReA, IBD)
7.	Previous uveitis (presence or history of prior uveitis confirmed by an ophthalmologist)
8.	Psoriasis (presence or history of psoriasis diagnosed by a physician)
9.	IBD (presence or history of Crohn's disease or ulcerous colitis diagnosed by a physician)
10.	HLA-B27 (positive test using standard laboratory techniques)
11.	Increase of CRP (elevated CRP in the presence of lumbar pain and after exclusion of other causes for CRP elevation)
B. Sacroiliitis in imaging studies	
1.	Sacroiliitis (radiological, MRI): definitive sacroiliitis according to the modified New York criteria or acute inflammation in MRI (highly suggestive of sacroiliitis)
C. Genetic predisposition	
1.	Positive HLA-B27

^aInterpretation: SpA are classified as axial if they meet the criteria of sacroiliitis in imaging studies, and at least one of the clinical criteria, or the criterion of positive HLA-B27 if associated with at least 2 clinical criteria.

^bInflammatory low back pain in patients with chronic low back pain (>3 months) if at least 4 of the following are met: 1) age of onset <40 years; 2) insidious onset; 3) improvement with exercise; lack of improvement with rest; 5) pain at night (with improvement after rising).

CRP indicates C reactive protein; ESR, erythrocyte sedimentation rate; IBD, inflammatory bowel disease; MRI, nuclear magnetic resonance; NSAID, nonsteroidal anti-inflammatory drugs; ReA, reactive arthritis; SpA, spondyloarthritis.

Table 2

ASAS (Ankylosing Spondylitis Assessment Study) Group classification criteria for peripheral spondyloarthritis (SpA)

Criteria for the classification of predominantly peripheral SpA in patients with age of onset of symptoms <45 years	
Arthritis, enthesitis or dactylitis (a necessary criterion) and:	
≥1 of the following:	
1.	Prior infection
2.	Sacroiliitis (Rx or MRI)
3.	Uveitis
4.	Psoriasis
5.	IBD
6.	HLA-B27
Or, alternatively, arthritis, enthesitis or dactylitis (a necessary criterion) and:	
≥2 of the following:	
1.	Arthritis
2.	Enthesitis
3.	Dactylitis
4.	Inflammatory lumbar pain
5.	Family history of SpA

IBD indicates inflammatory bowel disease; MRI, nuclear magnetic resonance; Rx, plain radiograph.

presence of bone marrow oedema and osteitis are considered essential for the definition of active sacroiliitis in MRI.

Throughout this document, the term SpA will be used to include all defined SpA (except PA) and what is traditionally defined as USpA.

Ankylosing spondylitis, the SpA paradigm, is a chronic inflammatory rheumatic disease characterised by predominantly axial symptoms (rachialgia/inflammatory lumbar pain) from sacroiliitis, spondylitis, spondylodiscitis¹² and formation of syndesmophytes leading to ankylosis. Frequently, it also presents peripheral arthritis (usually of the lower limbs), enthesitis and extra-articular manifestations such as acute anterior uveitis, psoriasis or IBD. Radiographic sacroiliitis (simple radiograph) defines its diagnosis, according to the modified New York criteria.¹

The SpA diseases as a whole have a significant impact on healthcare. Their prevalence is not low, at around 1.9% of the general population, with differences by race, prevalence of HLA B27 and geographic environment studied.^{13,14} The estimated annual incidence in Spain, calculated in the ESPIDEP study, is of 62.5 cases per 100,000 inhabitants.¹⁵ According to the National Validation Study of Spondyloarthropathies, they represent 13% of patients in Spanish rheumatology services.¹⁶

A considerable number of patients with SpA develop a disabling illness, with impairment of their functional capacity and quality of life,⁶ even from the beginning of the disease,¹⁷ leading to a loss of production capacity,^{6,17–19} Thus, SA causes an average annual loss of 62 working days per patient¹⁶ and leads 20% of patients to change careers and another 20%¹⁸ to permanent disability.

The basis of SpA treatment is still the same: education, physical therapy and treatment with non-steroidal anti-inflammatory drugs (NSAIDs); however, evidence of the effectiveness of tumour necrosis factor α (TNF- α) antagonists has increased notably.²⁰ Existing evidence supports the use of some disease-modifying antirheumatic drugs (DMARDs), such as methotrexate (MTX) or leflunomide (LEF) in the axial forms, but it cannot be ruled out in peripheral forms.²¹ Sulfasalazine (SSZ) has been shown to be effective, albeit modestly, on articular manifestations in controlled studies.²² However, it has not been shown that these treatments, except the continued use of NSAIDs, are beneficial in the progression of structural damage.²³

The purpose of these recommendations is to put in the hands of rheumatology specialists, and of all the technical specialists involved in SpA patient care, an instrument that can guide them in the therapeutic management of patients with BT. It should be noted that references to the monitoring of BT will be presented in another consensus document.

Methods

To elaborate this consensus, we used a modification of the RAND/UCLA²⁴ methodology. This document is based on the reviews and recommendations of *Espoguía*,²⁵ along with a critical review of the previous consensus.²⁶ A panel of 19 rheumatologists who belonged to the GRESSER group or who had taken part in the preparation of the *Espoguía* or the previous SpA consensus²⁶ was formed. These were sent a dossier containing the previous consensus and the *Espoguía* documentation. The entire consensus was prepared by distribution of tasks and comments to the parties.

Firstly, each panellist was assigned to work on one or several points of the consensus. Once completed, the work was circulated to all panellists for comment. After that, members of the SER research unit (RU) unified, categorised, classified and summarised all the comments for evaluation before the panel meeting.

A nominal group meeting was conducted, chaired by members of the SER RU. Proposed amendments to the document in relation

to format and content were discussed at this meeting, including recommendations.

Subsequently, the consensus recommendations were voted through a Delphi survey (completed anonymously online). Aggregate results were shown to all panellists (Delphi amended). The recommendations with a degree of consensus below 70% were re-edited and voted in a second round. Agreement was understood to exist when a panellist voted 7 or over 7 on a scale from 1 (totally disagree) to 10 (totally agree).

The level of evidence and degree of recommendation were classified according to the model of the Oxford Centre for Evidence Based Medicine²⁷ by SER RU members.

The final document was drafted using this information.

Prior considerations

Biological therapy available

Currently, the only option accepted as BT in AS and PA is still anti-TNF- α , specifically, etanercept (ETN), infliximab (IFX), adalimumab (ADA) and golimumab (Table 3). These can be used in monotherapy, without the need to combine them with MTX or SSZ.

Approved anti-TNF- α drugs are clinically effective in patients with SpA and axial and/or articular involvement refractory to NSAIDs and DMARDs.^{28–33} The clinical response is rapid and sustained over time, with longer survival of the drug than in RA,^{34,35} being effective at any stage of the disease, although the response is higher when there is more clinical activity and less evolution.^{36–40} They reduce the signs of vertebral and sacroiliac inflammation (objectified via MRI), but they have not been shown to alter structural damage.^{41–43} In addition, they are useful in extra-articular manifestations such as uveitis,⁴⁴ amyloidosis,^{45,46} IBD,^{47,48} osteoporosis,⁴⁹ and they may also aid in decreasing cardiovascular risk.⁵⁰ Their suspension is often associated with resurgence of the disease, although they have proven effective and safe after restoration.^{38,51–53}

Although there are no direct comparative studies between different anti-TNF- α agents, the response rate is similar among them, so the specific choice will depend on the medical criteria and the particular circumstances of each patient. However, there is evidence of differential effects in relation to some extra-articular manifestations of SpA, such as uveitis, in which monoclonal antibodies appear to be more effective in preventing recurrences.⁵⁴

Lastly, given their different structures, antigenicity and mechanisms of action, a lack of response to one of the antagonists does not necessarily imply the inefficiency of another.⁵⁵

Panel members believe that anti-TNF- α should be available for therapeutic practice, without any priority or hierarchy other than scientific evidence itself (NE 5; GR D; GA 93.7%).

Characteristics of available biological therapy

Etanercept (ETN)

This is a fusion protein with soluble p75 TNF receptor linked to the Fc portion of IgG (Table 3). The recommended dose is 50 mg a week (subcutaneously), although a single weekly dose is as effective as that of 25 mg twice a week in patients with AS.⁵⁶

In patients with active SpA refractory to NSAIDs and/or DMARDs, ETN is significantly more effective compared with placebo in variables such as: spinal pain, function, morning stiffness, spinal mobility, enthesitis, arthritis, composite indexes such as BASDAI (Bath Ankylosing Spondylitis Disease Activity Index), BASFI (Bath Ankylosing Spondylitis Functional Index), ASAS20/50/70, laboratory parameters (ESR, CRP) and quality of life.^{28,31,57–61}

The MRI of SpA patients treated with ETN has shown improvement in spinal inflammation.^{62,63}

Table 3Biological therapy available for the treatment of spondyloarthritis (SpA), according to their data sheets (updated in December 2010)^a

Active principle	Dosage and administration	Indications	Contraindications	Adverse events ^a
Adalimumab	- Dose: 40 mg - Via: subcutaneous - Frequency: every 2 weeks	- Severe active AS and insufficient response to conventional therapy	- Allergy to active principle or excipients - Active TBC, severe infections - Moderate to severe HF (NYHA classes III/IV)	- Very frequent: reaction at the site of injection (pain, redness) - Frequent: headache, respiratory/urinary infection, herpes, diarrhoea - Infrequent: SLE, arrhythmia, TBC, sepsis, cytopenia - Rare: CHF, multiple sclerosis, lymphoma, solid malignant tumour
Etanercept	- Dose: 25 mg or 50 mg - Via: subcutaneous - Frequency: 25 mg twice a week (interval of 72-96 hours); 50 mg once a week	- Severe active AS and insufficient response to conventional therapy	- Allergy to active principle or excipients - Sepsis or risk of sepsis - Active infections	- Very frequent: reaction at the site of injection, respiratory, urinary, cutaneous infection - Frequent: allergy, autoantibodies - Very frequent: severe infections, thrombopenia, psoriasis - Rare: pancytopenia, TBC, SLE
Golimumab	- Dose: 50 mg - Via: subcutaneous - Frequency: once a month, on the same day each month	- Severe active AS and insufficient response to conventional therapy	- Allergy to active principle or excipients - Active TBC or other severe infections like sepsis or opportunistic infections - Moderate or severe IC (NYHA classes III/IV)	- Very frequent: upper respiratory tract infection - Frequent: cellulitis, herpes, bronchitis, sinusitis, HT, superficial fungal infections, anaemia, antibodies, allergic reaction, depression, insomnia, headache - Infrequent: TBC, sepsis, neoplasms, ↑ glucose, lipids, CHF, thrombosis, arrhythmia, ocular alterations - Rare: reactivation of hepatitis B, lymphoma, pancytopenia
Infliximab	- Dose (depending on body weight): 5 mg/kg - Via: iv perfusion for 2 h - Frequency: after first dose, another at 2 and 6 weeks. After that, 1 every 6-8 weeks	- Severe active AS, in adult patients who have responded inadequately to conventional therapy - Should be administered in combination with MTX or monotherapy in case of contraindication or intolerance	- Allergy to active principle, excipients or other murine proteins - Active TBC, severe infections - Moderate to severe HF (NYHA classes III/IV)	- Very frequent: infusion reaction - Frequent: headache, respiratory infection, herpes, diarrhoea - Infrequent: SLE, TBC, sepsis, cytopenia - Rare: CHF, multiple sclerosis, lymphoma

AS indicates ankylosing spondylitis; CHF, congestive heart failure; DMARDs, disease-modifying antirheumatic drugs; HF, heart failure; HT, hypertension; iv, intravenous; MTX, methotrexate; NYHA, New York Heart Association; SLE, systemic lupus erythematosus; SpA, spondyloarthritis; TBC, tuberculosis; TNF, tumour necrosis factor. The data in this table are derived from the data sheet of the Spanish Medicine Agency (EMA).

^aAdverse events: very common (at least 1 in 10 patients); frequent (at least 1 in every 100 patients); infrequent (at least 1 in 1,000 and fewer than 1 in 100); rare (at least 1 in 10,000 and fewer than 1 in 1,000).

This biological agent has also shown low immunogenicity,⁶⁴ and improvement over biomarkers of cartilage degradation and bone remodeling,^{65,66} work disability⁶⁷ and microvascular dysfunction described in these patients.⁶⁸

One study has shown that it can reduce episodes of anterior uveitis associated to AS, in a manner similar to SSZ, in relation to the control group.⁶⁹

Lastly, several observational studies confirm that it remains effective for over 5 years.⁷⁰⁻⁷²

Infliximab (IFX)

This is a chimeric monoclonal antibody against TNF (Table 3). The recommended dose is 5 mg/kg every 6-8 weeks, intravenously. Some studies have shown that it is possible to achieve similar efficacy with lower doses, while maintaining the same interval.^{28,73,74}

Most studies have been conducted in AS, where, in patients with active disease and refractory to NSAIDs and/or DMARDs and compared to placebo, IFX has proven more effective for both axial and peripheral forms, improving clinical parameters such as arthritis, enthesitis, spinal pain, function, composite indexes,

such as BASDAI, BASFI, ASAS20,^{57,75-77} quality of life and laboratory parameters.^{78,79}

MRI imaging has found improvement of inflammation in the spine and sacroiliac joints.⁸⁰⁻⁸² There have also been reports of improvements in work disability,⁸³ bone mineral density⁸⁴ and, possibly, cardiovascular comorbidity.⁸⁵ It is also effective in reducing the number of outbreaks of uveitis^{44,86-90} and Crohn's disease.^{47,91}

Observational studies confirm the efficacy of IFX in the same parameters as those observed in clinical trials, an effect which is maintained with up to 5 years of treatment.^{92,93}

Adalimumab (ADA)

This is the first totally humanised monoclonal antibody with high affinity for human TNF (Table 3). The recommended dose is 40 mg once every 2 weeks by subcutaneous injection.

In patients with active SpA and refractory to NSAIDs and/or DMARDs, and compared with placebo, it has been found that ADA is statistically superior to placebo in improving overall and nocturnal spinal pain, function, fatigue, morning stiffness, spinal mobility, enthesitis, arthritis, composite indexes such as BASDAI, BASFI,

ASAS20/40/70, partial remission, laboratory parameters, quality of life and work disability.^{32,33,36,37,39,94–99}

MRI images show improvement of vertebral inflammation¹⁰⁰ and of some biomarkers that reflect structural damage.¹⁰¹ The antibody has proven effective in reducing the number of outbreaks of uveitis in different types of SpA.^{87,102} In Crohn's disease, ADA has proven effective in inducing and maintaining remission in these patients.^{47,91}

Several observational studies confirm the effectiveness of the ADA with up to 3 years treatment.¹⁰³

Golimumab

Golimumab is a new, monoclonal, anti-TNF- α antibody of human origin (Table 3), marketed for subcutaneous administration, at doses of 50 mg/4 weeks. The dose may be increased to 100 mg/month for patients weighing over 100 kg who have not achieved an adequate clinical response after 3 or 4 doses.

In patients with active SpA refractory to NSAIDs and/or DMARDs, it has been shown that at 3 months the use of golimumab produced a statistically greater improvement than placebo in ASAS20 (59.4%, 60% and 21.8%, respectively), and at 6 months in ASAS40 (43.5%, 54.3%, and 15.4%).^{104,105} Patients treated with golimumab also improved significantly in global patient assessment, lumbar pain, morning stiffness, CRP, and scores in SF-36, BASDAI, BASFI and the Jenkins Sleep Evaluation Questionnaire,¹⁰⁶ but not in the BASMI (Bath Ankylosing Spondylitis Metrology Index). Other outcomes such as enthesitis,¹⁰⁷ anaemia¹⁰⁸ and work productivity¹⁰⁵ also showed improvement with the use of golimumab.

Golimumab can be used in patients with an indication for biological therapy (NE 5; GR D; GA 100%).

Results

Therapeutic objective

The goal of SpA treatment is the remission of the disease or, failing that, minimising its inflammatory activity to achieve a significant improvement in symptoms and signs (joint swelling, pain, axial and peripheral stiffness, etc.), preservation of functional ability, maintenance of a good quality of life and structural damage control (NE 5; GR D; GA 93.7%).

To improve the prognosis of patients, it is essential to obtain a diagnosis and start treatment as early as possible (NE 5; GR D; GA 100%).

Ideally, the minimum clinical activity would correspond to:

- BASDAI ≤ 2 .
- General assessment of the disease by the patient ≤ 2 .
- Global assessment by the physician ≤ 2 .

These would indicate a virtual absence of joint pain and stiffness. Given the difficulty in achieving this objective, a BASDAI, overall disease assessment by the patient and the physician and nocturnal axial pain <4 are considered acceptable.

Indications of biological therapy in patients with spondyloarthritis

Biological therapy would be indicated in patients with active SpA refractory to conventional therapy (NE 5; GR D; GA 100%).

Such SpA treatment is indicated if, despite correct conventional treatment, the disease remains active according to the criteria mentioned previously. An extensive radiological condition or the absolute limitation of mobility, along with the presence of activity criteria, do not exclude the use of BT.³⁶ In any case, when establishing the definitive indication, the opinion of a rheumatologist or another physician with experience in SpA and BT is considered of utmost importance.

Several studies^{39,81} have recently shown that BT has greater efficacy when administered early. Although the technical sheet contains an indication only for AS, the panel considers it necessary to evaluate its indication in patients who meet the criteria for classification of SpA of the ASAS group (in both axial^{9,109} and peripheral^{9,10,109} forms) who appear active and are refractory to conventional therapy, as defined in previous sections.

Prior to the use of biological therapy in patients with SpA, it is necessary to provide appropriate treatment with NSAIDs and/or sulfasalazine and infiltration into peripheral tissues (NE 5; GR D; GA 87.5%).

In SpA cases with exclusive axial involvement, patients are considered refractory to conventional therapy when they have used at least 2 NSAIDs with proven anti-inflammatory potency over a period of 4 weeks (each NSAID), at the maximum recommended or tolerated dose, except if there is evidence of toxicity or contraindication to NSAIDs. Specific cyclooxygenase-2 inhibitors (coxibs) are a therapeutic alternative to conventional NSAIDs that have proven highly effective in some studies.^{110,111}

When the affection is peripheral, in addition to NSAID treatment, SSZ at a dosage of 2-3 g/day should have been used for at least 3 months in defined AS cases. Despite the lack of available scientific evidence, which does not allow the use of other DMARDs (MTX, LEF, cyclosporine A) to be a definitive requirement before using other forms of BT in peripheral SpA, the potential usefulness of these treatments should be assessed for each individual case.

Local infiltration with glucocorticoids should have also been tested in cases of enthesitis, dactylitis, monoarthritis or oligoarthritis. Although not necessary, radiation synovectomy is recommended in the case of monoarthritis, whenever possible.

With patients treated previously, before considering BT, whether they received an appropriate treatment according to the recommended doses and guidelines mentioned previously should be verified first. Treatment should then proceed according to the situation in each case, as follows:

- If they have been treated correctly and the criteria for activity persist, then initiating therapy with a TNF- α antagonist is recommended, as reported previously.
- If they have not been treated correctly, then completing or restarting treatment following the recommended guidelines is recommended before considering therapy with TNF- α antagonists.
- In the specific case of patients in whom SpA meets the criteria for response to a specific DMARD, this has been suspended and the disease has been reactivated, then a new cycle of treatment with that DMARD that previously elicited a response is recommended before considering therapy with TNF- α antagonists.

It is beyond the scope of this document to provide recommendations on the ophthalmologic treatment of SpA-associated uveitis, but it should be noted that, given the efficacy shown by this therapy in this situation,^{44,87} the treatment should be considered, in coordination with the ophthalmologist, for patients with uveitis refractory to conventional therapy and/or highly recurrent cases of uveitis (≥ 3 years). It should be remembered that the available evidence indicates that monoclonal antibodies against TNF- α would be more effective in the prevention of recurrences of SpA-associated uveitis than the soluble receptor at the usually recommended doses.^{44,87}

Rating: tools, criteria and definition of active disease

An initial systematic evaluation should be carried out to quantify the activity of the disease in all patients with SpA (NE 5; GR D; GA 100%).

This evaluation should include a minimum set of parameters such as:

1. Questionnaires completed by the patient, including visual (VAS) or numerical (NAS) analogue scales on the general state of the disease and of axial and nocturnal pain and the BASDAI as a composite disease activity index.
2. Physical function.
3. Acute phase reactants (ESR and CRP).
4. Rheumatologist assessment (VAS or NAS) based on clinical experience and imaging techniques (MRI and ultrasound).

There is also a recently-established composite index, the ASDAS (ASAS-Endorsed Disease Activity Score), which integrates assessment of subjective patient activity parameters included in the BASDAI and acute phase reactants. This index could soon be used in everyday clinical practice, after some cut-off values are validated and accepted, to establish the degree of disease activity.¹¹²⁻¹¹⁴

Evaluation tools

The continuous assessment to be carried out in SpA is fully detailed in the *Espoguía*.²⁵ Nevertheless, the tools to assess disease activity are reviewed in following sections.

Disease activity

A minimum set of parameters should be assessed in all patients with SpA to quantify disease activity (NE 5; GR D; GA 100%), including:

- BASDAI questionnaire¹¹⁵ in NAS (0-10) or VAS (0-10) format¹¹⁵ (questionnaires available on the SER website: <http://www.ser.es/catalina/?cat=13>).
- Overall disease rating by patients in NAS or VAS (0-10 in the last week).
- Nocturnal axial pain due to SpA in NAS or VAS (0-10 in the last week).
- CRP and ESR.
- When there is peripheral disease, joint count and number of symptomatic entheses.
- Overall assessment of the disease by the physician (NAS or VAS 0-10).

The parameters described make it possible to calculate the Ankylosing Spondylitis Disease Activity Score (ASDAS),¹¹³ which has also proved useful in evaluating the therapeutic response to BT.^{116,117} Joint counts were made on 44 joints.¹¹⁸

Function and quality of life

The panel recommends using the BASFI questionnaire as a measure of functional capacity (NE 5; GR D; GA 100%). This questionnaire¹¹⁹ (<http://www.ser.es/catalina/?cat=13>) is needed for calculating the ASAS response criteria: ASAS20, ASAS40, and partial remission.^{118,120,121} In special situations with predominance of peripheral arthritis, it may be more appropriate to use the HAQ disability questionnaire.

The use of questionnaires on quality of life of a specific (such as ASQoL) or a generic type (such as the SF-36 or SF-12), or of other tools such as the PASS question is left to the decision of the physician.

Imaging techniques

In cases requiring it, an MRI can help in the assessment of disease activity for therapeutic decisions (NE 5; GR D; GA 100%).

An MRI can be helpful in assessing activity for therapeutic decisions.¹²²⁻¹²⁴ In most cases, a sacroiliac MRI will suffice, while in 15%-24% of patients, a spinal MRI will show alterations not visible in

the sacroiliac MRI.^{125,126} The panel recommends reaching a consensus with radiologists about the diagnostic protocol to be used to maximise exploration effectiveness.¹²⁷

An ultrasound in expert hands can detect alterations in asymptomatic entheses from a clinical and explorative standpoint.^{128,129} One study showed the validity of an enthesitis ultrasound index (MASEI) for the evaluation of entheses with diagnostic purposes¹³⁰ and, more recently, for follow up.¹³¹ Taken together, these data support the use of ultrasound as a diagnostic support tool, with less information about its usefulness as a tool for evaluating activity.

Criteria and definition of active disease

The definition of disease activity depends on whether the disease is an axial or peripheral form. Although there are no validated and universally used criteria, we can consider disease activity in the axial forms if the following requirements are met for a period of at least 3 months (NE 5; GR D; GA 100%):

1. BASDAI ≥ 4 and global assessment by the physician ≥ 4 , along with at least one of the following:
 - Overall rating of the disease by the patient ≥ 4 .
 - Nocturnal spinal pain ≥ 4 .
 - Elevation of acute phase reactants (ESR and/or CRP).

Although the ASDAS¹¹³ is still not used routinely in clinical practice, it may be useful; consequently, it should be taken into account. Recently,¹³² 4 stages of activity have been proposed; inactive disease if ASDAS ≤ 1.3 ; low activity if ASDAS = 1.3- 2.1; high activity if ASDAS = 2.1-3.5 and very high activity if ASDAS > 3.5 .

In the peripheral forms (≤ 4 locations), there are no defined criteria for disease activity either. Therefore, we can consider disease activity in peripheral forms if the following requirements are met for a period of at least 3 months (NE 5; GR D; GA 93.7%):

1. Arthritis and/or enthesitis in one or more locations and global assessment by the physician ≥ 4 , along with at least one of the following:
 - Assessment of disease status by the patient ≥ 4 cm.
 - Elevation of acute phase reactants (ESR and/or CRP).

Assessment of therapeutic response

Patients with predominantly axial SpA are considered to respond to anti-TNF- α if, after 4 months of treatment, a reduction in BASDAI and global assessment by the physician of at least 50% is achieved (or an absolute decrease of more than 2 points compared with previous values) and a relative decrease of 50% (or an absolute decrease of more than 2 points compared with previous values) in at least one of the following: patient global assessment, nocturnal axial pain (if both of these were > 4 prior to treatment) or decrease in ESR and/or CRP if they were previously elevated (NE 5; GR D; GA 100%).

If there is a response, treatment will be continued indefinitely, carrying out evaluations every 3-4 months. If there is no response after 3-4 months or the patient fails to respond in subsequent evaluations, it may be possible to switch to another anti-TNF- α . In the case of IFX, the possibility of indicating the infusions every 6 weeks will be assessed.

Assessing response according to ASDAS result may also be suggested. A clinically important improvement will be considered if ASDAS improvement ≥ 1.1 and a great improvement when ASDAS improvement ≥ 2.0 .¹³²

A patient with peripheral predominance of SpA will be considered to respond to anti-TNF- α if a reduction of at least 50% in joint count

and global assessment by the physician is achieved after 4 months of treatment, along with one of the following: decrease of at least 50% of the overall assessment of the patient or decrease of at least 50% of the ESR and/or CRP, if they were previously elevated (NE 5; GR D; GA 93.7%).

There is no clear criterion of anti-TNF- α response in oligoarticular forms, so the physician should evaluate each patient individually, taking into account the type of joint involved and the impact it produces on the subject before making decisions.

As in the evaluation of non-biological treatments, regardless of the criteria described for changes during treatment with anti-TNF- α , certain situations (such as the presence of a single swollen joint [knee, hip, wrist, shoulder, etc.] that causes a marked loss of function or significantly alters the patient's work or professional activity despite treatment) may be considered as treatment failure. Patients with persistent enthesopathy or uncontrolled extra-articular manifestations such as recurrent acute anterior uveitis would be in a similar situation.

Changes between biological agents

Patients with SpA who have not responded to a first round of anti-TNF- α can switch to a second anti-TNF- α (NE 2a; GR B; GA 100%).

The previously-published SER document on the use of TNF- α antagonists in SpA²⁶ reached a consensus specifying that, if there was no response to treatment after 4 months or the patient became unresponsive after that period, it would be possible to switch to another anti-TNF- α .

Recent studies confirm the efficacy of substituting one biological agent for another in patients who are refractory to a first anti-TNF.^{55,133} If, despite the change in biological agents, it is not possible to achieve a therapeutic response as defined above, but there is an improvement greater than 20% in BASDAI and 20% in the assessment of the disease by the patient and the physician, it is considered that treatment should be maintained with the biological agent selected by the physician; however, if any of the previously used non-biological treatments had been more effective, assessing their reinstatement is recommended.

Changes in dosage

There is no evidence that a dose increase or a decrease in dose spacing enhances the response, so the panel considers that these are not recommended practices.

Decreasing the dose or prolonging the interval between doses could be considered in some patients with minimal criteria for clinical activity maintained over time (minimum of 2 consecutive assessments)^{74,134,135} (NE 2a; GR B; GA 100%).

Drug withdrawal

Discontinuation of the treatment could be assessed in patients with SpA who maintain a minimum clinical activity after a decrease in biological treatment; however, a reassessment of treatment reintroduction after about 12 weeks would be advised (NE 2a; GR B; GA 100%).

In a systematic review,^{52,53,136} 6 studies (including 2 clinical trials, 1 randomized study and 3 follow-up studies) were found that had analysed the result of suspending anti-TNF- α therapy in patients with AS who had previously responded to it. These studies observed that, after the drug withdrawal, most patients presented an outbreak of the disease in a relatively short time, but also that reintroduction was safe and effective. In a recent study in which BT was suspended only in patients with partial remission, 21% of patients remained inactive after 12 months of drug withdrawal.¹³⁷

Discussion

This document is part of the second update of the SER Consensus on the use of BT in SpA. It is based on the reviews and recommendations of the *Espoguía*²⁵ along with a critical review of the previous consensus,²⁶ following a scientific methodology through Delphi survey. In relation to the previous consensus, we highlight the separation of PsA on the basis of a decision by the panel, which felt that its differentiating characteristics, existing scientific evidence and current trends in the literature supported this differentiation.

This consensus has included subcutaneous golimumab as a new biological drug in SpA due to the high level of evidence. It has been added to the other three biologics available (ETN, IFX and ADA).

One of the most innovative, and therefore possibly the most controversial, aspects is the inclusion of patients with new ASAS criteria for axial SpA in the BT recommendation.⁹ The indication has been based on the fact that patients with early forms without a radiological condition present a degree of nocturnal pain, an activity index, functional capacity and presence of extra-articular manifestations similar to those of established forms of AS. In addition, these drugs have shown a high effectiveness when administered early in active cases refractory to conventional therapy.¹¹

Another contribution included in the consensus is the physician's global assessment of disease. The previous consensus had already highlighted the relevance of the opinion of a rheumatologist or another physician with experience in SpA and BT for the indication of these drugs; however, this consensus includes the visual numeric scale, based on clinical experience and imaging techniques (MRI and ultrasound). Therefore, the use of imaging techniques in assessing disease activity is recommended to help guide therapeutic decisions.^{62,111,125,138}

Unlike the previous consensus, this one has not included the section on prior evaluation and monitoring because the SER has decided to prepare another specific consensus document on BT monitoring. This will be published shortly and will include these aspects.

Lastly, we must note that, while there is currently not enough high-quality scientific evidence for many of the recommendations, the degree of agreement among panellists when evaluating them has been very high, which gives these recommendations a great value in daily practice. The large amount of data published in this context and the future introduction of new evidence, both in disease evaluation (ASDAS) and in biological agent use, will make it necessary to update this document on a regular basis.

Conflict of interest

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