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Clinical trials of new drugs for the treatment of rheumatoid arthritis: focus on early disease

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ABSTRACT

The European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases convened a task force of experts in rheumatoid arthritis (RA) and clinical trial methodology to comment on the new draft 'Guideline on clinical investigation of medicinal products for the treatment of RA' released by the European Medicines Agency (EMA). Special emphasis was placed by the group on the development of new drugs for the treatment of early RA. In the absence of a clear definition of early RA, it was suggested that clinical investigations in this condition were conducted in disease-modifying antirheumatic drugs naïve patients with no more than 1 year disease duration. The expert group recommended using an appropriate improvement in disease activity (American College of Rheumatology (ACR) or Simplified/Clinical Disease Activity Index (SDAI/CDAI) response criteria) or low disease activity (by any score) as primary endpoints, with ACR/European League Against Rheumatism remission as a secondary endpoint. Finally, as compelling evidence showed that the Disease Activity Score using 28-joint counts (DAS28) might not provide a reliable definition of remission, or sometimes even low disease activity, the group suggested replacing DAS28 as a measurement instrument to evaluate disease activity in RA clinical trials. Proposed alternatives included SDAI, CDAI and Boolean criteria.

provide comments on the new draft EMA guideline. Therefore, a panel of experts in the field of RA and clinical trial methodology was convened and a workshop was organised to discuss issues related to the design of clinical trials in RA. Furthermore, as the new ACR/EULAR classification criteria for RA allow for earlier treatment of the disease,⁵ particular attention was paid to defining the early RA population, together with the endpoints that should be implemented in clinical studies conducted in such a population. This document summarises the consensus of the expert group's recommendations following review of the draft EMA guideline on clinical investigation of medicinal products for the treatment of RA, with a particular focus on early RA.

EARLY RA POPULATION

The new draft guideline shows the willingness of the EMA to divide patients with RA into two populations: early RA and more advanced RA. The rationale behind this splitting is the introduction of the new ACR/EULAR classification criteria for RA⁵ that allow patients to be included earlier in their disease course than before. However, there is currently insufficient evidence that patients with early RA who have never been treated with disease-modifying antirheumatic drugs (DMARDs) behave much differently from DMARD-naïve patients with more established disease. Regardless of disease duration, patients who have previously experienced DMARDs usually respond to a lesser extent than patients who are DMARD naïve or have received only hydroxychloroquine or brief courses of glucocorticoids. Therefore, DMARD-experienced patients may have to be studied differently and with potentially different primary endpoints. Given the current focus on early RA, we suggest defining a trial population of DMARD-naïve patients with disease not exceeding 1 year duration from diagnosis as early RA. Such a population would not comply with the definition of early RA given in the 2015 ACR guideline for the treatment of RA (ie, RA with duration of disease/symptoms of <6 months, where duration denotes the length of time the patient has had symptoms/disease, not the length of time since RA diagnosis),⁹ but we think that it would be more appropriate to clinical research in terms of patient recruitment and population characterisation.

INTRODUCTION

The European Medicines Agency (EMA) has opened the public consultation for a draft guideline on the clinical investigation of medicinal products other than non-steroidal anti-inflammatory drugs (NSAIDs) for the treatment of rheumatoid arthritis (RA).¹ This much-awaited^{2 3} revision of the 2003 EMA 'Points to consider'⁴ had become necessary in light of the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for RA,⁵ the new ACR/EULAR remission criteria⁶ and the new EULAR recommendations for the management of RA.⁷

Considered as an interested party by the EMA,⁸ the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) was invited to



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Of note, the EULAR is currently updating its original consensus on early arthritis¹⁰ and it may be assumed that a definition of early RA will also be provided by these experts by the next EULAR Congress in June 2016.

PRIMARY ENDPOINT

The draft guideline suggests that the ACR response criteria are no longer endorsed as primary endpoints in early RA clinical trials, despite the fact that they have served the clinical trial landscape very well over the years. The ACR20, while not perfect, still constitutes a very sensitive and valid instrument to distinguish between efficacy rates of different anti-rheumatic treatments.^{11 12} Rather, the EMA recommends using remission as a primary endpoint, arguing that it is an established treatment target in the field and that disease activity is routinely monitored in patients in European clinical practice.

However, this recommendation raises two main issues. First, remission is still a relatively uncommon occurrence in clinical research, so that its power to detect differences in response between groups is reduced compared with the ACR20. Reaching such a challenging disease activity state would be likely to require increased numbers of patients for trials with the additional ethical concern that more individuals would be exposed to potentially ineffective treatment.

Therefore, we recommend choosing between ‘an appropriate improvement in disease activity’ and a disease activity state that is feasible to reach by a substantial proportion of patients as a primary endpoint. For maximum discriminative power,¹² this would be either the ACR20 or the profile of ACR response rates (none, 20, 50 and 70) tested together.¹³ With some loss of power, a single disease state such as low disease activity (LDA) or a single improvement rate such as the ACR50, ACR70 or SDAI/CDAI response criteria¹⁴ could also be acceptable. In addition, a minimum baseline level of disease activity should be introduced for studies to allow reliable measurement of improvement and LDA; the group suggests including patients with at least moderate disease activity and at least 6 out of 66 swollen joints and 6 out of 68 tender joints.

We think that remission is currently more appropriate as a secondary endpoint in early RA clinical trials.

MEASURING TOOLS TO ASSESS PRIMARY AND SECONDARY ENDPOINTS

A primary endpoint, whether defined as a treatment response or a favourable disease activity state, should be evaluated using validated instruments providing results that are consistent throughout a defined range and that do not favour specific classes of drugs. However, the EMA appears to regard DAS28<2.6 as remission, whereas the ACR and EULAR abandoned this criterion and introduced a new definition of remission based on SDAI (≤ 3.3) and Boolean criteria (≤ 1 on all following scores: tender joint count, swollen joint count, C-reactive protein (CRP) and patient global assessment on a 0–10 scale).^{6 15–17} The most important reason for this change is that the DAS28 remission cut-point allows for significant residual disease activity and progression of structural damage.^{6 15–18} Furthermore, the formula used to calculate DAS28 provides excess weighting to acute phase reactants, especially in the LDA range (values below 3.2),¹⁹ and may give an unfair advantage to agents that inhibit interleukin (IL) 6 pathways when DAS28<2.6 (and also DAS28<3.2) are used as primary trial outcomes. For example, patients on such agents have been shown to reach DAS28<2.6 while not meeting ACR70,²⁰ and sometimes not even ACR50 response criteria,²¹ pointing to disease activity states that are

incompatible with clinical remission. In the ADACTA trial that compared tocilizumab and adalimumab monotherapies, the rates of DAS28<2.6 were almost fourfold higher with tocilizumab than adalimumab, while all other endpoints conveyed a less than twofold advantage for tocilizumab.²² In the FUNCTION trial that compared tocilizumab and methotrexate monotherapies, DAS28<2.6 rates were significantly higher for tocilizumab than methotrexate, in contrast to almost all other clinical and functional endpoints.²³ Such discrepancies were not observed in clinical trials evaluating biologics that do not target proinflammatory cytokines.^{24 25} Another issue is that certain drugs such as tofacitinib have differential effects on CRP and erythrocyte sedimentation rate (ESR), resulting in dramatic differences between rates of DAS28-ESR<2.6 or <3.2 and DAS28-CRP<2.6 or <3.2.^{26 27} In contrast, the SDAI has been shown to match DAS28 in terms of measurement properties but without the disadvantages noted with this measuring tool.¹⁷ Other candidates that may be more convenient in pragmatic trials and merit further exploration include Boolean criteria (no acute phase reactant), CDAI (no acute phase reactant) and in some instances possibly also Rapid3 (fully patient reported and without joint counts) that have both shown very good results in this context.^{16 22 23 27–30}

CONCLUSION

We acknowledge the importance of evaluating new drugs differently in patients with early RA than in patients with established disease. In this respect, we suggest considering DMARD-naïve patients with no more than 1 year disease duration as ‘early RA patients’ in clinical investigations of new medicinal products.

In light of the above and in contrast to the guidance document endorsing the use of DAS28<2.6 as a remission criterion, we recommend using ACR or SDAI/CDAI response criteria, or LDA by any score, as treatment targets and possible primary endpoints in early RA clinical trials. Furthermore, as we move our treatment target to lower and lower disease activity states, we also suggest that DAS28 is avoided as a core measurement instrument in RA clinical trials, because its responsiveness to agents that can affect acute phase reactants independently of clinical improvement is larger than for other drugs providing a similar, or possibly improved, clinical response. Alternatively, if DAS28 is maintained as a measurement tool in clinical trials with these drugs (ie, IL-6 or Janus kinase inhibitors), additional analyses should be presented to reassure readers that the overall outcome remains relevant despite concerns that DAS28 might misrepresent the effect.

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REFERENCES

1 European Agency for the Evaluation of Medicinal Products. Guideline on clinical investigation of medicinal products other than NSAIDs for treatment of rheumatoid arthritis. 20 March 2015. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/06/WC500187583.pdf (accessed 22 Jan 2016).

- 2 Smolen JS, Boers M, Abadie EC, *et al*. Updating the 2003 European regulatory requirements for registering disease-modifying drugs to be used in the treatment of rheumatoid arthritis. *Rheumatology (Oxford)* 2011;50:1732–6.
- 3 Smolen JS, Boers M, Abadie EC, *et al*. Recommendations for an update of 2003 European regulatory requirements for registration of drugs to be used in the treatment of RA. *Curr Med Res Opin* 2011;27:315–25.
- 4 European Agency for the Evaluation of Medicinal Products. Points to consider on clinical investigation of medicinal products other than NSAIDs for treatment of rheumatoid arthritis. 17 December 2003. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003439.pdf (accessed 22 Jan 2016).
- 5 Aletaha D, Neogi T, Silman AJ, *et al*. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Ann Rheum Dis* 2010;69:1580–8.
- 6 Felson DT, Smolen JS, Wells G, *et al*. American College of Rheumatology/European League against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. *Ann Rheum Dis* 2011;70:404–13.
- 7 Smolen JS, Landewé 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.
- 8 European Medicines Agency. Concept paper on the need for revision of the points to consider on the clinical investigation of medicinal products other than NSAIDs in rheumatoid arthritis (CPMP/EWP/556/95 REV. 1). 20 January 2010. <http://trbmossge:8801/sites/scientifique/Docs/Documents/E/Conceptpaperneedrevision.pdf> (accessed 22 Jan 2016).
- 9 Singh JA, Saag KG, Bridges SL Jr, *et al*. 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. *Arthritis Care Res (Hoboken)* 2016;68:1–25.
- 10 Combe B, Landewé R, Lukas C, *et al*. EULAR recommendations for the management of early arthritis: report of a task force of the European Standing Committee for International Clinical Studies Including Therapeutics (ESCIIT). *Ann Rheum Dis* 2007;66:34–45.
- 11 Felson DT. Whither the ACR20? *J Rheumatol* 2004;31:835–7.
- 12 Felson DT, LaValley MP. The ACR20 and defining a threshold for response in rheumatic diseases: too much of a good thing. *Arthritis Res Ther* 2014;16:101.
- 13 Boers M, Kostense PJ. Non-overlapping American College of Rheumatology response rates: a better way to report response in rheumatoid arthritis clinical trials. *Arthritis Rheum* 2010;62:3524–7.
- 14 Aletaha D, Martinez-Avila J, Kvien TK, *et al*. Definition of treatment response in rheumatoid arthritis based on the simplified and the clinical disease activity index. *Ann Rheum Dis* 2012;71:1190–6.
- 15 van der Heijde D, Klareskog L, Boers M, *et al*. Comparison of different definitions to classify remission and sustained remission: 1 year TEMPO results. *Ann Rheum Dis* 2005;64:1582–7.
- 16 Kavanaugh A, Fleischmann RM, Emery P, *et al*. Clinical, functional and radiographic consequences of achieving stable low disease activity and remission with adalimumab plus methotrexate or methotrexate alone in early rheumatoid arthritis: 26-week results from the randomised, controlled OPTIMA study. *Ann Rheum Dis* 2013;72:64–71.
- 17 Aletaha D, Ward MM, Machold KP, *et al*. Remission and active disease in rheumatoid arthritis: defining criteria for disease activity states. *Arthritis Rheum* 2005;52:2625–36.
- 18 Mäkinen H, Kautiainen H, Hannonen P, *et al*. Is DAS28 an appropriate tool to assess remission in rheumatoid arthritis? *Ann Rheum Dis* 2005;64:1410–13.
- 19 Bakker MF, Jacobs JW, Verstappen SM, *et al*. Tight control in the treatment of rheumatoid arthritis: efficacy and feasibility. *Ann Rheum Dis* 2007;66(Suppl 3):iii56–60.
- 20 Smolen JS, Beaulieu A, Rubbert-Roth A, *et al*. Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomised trial. *Lancet* 2008;371:987–97.
- 21 Emery P, Keystone E, Tony HP, *et al*. IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-tumour necrosis factor biologicals: results from a 24-week multicentre randomised placebo-controlled trial. *Ann Rheum Dis* 2008;67:1516–23.
- 22 Gabay C, Emery P, van Vollenhoven R, *et al*. Tocilizumab monotherapy versus adalimumab monotherapy for treatment of rheumatoid arthritis (ADACTA): a randomised, double-blind, controlled phase 4 trial. *Lancet* 2013;381:1541–50.
- 23 Burmester GR, Rigby WF, van Vollenhoven RF, *et al*. Tocilizumab in early progressive rheumatoid arthritis: FUNCTION, a randomised controlled trial. *Ann Rheum Dis* 2016;75:1081–91.
- 24 Genovese MC, Becker JC, Schiff M, *et al*. Abatacept for rheumatoid arthritis refractory to tumor necrosis factor alpha inhibition. *N Engl J Med* 2005;353:1114–23.
- 25 Cohen SB, Emery P, Greenwald MW, *et al*. Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy: Results of a multicenter,

- randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks. *Arthritis Rheum* 2006;54:2793–806.
- 26 Fleischmann R, Kremer J, Cush J, *et al*. Placebo-controlled trial of tofacitinib monotherapy in rheumatoid arthritis. *N Engl J Med* 2012;367:495–507.
- 27 Smolen JS, Aletaha D, Gruben D, *et al*. Remission rates with tofacitinib treatment in rheumatoid arthritis: a comparison of various remission criteria. *Arthritis Rheum* 2012;64(Suppl 10):S334.
- 28 Aletaha D, Nell VP, Stamm T, *et al*. Acute phase reactants add little to composite disease activity indices for rheumatoid arthritis: validation of a clinical activity score. *Arthritis Res Ther* 2005;7:R796–806.
- 29 Pincus T, Furer V, Keystone E, *et al*. RAPID3 (Routine Assessment of Patient Index Data 3) severity categories and response criteria: Similar results to DAS28 (Disease Activity Score) and CDAI (Clinical Disease Activity Index) in the RAPID 1 (Rheumatoid Arthritis Prevention of Structural Damage) clinical trial of certolizumab pegol. *Arthritis Care Res (Hoboken)* 2011;63:1142–9.
- 30 Curtis JR, Churchill M, Kivitz A, *et al*. A Randomized Trial Comparing Disease Activity Measures for the Assessment and Prediction of Response in Rheumatoid Arthritis Patients Initiating Certolizumab Pegol. *Arthritis Rheumatol* 2015;67:3104–12.



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