Is there a need for new thresholds to define remission and low disease activity by Disease Activity Score 28 calculated with C reactive protein? Real life data from a local registry

We read with great interest the recent article by Fleischmann *et al* which reports a *post hoc* analysis of five rheumatoid arthritis (RA) randomised clinical trials (RCTs) to evaluate the correlation between Disease Activity Score in 28 joints calculated by using erythrocyte sedimentation rate (DAS28-ESR) or C reactive protein (DAS28-CRP).[1] Since its introduction,[2] DAS28-CRP has been used to evaluate clinical response in RCTs and daily practice by applying the same DAS28-ESR thresholds to define remission and low disease activity (LDA). Consistently with some previous reports,[3–5] Fleischmann *et al* demonstrated that DAS28-CRP underestimates disease activity when using the same remission and LDA cut-off points validated for DAS28-ESR (2.6 and 3.2, respectively).[6] Based on these findings, the authors suggested new thresholds for DAS28-CRP (2.4 for remission and 2.9 for LDA) that significantly decrease the proportion of discordance between the two composite indices in defining remission and LDA.

Still several recent RCTs employ DAS28-CRP applying the DAS28-ESR cut-off points as a primary outcome measure, and many rheumatologists use DAS28-CRP over DAS28-ESR to assess RA disease activity and implement treat-to-target strategy in daily practice. Hence, we felt it would be very useful to validate the newly introduced DAS28-CRP thresholds in a real life setting.

In order to test the performance of standard versus new DAS28-CRP cut-offs, we extracted from a local registry data on all patients with RA treated with biological agents in our rheumatology unit between October 1999 and August 2013. The selected study population consisted of 562 patients receiving a total of 887 lines of biologic therapy (71 abatacept, 197 adalimumab, 15 anakinra, 45 certolizumab pegol, 230 etanercept, 18 golimumab, 237 infliximab and 74 rituximab) with a minimum follow-up period of 12 months. For each line of therapy DAS28-ESR and DAS28-CRP (using the old and the newly proposed thresholds) response rates were calculated at 6-month and 12-month checkpoints, carrying the last observation forward for patients who were missing the selected study end points.

As reported in table 1, the percentage of patients achieving remission or LDA at both the checkpoints was lower for DAS28-ESR than DAS28-CRP when using standard cut-offs for both measures. As a consequence, the proportion of discordance between the two composite indices at 6-month and 12-month evaluations was 9.1% and 9.7% for remission and 13.8% and 13.7% for LDA, respectively. When clinical response rates were recalculated using the new thresholds for DAS28-CRP, the discordance between the two measures decreased (7.1% and 7.2% for remission and 9.6% and 8.2% for LDA at 6 months and 12 months, respectively) and the k coefficient of agreement increased from 0.74 to 0.79 for remission and from 0.7 to 0.77 for LDA at 6 months and from 0.75 to 0.8 for remission and from 0.71 to 0.81 for LDA at 12 months.

In conclusion, our real life data confirm that the use of DAS28-ESR standard cut-offs for defining clinical response by DAS28-CRP overestimates the proportion of patients in remission or LDA, potentially affecting treatment strategies. In our daily clinical practice, the new thresholds proposed by Fleischmann *et al* seem to perform better, with a significant decrease of the discordance between the two indices. Additional studies are required to further validate these new DAS28-CRP cut-offs.

Ennio Giulio Favalli,[1] Andrea Becciolini,[2] Martina Biggioggero,[2] Antonio Marchesoni,[1] Pier Luigi Meroni[2]

[1]Department of Rheumatology, Gaetano Pini Institute, Milan, Italy
[2]Department of Clinical Sciences and Community Health, Division of Rheumatology, University of Milan, Gaetano Pini Institute, Milan, Italy

Correspondence to Dr Ennio Giulio Favalli, Department of Rheumatology, Gaetano Pini Institute, Milan 20122, Italy; ennio.favalli@gmail.com

Fleischmann R, van der Heijde D, Koenig AS, *et al*. How much does Disease Activity Score in 28 joints ESR and CRP calculations underestimate disease activity compared with the Simplified Disease Activity Index? *Ann Rheum Dis* 2014. doi: annrheumdis-2013-204920v1

Send letter to journal: Re: Is there a need for new thresholds to define remission and low disease activity by Disease Activity Score 28 calculated with C reactive protein? Real life data from a local registry

Competing interests EGF, AM and PLM have received lecture fees from BMS, Roche, MSD, UCB, Pfizer and AbbVie. MB has received lecture fees from BMS and UCB.

Provenance and peer review Not commissioned; internally peer reviewed.

To cite Favalli EG, Becciolini A, Biggioggero M, *et al*. *Ann Rheum Dis* 2015;**74**:e5.

Received 19 September 2014
Accepted 22 September 2014
Published Online First 10 October 2014

Table 1 Relative performance of DAS28 calculated with ESR or CRP

	Proportion of remission or LDA			Proportion of discordance	
	DAS28-CRP	DAS28-CRP*	DAS28-ESR	DAS28-CRP vs DAS28-ESR	DAS28-CRP* vs DAS28ESR
Remission					
6 months	240/887 (27%)	212/887 (23.9%)	181/887 (20.4%)	81/887 (9.1%)	63/887 (7.1%)
12 months	259/887 (29.1%)	228/887 (25.7%)	193/887 (21.7%)	86/887 (9.7%)	65/887 (7.2%)
LDA					
6 months	367/887 (41.3%)	306/887 (34.4%)	266/887 (29.9%)	123/887 (13.8%)	86/887 (9.6%)
12 months	388/887 (43.7%)	311/887 (35%)	282/887 (31.7%)	122/887 (13.7%)	73/887 (8.2%)

*Using the new thresholds proposed by Fleischmann *et al*.[1]
CRP, C reactive protein; DAS28, Disease Activity Score in 28 joints; ESR, erythrocyte sedimentation rate; LDA, low disease activity.

► http://dx.doi.org/10.1136/annrheumdis-2014-206669

Ann Rheum Dis 2015;**74**:e5. doi:10.1136/annrheumdis-2014-206651

REFERENCES

1 Fleischmann R, van der Heijde D, Koenig AS, *et al*. How much does Disease Activity Score in 28 joints ESR and CRP calculations underestimate disease activity compared with the Simplified Disease Activity Index? *Ann Rheum Dis* Published Online First: 20 August 2014. doi:10.1136/annrheumdis-2013-204920
2 Fransen J, Welsing PM, de Keijzer RM, *et al*. Disease activity scores using C-reactive protein: CRP may replace ESR in the assessment of RA disease activity [abstract]. *Ann Rheum Dis* 2004;62(Suppl 1):151.
3 Crowson CS, Rahman MU, Matteson EL. Which measure of inflammation to use? A comparison of erythrocyte sedimentation rate and C-reactive protein measurements from randomized clinical trials of golimumab in rheumatoid arthritis. *J Rheumatol* 2009;36:1606–10.
4 Hensor EM, Emery P, Bingham SJ, *et al*. Discrepancies in categorizing rheumatoid arthritis patients by DAS-28(ESR) and DAS-28(CRP): can they be reduced? *Rheumatology (Oxford)* 2010;49:1521–9.
5 Matsui T, Kuga Y, Kaneko A, *et al*. Disease Activity Score 28 (DAS28) using C-reactive protein underestimates disease activity and overestimates EULAR response criteria compared with DAS28 using erythrocyte sedimentation rate in a large observational cohort of rheumatoid arthritis patients in Japan. *Ann Rheum Dis* 2007;66:1221–6.
6 Prevoo ML, van't Hof MA, Kuper HH, *et al*. Modified Disease Activity Scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. *Arthritis Rheum* 1995;38:44–8.