

Spanish Rheumatology Society and Hospital Pharmacy Society Consensus on recommendations for biologics optimization in patients with rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis

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Abstract

Objective. The aim of this study was to establish guidelines for the optimization of biologic therapies for health professionals involved in the management of patients with RA, AS and PsA.

Methods. Recommendations were established via consensus by a panel of experts in rheumatology and hospital pharmacy, based on analysis of available scientific evidence obtained from four systematic reviews and on the clinical experience of panellists. The Delphi method was used to evaluate these recommendations, both between panellists and among a wider group of rheumatologists.

Results. Previous concepts concerning better management of RA, AS and PsA were reviewed and, more specifically, guidelines for the optimization of biologic therapies used to treat these diseases were formulated. Recommendations were made with the aim of establishing a plan for when and how to taper biologic treatment in patients with these diseases.

Conclusion. The recommendations established herein aim not only to provide advice on how to improve the risk:benefit ratio and efficiency of such treatments, but also to reduce variability in daily clinical practice in the use of biologic therapies for rheumatic diseases.

Keywords

Rheumatoid arthritis, Psoriatic arthritis, Ankylosing spondylitis, Biologics, Optimization, Dose reduction, bDMARD, cDMARD, Risk/benefit ratio

Introduction

RA, PsA and AS are common chronic inflammatory joint diseases that have a major health care and social impact. Between 1% and 3% of the population may be affected by one or more of these diseases [1–4]. While the clinical spectrum of RA, PsA and AS is very heterogeneous, for a significant number of patients, these diseases can severely affect their quality of life and are associated with increased morbidity and mortality [5–11]. All of this leads to a substantial socio-economic burden in terms of both labour costs, due to the higher incidence of these diseases in the 20- to 60-year-old age range, and health care expenditure and social dependence, particularly in elderly patients [12, 13].

This scenario has changed, thanks to a transformation in the diagnostic/therapeutic approach. First, and most importantly, these diseases are no longer considered benign [5, 14, 15]. Second, there is now a more proactive attitude, leading to intensive and earlier treatment until optimal disease control is attained [16–24]. The availability of biologic therapies (BTs) has proved of enormous benefit in helping rheumatologists attain better disease control and, consequently, improving the functional capacity and quality of life for patients with RA, PsA and AS [25–27].

In terms of safety, current evidence suggests that the increased risk of infection [28–33] associated with BT can be prevented or better managed [34, 35]. Nevertheless, this drawback has been accepted for those cases in which a patient's disease activity cannot be controlled by other standard therapeutic means, since in these individuals the BT's risk:benefit ratio improves considerably [25–27].

Rationale

In recent years, the tapering of BT when a patient has reached a stable therapeutic goal (TG) has been gaining ground in daily clinical practice [36–42]. Nonetheless, some degree of variability in the use of BT is implicit here, because until now there have been no specific recommendations for clinicians to follow.

The reasons for optimizing the use of BT are manifold. First, there is a need to improve the risk:benefit ratio. Rheumatologists regularly decrease drug dosages (particularly when using drugs with potentially serious adverse effects) once a TG has been reached and consolidated [43]. Current information suggests that BT use involves a dose-dependent effect on the risk of infection [44–47], especially when various BTs are used in combination therapy [48], as this is not approved practice. Nonetheless, comorbidities and the use of glucocorticoids also account for higher risk of infection [49–51]. Second, physicians are obliged to maximize the quality of care and patient satisfaction, while keeping costs to a minimum [52]. Pharmacokinetic studies of various BTs have revealed significant interindividual variability, with serum concentrations tending to overlap in populations receiving different doses, a situation that can be observed even at doses below the recommended level [53–58]. Thus, it seems reasonable to try to identify the minimum dose that would provide adequate disease control once inflammatory activity has been resolved.

Finally, there is the issue of equity of care. In this sense, public sector managers are obliged to ensure equal access at the lowest possible cost, avoiding the paradoxical situation of being unable to initiate new treatments for patients who need them, while other patients with adequate disease control may be effectively overtreated. On the other hand, the emAR II study demonstrated that significant variability in the use of BT persists, in both RA and SpA patients [59]. Such heterogeneous practices, as observed in a number of rheumatology units throughout the country, may have repercussions on the equity of care provided for patients with RA, PsA and AS.

For all of these reasons, the Spanish Rheumatology Society (Sociedad Española de Reumatología, SER) and the Hospital Pharmacy Society have promoted the development of a series of recommendations for optimizing BT use in patients with RA, PsA and AS. The intention of the panel is to offer some general recommendations that can then be adapted on an individual case basis, with the aim of providing quality health care based on safety, efficiency and equity criteria.

Finally, the panellists are aware that some of the recommendations could be considered off-label practice, and this may have legal consequences, depending on the Health System regulations. The panellists are convinced that informing the patient about the optimizing procedure—its objectives, benefits and possible risks—is essential.

An extended version of this section is provided as supplementary material, available at *Rheumatology Online*. This includes the preliminary considerations, describing several relevant issues for optimizing BT, and also summaries of the three systematic reviews (SRs) supporting BT down-titration (our unpublished data).

Methods

These recommendations were drawn up via the consensus of an expert panel using the modified RAND/UCLA method [60]. Their consensus was based on SRs of the available scientific evidence, as well as on clinical experience, for which a nominal group was formed and Delphi surveys were conducted.

The panel included 16 BT experts, of whom 10 were rheumatology experts and 6 were hospital pharmacists. Panellists were sent a set of data and selected publications that included SER consensus papers on BT, and literature provided by biopharmaceutical companies (Abbvie, Bristol-Myers Squibb, Merck Sharp & Dohme, Pfizer, Roche and UCB Pharma). There were three nominal group meetings. At the first one, it was agreed that a general literature search on optimization and BT in RA, AS and PsA should be conducted in order to define the focus of the SRs to be carried out at a later stage.

At the second panel meeting, following formal consensus on methodology, the structure and content of the project were established, and one or more sections were distributed among the experts. The project consisted of an introduction and rationale, preliminary questions, definitions and six basic recommendations (see supplementary material for rationale, preliminary questions, definitions of TG and relapse, and future perspectives sections, available at *Rheumatology Online*). Four clinical questions were identified and agreed upon, formulated in PICO (Population, Intervention, Comparator and Outcome) format, and these were then used to conduct the SRs. The questions referred to the consequences of stopping or reducing the BT dose: (i) rate of relapse in the three diseases of interest; (ii) patient response to reintroducing the BT post-relapse due to a dose reduction or suspension; (iii) radiographic progression in patients with RA in whom the BT dose was suspended or decreased; and (iv) optimization of rituximab

(RTX). In the first three SRs, the level of evidence (LE) for the references included were classified according to the Scottish Intercollegiate Guidelines Network (SIGN) scale [61]; in the RTX review, however, evidence was classified according to the Oxford Centre for Evidence-Based Medicine (CEBM) scale [62], allowing establishment of the degree of the recommendations (DRs).

The first draft of the recommendations was subjected to an individual, anonymous and independent assessment by experts using a Delphi survey, with an online platform establishing the degree of agreement between panellists (DAP). To compare the opinions of those experts with those of rheumatology professionals, a Delphi survey was also conducted among those SER members who agreed to receive this questionnaire, allowing the degree of agreement among SER members (DAM) to be established. A total of 834 SER members were sent the survey, with a valid response rate of 33.7%.

The level of agreement with the recommendations in the various surveys was estimated both as the mean score on a scale of 1–10 (1 being total disagreement and 10 total agreement) and as the percentage of panellists or rheumatologists who scored each recommendation ≥ 7 . The level of agreement was regarded as high if the recommendations attained a mean > 7 and the percentage of panellists and rheumatologists scoring ≥ 7 was over 70%. Recommendations that did not meet these conditions in the panellist or member surveys were reformulated by the panel of experts, and subjected to a second Delphi round among members of the panel.

In the third meeting, the results of the available scientific evidence obtained in the SRs were discussed in order to formulate the final recommendations, also taking into account the consensus obtained from the survey results. The four SRs are readily available in Spanish upon request from: proyectos@ser.es (our unpublished data).

Recommendations

Each recommendation is presented as: the clinical question, the panel recommendation, and observations. See Table 1 and supplementary material, available at *Rheumatology* Online, for definitions of TG and relapse for each disease.

Table 1. Definitions of therapeutic goal and relapse

	Therapeutic goal	Relapse	
		Mild	Severe
RA and poly-articular PsA	DAS28 (ESR) < 3.2 SDAI < 11 HUPI < 5	DAS28 increase > 0.6 + final DAS28 > 3.2	DAS28 increase > 1.2
AS and axial PsA	BASDAI < 4 ASDAS < 2.1	BASDAI increase > 1 (ASDAS increase > 1.1) + 2 $<$ final BASDAI < 4 (final ASDAS < 2.1)	BASDAI increase > 2 (ASDAS increase > 2) or Final BASDAI > 4 (Final ASDAS > 2.1) or Mild relapse + CRP $>$ UNL
Oligoarticular or enthesitic PsA	TJC and SJC ≤ 1 VAS Pain ≤ 1.5 (0–10) GDA Patient ≤ 2 TEC ≤ 1		SJC > 3 or TEC > 3 + CRP $>$ UNL

A detailed explanation of definitions is available as supplementary material, available at *Rheumatology* Online. SDAI: simplified disease activity index; HUPI: Hospital Universitario la Princesa Index; ASDAS: ankylosing spondylitis disease activity score; TJC: tender joint count; SJC: swollen joint count; GDA: global disease assessment; TEC: tender entheses count; UNL: upper normal limit.

The first five recommendations refer to all BTs except RTX. The panel decided that a specific recommendation for RTX should be developed, given that its mechanism of action and dose are completely different from those of other BTs.

How long after reaching the TG should BT optimization be considered?

Recommendation.

The process of BT optimization can be initiated in patients who have maintained their TG for at least 6 months (DAP: 9.1, 100%; DAM: 7.5, 74%; DR D).

The time span between starting BT treatment and the initiation of BT optimization should be assessed on an individual patient basis. A prolonged disease history prior to starting BT is a variable that appears repeatedly among the factors associated with greater relapse frequency in various studies in which BT was discontinued [63, 64]. Other factors similarly associated with post-optimization relapse include advanced age and higher disease activity [64]. Glucocorticoid dependence, time-to-reach TG and other factors reflecting disease severity could also serve as a guide when deciding how long a patient should proceed towards his/her TG before reducing the BT dose. In the survey of SER members, a large number of respondents specified a period of 1 year at TG before embarking on optimization.

How should optimization be approached in terms of dose reductions?

Recommendation

The dose indicated in the summary of product characteristics (SPC) may be reduced initially by 20–50%, by either reducing the initial dose or increasing the interval between doses (DAP: 8.6, 86%; DAM: 8.2, 88%; DR D).

Aside from etanercept, the only way to reduce the dose in cases of s.c. administration is by increasing the dosing interval. Conversely, the dose of drugs administered intravenously may be lowered either by reducing the amount administered in each infusion or by reducing the frequency of infusions. The selection of one over the other depends on patient preference, the previous experience of the team and/or other circumstances regarding the logistics of the centre where the BT is administered.

Regarding the percentage of reduction, except in the PRESERVE trial, in which the dose of etanercept was reduced by 50% in a pre-established manner [65], all other publications refer to a 10–50% dose reduction, both in general clinical practice [36, 37, 39] and in studies that used a pre-established protocol [17, 41, 66]. Taking into account that the majority of patients who undergo BT in a daily clinical practice setting do so because of high disease activity [59], the panel suggests prudent dose reductions, tailored to each medicine, but which should never initially exceed 50%. As with the previous recommendation, the dose reduction must be adapted to each patient based on variables such as disease activity (low activity vs remission), age, long- or short-term disease, presence of poor prognosis factors and other patient characteristics.

How should follow-up be conducted once BT optimization has been initiated?

During the BT optimization process, the panel estimates that each time a dose reduction is made, the first clinical control should occur after 8 weeks, and that if a patient continues towards his/her TG, then successive visits may be made every 12–16 weeks (DAP: 8.9, 93%; DAM: 7.9, 82%; DR D).

Only a few of the studies that evaluated relapse following discontinuation of BT [63, 67, 68] provided details on the mean time to relapse, which ranged from 4 to 15 weeks. Important as it is to determine the frequency of patient follow-up visits, so too is the need for ready access paths to the doctor in charge should any relapse occur between visits. Based on feedback from SER members, the availability of additional medical support, such as nurse consultations, telephone consultations and contact via email or other new technologies, could be an effective way of resolving this issue.

What should be done if a relapse occurs during the optimization process?

Recommendation A

In patients with RA or polyarticular PsA who suffer a relapse during the optimization process, the BT dose or dose interval should be readjusted in order to re-attain the TG; the decision of whether to prescribe the dose indicated in the medication guide or to return to the dose used before the dose reduction that provoked the relapse should be assessed on an individual basis depending on the severity and nature of the relapse (DAP: 8.9, 100%; DAM: 8.9, 97%; DR D).

Two relapse intensity criteria were defined because, in the experience of the panellists with patients who have undergone successive BT dose reductions, mild forms of disease reactivation can be managed successfully by returning to the previous dose, even if this is lower than the dose or frequency recommended in the medication guide. However, if the patient suffers a severe relapse (Table 1), it would be reasonable to return to the dose indicated in the SPC.

Recommendation B

In patients with AS and PsA for whom BT was indicated for axial involvement and who suffer a mild relapse during the optimization process, full dose (or maximum tolerated) of NSAIDs is recommended for at least 4 weeks, followed by another clinical assessment. If at this stage the TG is not reached, the previous BT dose or the dose recommended in the SPC should be prescribed, following an individual patient assessment by the doctor in charge. If patients present with a severe relapse, then the recommendation is to return to the BT dose specified in the SPC (DAP 8.9, 94%; DR D).

The reasoning behind developing one recommendation for RA and PsA (with peripheral polyarthritis involvement) and another for AS and PsA (with axial involvement) is that the use of NSAIDs has not been shown to decrease structural progression in RA, while there is evidence that in AS patients treated continuously with NSAIDs, radiographic progression can be delayed [69, 70].

The initial version of this recommendation was poorly endorsed in the SER member survey (DAM: 6.9, percentage scores >7: 63%) and thus it had to be reformulated. The problem was that it did not distinguish between mild or severe relapses, and proposed the use of NSAIDs for at least 8 weeks in all cases.

Finally, it is important to take into account the CRP value in order to gauge what type of relapse the patient is experiencing (Table 1). Data from clinical trials suggest a better response to TNF-blocking agents, both from a clinical point of view and in MRI of bone oedema, in patients with elevated CRP [71–74].

When should BT discontinuation be considered for patients undergoing optimization?

Recommendation

BT discontinuation may be considered in patients undergoing gradual BT optimization if the following criteria are met: (i) the patient is receiving a minimal optimization dose, (ii) the patient remains at the TG for 6–12 months after the last dose decrease, and (iii) there is no evidence of significant radiographic progression since initiation of optimization, and/or there is no US evidence of active disease (DAP: 8.4, 100%; DAM: 8, 82.5%; DR D).

Panel members explicitly expressed that discontinuing BT is not, in itself, an objective of the optimization process, but rather a consequence of permanent and effective disease control through successive dose reductions. General experience collected from the panel and SER member surveys regarding this recommendation is that stopping BT is uncommon. The possibility of stopping BT is especially remote in patients with severe and/or long-term disease, in which the BT was prescribed due to the failure of several DMARDs. In addition, studies on BT discontinuation describe a relapse in virtually all patients during the first year of follow-up [63–65, 67, 68], although there was some variability in how these studies were conducted, and prior dose-reduction regimens had not been instigated. However, in patients in whom BT was used at an early disease stage [75, 76] or because of moderate disease activity [65], or in those who have maintained their TG for long periods following successive BT dose reductions without relapse [66], stopping BT could be an option. In such cases, patients should be informed of the risks and benefits of stopping treatment, and they should be involved in the decision-making process.

The main obstacle in applying this recommendation concerns the question of how to best define minimal optimization dose. The panel suggests that this dose is reached when successive BT dose reductions result in serum drug levels being non-therapeutic or absent.

From a pharmacokinetic perspective, the minimal optimization dose can be calibrated by widening the administration interval by three times the drug elimination half-life, or by prescribing 25% of the dose shown in the SPC; in either case, 12.5% (trough concentration) of the drug should remain in the patient's body. However, the absence of pharmacokinetic studies in this optimization scenario, together with BT pharmacokinetic variability—even among individuals of the same age, sex, BMI or ethnicity—makes it difficult to establish a minimum dose for any given patient. Table 2 shows, merely as a guide, the elimination half-life and dosing intervals recommended in the SPC of the various BTs available.

Table 2. Elimination half-life of various biologic therapies

	Elimination half-life (t _{1/2})	Frequency of administration indicated in the SPC
Golimumab	12 (s.d. 3) days	Monthly
Etanercept	70 h, range (7–300 h)	50 mg: weekly 25 mg: 72 h
Adalimumab	2 weeks	Every 2 weeks
Anakinra	4–6 h	Daily
Certolizumab	2 weeks	Every 2 weeks
Infliximab	8–10 days	Every 8 weeks
Tocilizumab	10–16 days depending on dose and age	Every 4 weeks
Abatacept	8–25 days	i.v.: every 4 weeks s.c.: weekly

These data were obtained from the SPC of each medicine available from the EMA.
SPC: summary of product characteristics; EMA: European Medicines Agency.

In view of this uncertainty, monitoring BT plasma levels, as is often done with certain antibiotics, anti-epileptics, etc., would be of enormous benefit, not only in assessing the effectiveness of the treatment, but also in determining when a BT could be discontinued. A reasonable approach would be to suspend the drug in those patients who remain within their TG for prolonged periods (6–12 months) and whose trough levels of BT, following successive dose-reduction phases, become undetectable.

In RA, radiographic progression in patients who are well controlled with BT (including those on low BT dose regimens) is rare [65, 77–84]. Some clinical trials have demonstrated the cessation of structural damage, even in RA patients who lacked a satisfactory clinical response to the drug [45].

Conversely, there may be radiographic progression in cases of AS axial structural damage, despite the fact that clinical activity is well controlled with a BT [85]. The need for more prolonged BT treatment to delay radiographic progression has recently been described [86]. Nonetheless, there is a strong correlation between disease activity and MRI evidence of sacroiliac or spinal inflammation [71]. Therefore, an axial MRI may assist clinicians when deciding whether or not to discontinue BT in patients with AS.

How can RTX use be optimized?

Recommendation

To optimize the use of RTX in patients with RA, it is advisable to: (i) preferentially treat seropositive forms of the disease [87] (LE 1a, DR A) and (ii) use a tailored dosing schedule according to a treat-to-target strategy based on the TG or relapse definitions (Table 1) [87, 88] (LE 2b, DR B). Although the SPC recommended two 1000-mg infusions 15 days apart (2000 mg), there is evidence that a significant number of patients respond adequately to a single infusion of 1000 mg [89] (LE 1a, DR A) (DAP 9.1, 100%; DAM 7.9, 86%).

The most recent study involving long-term follow-up in patients treated with RTX during clinical trials included analysis of a subset (n = 627) of patients treated for longer than 5 years, some of whom had been treated for up to 9.5 years (more than 17 cycles) [90]. Bearing in mind that the presence of low immunoglobulin levels was an exclusion criterion in these clinical trials, no significant increases in infections were detected, although there was a tendency towards a reduction in serum IgG levels [90]. The information available on the use of RTX in daily clinical practice (AIR registry from the French Rheumatology Society) suggests that infections are more common in patients with IgG levels <6 g/l, although the presence of pulmonary and cardiac comorbidities, as well as extra-articular RA manifestations, was also associated with an increased risk of infection [50]. Finally, various studies have shown that reduced IgG and IgM levels are associated with cumulative RTX dose, especially in patients with decreased immunoglobulin levels prior to the start of treatment [44, 91].

Based on these preliminary findings, the panel believes RTX to be a safe long-term therapy, although potentially high cumulative doses over short periods have been associated with decreased IgG levels and increased infections in patients with a long history of complications and pulmonary or cardiac comorbidities. One way of improving the risk:benefit ratio is to administer the drug to those patients who present a more pronounced and longer-lasting clinical response. This is more likely to occur in seropositive patients, those who are either RF or ACPA-positive or both [87]. Furthermore, the response

should be evaluated 3–4 months post-rituximab infusion. Indeed, in those patients who respond well, it should be administered again once the TG is lost (DAS28 <3.2), without allowing the disease to reach a high activity stage. This approach has proved effective [88] and can reduce the cumulative RTX dose in these patients compared with those receiving the drug regularly every 6 months.

It is true that the efficacy in patient groups treated with 2-g cycles vs those who received only 1 g was quite similar [92]. The efficacy of RTX has been shown to be not so much dependent on the dose used, as on the extent of B-lymphocyte depletion below the detection limit of highly sensitive cytometers (<0.1 × 10⁶ cells/l) [93]. Some patients may require higher doses because the efficacy of B cell depletion appears to depend upon CD16 (a receptor for the Fc fraction of IgG) genetic variants [94–96]. It could be that only patients homozygous for the low-affinity genotype would require high-dose cycles, although this hypothesis would have to be confirmed in controlled studies.

Finally, an increasing number of randomized clinical trials are exploring the efficacy and safety of dose reduction in those patients who have attained their TGs with the standard dose. The results of these trials will help shed some light on the uncertainty surrounding current optimization practices and will contribute towards the inevitable updating of this consensus.

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References

1. Braun J, Bollow M, Remlinger G, et al. Prevalence of spondylarthropathies in HLA-B27 positive and negative blood donors. *Arthritis Rheum* 1998;41:58-67.
2. Carmona L, Ballina J, Gabriel R, Laffon A. The burden of musculoskeletal diseases in the general population of Spain: results from a national survey. *Ann Rheum Dis* 2001;60:1040-5.
3. O'Neill T, Silman AJ. Psoriatic arthritis. Historical background and epidemiology. *Baillieres Clin Rheumatol* 1994;8:245-61.
4. Scott DL, Wolfe F, Huizinga TW. Rheumatoid arthritis. *Lancet* 2010;376:1094-108.
5. Braun J, Pincus T. Mortality, course of disease and prognosis of patients with ankylosing spondylitis. *Clin Exp Rheumatol* 2002;20:S16-22.
6. Carmona L, Gonzalez-Alvaro I, Balsa A, et al. Rheumatoid arthritis in Spain: occurrence of extra-articular manifestations and estimates of disease severity. *Ann Rheum Dis* 2003;62:897-900.
7. Gladman DD, Farewell VT, Wong K, Husted J. Mortality studies in psoriatic arthritis: results from a single outpatient center. II. Prognostic indicators for death. *Arthritis Rheum* 1998;41:1103-10.
8. Lehtinen K. Mortality and causes of death in 398 patients admitted to hospital with ankylosing spondylitis. *Ann Rheum Dis* 1993;52:174-6.
9. Sokka T, Abelson B, Pincus T. Mortality in rheumatoid arthritis: 2008 update. *Clin Exp Rheumatol* 2008;26:S35-61.
10. Wong K, Gladman DD, Husted J, Long JA, Farewell VT. Mortality studies in psoriatic arthritis: results from a single outpatient clinic. I. Causes and risk of death. *Arthritis Rheum* 1997;40:1868-72.
11. Bakland G, Gran JT, Nossent JC. Increased mortality in ankylosing spondylitis is related to disease activity. *Ann Rheum Dis* 2011;70:1921-5.
12. Ariza-Ariza R, Hernandez-Cruz B, Collantes E, et al. Work disability in patients with ankylosing spondylitis. *J Rheumatol* 2009;36:2512-6.
13. Lajas C, Abasolo L, Bellajdel B, et al. Costs and predictors of costs in rheumatoid arthritis: a prevalence-based study. *Arthritis Rheum* 2003;49:64-70.
14. Gladman DD, Antoni C, Mease P, Clegg DO, Nash P. Psoriatic arthritis: epidemiology, clinical features, course, and outcome. *Ann Rheum Dis* 2005;64 Suppl 2:ii14-7.
15. Pincus T, Callahan LF, Sale WG, et al. Severe functional declines, work disability, and increased mortality in seventy-five rheumatoid arthritis patients studied over nine years. *Arthritis Rheum* 1984;27:864-72.
16. Descalzo MA, Carbonell J, Gonzalez-Alvaro I, et al. Effectiveness of a clinical practice intervention in early rheumatoid arthritis. *Arthritis Care Res* 2012;64:321-30.
17. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, et al. Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): a randomized, controlled trial. *Arthritis Rheum* 2005;52:3381-90.
18. Gremese E, Salaffi F, Bosello SL, et al. Very early rheumatoid arthritis as a predictor of remission: a multicentre real life prospective study. *Ann Rheum Dis* 2013;72:858-62.
19. Grigor C, Capell H, Stirling A, et al. Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. *Lancet* 2004;364:263-9.
20. Mottonen T, Hannonen P, Leirisalo-Repo M, et al. Comparison of combination therapy with single-drug therapy in early rheumatoid arthritis: a randomised trial. FIN-RACo trial group. *Lancet* 1999;353:1568-73.
21. Nell VP, Machold KP, Eberl G, et al. Benefit of very early referral and very early therapy with disease-modifying anti-rheumatic drugs in patients with early rheumatoid arthritis. *Rheumatology* 2004;43:906-14.
22. O'Dell JR. Treating rheumatoid arthritis early: a window of opportunity? *Arthritis Rheum* 2002;46:283-5.
23. Sieper J, Braun J. How important is early therapy in axial spondyloarthritis? *Rheum Dis Clin North Am* 2012;38:635-42.
24. Verstappen SM, Jacobs JW, van der Veen MJ, et al. Intensive treatment with methotrexate in early rheumatoid arthritis: aiming for remission. Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA, an open-label strategy trial). *Ann Rheum Dis* 2007;66:1443-9.
25. Machado MADA, Barbosa MM, Almeida AM, et al. Treatment of ankylosing spondylitis with TNF blockers: a meta-analysis. *Rheumatol Int* 2013;33:2199-213.
26. Singh JA, Christensen R, Wells GA, et al. A network meta-analysis of randomized controlled trials of biologics for rheumatoid arthritis: a Cochrane overview. *CMAJ* 2009;181:787-96.
27. Ash Z, Gaujoux-Viala C, Gossec L, et al. A systematic literature review of drug therapies for the treatment of psoriatic arthritis: current evidence and meta-analysis informing the EULAR recommendations for the management of psoriatic arthritis. *Ann Rheum Dis* 2012;71:319-26.
28. Carmona L, Descalzo MA, Perez-Pampin E, et al. All-cause and cause-specific mortality in rheumatoid arthritis are not greater than expected when treated with tumour necrosis factor antagonists. *Ann Rheum Dis* 2007;66:880-5.
29. Garcia-Doval I, Perez-Zafrilla B, Descalzo MA, et al. Incidence and risk of hospitalisation due to shingles and chickenpox in patients with rheumatic diseases treated with TNF antagonists. *Ann Rheum Dis* 2010;69:1751-5.
30. Gomez-Reino JJ, Carmona L, Valverde VR, Mola EM, Montero MD. Treatment of rheumatoid arthritis with tumor necrosis factor inhibitors may predispose to significant increase in tuberculosis risk: a multicenter active-surveillance report. *Arthritis Rheum* 2003;48:2122-7.

31. Pena-Sagredo JL, Farinas MC, Perez-Zafrilla B, et al. Non-typhi Salmonella infection in patients with rheumatic diseases on TNF-alpha antagonist therapy. *Clin Exp Rheumatol* 2009;27:920-5.
32. Pena-Sagredo JL, Hernandez MV, Fernandez-Llanio N, et al. Listeria monocytogenes infection in patients with rheumatic diseases on TNF-alpha antagonist therapy: the Spanish Study Group experience. *Clin Exp Rheumatol* 2008;26:854-9.
33. Perez-Sola MJ, Torre-Cisneros J, Perez-Zafrilla B, et al. Infections in patients treated with tumor necrosis factor antagonists: incidence, aetiology and mortality in the BIOBADASER registry. *Med Clin (Barc)* 2011;137:533-40.
34. Carmona L, Gomez-Reino JJ, Rodriguez-Valverde V, et al. Effectiveness of recommendations to prevent reactivation of latent tuberculosis infection in patients treated with tumor necrosis factor antagonists. *Arthritis Rheum* 2005;52:1766-72.
35. Gomez Reino J, Loza E, Andreu JL, et al. [Consensus statement of the Spanish Society of Rheumatology on risk management of biologic therapy in rheumatic patients]. *Reumatol Clin* 2011;7:284-98.
36. Martínez-Pérez R, Rodríguez-Montero S, Muñoz A, et al. Effectiveness of dose reduction of etanercept and adalimumab in patients with rheumatoid arthritis. *J Transl Med* 2011;9:P44.
37. Navarro-Compan V, Moreira V, Ariza-Ariza R, et al. Low doses of etanercept can be effective in ankylosing spondylitis patients who achieve remission of the disease. *Clin Rheumatol* 2011;30:993-6.
38. Escudero-Vilaplana V, Ramirez-Herraiz E, Trovato-Lopez N, et al. Influence on effectiveness of early treatment with anti-TNF therapy in rheumatoid arthritis. *J Pharm Pharm Sci* 2012;15:355-60.
39. Ramirez-Herraiz E, Escudero-Vilaplana V, Alanon-Plaza E, et al. Efficiency of adalimumab, etanercept and infliximab in rheumatoid arthritis patients: dosing patterns and effectiveness in daily clinical practice. *Clin Exp Rheumatol* 2013;31:559-65.
40. Ramírez Herráiz E, Escudero Villaplana V, Alañón Plaza E, et al. Uso real de antagonistas del TNF en la práctica clínica: Optimización de dosis y costes asociados en pacientes con Espondilitis Anquilosante en 2 hospitales generales universitarios. *Reumatol Clin* 2013;9:26-7.
41. Maneiro JR, Perez-Pampin E, Salgado E, Carmona L, Gomez-Reino JJ. Observational study of optimization of biologic therapies in rheumatoid arthritis: a single-centre experience. *Rheumatol Int* 2014;37:1059-63.
42. Inciarte-Mundo J, Hernandez MV, Rosario V, et al. Reduction of biological agent dose in rheumatic diseases: descriptive analysis of 153 patients in clinical practice conditions. *Reumatol Clin* 2013;10:10-6.
43. Smolen JS, Landewe R, Breedveld FC, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. *Ann Rheum Dis* 2014;73:492-509.
44. Isvy A, Meunier M, Gobeaux-Chenevier C, et al. Safety of rituximab in rheumatoid arthritis: a long-term prospective single-center study of gammaglobulin concentrations and infections. *Joint Bone Spine* 2012;79:365-9.
45. Lipsky PE, van der Heijde DM, St Clair EW, et al. Infliximab and methotrexate in the treatment of rheumatoid arthritis. Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. *N Engl J Med* 2000;343:1594-602.
46. Maini RN, Breedveld FC, Kalden JR, et al. Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor alpha monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. *Arthritis Rheum* 1998;41:1552-63.
47. Maini RN, Taylor PC, Szechinski J, et al. Double-blind randomized controlled clinical trial of the interleukin-6 receptor antagonist, tocilizumab, in European patients with rheumatoid arthritis who had an incomplete response to methotrexate. *Arthritis Rheum* 2006;54:2817-29.
48. Genovese MC, Cohen S, Moreland L, et al. Combination therapy with etanercept and anakinra in the treatment of patients with rheumatoid arthritis who have been treated unsuccessfully with methotrexate. *Arthritis Rheum* 2004;50:1412-9.
49. Dixon WG, Abrahamowicz M, Beauchamp ME, et al. Immediate and delayed impact of oral glucocorticoid therapy on risk of serious infection in older patients with rheumatoid arthritis: a nested case-control analysis. *Ann Rheum Dis* 2012;71:1128-33.
50. Gottenberg JE, Ravaud P, Bardin T, et al. Risk factors for severe infections in patients with rheumatoid arthritis treated with rituximab in the autoimmunity and rituximab registry. *Arthritis Rheum* 2010;62:2625-32.
51. Listing J, Gerhold K, Zink A. The risk of infections associated with rheumatoid arthritis, with its comorbidity and treatment. *Rheumatology* 2013;52:53-61.
52. Ortún Rubio V. ¿Qué debería saber un clínico de Economía? [What should a doctor know about economy?]. In: Millan Núñez-Cortes J, del Llano Señarís JE, editors. *Ser médico Los valores de una profesión [Being a doctor: The values of a profession]*. Alcobendas, Madrid (Spain): Unión Editorial, SA; 2012.
53. den Broeder A, van de Putte L, Rau R, et al. A single dose, placebo controlled study of the fully human anti-tumor necrosis factor-alpha antibody adalimumab (D2E7) in patients with rheumatoid arthritis. *J Rheumatol* 2002;29:2288-98.
54. European Medicines Agency. London: EMA; 2010. Assessment Report For Mabthera (rituximab): Procedure No.: EMEA/H/C/000165/II/0065.
55. Frey N, Grange S, Woodworth T. Population pharmacokinetic analysis of tocilizumab in patients with rheumatoid arthritis. *J Clin Pharmacol* 2010;50:754-66.

56. Korth-Bradley JM, Rubin AS, Hanna RK, Simcoe DK, Lebsack ME. The pharmacokinetics of etanercept in healthy volunteers. *Ann Pharmacother* 2000;34:161-4.
57. Nishimoto N, Yoshizaki K, Maeda K, et al. Toxicity, pharmacokinetics, and dose-finding study of repetitive treatment with the humanized anti-interleukin 6 receptor antibody MRA in rheumatoid arthritis. Phase I/II clinical study. *J Rheumatol* 2003;30:1426-35.
58. St Clair EW, Wagner CL, Fasanmade AA, et al. The relationship of serum infliximab concentrations to clinical improvement in rheumatoid arthritis: results from ATTRACT, a multicenter, randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2002;46:1451-9.
59. Sociedad Española de Reumatología. Proyecto EMAR II. Variabilidad en el manejo de la artritis reumatoide y las espondiloartritis en España. Informe de resultados. Madrid: SER, 2011 [updated February 2011]. http://www.ser.es/ArchivosDESCARGABLES/Proyectos/Emar/EMAR_Informe.pdf (5 September 2013, date last accessed).
60. Fitch K. Santa Monica: Rand; 2001. The Rand/UCLA appropriateness method user's manual.
61. Scottish Intercollegiate Guidelines Network. A guideline developer's handbook: SIGN 50. Edinburgh: SIGN (NHS Quality Improvement Scotland), 2008. <http://www.intute.ac.uk/healthandlifesciences/cgi-bin/fullrecord.pl?handle=20080207-11330481> (28 August 2013, date last accessed).
62. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996;17:1-12.
63. Saleem B, Keen H, Goeb V, et al. Patients with RA in remission on TNF blockers: when and in whom can TNF blocker therapy be stopped? *Ann Rheum Dis* 2010;69:1636-42.
64. Tanaka Y, Takeuchi T, Mimori T, et al. Discontinuation of infliximab after attaining low disease activity in patients with rheumatoid arthritis: RRR (remission induction by Remicade in RA) study. *Ann Rheum Dis* 2010;69:1286-91.
65. Smolen JS, Nash P, Durez P, et al. Maintenance, reduction, or withdrawal of etanercept after treatment with etanercept and methotrexate in patients with moderate rheumatoid arthritis (PRESERVE): a randomised controlled trial. *Lancet* 2013;381:918-29.
66. van der Maas A, Kievit W, van den Bemt BJ, et al. Down-titration and discontinuation of infliximab in rheumatoid arthritis patients with stable low disease activity and stable treatment: an observational cohort study. *Ann Rheum Dis* 2012;71:1849-54.
67. Brocq O, Millasseau E, Albert C, et al. Effect of discontinuing TNFalpha antagonist therapy in patients with remission of rheumatoid arthritis. *Joint Bone Spine* 2009;76:350-5.
68. Baraliakos X, Listing J, Brandt J, et al. Clinical response to discontinuation of anti-TNF therapy in patients with ankylosing spondylitis after 3 years of continuous treatment with infliximab. *Arthritis Res Ther* 2005;7:R439-44.
69. Poddubnyy D, Rudwaleit M, Haibel H, et al. Effect of non-steroidal anti-inflammatory drugs on radiographic spinal progression in patients with axial spondyloarthritis: results from the German Spondyloarthritis Inception Cohort. *Ann Rheum Dis* 2012;71:1616-22.
70. Wanders A, Heijde D, Landewe R, et al. Nonsteroidal antiinflammatory drugs reduce radiographic progression in patients with ankylosing spondylitis: a randomized clinical trial. *Arthritis Rheum* 2005;52:1756-65.
71. Braun J, Baraliakos X, Golder W, et al. Magnetic resonance imaging examinations of the spine in patients with ankylosing spondylitis, before and after successful therapy with infliximab: evaluation of a new scoring system. *Arthritis Rheum* 2003;48:1126-36.
72. Sieper J, van der Heijde D, Dougados M, et al. Efficacy and safety of adalimumab in patients with non-radiographic axial spondyloarthritis: results of a randomised placebo-controlled trial (ABILITY-1). *Ann Rheum Dis* 2013;72:815-22.
73. Song IH, Weiss A, Hermann KG, et al. Similar response rates in patients with ankylosing spondylitis and non-radiographic axial spondyloarthritis after 1 year of treatment with etanercept: results from the ESTHER trial. *Ann Rheum Dis* 2013;72:823-5.
74. Visvanathan S, Wagner C, Marini JC, et al. Inflammatory biomarkers, disease activity and spinal disease measures in patients with ankylosing spondylitis after treatment with infliximab. *Ann Rheum Dis* 2008;67:511-7.
75. Quinn MA, Conaghan PG, O'Connor PJ, et al. Very early treatment with infliximab in addition to methotrexate in early, poor-prognosis rheumatoid arthritis reduces magnetic resonance imaging evidence of synovitis and damage, with sustained benefit after infliximab withdrawal: results from a twelve-month randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2005;52:27-35.
76. van den Broek M, Klarenbeek NB, Dirven L, et al. Discontinuation of infliximab and potential predictors of persistent low disease activity in patients with early rheumatoid arthritis and disease activity score-steered therapy: subanalysis of the BeSt study. *Ann Rheum Dis* 2011;70:1389-94.
77. Bresnihan B, Newmark R, Robbins S, Genant HK. Effects of anakinra monotherapy on joint damage in patients with rheumatoid arthritis. Extension of a 24-week randomized, placebo-controlled trial. *J Rheumatol* 2004;31:1103-11.
78. St Clair EW, Heijde DM, Smolen JS, et al. Combination of infliximab and methotrexate therapy for early rheumatoid arthritis: a randomized, controlled trial. *Arthritis Rheum* 2004;11:3432-43.
79. Emery P, Fleischmann R, van der Heijde D, et al. The effects of golimumab on radiographic progression in rheumatoid arthritis: results of randomized controlled studies of golimumab before methotrexate therapy and golimumab after methotrexate therapy. *Arthritis Rheum* 2011;63:1200-10.

80. Keystone EC, Combe B, Smolen J, et al. Sustained efficacy of certolizumab pegol added to methotrexate in the treatment of rheumatoid arthritis: 2-year results from the RAPID 1 trial. *Rheumatology* 2012;51:1628-38.
81. Kremer JM, Blanco R, Brzosko M, et al. Tocilizumab inhibits structural joint damage in rheumatoid arthritis patients with inadequate responses to methotrexate: results from the double-blind treatment phase of a randomized placebo-controlled trial of tocilizumab safety and prevention of structural joint damage at one year. *Arthritis Rheum* 2011;63:609-21.
82. Maini RN, Breedveld FC, Kalden JR, et al. Sustained improvement over two years in physical function, structural damage, and signs and symptoms among patients with rheumatoid arthritis treated with infliximab and methotrexate. *Arthritis Rheum* 2004;50:1051-65.
83. Tada M, Koike T, Okano T, et al. Comparison of joint destruction between standard- and low-dose etanercept in rheumatoid arthritis from the Prevention of Cartilage Destruction by Etanercept (PRECEPT) study. *Rheumatology* 2012;51:2164-9.
84. Tak PP, Rigby W, Rubbert-Roth A, et al. Sustained inhibition of progressive joint damage with rituximab plus methotrexate in early active rheumatoid arthritis: 2-year results from the randomised controlled trial IMAGE. *Ann Rheum Dis* 2012;71:351-7.
85. Baraliakos X, Listing J, Rudwaleit M, et al. Radiographic progression in patients with ankylosing spondylitis after 2 years of treatment with the tumour necrosis factor alpha antibody infliximab. *Ann Rheum Dis* 2005;64:1462-6.
86. Baraliakos X, Haibel H, Listing J, Sieper J, Braun J. Continuous long-term anti-TNF therapy does not lead to an increase in the rate of new bone formation over 8 years in patients with ankylosing spondylitis. *Ann Rheum Dis* 2014;73:710-5.
87. Teng YK, Tekstra J, Breedveld FC, et al. Rituximab fixed retreatment versus on-demand retreatment in refractory rheumatoid arthritis: comparison of two B cell depleting treatment strategies. *Ann Rheum Dis* 2009;68:1075-7.
88. Emery P, Mease PJ, Rubbert-Roth A, et al. Retreatment with rituximab based on a treatment-to-target approach provides better disease control than treatment as needed in patients with rheumatoid arthritis: a retrospective pooled analysis. *Rheumatology* 2011;50:2223-32.
89. Mariette X, Rouanet S, Sibilia J, et al. Evaluation of low-dose rituximab for the retreatment of patients with active rheumatoid arthritis: a non-inferiority randomised controlled trial. *Ann Rheum Dis* 2014;73:1508-14.
90. van Vollenhoven RF, Emery P, Bingham CO III., et al. Long-term safety of rituximab in rheumatoid arthritis: 9.5-year follow-up of the global clinical trial programme with a focus on adverse events of interest in RA patients. *Ann Rheum Dis* 2013;72:1496-502.
91. De La Torre I, Leandro MJ, Valor L, et al. Total serum immunoglobulin levels in patients with RA after multiple B cell depletion cycles based on rituximab: relationship with B cell kinetics. *Rheumatology* 2012;51:833-40.
92. Bredemeier M, de Oliveira FK, Rocha CM. Low- versus high-dose rituximab for rheumatoid arthritis: a systematic review and meta-analysis. *Arthritis Care Res* 2014;66:228-35.
93. Vital EM, Rawstron AC, Dass S, et al. Reduced-dose rituximab in rheumatoid arthritis: efficacy depends on degree of B cell depletion. *Arthritis Rheum* 2011;63:603-8.
94. Kastbom A, Coster L, Arlestig L, et al. Influence of FCGR3A genotype on the therapeutic response to rituximab in rheumatoid arthritis: an observational cohort study. *BMJ Open* 2012;2:e001524.
95. Ruysse-Witrand A, Rouanet S, Combe B, et al. Fcgamma receptor type IIIA polymorphism influences treatment outcomes in patients with rheumatoid arthritis treated with rituximab. *Ann Rheum Dis* 2012;71:875-7.
96. Dall'Ozzo S, Tartas S, Paintaud G, et al. Rituximab-dependent cytotoxicity by natural killer cells: influence of FCGR3A polymorphism on the concentration-effect relationship. *Cancer Res* 2004;64:4664-9.