Adv Ther (2022) 39:1490–1501
https://doi.org/10.1007/s12325-022-02064-x

REVIEW

Treatment Failure in Axial Spondyloarthritis: Insights for a Standardized Definition

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Received: December 7, 2021 / Accepted: January 26, 2022 / Published online: February 24, 2022

ABSTRACT

Axial spondyloarthritis is a chronic inflammatory rheumatic disease that affects the axial skeleton and causes severe pain and disability. It may be also associated with extra-articular manifestations. Early diagnosis and appropriate treatment can reduce the severity of the disease and the risk of progression. The biological disease-modifying antirheumatic drugs (bDMARDs) tumor necrosis factor alpha (TNFα) inhibitors (TNFi) and the anti-interleukin (IL)-17A antibodies secukinumab and ixekizumab are effective agents to reduce disease activity and minimize the inflammation that damages the joints. New alternatives such as Janus kinase (JAK) inhibitors are also available. Unfortunately, response rates to bDMARDs are far from optimal, and many patients experience so-called treatment failure. The definition of treatment failure definition is often vague and may depend on the rigorousness of the therapeutic goal, the inclusion or not of peripheral symptoms/extra-articular manifestations, or patients' overall health. After an exhaustive bibliographic review, we propose a definition based on loss of the following status: low disease activity assessed by Ankylosing Spondylitis Disease Activity Score (ASDAS)-CRP, absence of extra-articular manifestations, and low disease impact on the patients' general health. Apart from discontinuing the therapy because of safety or intolerance reasons, two types of treatment failure can be differentiated depending on when it occurs: primary failure (no response within 6 months after treatment initiation, or lack of efficacy) and secondary failure (response within 6 months but lost thereafter, or loss of efficacy over time). Physicians should carefully consider the moment and the reason for the treatment failure to decide the next therapeutic step. In the case of primary failure on a first TNFi, it seems reasonable to switch to another class of drugs, i.e., an anti-IL-17 agent, as phase III trials showed that the response to

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12325-022-02064-x.

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IL-17 blockade was higher than to placebo in patients previously exposed to TNFi. When secondary failure occurs, and loss of efficacy is suspected to be caused by antidrug antibodies (ADAs), it is advisable to analyze serum TNFi and ADAs concentrations, if possible; in the presence of ADAs and low TNFi levels, changing the TNFi is rational as it may restore the TNFα blocking capacity. If ADAs are absent/low with adequate drug therapeutic levels, switching to another target might be the best strategy.

Keywords: Axial spondyloarthritis; Treatment failure; TNF inhibitors; Secukinumab; Ixekizumab; Disease activity

Key Summary Points

Axial spondyloarthritis is a chronic inflammatory disease that causes severe pain and disability.

The biologic agents TNFα inhibitors (TNFi) and anti-interleukin (IL)-17A antibodies have demonstrated efficacy to reduce disease activity and risk of progression, but some patients experiment lack (primary treatment failure) or loss (secondary treatment failure) of response.

As the definition of treatment failure is often vague, here we propose a definition based on loss of the following status: low disease activity according to Ankylosing Spondylitis Disease Activity Score (ASDAS)-CRP, absence of extra-articular manifestations, and low disease impact on the patients' general health.

Physicians should carefully consider the moment and the reason for the treatment failure to decide the next therapeutic step. The main options are targeting the same biologic pathway (changing between TNFi) or switching to another class of drug (anti-IL-17).

INTRODUCTION

The term spondyloarthritis (SpA) designates a group of chronic inflammatory conditions that share pathophysiological, genetic, and clinical characteristics. The global prevalence of SpA ranges from 0.2% to 1.61% in the general population, with higher rates in North America and Europe which may correspond to the prevalence of the *HLA-B27* allele, the most important genetic predisposition factor in SpA [1, 2]. The Assessment of Spondyloarthritis International Society (ASAS) classified SpA as either axial or peripheral depending on the predominant involvement: while axial SpA mostly affects the spine and sacroiliac joints (axial skeleton), peripheral SpA predominantly affects the peripheral skeleton (arthritis, enthesitis, or dactylitis). In line with the ASAS classification, axial SpA encompasses two subsets of patients: those with radiographic sacroiliitis visible on X-rays (ankylosing spondylitis [AS] or radiographic axial SpA [r-axSpA]) and those without evidence of radiographic damage of the sacroiliac joints (non-radiographic axial SpA [nr-axSpA]) [3]. Additionally, axial SpA may be associated with extra-articular manifestations, including uveitis, psoriasis, and inflammatory bowel disease [4].

Axial SpA has a significant impact on a patient's life, leading to reduction of physical function and health-related quality of life. In addition, it generates substantial societal and economic burden for the healthcare systems because of the high direct costs derived from the frequent use of health resources and the indirect costs associated with the loss of work productivity [5, 6]. Thus, early diagnosis and treatment to prevent progressive structural damage and disability are crucial for managing patients with axial SpA. Nonsteroidal anti-inflammatory drugs (NSAIDs), regular exercise, and physical therapy are the recommended first-line interventions for patients with active disease [7, 8]; however, not all patients achieve adequate control of the disease with this strategy or tolerate high and/or prolonged doses of NSAIDs, so a significant number of them will require therapy escalation. The most effective

agents currently available are biological disease-modifying antirheumatic drugs (bDMARDs): tumor necrosis factor alpha inhibitors (TNFi) and the monoclonal antibodies against interleukin (IL)-17A secukinumab and ixekizumab. A new therapeutic class for the treatment of axial SpA, Janus kinase inhibitors (JAKi), has also been approved. Unfortunately, response rates to bDMARDs are far from optimal, and many patients (about 40%) experience treatment failure [9]. Subsequent management is challenging, and the practicing clinician should carefully consider the moment and the reason for discontinuing the first bDMARD to decide the next therapeutic step [10].

In order to facilitate this process, we provide a narrative review based on a focused literature search (see the appendix in the electronic supplementary material) of available therapies and treatment strategies used in the management of axial SpA, and we propose a definition of treatment failure according to disease activity. We also discuss the different approaches to address treatment failure and areas of uncertainty related to this matter. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

SECOND-LINE THERAPY IN AXIAL SPA: BDMARDS AND JAK1I

The TNFi approved for patients with axial SpA are infliximab (and its biosimilars, although this one is not approved for the use in nr-axSpA), etanercept (and its biosimilars), adalimumab (and its biosimilars), golimumab, and certolizumab pegol. As shown in Table 1, all the TNFi currently authorized for the indication of active axial SpA with inadequate response to NSAIDs showed a significant superiority compared to placebo in terms of ASAS20 response rates and other outcomes in clinical trials of 12–24 weeks of duration [11–16]. Additional studies indicated that TNFi maintain their safety and efficacy for several years [17–19], and delayed structural progression [20, 21], whereas the rates of discontinuing the first TNFi owing to lack of or loss of efficacy range from 13% to 68% [22].

With an alternative mechanism for disrupting inflammation, anti-IL-17 agents extended the therapeutic options for patients with both radiographic and non-radiographic axial SpA. The efficacy of the IL-17 blockade in r-axSpA was demonstrated in several phase III clinical trials (Table 1). Firstly secukinumab [23], and later ixekizumab [24], showed efficacy for the treatment of axial SpA, with similar magnitude to that observed with TNFi. In the first studies exploring the anti-IL-17 effect after TNFi failure, higher response rates were obtained with anti-IL-17 drugs than with placebo [25, 26]. Furthermore, absence of radiographic progression was observed in 79–89% of patients treated with anti-IL-17 agents [27, 28]. Recent studies in patients with nr-axSpA showed that secukinumab [29] and ixekizumab [30] demonstrated similar efficacy to that in patients with r-axSpA (Table 1).

Upadacitinib, a selective JAK1i, is currently the only agent of this therapeutic class approved for r-axSpA, on the basis of a randomized, double-blind, placebo-controlled phase II/III study [31]. Significantly more patients treated with upadacitinib (vs placebo) achieved an ASAS40 response (Table 1), showing a rapid onset of benefit. The trial did not include biologic-exposed patients nor patients with nr-axSpA [31], although preliminary data of the SELECT-AXIS 2 (NCT04169373) supports its efficacy in this latest population.

The ASAS/European League Against Rheumatism (EULAR) [7] and the American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network (ACR/SAA/SPARTAN) [8] guidelines recommended TNFi as first-line bDMARDs, mainly owing to longer clinical experience and greater familiarity with their safety profile. However, subsequent guidelines updates should consider the latest evidence, and this advice may change when new real-life data and long-term results of clinical trials on anti-IL-17 agents and JAKi are taken into account. There is also a lack of data regarding the use of TNFi after anti-IL-17 blockade.

Table 1 Characteristics of clinical trials with bDMARDs and JAKi currently approved for active axial SpA

	Patient sample	Primary endpoint	Primary endpoint (vs placebo)
Radiographic axial SpA			
Infliximab	*N* = 279	ASAS20 at week 24	61.2% (vs 19.2%)
Etanercept	*N* = 277	ASAS20 at week 12	59% (vs 28.0%)
Adalimumab	*N* = 315	ASAS20 at week 12	58.2% (vs 20.6%)
Golimumab	*N* = 216	ASAS20 at week 14	59.4% (vs 21.8%)
Certolizumab pegol	*N* = 178 (20.2% with prior TNFi exposure)	ASAS20 at week 12	200 mg every 2 weeks: 56.9% 400 mg every 4 weeks: 64.3% (vs 36.8%)
Secukinumab	*N* = 590 (26.0–39.0% of patients had inadequate responses/intolerance to TNFi)	ASAS20 at week 16	61% (vs 29.0%) TNFi-naïve: 68.2% (vs 31.1%) TNFi-exposed: 50.0% (vs 24.1%)
Ixekizumab	*N* = 251 (not previously been treated with bDMARDs) *N* = 316 (previously treated with TNFi)	ASAS40 at week 16	48.0% (vs 18.0%) 25.4% (vs 12.5%)
Upadacitinib	*N* = 187	ASAS40 at week 14	52% (vs 26.0%)
Non-radiographic axial SpA			
Adalimumab	*N* = 185	ASAS40 at week 12	36% (vs 15.0%)
Etanercept	*N* = 215	ASAS40 at week 12	32% (vs 16.0%)
Golimumab	*N* = 197	ASAS20 at week 16	71.1% (vs 40.0%)
Certolizumab pegol	*N* = 147 (10.9% with prior TNFi exposure)	ASAS20 at week 12	200 mg every 2 weeks: 58.7% 400 mg every 4 weeks: 62.7% (vs 40.0%)
Secukinumab	*N* = 371 (9.7% patients previously exposed to TNFi)	ASAS40 at week 16 naïve population	41.5% (vs 29.2%)
Ixekizumab	*N* = 201	ASAS40 at week 16	35% (vs 19.0%)

Data correspond to the approved dosing regimen of each agent
ASAS Assessment of Spondyloarthritis International Society, *SpA* spondyloarthritis, *TNFi* TNFα inhibitor

DISEASE ACTIVITY MEASURES IN AXIAL SPA

The drug efficacy evaluated in the aforementioned clinical trials described was based on ASAS20 or ASAS40 response rates, but these endpoints do not reflect the final disease states of the patients after a period of treatment. Ideally, the measures used to assess disease activity in ax-SpA should be easily implementable in clinical practice and relevant for both patients and physicians. A classic composite measure of disease activity is the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), which collects six patient-reported variables evaluating clinical symptoms of inflammation. Historically, active disease has been defined by a BASDAI level of at least 4 [32]. The more recent Ankylosing Spondylitis Disease Activity Score (ASDAS) incorporates laboratory evaluation of inflammation (using C-reactive protein [CRP] or erythrocyte sedimentation rate [ESR]), with good discriminatory properties and sensitivity to change [33]. ASDAS may be a surrogate marker of spinal inflammation and it has been shown that is longitudinally linked to progression of the structural damage [34, 35]. Moreover, ASDAS has validated cutoff levels for disease activity states: a value below 1.3 is considered inactive disease or remission, between 1.3 and 2 as low disease activity, between 2.1 and 3.5 as high disease activity, and above 3.5 as very high disease activity [36, 37].

On the basis of this scale, several international and national guidelines advocate treatment to the target of achieving clinical remission (ASDAS < 1.3) or at least low disease activity (ASDAS < 2.1) [7, 38, 39]. The ASDAS cutoff for minimal clinically important improvement between examinations is 1.1 or higher, and a change at least 2.0 units is considered a major improvement [36]. On the other hand, an increase of at least 0.9 points is the ASAS definition for clinically important worsening [40]. In general terms, treatment should be individualized considering other symptoms and signs of the disease (axial, peripheral, extra-articular), comorbidities, psychosocial factors, and patients' opinions.

BIOLOGICAL TREATMENT FAILURE: WHEN, WHY, AND CONTROVERSIES

Failure on bDMARDs can be detected or revealed both by objective measures (e.g., the presence of active manifestations of the disease on examination, raised CRP levels attributable to disease activity, or inflammatory lesions detected by magnetic resonance imaging [MRI]) or by the results of the patient-reported outcomes (PROs). However, sometimes there is discordance between the results of the objective measures and the results of the PROs. This is probably due to factors such as persistence of pain in some patients without evidence of inflammation and the influence of other aspects affecting the patient's well-being and pain perception such as sleep disturbances or fatigue, as has been observed in patients with rheumatoid arthritis [41, 42]. The fact that some factors such as age, education level, gender, radiographic damage, or comorbidities influence the way in which the patients handle, or report, their disease process cannot be dismissed [43, 44]. Since treatment compliance and continuation is essential for its success, it must be verified that the patient's adherence to therapy is adequate before definitively establishing the failure. An important issue to consider is that one drug can cause adverse events or undesirable effects (even when it is effective), so the treatment failure and drug discontinuation are not exclusively based on disease activity.

Apart from stopping the therapy because of safety or intolerance reasons, two types of treatment failure are usually differentiated depending on when it occurs: primary failure (no response within 6 months after treatment initiation, or lack of efficacy) and secondary failure (response within 6 months but lost thereafter, or loss of efficacy over time) [8]. The distinction between lack or loss of response is often vague and is conditioned by the rigorousness of the therapeutic goal (remission, low disease activity, ASAS response as used in clinical trials) and the drug used and its speed of action/effect (Table 2). Other factors that can modify the treatment failure definition are the

Table 2 Time of response assessment according to each summary of product characteristics

Drug	
Infliximab	If a patient does not respond by 6 weeks (i.e., after 2 doses), no additional treatment with infliximab should be given
Etanercept	Available data suggest that a clinical response is usually achieved within 12 weeks of treatment. Continued therapy should be carefully reconsidered in a patient not responding within this time period
Adalimumab	Available data suggest that a clinical response is usually achieved within 12 weeks of treatment. Continued therapy should be carefully reconsidered in a patient not responding within this time period
Golimumab	Available data suggest that clinical response is usually achieved within 12–14 weeks of treatment (after 3–4 doses). Continued therapy should be reconsidered in patients who show no evidence of therapeutic benefit within this time period
Certolizumab pegol	Available data suggest that clinical response is usually achieved within 12 weeks of treatment. Continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit within the first 12 weeks of treatment
Secukinumab	Available data suggest that a clinical response is usually achieved within 16 weeks of treatment. Consideration should be given to discontinuing treatment in patients who have shown no response by 16 weeks of treatment. Some patients with an initial partial response may subsequently improve with continued treatment beyond 16 weeks
Ixekizumab	Consideration should be given to discontinuing treatment in patients who have shown no response after 16–20 weeks of treatment. Some patients with initially partial response may subsequently improve with continued treatment beyond 20 weeks
Upadacitinib	Consideration should be given to discontinuing treatment in patients with ankylosing spondylitis who have shown no clinical response after 16 weeks of treatment. Some patients with initial partial response may subsequently improve with continued treatment beyond 16 weeks

inclusion or not of peripheral symptoms/extra-musculoskeletal manifestations or the health status in the assessment of the response. In fact, ASAS recommended a validated tool for evaluating the health of patients with axial SpA, the ASAS Health Index (ASAS-HI), to test real-life functioning both in clinical trials and daily practice [45]. The TICOSPA trial (Tight Control in Spondyloarthritis), the first study evaluating the potential benefits of tight control and a treat to target approach in patients with axial SpA, has shown a favorable effect in terms of improvement of ASAS-HI, compared to usual care, although it was not statistically significant [46].

Another aspect to take into account to determine treatment failure is the possible occurrence of radiographic progression. Although a 2-year period is required before changes can be reliably detected with the modified Stoke Ankylosing Spondylitis Spine Scoring (mSASSS) [47], imaging methods other than plain radiographs, such as low-dose computed tomography (CT), have the potential to identify earlier vertebral and/or sacroiliac progression in axial SpA [48, 49]. On the other hand, CT or MRI may help to support the decision whether the appearance or worsening of symptoms reflects the failure of therapy or an alternate source of pain such as degenerative or

prolapsed disc pain [50]. In certain clinical scenarios the findings of active lesions on MRI could reinforce the treatment failure suspicion.

THERAPEUTIC STRATEGIES AFTER TREATMENT FAILURE

One of the dilemmas faced by physicians caring for patients with axial SpA is what to do in the event of a biological treatment failure. Although it is great news, the introduction of more alternatives to TNFi has made this decision even more complicated to make. Usually, population-based studies indicate that clinical response after switching to a second bDMARD (either a TNFi or anti-IL-17) is lower than the one experienced by patients naïve to biologic therapies [51, 52]. Nonetheless, drug switching is required (and recommended) when there is treatment failure or intolerance. According to the ASAS-EULAR recommendations, in patients with a primary failure on the first TNFi, it is more reasonable to switch to another class of drugs, i.e., an anti-IL-17, always after reconsidering if the diagnosis and the indication for the start of the first TNFi were correct [7]. Supporting this suggestion, the results of the phase III trials with secukinumab and ixekizumab showed that, among patients previously exposed to TNFi, the response to the anti-IL-17 agents was higher than to placebo [25, 26]. However, at least one study has shown that secukinumab has comparable effectiveness versus an alternative TNFi after prior TNFi failure [53]. In the case of failure on IL-17 blockade, there is no solid data regarding the switch from anti-IL-17 to TNF inhibition.

Of note, biological agents may induce an unwanted immune response (immunogenicity), which may alter the bioavailability of the drug causing a loss of efficacy. The development of antidrug antibodies (ADAs) on treatment with TNFi may represent one of the main causes for secondary treatment failure [54]. Thus, determination of serum ADAs or drug levels could identify the reason for poor response and assist in deciding the selection of the subsequent treatment [55]. In the presence of ADAs and low TNFi levels, cycling between TNFi is rational as it may restore the TNFα blocking capacity. In fact, the failure to respond to a first TNFi as a result of the development of ADAs seems to be predictive for a better clinical response to a second TNFi in SpA [56]. If ADAs are absent/low with adequate therapeutic levels of the TNFi, inefficacy is probably not due to the neutralization of the therapeutic effect, but because TNFα is not the main cytokine instigating disease activity. In this case, switching to another target might be the best strategy (Fig. 1) [57]. However, it is not always feasible to perform ADAs determinations and its use in clinical practice is yet limited. Stronger evidence from larger series is still lacking to support the systematic implementation of this measure in clinical practice.

DISCUSSION AND PERSPECTIVES

Despite the difficulty of establishing a concise definition of treatment failure, it is necessary to set a general criterion that allows decisions to be made on the basis of objective parameters. We propose a definition based on Ankylosing Spondylitis Disease Activity Score (ASDAS)-CRP, absence of extra-articular manifestations and low disease impact on the patients' general health (ASAS-HI). However, this standard definition must be individualized to each patient's condition, ruling out additional causes of treatment failure, such as comorbidities deteriorating patients' function and well-being [43] and other causes of chronic pain unrelated to the SpA, such as fractures and degenerative conditions. In the future, and based on the most advanced imaging techniques, findings of rapid radiographic progression may support a definitive failure, but the current (lack of) evidence precludes the ability to establish a precise definition or cutoff point. In this regard, what has been established is a clear longitudinal relationship between disease activity and radiographic progression, and that reinforces the need to achieve a level of low disease activity/inactive disease [20, 34, 35]. Thus, in patients with a primary failure on a first TNFi, switching to a drug with a different mechanism of action seems reasonable, trying to avoid

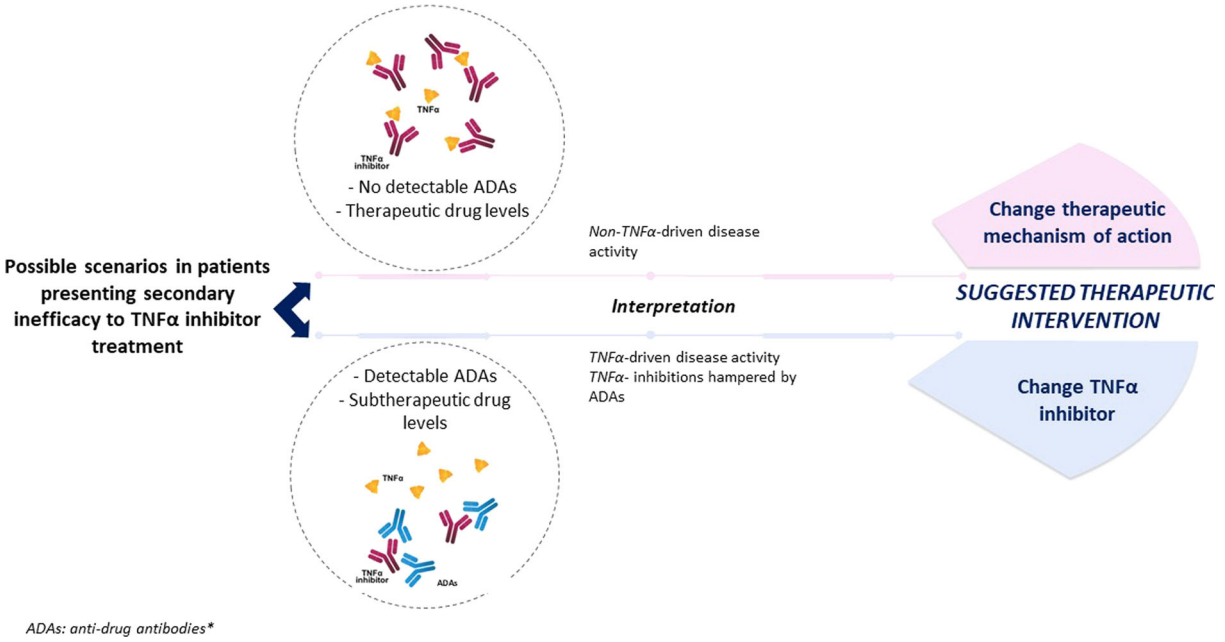

Fig. 1 Possible scenarios for management of secondary treatment failure on TNFi. *ADAs determination is recommended, if available

long-lasting active disease. This may be the best option also when secondary failure occurs in the absence of ADAs; if loss of efficacy is confirmed to be caused by immunogenicity, it is advisable to use a different TNFi, although the lack of clinical trials comparing TNF blockers makes it difficult to decide which is the optimal therapeutic step. Secukinumab dose escalation is being evaluated in those patients not achieving inactive disease at week 16 according to ASDAS (NCT03350815), but the results are pending. Patients with obesity/overweight usually present higher disease activity and reduced response to TNFi, and may benefit from dose intensification, if ADAs are absent [58, 59], similar to the weight-based dosing of secukinumab proposed for patients with psoriasis [60]; however, weight reduction should be always advised in all patients with obesity. Most importantly, we should also remind the patients that exercise is a cornerstone of the treatment, and it is indicated in all stages of the disease. Finally, the concomitant use of conventional DMARDs or the combination of bDMARDs with JAKi has been scarcely investigated in the setting of biologic treatment failure, so future studies should address this gap.

In conclusion, there are still many unknowns to resolve in the event of a treatment failure. More clinical trials and real-life studies are needed, as well as updated guidelines or consensus algorithms to optimize patient care. The final objective must be to improve patients' quality of life and avoid harm, and this is only achieved with an informed decision in the case of treatment failure, making the consequent change of drug or therapeutic target.

ACKNOWLEDGEMENTS

Funding. Novartis Pharmaceuticals provided economic funding for this work. The sponsor had no role in the design, the analysis and the interpretation of the data, the wording of the article or the decision to send the article for publication. The journal's Rapid Service Fee was funded by Springer Healthcare Ibérica.

Medical Writing Assistance. The authors would like to acknowledge Anabel Herrero PhD., who provided medical writing support on behalf of Springer Healthcare, with funding from Novartis Pharmaceuticals.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Authorship Contributions. All authors (XJ, MJMR, JMB, CFC, and JG) contributed to the design of the bibliographic research and revised the literature. All authors (XJ, MJMR, JMB, CFC, and JG) critically revised all versions of the manuscript, and read and approved the final manuscript.

Disclosures. Xavier Juanola has received unrelated honoraria or research grants from Abbvie, Lilly, Janssen, Novartis, Pfizer, and UCB. Manuel J. Moreno Ramos has received unrelated honoraria or research grants from Abbvie, Celgene, Janssen, Lilly, MSD, Novartis, Pfizer and UCB, and advisor's honoraria from Abbvie, Celgene, Janssen, Lilly, Novartis, Pfizer and UCB unrelated to the present work. Joaquin Maria Belzunegui has received unrelated honoraria from Janssen, Lilly, Novartis, Abbvie, BMS and UCB. Cristina Fernández-Carballido has received payments or speaker's honoraria from Abbvie, Celgene, Janssen, Lilly, MSD, Novartis, Pfizer, Roche and UCB and advisor's honoraria from Abbvie, Celgene, Janssen, Lilly, Novartis, Pfizer and UCB unrelated to the present work. Jordi Gratacós has received unrelated honoraria or research grants from Abbvie, BMS, Lilly, MSD, Novartis, Pfizer, Roche, and UCB.

Compliance with Ethical Guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Data Availability. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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