Monitoring of rheumatoid arthritis disease activity in individual patients: still a hurdle when implementing the treat-to-target principle in daily clinical practice

Monitoring disease activity in individual RA patients

It is generally assumed that composite measures such as the DAS assessing 28 joints \([\text{DAS28; } 0.7\text{ln} (\text{ESR}) + 0.0142(\text{VAS}) + 0.555(28\text{TJC}) + 0.284(28\text{SJC})]\); VAS: visual analogue scale; TJC: tender joint count; SJC: swollen joint count) have been widely validated for use in individual RA patients. This assumption is false. The DAS28 has been validated for evaluations at group level, i.e. for measuring effects in clinical trials, but not for evaluations at individual patient level, i.e. for use in clinical practice. Is this only a theoretical, methodological issue or a relevant problem for daily practice?

The DAS28 has serious drawbacks, especially when used for applying the treat-to-target principle in an individual RA patient \([1]\), which requires precise and valid measurement of disease activity. Joints of the ankles and feet are not included in the DAS28. At group level, this is not a major problem, but at the individual patient level, this may lead to misclassification regarding states of low disease activity or remission \([2]\). One could argue, first, that in the absence of a generally accepted gold standard of remission, misclassification of remission more or less is arbitrary, and second, that according to the 2011 remission criteria, the absence of involved joints is not required \([3]\). However, among RA patients in DAS28 remission, several have more than five swollen joints (SJs) and some more than 10 SJs, especially joints of ankles and feet \([4]\). This cannot be easily ignored.

Issues with ankle and foot involvement aside, theoretically a patient can have 24 SJs of the 28 joints assessed for the DAS28 and still be in DAS28 remission. In contrast, a patient clinically in remission with four tender joints (TJs), zero SJs, a VAS global of 15 mm (range 0–100 mm) and an ESR of 15 mm/h is classed as having moderate disease activity according to the DAS28.

Furthermore, concomitant (secondary) FM or tender points in the non-FM range may result in a high DAS28 \([5\), 6\]. This is due to a positive association of tender points with the VAS global and TJ scores \([6]\). This too might lead to misclassification, for instance, falsely rejecting remission in an RA patient who is clinically in remission. Concomitant FM is not rare; it is present in 12–17% of patients with RA \([6]\).

Another issue arises when comparing individual patients’ DAS28. Similar scores may reflect different grades of disease activity and stages of RA. A DAS28 of 3.9 (moderate disease activity) can be based on 8 TJs, 0 SJs, a VAS of 30 mm and an ESR of 15 mm/h, but also on 0 TJs, 12 SJs, a VAS of 30 mm and an ESR of 35 mm/h.

There are also problems related to individual DAS28 components, in part caused by their relative weightings and conversions. Because in the DAS28 formula a TJ has a weight of 1.95 times that of a SJ and because square roots are applied, three TJs contribute more than seven SJs to the overall score. ESR is not just a measure of acute phase reaction, it is also increased by conditions such as obesity (also associated with difficult clinical assessment of disease activity) and hyperlipidaemia. ESR is frequently slightly elevated in elderly patients. Would a slight increase really matter? Well yes, because changes in the lower range of the ESR influence DAS28 most (Fig. 1), due to its log conversion. A non-specifically raised ESR might lead to a false conclusion that remission is absent. In comparison with ESR, CRP is less influenced by other conditions; it can be applied in the DAS28 instead of ESR, as 0.36\text{ln}(\text{CRP} + 1), with CPR in milligrams per litre. However, CRP then has the same drawback as ESR, i.e. changes in its lower range influence DAS28 most (Fig. 1).

The clinical disease activity index and the simplified disease activity index have no weightings or arithmetic conversions of individual components and each includes a physician’s global assessment. Therefore they are not subject to some of the flaws described above and also are much easier to calculate. However, they also assess only 28 joints \([7]\).

Based on the issues described above, we decided not to use the DAS28 for individual patients’ strategy steps in our treat-to-target computer-assisted management in early RA (CAMERA) trials \([8\), 9\]. The DAS28 and other indexes have too many flaws to apply them as sole determinants of RA activity for treat-to-target strategies or as criterion for access to biologic therapy. What is really needed is a composite measure of disease activity without the flaws mentioned above and validated for use in individual patients. Until that time we do not argue against the use of a composite index in daily practice, or the scoring of joint counts for that matter. However, we do recommend that more than 28 joints should be assessed and that the individual components should be taken into account too. The scores should be interpreted in the light of
particularities of the patient (e.g. age, BMI, co-morbidities and stage of the disease). For a patient with elevated ESR not related to disease activity, one could choose an index with CRP instead. To improve the specificity of assessing remission, one could add to the DAS28 criterion of remission the requirement of absence of any SJs, including ankles and feet. Alternatively, one might allow one SJ, according to the Boolean definition of the 2011 remission criteria [3]. US may be applied to assist clinical decision making. Some US issues remain to be resolved. At the moment there is no consensus on clinically relevant cut-off scores and the selection of joints to scan. Nevertheless, power Doppler US has added value when diagnosing RA and when evaluating remission of RA [10]. Another argument for applying US in clinical decision making in individual patients is that power Doppler signs of synovitis predict the progression of radiological joint damage and future flare in RA patients clinically in remission [10].

In conclusion, monitoring of RA disease activity in daily clinical practice demands a personalized approach; clinical decision making based only on an aggregate value of a composite index such as DAS28 is insufficient.

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