RAPID3? Aptly named!

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ABSTRACT

The RAPID3 score is the sum of three 0–10 patient self-report scores: pain, functional impairment on MDHAQ, and patient global estimate. It requires 5 seconds for scoring and can be used in all rheumatologic conditions, although it has mostly been used in rheumatoid arthritis where cutoffs for low disease activity (<6/30) or high disease activity (>12/30) have been set. A RAPID3 score of ≤3/30 with 1 or 0 swollen joints (RAPID3≤3+≤SJ1) provides remission criteria comparable to Boolean, SDAI, CDAI, and DAS28 remission criteria, in far less time than a formal joint count. RAPID3 performs as well as the DAS28 in separating active drugs from placebos in clinical trials. RAPID3 also predicts subsequent structural disease progression. RAPID3 can be determined at short intervals at home, allowing the determination of the area under the curve of disease activity between two visits and flare detection. However, RAPID3 should not be seen as a substitute for DAS28 and face to face visits in routine care. Monitoring patient status with only self-report information without a rheumatologist's advice (including joints and physical examination, and consideration of imaging and laboratory tests) may indeed be as undesirable for most patients than joint examination without a patient questionnaire. Conversely, combining the RAPID3 and the DAS28 may consist in faster or more sensitive confirmation that a medication is effective. Similarly, better enquiring of most important concerns of patients (pain, functional status and overall opinion on their disorder) should reinforces patients' confidence in their rheumatologist and treatments.

What is RAPID3 ?

The RAPID3 (Routine Assessment of Patient Index Data 3) score is the sum of three 0–10 patient self-report scores included in the rheumatoid arthritis (RA) core dataset (1-3): pain intensity on a 0–10 visual analogue scale (VAS); functional impairment of 10 activities on a Multidimensional Health Assessment Questionnaire score (MDHAQ), scored 0–3 for a total of 0-30, converted to 0–10; and patient global estimate, as rated by the patient on a 0–10 VAS. Scoring by a health professional requires 5 seconds.

This patient reported outcome (PRO) score thus ranges from 0 to 30, and can be used in all rheumatologic conditions, including ankylosing spondylitis (AS) and SLE (for which it is comparable to SLEDAI or BILAG) (2-3). In the initial development of RAPID3 (see references 4-5) indices with 2, 3, 4, or 5 measures were studied, which were termed RAPID2, RAPID3, RAPID4, and RAPID5; all scores were recalculated to 0–10, including RAPID3, so that all could be comparable. However, RAPID3 provided as much information as other versions, which also required more time to score. Indeed, conversion of a 0–30 RAPID3 score to 0–10 required an additional 5 seconds for a total of 10 seconds, which appeared unnecessary. Therefore, since 2008, a 0–30 scale has been advocated.

RAPID3 has been studied primarily in rheumatoid arthritis (RA), to complete physician's assessment of the activity/severity of the disorder. RAPID3 cutoffs indicating low (<6/30) or high levels (>12/30) of RA activity have been defined (5-6), as well as changes indicating significant improvements (>3.6/30) (7). RAPID3 has therefore gained acceptance, even as an evaluation tool in various trials.

Limitations of DAS28 in daily practice

RA activity should not be restricted to tender and swollen joint counts, or the DAS28 score (even though this last score includes patient's global estimate). Indeed, DAS28 is most widely used in clinical research and clinical trials in RA (8), but includes several

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limitations, particularly for use in busy clinical settings.

First, whereas RAPID3 takes only 5 seconds, DAS28 is more time consuming, with a mean of 112 seconds (9). This partly explains why most visits of most patients with rheumatoid arthritis to most rheumatologists do not include a formal quantitative joint count (10-11).

Second, ESR (or CRP), which is the more weighted parameter in the DAS28 algorithm, can rise for other reasons than RA. This may lead to over-estimation of RA activity, especially in older patients and/or those who could not qualify for clinical trials because of their co-morbidities. Conversely, ESR (or CRP) is normal in 40% of RA even 10 and 20 years ago (12-13), so that CDAI is often a better measure than DAS28.

Third, although subjective measure often are considered less reliable than supposedly objective evaluations by the physician, a reappraisal of the objective nature of the clinical evaluation has shown that joint scores are far from completely reproducible (14-16), and are imperfectly correlated with gold-standard like ultrasound (17). In fact, other studies concluded that patient questionnaire scores are more reliable than joint counts (18), or showed that joint count measures are more likely to improve with placebo treatment than patient reported outcome tools (19). It could also be recalled that in DAS28 all joints are equally weighted (while synovitis of a knee or ankle is usually much more severe and bothersome than synovitis of an inter-phalangeal joint, and involvement of shoulders, hips, and knees is as prognostic of mortality as 28 joints (20)).

Fourth, DAS28 is mostly a doctor-reported outcome (DRO), which does not include global pain and function, when patient's perception of his/her disorder may be somewhat different, leading to disagreement between the two, especially when estimating the efficacy or risk-toxicity ratio of treatments. For example, the practice-based DUO study showed that DMARD intensification was predominantly based on PROs compared with DROs, most RA patients with DAS28 >3.2 preferring not to experience DMARD intensification (21). Likewise, other reports on discordances between patient global and doctor global estimates have been recently published (22).

Fifth, DAS28 is directed to be performed by the same physician at each visit, leading to limitations in tight monitoring when that physician is not available. Pooled and averaged data from clinical trials can also misleadingly lead to the conclusion that changes in the activity of rheumatoid arthritis (RA) between physician visits are very small and gradual. In fact, at the individual level, disease-activity peaks often occur, including short-term exacerbation of pain and disability, and perhaps long-term structural progression (23), despite apparent remission during visits. Those transient flares are often missed if patient follow-up only relies on DAS28 scores performed every 3 to 6 months. Closely spaced assessments could be achieved by providing patients with self-assessment tools like RAPID3 for use at home between visits to healthcare professionals (24-26).

Advantages of RAPID3

RAPID3 brings useful information to physicians, and complies with requests from the OMERACT groups who highlighted since 2002 the importance of incorporating the patient perspective into outcome assessment (27-28).

First, RAPID3 puts emphasis on patient's pain, which often is not quantitatively assessed by many rheumatologists, whereas it remains the main concern for patients (29). Indeed DAS28 in RA (as well as ASDAS in spondyloarthropathies (SpA)) mostly reflects the number of tender sites, and do not directly measure pain intensity, while a single joint can be painful enough to make a patient in *low disease activity* still disappointed by his treatment. This is one of the reasons why the subgroups of patients classified as responders are not exactly identical when using either DAS28 or RAPID3 (23, 30). All components of RAPID3 have an equal importance, and in a longitudinal study, mean variance was 1.72 for the VAS pain sub-score, *versus* 1.79 for the function sub-score, and 1.91 for the VAS global sub-score (25).

A second strength of the RAPID3 score is that it better reflects functional impairment and overall perception than do most other scores (31). RAPID3 also reflects the actual activity of RA more faithfully than the DAS28 in patient populations (24), as well as social consequences of RA. For instance, in patients combining RA and other musculo-skeletal co-morbidities, a low RAPID3 score probably indicates levels of work ability and quality of life as good (or even better) than those of patients whose DAS28 or BASDAI/ASDAS indicate a disease remission. RAPID3 (which includes MDHAQ) might also correlate more closely than does the DAS28 with subsequent functional outcomes and premature death (32).

A third strength of RAPID3 is that it has been shown in studies of the French ESPOIR early arthritis cohort that a RAPID3 score of ≤3/30 with 1 or 0 swollen joints (RAPID3≤3+≤SJ1) provides remission criteria comparable to Boolean (33), SDAI (Simplified Disease Activity Index), CDAI, and DAS28 remission criteria, in far less time than a formal joint count (34). It might also be recalled that patient questionnaire scores are more reproducible than formal joint counts (14-16, 35).

A fourth strong point of RAPID3 is that, as also observed for other PROs (36), it performs as well as the DAS28 in separating active drugs from placebos in clinical trials (37-38). This is not surprising since: 1-the individual measures do better than composite indices in groups (not individuals) to distinguish active from control treatments; 2-RAPID3 score correlates well with the DAS-28, Simplified Disease Activity Index (SDAI), and Clinical Disease Activity Index (CDAI) (24). RAPID3 also predicts subsequent structural disease progression (39).

Fifth, as already emphasised, a main strength of RAPID3 is its simplicity. RAPID3 requires 5 seconds and can be computed without blood tests or a physician's assessment. Consequently, RAPID3 can be determined at short intervals (weekly (25), or monthly (26)), if needed. Closely spaced RAPID3 collection by the patients at home, currently restricted to clinical research, would allow closer monitoring (6, 30)

of RA (and SpAs) via the determination of the area under the curve of disease activity between two visits (40). Regular self-evaluation using RAPID3 may also ensure prospective flare detection (41), although other approaches (questionnaire completed during physician visits) have been suggested to identify transient flares retrospectively (42). In a past longitudinal weekly self-assessment of 26 RA patients at home during a 6-month period with the RAPID3 score, each of the 26 patients had a difference between the highest and lowest RAPID-3 values during the study period that was considerably larger than 1.2/10 (25) (which is the difference previously defined as clinically significant) (2). The differences between the highest and lowest RAPID3 values ranged from 1.6/10 to 5.5/10, and the mean difference was 2.95±0.71. Furthermore, several patients had RAPID3 score changes greater than 2.5/10 from one week to the next. Rather similar fluctuations were found by Walter *et al*. who asked Dutch RA patients to self-assess monthly (26). As in the previous study (25), most fluctuations improved to earlier levels spontaneously, so that self-assessment of RAPID3 were of limited value to predict DAS28 scores during visits in individual patients (26). However, filling RAPID3 scores on a regular basis might help patients better recall past peaks of RA, and could give physicians a better overview of the real activity of the arthritis during the period between two visits. Even transient flares are indeed a concern for many patients, and fluctuations of RA activity could impact the long term prognosis of RA, especially in the youngest. Indeed, a previous *post-hoc* study showed that RA patients with habitually moderate DAS28 scores and transient peaks in disease activity had similar levels of structural damage to those seen in patients with higher but stable DAS28 scores at all assessments (43).

A sixth advantage of RAPID3 might be the counterpart of its poor specificity. Indeed, RAPID3 could be used in all rheumatic diseases (and/or other conditions responsible for pain and functional impairment), allowing comparative studies of its values in various settings (44). After adjustment on age, sex, and other co-morbidities, such studies could help and position the impact of various disorders (*e.g*. fibromyalgia, SpAs, systemic diseases like SLE, and osteoarthritis) on health status as perceived by the patients. RAPID3 may also provide a means of comparing patient acceptable symptom state levels according to age and in various disorders, since they may vary from one condition to the next. Conceivably, the treatment costs that patients or society would be willing to accept to obtain a predefined RAPID3 score improvement (willingness to pay) may also vary across diseases and ages, but other generic instruments have been considered as (much) more appropriate than RAPID3 for that purpose.

RAPID3 also has limitations

The first weakness of RAPID3 is the incomplete accuracy of the MDHAQ score for evaluating the impact of rheumatic diseases on patients' life. Other activities may be better weighted in by scores like RAID for RA, although this has not yet been demonstrated in routine care (45).

The second limitation of the RAPID3 is its subjective nature, and the possible influence of physicians, relatives, or patient's mood on the scoring (although this last prejudice has been challenged) (25). However, this might also be a strength, when other scores like DAS28 underestimate RA activity (for instance severe pain or limitation due to synovitis of a single ankle in patients with DAS28 <2.6).

The third limitation of RAPID3 is the inter-individual variability in patient self-evaluation of disease activity and pain intensity. Consequently, for a given level of either, some patients with RA may overestimate, and others may underestimate their pain and/or the activity of their disease. Even in populations of healthy individuals, it has been shown that RAPID3 values could vary a lot across individuals (46). Values of RAPID3 are also higher in females (46). However, variability similarly impacts so-called *objective* scores like DAS28, and this inter-individual variability is somewhat overcome by the fact that patients are their own controls. Those inter-individual variations in quoting or experiencing pain and limitations could be kept in mind when using the cut-offs for low disease activity (<6/30) or high disease activity (>12/30), moreover, as the accumulation of musculoskeletal abnormalities with advancing age contributes to the increase in RAPID3 scores for other reasons than RA or SpA (46). The same holds true for the cut-offs uses for other scores like DAS28, which partly explains why no adjustment to achieve clinical remission was made in most of the 37.5% of 4,037 Australian RA patients with DAS28-ESR over 3.2 recently seen by their rheumatologists (47).

Lastly, limitations of RAPID3 include the need for appropriate translation and adaptation to various cultural contexts, as well as issues linked to patient functional and actual illiteracy.

RAPID3 (DRO) does not aim to substitute DAS28 or AS-DAS (PROs) but to synergise with them

In the same way as biologics synergise with classical DMARDs, PROs like RAPID3 should not be seen as a substitute to DROs and face to face visits. Monitoring patient status with only self-report information without rheumatologist's advice (including joints and general physical examination and consideration of imaging and laboratory tests) may indeed be as undesirable for most patients than joint examination without a patient questionnaire (48). Moreover, a discussion with patients is required to interpret RAPID3 scores (48): indeed some fluctuations are sometimes best explained by unusual exhausting activities than by transient RA flares.

In fact, RAPID3 should rather be seen as a very useful complement of DAS28 (or ASDAS for SpA), both for transversal of longitudinal studies/assessments. For instance, although the DAS28 usually plateaus within the first 6 months of treatment with a disease-modifying anti-rheumatic drug combined with a biologic agent, the RAPID3 score can continue to improve significantly until month 24, regardless of the biotherapy used (49). Another advantage of combining the RAPID3 and the DAS28

may consist in faster or more sensitive confirmation that a medication is effective, which would allow the inclusion of fewer patients, thereby decreasing study costs (9, 30).

Other contributions of RAPID3 assessment can still be expected (50). Indeed, better enquiring of most important concerns of patients (pain, functional status and overall opinion on their disorder) should reinforces patients' confidence in their rheumatologist and treatments. RAPID3 scoring might even have a positive influence on treatment compliance. Finally, RAPID3 could also remind busy physicians that besides DMARDs and/or biologics, other treatments can be felt as very helpful by patients, including painkillers, anti-inflammatory drugs (or very low dose prednisone (51-52)) and local injections of steroids. They should not be seen as outmoded weak competitors of recent DMARDs/biologics, but rather as stooges of our modern therapeutic armamentarium.

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