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Title: Time to modify the DAS28 to make it fit for purpose(s) in rheumatoid arthritis?

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1. Introduction

In rheumatoid arthritis, the disease activity score (DAS) is a composite measure widely used in research and clinical practice to assess disease status and therapeutic response. However, the DAS has limitations, notably a mismatch in some people between the level of disease activity indicated by the score and the extent of objectively assessed inflammation. Recent work has shown that not all DAS28 components are independent predictors of imaging-detected inflammation, and that updated DAS28 definitions that exclude TJC28 and patient global VAS are better associated with inflammation. We propose that the time has come to modify the current DAS to make it more reflective of true inflammation, and consider adding other tools if a more comprehensive evaluation of patient well-being is required.

2. Why do we use a disease activity score?

Modern treat-to-target strategies for rheumatoid arthritis (RA) management improve patient outcomes. Such strategies require serial evaluation of disease activity. When assessing RA there are a range of constructs that are important to both patients and clinicians, including pathophysiological manifestations and impacts on both patients and wider society [1]. Disease activity measurement is therefore complex; depending on the situation, investigators and clinicians may require a specific measure of active RA inflammation to assess treatment response and/or a more global indication of how an individual patient feels at a given time point. Composite measures, incorporating outcomes important to both clinicians and patients, can provide a simplified, generalizable metric that facilitates funding approval and access to treatment.

The Disease Activity Score (DAS) is a commonly used tool for disease monitoring. The current DAS used in clinical studies and practice (comprising tender and swollen joints assessments, acute phase reactants - either CRP or ESR - and patient global visual analogue scale (VAS)) was derived from clinical examination and expert opinion [2]. However, years of use and the development of modern objective assessments of inflammation with imaging have raised some concerns about the existing DAS formulations.

3. Existing DAS has limitations

Each of the DAS components has potential issues regarding measurement validity. There can be considerable inter-observer variation in tender joint and swollen joint counts (TJC and SJC) [3]. In clinical trials, inter-assessor variation results in noisy measurement – particularly in multicentre trials using hundreds of evaluators. Although composite score components should not be so closely correlated as to be redundant, we expect them to be moderately correlated [2]. However, acute

phase reactants may be normal in the presence of quite florid swollen joints, perhaps due to altered immunological profile [4]. ESR varies by sex and age, and CRP is considered a more responsive inflammatory measure than ESR [5]. The patient global component probably captures a broader concept than RA disease activity. In a T2T era aiming for remission, recent work suggests that a patient global VAS is common element for not achieving DAS remission [6], so we may risk over-treating patients.

Importantly, it is often difficult to understand which disease process underlies symptoms. In patients with longer-standing RA, especially those who haven't received modern therapies using T2T strategies, there will be secondary osteoarthritis and joint problems contributing to ongoing symptoms and signs. What's more, with some data suggesting age at onset of RA is increasing [7], patients are very likely to have co-present osteoarthritis, tendinitis and rheumatoid arthritis. Many of the causes of mechanical joint pain will not be modifiable with existing DMARDs.

If the major aim of assessing RA disease activity is to understand whether the inflammatory (DMARD-responsive) disease component is controlled, clinicians may be more influenced in treatment decisions by some DAS components than others. The original (1990s) weighting of DAS suggested that TJC was prioritised [2]. Subsequent appreciation of the limitations of DAS may have changed this view: one study found that only SJC was predictive of treatment decision [8]; another reported that in patients with high DAS28 comprising low SJC, high TJC and high patient global VAS, treatment was often left unchanged [9].

Ongoing inflammation results in deteriorating patient function and structural outcomes; a stricter Boolean definition of remission predicts better outcomes than DAS remission. Modern imaging suggests DAS and other composite tools may be inaccurate in detecting ongoing inflammation.

Clinically tender and/or swollen joints may show no imaging-detectable inflammation; conversely, joints that are neither tender nor swollen can have synovial hypertrophy and/or vascularisation present [10-14]. Such 'subclinical' inflammation has been associated with continued structural progression in patients in DAS remission [15-18].

4. Recent studies show modified DAS formulae are better related to inflammation and joint damage

Two recent papers have shown that the only DAS28 components that independently predict objective measures of inflammation – either MRI [19] or ultrasound-detected [20] synovitis/osteitis – are SJC and ESR/CRP (Table 1), and that modified DAS formulae that exclude TJC28 and patient global VAS are more strongly associated with radiographic damage.

Baker et al. used clinical trial data to assess associations between each DAS28 component and total MRI-derived synovitis and bone oedema/osteitis scores for the dominant side metacarpophalangeal joints (MCPJs) and wrist [19]. They also included evaluator's global assessment VAS (EvGA) as a predictor. They showed that only CRP, ESR, SJC28 and EvGA predicted each of the MRI outcomes, and produced modified DAS28 scores (each including SJC and EvGA with either CRP or ESR). They then used independent data to validate that the new definitions were more strongly associated with MRI synovitis and oedema/osteitis than the equivalent original DAS28 scores, and were better at predicting radiographic progression. However, of the individual components/predictors collected in the independent dataset, only SJC28, ESR and CRP (not EvGA) correlated with the MRI outcomes.

Recent work conducted in collaboration with a large RA consortium built on these findings. Hensor et al. used data from two observational cohorts and a clinical trial to show that in each dataset, only

SJC28 and CRP predicted an US-detected composite score (combined grey scale and power Doppler evaluation, GSPD), despite differences between the cohorts in US methodology [20]. The authors did not consider EvGA, reasoning that it was not available in many existing large-scale datasets and it may be subject to inter-evaluator variability. ESR was not predictive of GSPD in any of the cohorts. A re-weighted 2-component (2C) DAS28 (√SJC28+0.6*ln(CRP+1)) outperformed original DAS28CRP, DAS28ESR and partial SDAI and CDAI (calculated without adding EvGA) in its degree of association with GSPD in each dataset. In an external validation dataset, the Norfolk Arthritis Register, 2C-DAS28CRP was more strongly predictive of Larsen score than original 3C-DAS28 (which includes TJC28), and was associated with presence of erosions, whereas 3C-DAS28 was not.

5. How do we move forward?

Given the evidence suggesting that DAS(28) is inaccurate in detecting active inflammation, how can we improve assessment and monitoring of disease activity in RA? One option could be to use CDAI or SDAI instead. However, both scores give equal weight to TJC28 and SJC28, and include patient global VAS, when both studies highlighted above [19,20] have shown neither TJC28 nor patient global VAS are associated with imaging inflammation. In addition, 2C-DAS28 outperformed partial SDAI and CDAI in its association with US synovitis [20]. A 2014 meta-analysis showed rates of subclinical (USPD) inflammation in patients in remission were similar irrespective of whether DAS, SDAI or ACR definitions of remission were used [18].

The DAS is a well-established tool that has revolutionised RA management. Further progress is now achievable with a revised DAS. We recommend moving to a more accurate assessment of inflammation using one of the recent modified DAS definitions [19, 20], which include commonly accepted components, and which better reflect aspects of disease activity that are modifiable by therapies targeted primarily at synovial inflammatory pathways. Further work, feasibly using existing

datasets, could inform the choice between the two proposed options, define cut-offs and explore definitions of Boolean remission that do not include TJC or patient VAS. Such work should evaluate the implications of the new definitions for long-term outcomes in randomised controlled trials.

Were either of the new definitions to be adopted, we would need to consider how to capture the patient experience separately, in more depth [1]. Joint tenderness and the constructs captured by the patient global assessment such as pain, stiffness and fatigue are important to both patients and clinicians. However, the lack of correlation with imaging-detected inflammation suggests that these constructs may not be adequately treated by existing DMARDs. It may be that a dedicated, detailed assessment of patient-reported symptoms, using existing or novel tools, and consequent specific therapeutic targeting would improve patient outcomes.

We are aware that removing TJC28 and patient global VAS would, at first glance, seem to remove the patient's perspective from the disease activity assessment. This is not our intention; we believe that it would be in patients' best interests to use disease activity measures that most accurately reflect the manifestations targeted by current therapies. Measuring and treating other aspects of the disease independently could both improve the signal-to-noise ratio in clinical trials of new DMARDs, requiring fewer participants, and encourage the development of a more integrated approach to the management of rheumatoid arthritis.

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*Original DAS development paper that provides detail on the relative weighting of each component when using rheumatologist treatment decision as the target

**The first of two recent papers to re-evaluate the DAS components against modern imaging, using MRI-detected synovitis and osteitis as the target

***The second recent paper to re-evaluate the DAS components against modern imaging, using US-detected synovitis as the target

Table 1: This table summarises the results obtained by Baker et al [19] and Hensor et al [20]. Baker et al used generalised estimating equations to look for associations between DAS28 components, including both CRP and ESR, and MRI RAMRIS synovitis score; they also included evaluator global VAS. Hensor et al used linear mixed models that included either CRP or ESR, with combined grey scale power Doppler score as the outcome. Although the size of the coefficients themselves are not directly comparable between cohorts due to differences in methods, this table shows that neither TJC28 nor patient general health VAS were independently associated with imaging-detected synovitis in any of the four cohorts included. Baker et al found that both CRP and ESR were associated with MRI synovitis, whereas Hensor et al reported that models that included ESR (including one that included both CRP and ESR) did not outperform a model that only included CRP and SJC28.

	Coefficient* (95% CI)						
	Baker et al	**Hensor et al (CRP model)**			**Hensor et al (ESR model)**		
Component	**Cohort 1**	**Cohort 2**	**Cohort 3**	**Cohort 4**	**Cohort 2**	**Cohort 3**	**Cohort 4**
ln(CRP+1)	0.50 (0.28, 0.72)	15.79 (9.95, 21.62)	39.64 (23.39, 55.89)	4.28 (2.65, 5.92)	-	-	-
lnESR	0.20 (0.03, 0.36)	-	-	-	11.91 (4.87, 18.94)	10.68 (-6.53, 27.88)	1.54 (-0.22, 3.31)
(√)SJC28**	0.15 (0.10, 0.20)	30.48 (24.49, 36.47)	25.70 (6.04, 45.36)	4.54 (2.58, 6.49)	32.08 (26.06, 38.09)	35.41 (14.21, 56.60)	5.66 (3.59, 7.74)
(√)TJC28**	0.01 (-0.02, 0.04)	0.62 (-4.43, 5.67)	6.72 (-9.57, 23.01)	0.70 (-1.00, 2.40)	0.49 (-4.61, 5.58)	10.11 (-7.21, 27.43)	0.15 (-1.64, 1.95)
GHVAS	0.03 (-0.04, 0.10)	-0.07 (-0.32, 0.17)	-0.06 (-0.71, 0.60)	-0.04 (-0.10, 0.02)	-0.03 (-0.28, 0.22)	0.25 (-0.43, 0.94)	-0.02 (-0.09, 0.05)
EvGA	0.20 (0.12, 0.28)	-	-	-	-	-	-

CRP=C-reactive protein; ESR=erythrocyte sedimentation rate; EvGA=Evaluator global assessment; GHVAS=general health visual analogue scale; SJC28=28 swollen joint count; TJC28=28 tender joint count *Different sets of joints were scanned in the different cohorts, and the outcome varied, therefore the coefficients are not directly comparable across all cohorts **Hensor et al used √SJC28 and √TJC28 whereas Baker et al used SJC28 and TJC28 (native scaled)