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REDOSER project: optimising biological therapy dose for rheumatoid arthritis and spondyloarthritis patients

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Abstract

Background: Reducing the dose of biological therapy (BT) when patients with immune-mediated arthritis achieve a sustained therapeutic goal may help to decrease costs for national health services and reduce the risk of serious infection. However, there is little information about whether such a decision can be applied universally. Therefore, the objective of this study was to develop appropriateness criteria for reducing the dose of BT in patients with rheumatoid arthritis (RA), axial spondyloarthritis (axSpA), and peripheral spondyloarthritis (pSpA).

Methods: The RAND/UCLA appropriateness method was coordinated by experts in the methodology. Five rheumatologists with clinical research experience in RA and/or SpA selected and precisely defined the variables considered relevant when deciding to reduce the dose of BT in the 3 diseases, in order to define patient profiles. Ten rheumatologists with experience in prescribing BT anonymously rated each profile on a scale of 1 (completely inappropriate) to 9 (completely appropriate) after revising a summary of the evidence obtained from 4 systematic literature reviews carried out specifically for this project.

Findings: A total of 2,304 different profiles were obtained for RA, 768 for axSpA, and 3,072 for pSpA. Only 327 (14.2%) patient profiles in RA, 80 (10.4%) in axSpA, and 154 (5%) in pSpA were considered appropriate for reducing the dose of BT. By contrast, 749 (32.5%) patient profiles in RA, 270 (35.3%) in axSpA, and 1,243 (40.5%) in pSpA were considered inappropriate. The remaining profiles were considered uncertain.

Interpretation: Appropriateness criteria for reducing the dose of BT were developed in 3 inflammatory conditions. These criteria can help clinicians treating these disorders to optimize the BT dose. However, further research is needed, since more than 50% of the profiles were considered uncertain and the real prevalence of each profile in daily clinical practice remains unknown.

Keywords: Pharmaceutical science, Evidence-based medicine, Medicine

1. Background

Clinical trials have shown that biological therapy (BT) is of enormous benefit for improving disease control and, consequently, physical function and quality of life in patients with inflammatory arthropathy [1, 2, 3]. However, during the last 10 years, clinicians have been aware of the increased risk of infection with BT, as well as the high cost for national health services. These concerns have led to an optimization approach, namely, reducing the dose of BT when the patient achieves a sustained therapeutic goal (TG). This approach has been justified in terms of safety [4] and efficacy [5]. The Spanish Society of Rheumatology (SER) and the Spanish Society of Hospital Pharmacy recently published recommendations on how to reduce the dose of BT in clinical practice [6]. A panel of experts proposed

that the ideal candidate for this approach needed to have sustained the TG for at least 6 months before the reduction. However, the experts cast doubts on whether their recommendations could be applied universally. Therefore, there is no solid evidence on the appropriateness of reducing the dose of BT at the individual level, since the patients included in clinical trials differ somewhat from those treated in daily clinical practice [7]. Clinical trials analyzing BT dose reduction are subject to the same limitations [8].

The RAND/UCLA appropriateness method (RAM) combines evidence-based medicine and clinical practice by engaging a working group, a literature review group, and a rating panel in a modified Delphi exercise, as previously described by RAND [9]. This method is considered the best option for analyzing the appropriateness of a medical procedure for various patient profiles when there is no solid evidence for the procedure. Following the original definition of “appropriate” [9], we define “appropriate” as meaning that the benefits for the patient outweigh the risks if the dose of BT is reduced, “inappropriate” as meaning that the risks outweigh the benefits, and “uncertain” as meaning that the risk/benefit balance is similar whether the dose is reduced or not.

Therefore, the objective of this study was to develop appropriateness criteria for reducing the dose of BT in patients with rheumatoid arthritis (RA), axial spondyloarthritis (axSpA), and peripheral spondyloarthritis (pSpA). We aimed to establish the optimal balance between reducing the frequency of serious infection and maintaining effectiveness, regardless of cost considerations.

2. Methods

The RAM includes 4 independent stages [9], which, for this project, were coordinated by 2 researchers with experience in the field (AJB, PL) and a methodologist from the SER Research Unit (CS-P).

2.1. Development of the list of indications

In this study, the term “indication” is used as a “clinical scenario” or “patient profile”, that is, it does not mean that the dose reduction is indicated.

According to the RAM, the indications are as follows: 1) comprehensive (all patients must be able to be classified); 2) mutually exclusive (no patient can be classified in more than 1 indication); and 3) homogeneous (the appropriateness of dose reduction would apply equally to all persons classified in a particular indication).

In order to develop the list of indications, at the initial meeting, a working group of 5 rheumatologists (see Supplementary File 1 for composition and selection criteria) supported by researchers experienced in RAM identified the variables to be taken

into consideration when classifying candidates for BT dose reduction, suggested definitions of the variables, and drafted the structure of the indications list. After contact by e-mail and a second meeting, the variables, definitions, and indications were established.

2.2. Literature review and synthesis of the scientific evidence

To provide the members of the rating panel with the best available scientific evidence to help them determine the extent to which the clinical decision to reduce the BT dose is appropriate, a literature review was performed by members of the SER Evidence-Based Rheumatology group (see Supplementary File 1). The synthesis involved 4 systematic reviews to answer the following research questions: 1) What is the relapse rate in patients with RA who have achieved clinical remission when their BT dose is reduced? 2) What is the extent of radiological progression in patients with RA when the BT dose is reduced? 3) What is the relapse rate in patients with spondyloarthritis on BT who have achieved remission when the BT dose is reduced? 4) What is the extent of radiological progression in patients with spondyloarthritis when the BT dose is reduced? These systematic reviews are available on the SER Web site (<http://www.ser.es/redoser/>). In addition, a systematic review [10] published after the development of those previously mentioned was added to the evidence synthesis.

2.3. Rating the appropriateness of each indication

The rating panel comprised 10 rheumatologists with experience in prescribing BT (see Supplementary File 1). The rating panel members received the indications list, the literature review, and the instructions for the rating process by e-mail. Considering that reducing the BT dose is appropriate if the expected health benefit (e.g., decreased adverse events, decreased infections) exceeds the expected negative consequences (e.g., risk of relapse, pain) by a sufficiently wide margin that the BT dose can be reduced, irrespective of cost which is an adaptation of the general definition of appropriate [9] to the particular characteristics of this project. The rating panel was asked to rate the appropriateness of the dose reduction for each indication on a scale of 1 to 9, where 1 is highly inappropriate and 9 highly appropriate. In addition, the rating panel was warned that in the case of patients with illnesses that also improve with BT (e.g., psoriasis, inflammatory bowel disease), it had to be assumed that this second disease was in remission.

In a first round, the rating panel rated the indications anonymously without interacting. Then, the degree of agreement between the panelists was calculated using the Interpercentile Range Adjusted for Symmetry method [9]. Mathematically, disagreement means that at least one third of the panelists rated the indication in the 1–3 region, and at least one third of the panelists rated it in the 7–9 region.

Thus, each indication was categorized as having been rated with or without disagreement.

After 2 months, the rating panel discussed the definitions, the structure of the indications list prepared by the working group, and their own first-round ratings during a 2-day face-to-face meeting. The ratings discussion focused mainly on those indications rated with disagreement. At the meeting, each panelist received a personalized rating form indicating his/her first-round rating for each indication and the anonymous ratings distribution of the other members of the panel. In addition, the moderator (PL) received a summary rating form with similar information (including panelist identification), along with other statistics reflecting the level of agreement between panel members. After a discussion in which consensus was not forced, rating panel members independently provided their definitive ratings for each indication. Each panel member had equal weight in producing the final result for the indications.

2.4. Defining “appropriate”, “uncertain”, and “inappropriate” for definite appropriateness criteria in each indication

Each indication was classified as “appropriate”, “inappropriate”, or “uncertain” according to the median and the degree of agreement between the panelists. Indications with a median score of <3.5 rated without disagreement were classified as inappropriate. Indications with a median score of >6 rated without disagreement were classified as appropriate. Indications with a median of 3.5 to 6, as well as all indications rated with disagreement, were classified as uncertain.

2.5. Statistics

To determine the contribution of each variable in the scoring of appropriateness for each indication, we constructed 3 multivariable linear regression models, 1 for each disease, using command *glm* in Stata 12.1 (Stata Corp LP, College Station, Texas, USA). In these models, the dependent variable was the median appropriateness score for each indication and the independent variables were those used for defining the list of indications in each disease. Therefore, the beta coefficients represent the extent to which this variable contributed to the average appropriateness score. All coefficients are negative, since the option considered most likely to reduce the dose of BT was set as a reference for each variable.

3. Results

3.1. Rheumatoid arthritis

The working group identified and defined 10 variables (Table 1; for definitions see Supplementary File 2), which generated 2,304 clinical profiles for RA. All

Table 1. Variables selected by the working group to develop the list of the 2,304 indications for Rheumatoid Arthritis and percentages of appropriate indications (AI), uncertain indications (UI), and inappropriate indications (II).

Variables	Options	AI (%)	UI (%)	II (%)
DA at BT dose reduction	Remission/ Low	23.1 / 5.1	46.5 / 60.2	30.4 / 34.5
Time since TG was reached	>12 months / 6-12 months	16.6 / 11.7	52.5 / 54.3	30.9 / 34
DA at initiation of BT	Moderate / High	17.7 / 10.6	52.5 / 54.2	29.8 / 35.2
Disease duration	<5 years / ≥5 years	18.6 / 9.7	49.7 / 57	31.7 / 33.3
Age	≤70 years / >70 years	11.1 / 17.3	55 / 51.7	33.9 / 31
Time to achieve TG	<6 months / ≥6 months	18.9 / 9.4	50.2 / 56.6	30.9 / 34
Previous BT failures	0 / 1 / ≥2	22.7/12.6/7.2	47.5/56.1/56.5	29.8/31.2/36.3
BT use	Combined with DMARD / Monotherapy	20 / 8.3	49.7 / 57.3	30.3 / 36.4
Dependence on corticosteroids	No / Yes	20.7 / 7.6	50.4 / 56.3	28.9 / 36
Active synovitis by US	No / Yes / US not available	33.3 / 0 / 9.1	66 / 6.9 / 87.2	0.7 / 93.1 / 3.3

Abbreviations: DA, disease activity; BT, biological therapy; TG, therapeutic goal; DMARD, disease-modifying anti-rheumatic drugs; US, ultrasonography; CRP, C-reactive protein.

variables and definitions were accepted by the rating panel except for “subclinical synovitis by ultrasonography”, which was changed by the rating panel to “active synovitis by ultrasonography”.

After the first rating round, 54 (2.34%) indications were rated with disagreement, although only 8 (0.35%) remained at disagreement after the second round. Reduction of the BT dose was considered appropriate in 327 indications (14.2%), uncertain in 1,228 (53.3%), and inappropriate in 749 (32.5%). The indication with the highest appropriateness score corresponded to a patient with the following characteristics: age <70 years, disease duration <5 years, moderate disease activity at initiation of BT used in combination with a conventional DMARD, no dependence on corticosteroids, having achieved the TG <6 months after the first BT prescription, and in remission for >12 months without active synovitis by ultrasonography before BT was tapered. By contrast, the rating panel considered to have the least appropriate profile for dose reduction was as follows: elderly patient with long-term disease and previous failure of >2 BT, dependence on corticosteroids, high disease activity at prescription of the current BT (used in monotherapy), and achieving low disease activity after >6 months, but having low disease activity only for the last 6 months and showing active synovitis by ultrasonography at some joints.

Although the appropriateness criteria for each indication are shown in the “Results” section of Supplementary File 2, the upper panel of Fig. 1 shows how much each variable influenced the rating panel when the appropriateness of the indications was scored. Interestingly, the rating panel considered that no indication

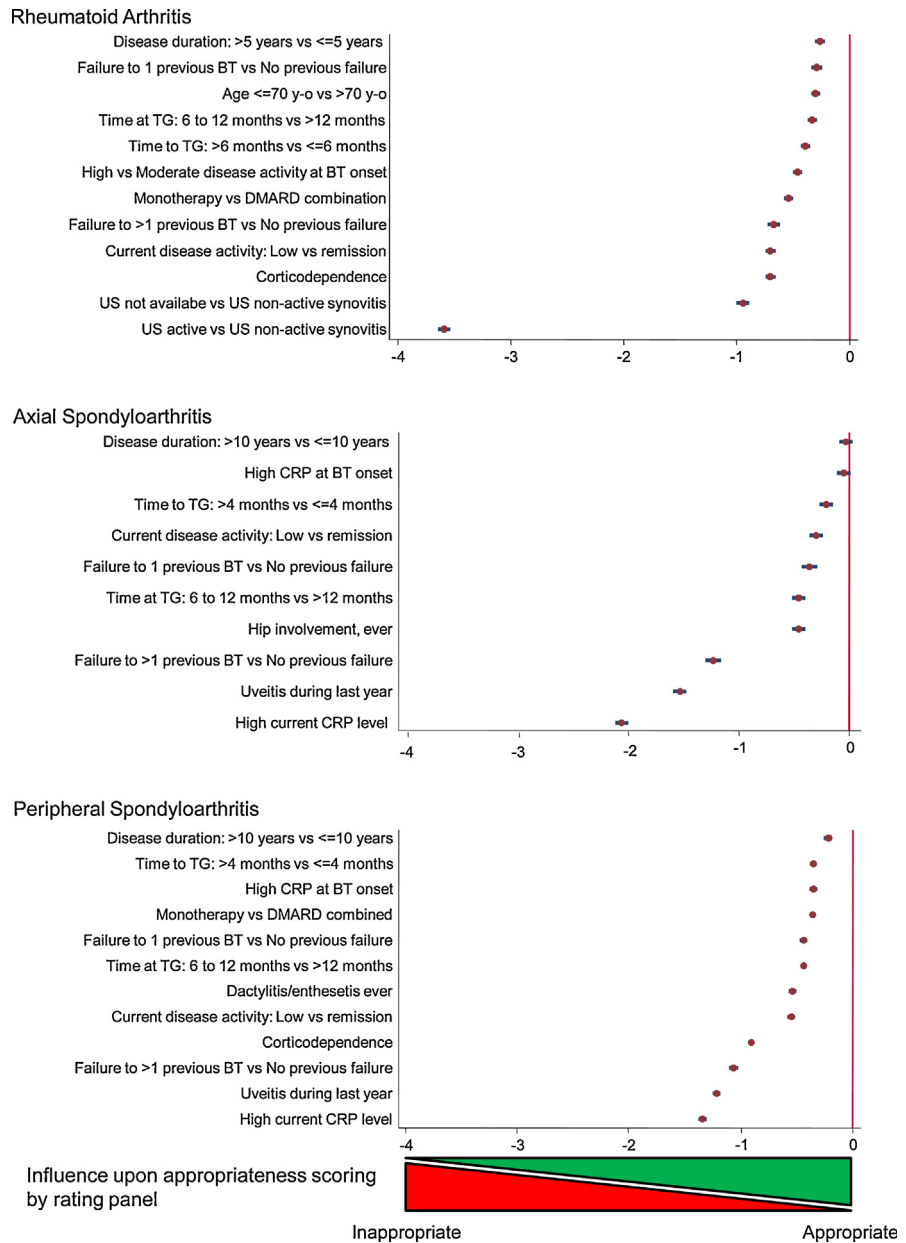


Fig. 1. Influence of the variables used to define patient profiles on the score provided for each profile by members of the rating panel. The data are shown as the b coefficient (brown point) and the 95% confidence interval (blue bar) of each option in the multivariable analysis (see Methods, Statistics). For each variable, the option considered most likely to reduce the BT dose was used as a reference; therefore, all b coefficients are negative. The more the brown point shifts to the left, the less appropriate this condition was considered by the panelists in the different profiles.

with active synovitis by ultrasound was appropriate for BT dose reduction, whereas without active synovitis by ultrasound, the dose reduction was considered appropriate in 33.3% of the indications (Table 1).

Table 2. Variables selected by the working group to develop the list of the 768 indications for **Axial Spondyloarthritis** and percentages of appropriate indications (AI), uncertain indications (UI), and inappropriate indications (II).

Variables	Options	AI (%)	UI (%)	II (%)
DA at BT dose reduction	Remission / Low	13.3 / 7.6	56.7 / 53.9	32 / 38.5
Time since TG was reached	>12 months / 6-12 months	13.3 / 7.6	57.3 / 51.3	29.4 / 41.1
Disease duration	<10 years / ≥10 years	11.5 / 9.4	55.1 / 55.5	35.4 / 35.2
CRP at BT dose reduction	Normal / High	20.8 / 0	70.8 / 37.8	8.3 / 62.2
CRP at initiation of BT	Normal / High	10.7 / 10.2	54.2 / 54.4	35.2 / 35.4
Time to achieve TG	<4 months / ≥4 months	11.7 / 9.1	56.8 / 51.8	31.5 / 39.1
Hip involvement ever	No / Yes	13.3 / 7.5	55.7 / 52.9	31 / 39.6
Previous BT failures	0 / 1 / ≥2	18.4/11.7/1.2	57.8/62.9/42.2	23.8/25.4/56.6
Uveitis during previous year	No / Yes	20.8 / 0	64.1 / 44.5	15.1 / 55.5

Abbreviations: DA, disease activity; BT, biological therapy; TG, therapeutic goal; CRP, C-reactive protein.

3.2. Axial spondyloarthritis

The working group identified and defined 9 variables (Table 2; for definitions see the Supplementary File 3), which generated 768 clinical profiles for axSpA. All variables and definitions were accepted by the rating panel. Two of the 768 indications (0.26%) were rated with disagreement after the first round, and no indications were rated with disagreement after the second round. Dose reduction was considered appropriate in 80 indications (10.42%), uncertain in 418 (54.43%), and inappropriate in 270 (35.16%). The appropriateness criteria for each indication are shown in the “Results” section of Supplementary File 3.

The middle panel of Fig. 1 shows that disease duration and C-reactive protein (CRP) level at initiation of BT had almost no influence on how the rating panel rated the appropriateness of dose reduction for axSpA. By contrast, the presence of uveitis during the previous year or current high CRP level had the highest negative influence on appropriateness scoring for axSpA profiles. Therefore, no indication including these clinical situations was considered appropriate for dose reduction. By contrast, the best profile for tapering the BT dose was that of a patient with no history of hip involvement or uveitis who achieved early remission (<4 months) lasting >12 months with her/his first BT and had normal CRP levels.

3.3. Peripheral spondyloarthritis

The working group identified and defined 11 variables (Table 3; see Supplementary File 4 for definitions), which generated 3,072 clinical profiles for pSpA. All variables and definitions were accepted by the rating panel. No indication was rated with disagreement. Dose reduction was considered appropriate

Table 3. Variables selected by the working group to develop the list of the 3,072 indications for **Peripheral Spondyloarthritis** and percentages of appropriate indications (AI), uncertain indications (UI), and inappropriate indications (II).

Variables	Options	AI (%)	UI (%)	II (%)
DA at BT dose reduction	Remission / Low	8.3 / 1.7	59.7 / 49.4	32 / 48.9
Time since TG was reached	>12 months / 6-12 months	7 / 3.1	58.7 / 50.4	34.3 / 46.5
Disease duration	<5 years / ≥5 years	6.1 / 3.9	56.3 / 52.9	37.6 / 43.2
CRP at BT dose reduction	Normal / High	10 / 0	70.4 / 38.7	19.6 / 61.3
CRP at initiation of BT	Normal / High	5.8 / 4.2	60.5 / 48.6	33.7 / 47.2
Time to achieve TG	<6 months / ≥6 months	6.3 / 3.7	58.7 / 50.4	35 / 45.9
Dactylitis-enthesitis ever	No / Yes	7.4 / 2.7	60 / 49.1	32.7 / 48.2
Previous BT failures	0 / 1 / ≥2	9.4 / 4.2 / 1.5	65.3/58.9/39.4	25.3/36.9/59.1
BT use	Combined with DMARD / Monotherapy	6.2 / 3.8	59.3 / 49.8	34.5 / 46.5
Dependence on corticosteroids	No / Yes	8.7 / 1.4	64.9 / 44.2	26.4 / 54.4
Uveitis during last year	No / Yes	9.7 / 0.3	67.7 / 41.4	22.6 / 58.3

Abbreviations: DA, disease activity; BT, biological therapy; TG, therapeutic goal; DMARD, disease-modifying anti-rheumatic drugs; CRP, C-reactive protein.

in 154 indications (5.01%), uncertain in 1,675 (54.52%), and inappropriate in 1,243 (40.46%). The appropriateness criteria for each indication are shown in the “Results” section of Supplementary File 4.

The lower panel of Fig. 1 shows that high CRP level at the time of dose reduction and presence of uveitis in the previous year had the strongest influence on appropriateness scoring. However, only clinical profiles with high CRP levels were considered inappropriate for BT dose reduction in all cases.

4. Discussion

Reducing the BT dose under certain circumstances, especially in RA patients, is recommended in international guidelines for the management of immune-mediated diseases [11, 12]. Although rheumatologists face this situation commonly in daily clinical practice, there is no solid evidence to determine which profiles are most likely to be successful after tapering BT [13]. This is the first study to address this problem using RAM. After identifying more than 6,000 profiles, we considered that tapering the BT dose was appropriate in 561 (9.1%) clinical situations, inappropriate in 2,262 (36.8%), and uncertain in more than half. Consequently, we were able to take a position in 46% of the clinical profiles considered.

Several issues must be taken into account to ensure that these results are interpreted appropriately. First, in the case of RA, the appropriateness criteria do not apply to rituximab, since it is administered differently from other BT agents. Furthermore,

recommendations for optimized use of this drug are based on solid scientific evidence [6]. Second, and of particular concern, is the prevalence of real cases from daily clinical practice among the theoretical indications developed using the RAM. Previous studies based on this methodology reported that 60% to 80% of the indications do not represent actual patients in clinical practice [14, 15]. In fact, in a study assessing the validity of RAM criteria for performing carotid endarterectomy, Shekelle et al. found that most patients were concentrated in 32% of indications [15]. The interpretation of indications classified as uncertain is also a crucial aspect of the RAM. With current knowledge, uncertain means that the risk and benefits of BT dose reduction in patients who reach the TG are similar. Considering that most relapses after reducing the dose of BT can regain TG by restarting the full BT dose [15, 16, 17, 18, 19, 20, 21], we displayed the median score provided by the rating panel for each indication in the tables of appropriateness criteria (Supplementary Files 2 to 4). Since the scores for uncertain indications ranged from 3.5 to 6, this information may help physicians who are deciding whether or not to reduce the dose of BT in uncertain clinical profiles.

In the future, the prevalence of clinical profiles will be studied and the criteria will be validated in retrospective studies in which BT doses have been already optimized or prospective studies.

Our study is subject to a series of limitations. First, although the RAM is not a perfect method, the evidence about its strengths and limitations suggests that the RAM has enough validity and reliability to be used for developing appropriate use criteria [9, 15, 22, 23, 24]. Second, management of appropriateness criteria, as they are shown in the Supplementary Files 2 to 4, is complex. However, the identification of clinical profiles makes it possible to establish a hierarchical decision tree that facilitates development of software that in turn aids decision making by using fewer than 12 dichotomy options. While it is true that the selection of items used to develop the lists of indications was based on the experience of working group members, no solid evidence was available about biomarkers that were predictive of success when BT was tapered, as recently reported in RA by Tweehuysen et al [13], who analyzed ultrasonography only for the prediction of successful discontinuation of BT but not for reducing the dose of BT in RA [13]. Nevertheless, the rating panel was most influenced by this variable, although ultrasonography experts agreed that more research is needed in order to provide accurate and solid evidence on how this technique can be used to taper BT [25]. Since the working group considered that this knowledge will be gained in the near future, a variable with 3 options (active or inactive synovitis by ultrasonography and no ultrasonography available) was included. Lastly, we decided not to include measurement of serum BT levels, which would also complement these criteria, to develop clinical profiles of the 3 diseases, since the

working group considered that a deeper understanding of the role of this information is needed before measurement of BT levels is included in the decision to taper BT [26]. Nonetheless, in the future, measurement of BT levels may play a role in the decision to taper the BT dose [27].

In summary, the publication of these appropriateness criteria for BT dose reduction can provide support to clinicians making decisions on issues that are not based on robust data and that might be considered off-label practice by some physicians. Furthermore, these criteria can help to reduce administrative pressure on rheumatologists to reduce the BT dose in inappropriate clinical profiles. They can also broaden the scope of management of BT in other medical specialties treating immune-mediated inflammatory disorders: the focus can shift to tapering rather than stopping BT once remission has been achieved, since discontinuation has led to more frequent relapses [28].

Declarations

Author contribution statement

Isidoro González Álvaro, Antonio Blasco, Pablo Lazaro, Carlos Sánchez-Piedra: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Raquel Almodovar, Javier Bachiller-Corral, Alejandro Balsa, Rafael Caliz, Gloria Candelas, Cristina Fernández-Carballido, Angel García-Aparicio, Blanca Garcia Magallon, Rosario Garcia-Vicuña, Antonio Gómez-Centeno, Ana Ortiz, Raimon Sanmartí, Jesús Sanz, Beatriz Tejera: Contributed reagents, materials, analysis tools or data; Wrote the paper.

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Competing interest statement

The authors declare the following conflict of interests:

Dr. Gonzalez-Alvaro reports grants from Instituto de Salud Carlos III, during the conduct of the study; personal fees from Lilly, grants, personal fees and non-financial support from UCB, personal fees and non-financial support from BMS, personal fees and non-financial support from Pfizer, grants from Roche, personal fees and non-financial support from Abbvie, non-financial support from MSD,

outside the submitted work; In addition, Dr. Gonzalez-Alvaro has a patent PCT/ES2015/070182 issued.

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Dr. Lazaro reports personal fees from Spanish Society of Reumatology, during the conduct of the study; grants from AbbVie, outside the submitted work.

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Dr. García-Magallón reports personal fees from MSD, non-financial support from Pfizer, personal fees from MSD, non-financial support from MSD, non-financial support from JANSSEN, outside the submitted work.

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Additional information

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