RADAI-5 and electronic monitoring tools

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ABSTRACT

Tighter monitoring of patients is regarded one of the key approaches to improve management of rheumatoid arthritis (RA). It could be demonstrated that the patient relevant disease course is not simply the linear link between two observation points, but fluctuates significantly in up to 80% of patients surveyed three times over two months, which understandably compromises quality of life. Patient self-report questionnaires such as the Rheumatoid Arthritis Disease Activity Index-Five (RADAI-5) have been shown to provide reliable information about disease activity, functionality, and other important aspects of daily life. The internal consistency of such questionnaires was shown to be significantly higher than the one of the DAS28 or the CDAI. Innovative electronic tools can be easily foreseen to constitute the media to enhance the dialogue between healthcare professionals and patients to improve disease care.

These tools collect patient-recorded outcomes (PROs) data, through which physicians can monitor the course of the individual disease. Electronic versions can enable patients to receive additional medical attention between visits and provide a more detailed record of disease course over time.

Applying the RADAI-5 or other questionnaires in electronic assessment tools will allow for the individual assessment of health levels, well-being, joint pain and the quality of life. Such tools will enable more frequent patient monitoring, with the potential to improve the patient's situation as well as to enhance physicians' time management, and to prioritise patients who may need further attention.

Introduction

Inflammatory rheumatic diseases such as rheumatoid arthritis (RA) are chronic progressive diseases, which, in the absence of adequate treatment, lead to serious functional deficiencies, work disability, and premature mortality (1). Irreversible damage may occur within a short time, and early diagnosis and treatment are needed. (2-4). There has been a paradigm shift to adapted early-aggressive treatment of arthritis, with a goal of therapeutic efforts to achieve remission, which also may be defined as a symptom free status (5, 6).

Tighter monitoring of patients is regarded one of the key measures to improve management of inflammatory arthritis (7). In 2015, a group of Austrian rheumatologists demonstrated that the patient course in RA usually is not a simple linear link between two observations, but fluctuates in up to 80% of patients, in about the half remarkably, surveyed three times over two months. The resulting unpredictability of patients' daily situation compromises quality of life (8). Similar observations have been reported recently for spondyloarthritis (SpA) patients by a Dutch group, which observed relevant changes might be missed without frequent monitoring between visits (9).

A tight control or treat-to-target (T2T) management strategy has become the standard of care for rheumatic diseases. Integral to this principle is that disease activity is measured regularly, and therapy is adjusted accordingly to achieve or maintain the target agreed to in shared decisions between the physician and the patient (10, 11). T2T in rheumatic disease utilises composite disease activity indexes such as the disease activity score (DAS), or including a 28 joint count (DAS28) (10). Most of the widely used indexes do not record patients' wishes, beliefs, fears, coping mechanisms, or gains. Furthermore, patient's assessment has been shown to exert lesser importance on the final result of the DAS28 and the SDAI than the joint counts or physician's assessment but more than acute phase reactants (12). However, querying patient variables regularly contributes to ap-

proaching the true target, namely the best possible individual outcome. Such information may be captured optimally by querying and listening to the patient, which can be carried out feasibly by collecting patient related outcomes (PROs) (13). Instruments such as the Routine Assessment of Patient Index Data 3 (RAPID-3) on a multi-dimensional health assessment questionnaire (MDHAQ), or the Rheumatoid Arthritis Disease Activity Index-Five (RADAI-5) have been shown to provide reliable information about disease activity, functionality, and other important aspects of daily life (14, 15). The internal consistency of the RAPID-3 and RADAI-5 was shown significantly higher than the one of the DAS28ESR and the CDAI (16).

Moreover, the patient's perspective with respect to improvement or worsening of RA status has been shown to be discordant with the physicians' perspective in many cases. Patients often require greater improvement to be satisfied and less deterioration to be dissatisfied (17, 18), which provides additional guidance for application of PROs to assess response and non-response in RA.

The RADAI-5

The food and drug administration (FDA) defined PROs as follows: "*A patient-reported outcome is any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else*". Thus, PRO variables are for instance pain, quality of life, medical care, coping mechanisms, subjective health status, physical activity and working ability (19).

The RADAI-5 is a short and easy to complete questionnaire containing five items in a numerical rating scale format from 0 to 10. The respective questions are "How active was your arthritis the last six months?" (0 = completely inactive to 10 = extremely active), "How active is your arthritis today with respect to joint tenderness and swelling?" (0 = completely inactive to 10 extremely active), "How severe is your arthritis pain today?" (0 = no pain to 10 unbearable pain), "How would you de-
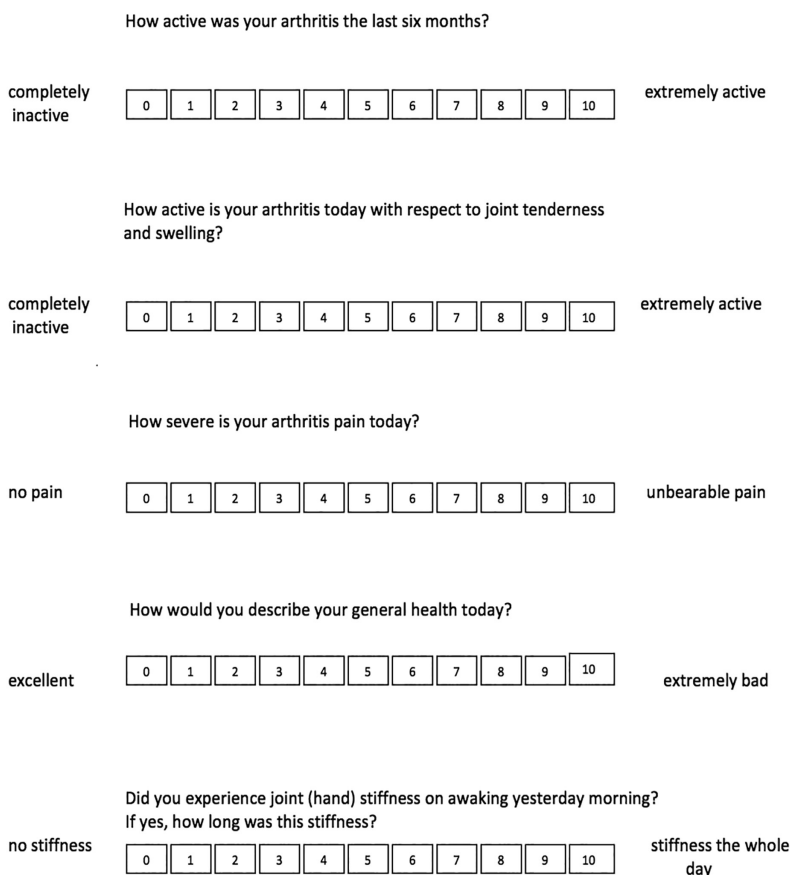

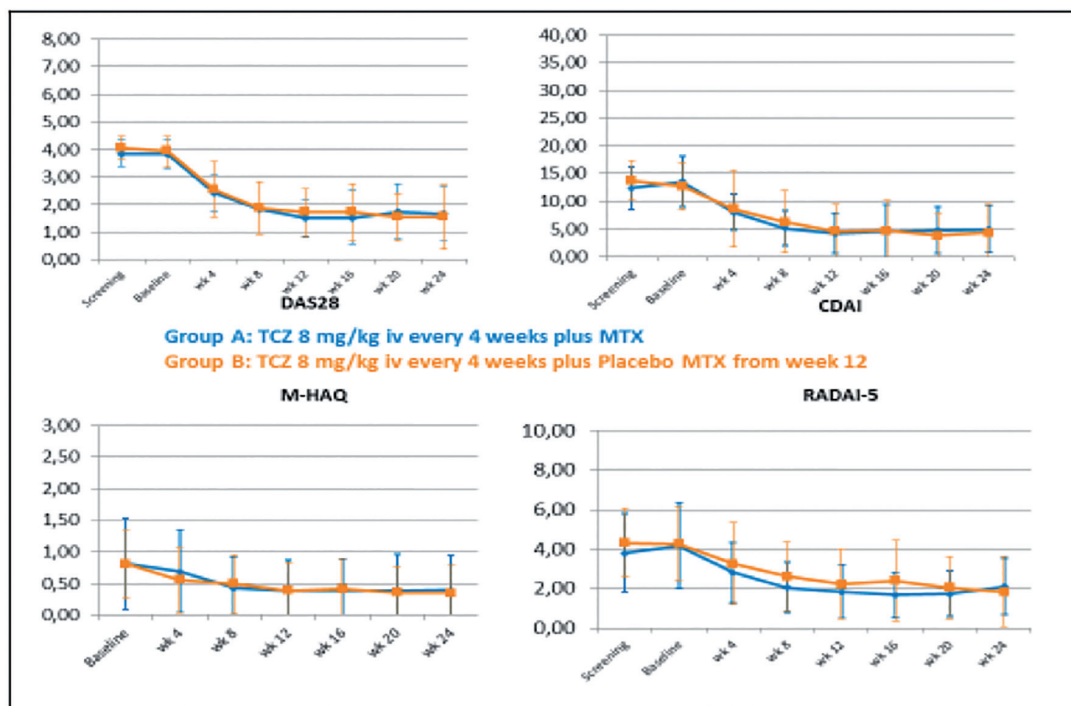**RADAI-5**

Fig. 1. The RADAI-5 questionnaire (12).

scribe your general health today? (0 = very good to 10 = very bad), and "Did you experience joint (hand) stiffness on awaking yesterday morning? If yes, how long was this stiffness?" (0 = no stiffness to 10 stiffness the whole day). The final result can be easily calculated: (Q1 + Q2 + Q3 + Q4 + Q5)/5 (15). Ease of calculation is of lesser importance in case of electronic assessment tools (see Fig. 1).

The single questions are intended to target different disease variables. Question one strongly relates to the dimension of time more than to the exact time in the individual course of an RA patient as many studies suggest that asking about "6 months" is not always interpreted accurately by many patients. Question two directly covers joint involvement, while question three queries pain, which is known to be a critical determinant of most patients' wellbeing and functionality (20). Question four, queries the patient's general health,

also targeting co-morbidities as well as coping strategies, while question five queries stiffness, relevant to physical activity, and working capacity,

Tender joint counts (TJC), swollen joint counts (SJC), and physician's global assessment (PhGA) were found to be highly statistically significantly correlated to the RADAI-5 (rho=0.747; $p<0.001$ for TJC; rho=0.598; $p<0.001$ for SJC; rho=0.603; $p<.001$ for PhGA), while no significant relationship could be found with the ESR and CRP values (15).

Factorial analysis according to principal component indicated that RADAI-5, as other PROs such as the RAPID-3, is a mono-dimensional instrument. The respective Eigenvalue was 3.65 for the RADAI-5, indicating that all questions contribute significantly and well-balanced to the final result, as the average item loading for the RADAI-5 was 0.849 ranging from 0.775 to 0.934. While the DAS28-ESR

Fig. 2. Course of the DAS28, the CDAI, the M-HAQ, and the RADAI-5 in the OPTI-MISE trial (24).

Group A: TCZ 8 mg/kg iv every 4 weeks plus MTX
Group B: TCZ 8 mg/kg iv every 4 weeks plus Placebo MTX from week 12

Fig. 3. The RADAI-5 (German version) as part of the iMonitor (with permission).

also proved to be, a mono-dimensional instrument in the resepctive patient cohort, the CDAI was found to be bi-dimensional (16).

In a recent review, the four PROs with the most extensive validations and strongest levels of evidence were: Pt-DAS28, RADAI, RADAI-5 and RAPID-3. The RADAI-5 in particular was shown to have the highest internal consistency of all instruments investigated, as expressed by a Cronbach's alpha of 0.91 to 0.92 (21).

The questionnaire's structural validity, and also its hypothesis testing were taken into account positively, while, like with other PROs, its cross-cultural validity, and its responsiveness were regarded not fully proven. In the meantime the RADAI-5 was applied in the OPTIMISE-trial (a multicentre study of the safety and effect on disease activity of tocilizumab (TCZ) in combination with methotrexate (MTX) *versus* TCZ monotherapy in patients with mild to moderate rheumatoid arthritis, with inadequate response to MTX [defined as DAS 28 (<4.5 and >2.6)], and performed in a parallel way compared to composite scores and the Health Assessment Questionnaire (see Fig. 2) (22).

Regarding cross-cultural validity, it should be noted that such properties have not been proven for any instrument yet, however, the RADAI-5 and the SJC were found to be the independent variables of disease activity associated with sexual dysfunction in Moroccan women with RA (23).

The RADAI-5 appears well-suited for use in assessment as an electronic monitoring tool. One approach is to provide coloured flags including red or yellow flags enabling alerts classifying RA-patients who require particular attention. A remission like state would be indicated by a green flag, mild disease by a yellow flag, moderate as well as high by a red flag, for urgent action as soon as possible. The thresholds for patient classification are: 0.0–1.4 for remission-like, 1.6–3.0 for mild disease activity, 3.2–5.4 for moderate and 5.6–10.0 for high disease activity (20). Electronic assessment tools aim to provide the physician with alerts, such as thresholds for improvement and worsening were elaborated (improvement >1.7, worsening >1.5). Since the RADAI-5 is expressed by a number with an even first decimal, it was decided, that changes in disease activity should be expressed by a number with an odd decimal to avoid misinterpretation of the result. In one study DAS28- and RADAI-5 improvement proved to be significantly correlated (24). More recently, these thresholds could be provisionally validated by analysing data from BioReg, the Austrian registry for biological treatment in rheumatology (25).

In 2011 the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) defined remission in rheumatoid arthritis for clinical trials. A study in a daily routine setting was performed to assess whether the RADAI-5 remission criterion meets ACR/EULAR remission definitions (26). Remission according to the RADAI-5 had a positive predictive value (PPV) of 45% and a negative predictive value (NPV) of 96% indicated remission according to the Boolean based-definition, while the values were 66% PPV, and 90% NPV respectively for also indicating remission according to the SDAI-based definition. Kappa statistics show fair to good agreement for all three definitions (26).

An electronic RADAI-5

In times of shrinking resources, innovative electronic tools can be easily foreseen to constitute media to enhance dialogue between healthcare professionals and patients to improve disease care. The tools, and there are various remote monitoring tools for inflammatory arthritis in use or being developed, aim to reduce the number of direct consultations between healthcare professionals and patients and, empower patients by encouraging them to take an active role in their disease management (27, 28). These tools collect patient-recorded outcomes (PROs) data through which physicians can monitor the course of the individual disease. Doing so enables patients to receive additional medical attention between visits and provides a more detailed record of their disease course over time. In case the PROs' values exceed pre-specified thresholds, the tool alerts the physician enabling immediate adaption of therapeutic measures in patients whose disease course is unfavorable and therefore require particular attention.

The RADAI-5 such as other questionnaires provides an advantage that the patient is given the key role in activity assessment. Moreover, inter-physician variations in assessing joints or global disease activity are avoided (15). Application of RADAI-5 or other questionnaires in electronic assessment tools will allow for the individual assessment of health levels, well-being, joint pain and the quality of life, which are known to be still quite variable in many patients even within a short timeframe of about two months (8). Because of disease fluctuations, predictions of health levels, personal well-being, joint pain as well as the quality of life for the individual patient remain in need of improvement. This of course has major consequences for the individual patient; even planning of activities for the nearest future could be a hard task for the patient (8). These capacities will stimulate further development of such tools, in addition to shrinking personal and financial resources for both physicians and patients. However, the ideal frequency of monitoring visits has not been elucidated yet, too frequent monitoring may result in spurious changes that may not be indicated. Such studies have to be unquestionably part of the research agenda with respect to electronic monitoring tools.

Electronic remote monitoring tools can offer additional data to support clinical decision-making, and may improve the quality of care by effective doctor-patient communication without traveling and waiting times. The patients as well as health professionals may choose their time to deal with the monitoring tool (27). For rheumatologists, such instruments provide the advantage of supporting tight control, based on a rationale for tight disease control to prevent symptoms, recognise complications early, and maintain functionality. Such monitoring tools comply with the KISS (keep it simple, stupid) principle with the overall goal to be practical to

use, and they should be as fully automated as possible in order to spare personal and financial resources.

A recent study revealed that manual deficiencies in RA patients do not constitute a barrier for the use of mobile applications (29). The simpler the questionnaire, the fewer problems for patients, and RADAI-5 meets these goals. Remote data entry has been shown to be regarded comfortable by the majority of 153 patients with RA, systemic lupus erythematosus, or SpA, and the results did not differ from the ones obtained by completing a sheet of paper (29).

Electronic patient monitoring tools are meanwhile well accepted in many chronic diseases, such as diabetes, and congestive heart failure; they have already found their way into rheumatology, where different instruments are available. The RADAI-5 was incorporated aside other questionnaires, and a pat-DAS28 into the iMonitor, an instrument applicable in RA and SpA patients (see Fig. 3) (28).

Concluding remarks

As individualised treatment strategies become increasingly important, such electronic assessment tools may provide substantial advantages in identifying patients requiring particular attention. Applying the RADAI-5, and its derivative for psoriatic arthritis, the SASPA (Stockerau Activity Score for Psoriatic Arthritis) can be regarded a substantial step forward in this respect as these instruments are capable of expressing great parts of the patient's perspective of the disease process (15, 30). Stable low RADAI-5 values are indicators of an uncomplicated disease course, as it is the case with other instruments. A remission-like state, and above all a stable remission according to the RADAI-5, definitely indicate different, incremental information from remission according to the DAS28 or CDAI, as question one includes the dimension of time, as a result meeting the RADAI-5 remission-like state cannot be expected after a short time period (15).

No single measure can serve as a "gold standard" in diagnosis and assessment of individual patients with most rheumatic diseases (31). The RADAI-5 questionnaire constitutes one easily applicable option for routine RA monitoring, which enables physicians to get reliable information about the disease course and is sensitive enough to sound the alarm if deteriorations occur (15). Clinical rheumatologists feel necessity need for tighter patient monitoring, to improve the outcome of the disease without increasing pressure on specialists. Furthermore, better information concerning disease course, which is far more than just the linear path between two consecutive observation points (8, 9, 13), will greatly improve documentation. Such tools doubtlessly will enable more frequent monitoring with the potential to improve a patient's situation, to support physician time management, to prioritise patients who may need further attention, and contribute to better public health for the society and improve patient outcomes.

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