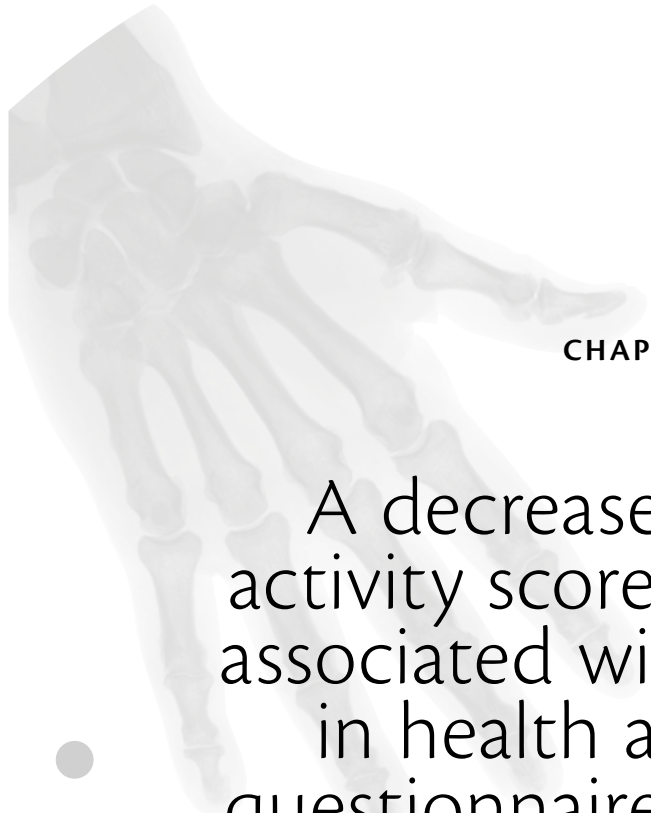

CHAPTER 5

A decrease in disease activity score (DAS) level is associated with a decrease in health assessment questionnaire (HAQ) score, independent of follow-up duration

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ABSTRACT

Objective: To assess the relationship between a decrease in disease activity score (DAS) and functional ability during 5 years of DAS-steered treatment in recent-onset rheumatoid arthritis (RA) patients, taking into account absolute DAS levels and follow-up duration.

Methods: Data from the BeSt study were used, in which treatment was aimed at achieving DAS ≤2.4. The longitudinal relationship between 3-monthly measured DAS and health assessment questionnaire (HAQ) score was assessed using linear mixed modelling during 5 years of treatment, with DAS and HAQ 3 months earlier, change in DAS in last 3 months (delta DAS), time (log-transformed) and their interactions as determinants.

Results: Predictors for HAQ were: previous DAS, delta DAS, ln time, the interaction previous DAS*delta DAS, and previous HAQ. The interaction ln time*delta DAS was non-significant, indicating that the association between delta DAS and HAQ was independent of follow-up duration. A decrease from a higher DAS was associated with a smaller HAQ decrease than for a similar decrease from a lower DAS, indicating a non-linear relationship between DAS and HAQ.

Conclusion: At any time during 5 years of follow-up, a decrease in DAS was associated with a better functional ability. The magnitude of HAQ improvement depends on the DAS decrease and on the absolute DAS level.

INTRODUCTION

The introduction of (combinations) of disease-modifying antirheumatic drugs (DMARDS), corticosteroids and biologicals early in the disease course has improved the clinical and radiological outcomes of rheumatoid arthritis (RA) patients considerably.[1–6] Further improvement has been made by treating patients according to a predefined target and adjusting therapy until that goal is reached.[7,8].

An frequently used tool for treating to target is the disease activity score (DAS) and its simplifications, originally developed to compare treatment outcomes in clinical trials.[9] The DAS can be used as a tool to guide treatment decisions in individual patients.[7]

Furthermore, it is known from previous research that the DAS is related to the functional capacity of RA patients.[10–12] It remains unclear whether actively aiming at a decrease in DAS will, independent of follow-up duration and even if the DAS level is already low, results in improvement in functional ability. Therefore, the objective of this analysis was to assess the association between a change in DAS and functional ability (as measured with the health assessment questionnaire (HAQ)) during 5 years of DAS-steered treatment in patients with recently diagnosed RA, while taking into account the absolute level of disease activity and follow-up duration.

PATIENTS AND METHODS

We used 5-year follow-up data from a cohort of 508 patients with active RA, all fulfilling the American College for Rheumatology (ACR) classification criteria for RA[13] and a disease duration ≤2 years, treated with the aim of achieving low disease activity.[14] Treatment adjustments were made based on 3-monthly DAS calculations done by a research nurse blinded for treatment allocation. If the DAS was >2.4, the rheumatologist adjusted medication according to the previously described protocol per treatment arm.[14] If the DAS was ≤2.4 for at least 6 consecutive months, medication was tapered until monotherapy at a low maintenance dose was achieved. Once this was done, and if DAS was <1.6 for at least 6 consecutive months, the last medication was tapered and stopped, but restarted again as soon as DAS was ≥1.6. Functional capacity was measured every 3 months using the Dutch version of the HAQ.[15] A decrease in HAQ of at least 0.22 is considered to be a clinically meaningful improvement.[16]

Statistical analysis

A linear mixed model (LMM), which combines multiple measurements per patient, uses all available data during follow-up, takes into account missing values and corrects for within-patient correlation, was used to assess the longitudinal relationship between DAS and HAQ. Twenty follow-up measurements of HAQ per patient, collected during 5 years follow-up, were used as outcome.

The DAS 3 months earlier (previous DAS), the change in DAS in the preceding 3 months (delta DAS), and the time since baseline (log-transformed to approach linearity) were

added to the model as explanatory variables, as well as the two-way interactions previous DAS*delta DAS, delta DAS*ln time and previous DAS*ln time and the three-way interaction previous DAS*delta DAS*ln time. The previous HAQ (3 months earlier) was added to the model (first order autoregression) to model change in HAQ rather than absolute HAQ scores. This allows a longitudinal interpretation of the data (ie, a change in DAS is associated with a change in HAQ) rather than a cross-sectional interpretation (patients with a high DAS have on average high HAQ). The following potential confounders were added one by one: treatment strategy, baseline body mass index (BMI), age, sex, symptom duration, anti-citrullinated peptide antibody (ACPA) status, rheumatoid factor (RF) status, baseline C-reactive protein (CRP) and Sharp-van der Heijde Score (SHS) at baseline and in the following years. As well as the variables described above added as fixed effects, two random effects were added (random slope with ln time and a random intercept) to correct for between-patients variance. The covariance structure with the lowest Akaike value was used (unstructured), that is, the covariance structure that fitted the model best, while taking into account the number of estimated parameters. SPSS version 16.0 (SPSS Inc., Chicago, Illinois, USA) was used for the analyses.

RESULTS

In the first LMM with all covariates and interactions, the three-way interaction previous DAS*delta DAS*ln time was not significantly associated with HAQ (p=0.25) and hence omitted from the analysis. In the next analysis the covariates and two-way interactions were added one by one. The previous DAS, delta DAS, ln time, and the previous HAQ significantly predicted HAQ *(table 1)*. Furthermore, the two-way interaction previous DAS*delta DAS was significantly associated with HAQ, indicating that the association with delta DAS depends on the absolute level of DAS and that there was a non-linear relationship between DAS and HAQ. The two-way interaction delta DAS*ln time showed no significant association, indicating that the relationship of delta DAS with HAQ was not dependent on the progression of time since the start of treatment. Treatment strategy, sex, baseline BMI, age, symptom duration, ACPA, RF, CRP and SHS and SHS in the following years did not change the ß values nor the p values of the variables of interest (data not shown) and were therefore excluded from the analysis. The regression formula to predict the next HAQ is as follows:

Outcome HAQ = -0.037 + (0.044*ln time) + (0.213*previous DAS) + (0.183*delta DAS) + (0.022*previous DAS*delta DAS) + (0.234*previous HAQ) + [corr] + error

in which the regression coefficients of the LMM *(table 1)* are filled in and [corr] represents the correction for random patient effects (mean zero). To visualise the effect of this formula, a matrix was constructed, showing the estimated improvement in HAQ for various levels of DAS, delta DAS, and previous HAQ at different time points *(figure 1)*. Clinically significant HAQ improvements are shown in dark grey boxes, clinically non-significant HAQ improvements in white and less common or impossible combinations of variables (for instance DAS decrease more than previous DAS) are shown in

TABLE 1 Linear mixed model (LMM) results of predictors of outcome HAQ during 5 years of DAS-steered treatment.

Variable	ß	95% CI	Explained variance* (%)
Ln (time)	0.044	0.031-0.057*	20
Previous HAQ	0.234	0.213-0.255*	20
Previous DAS	0.213	0.200-0.226*	28
Delta DAS (current DAS – previous DAS)	0.183	0.166-0.200*	37
Previous DAS*delta DAS	0.022	0.016-0.027*	37

DAS, disease activity score; HAQ, health assessment questionnaire; ln (time), natural logarithm of time since baseline; LMM, linear mixed model.
The intercept is -0.037 with a p-value of 0.15 ß represents results of final multivariable LMM. In the right-hand column the increasing explained variance of the model is given (compared to a LMM with only a random intercept), by adding first a random slope with ln time (explained variance 18%), and then one by one variables as shown in the table.
*p<0.05.

'lighter grey. The matrix illustrates the positive association between delta DAS and HAQ, indicating that with a larger decrease in DAS, the outcome HAQ will be lower. This positive relationship did not change significantly during 5 years follow-up. The model also shows that a decrease in DAS resulting in a still high DAS has less impact on improving

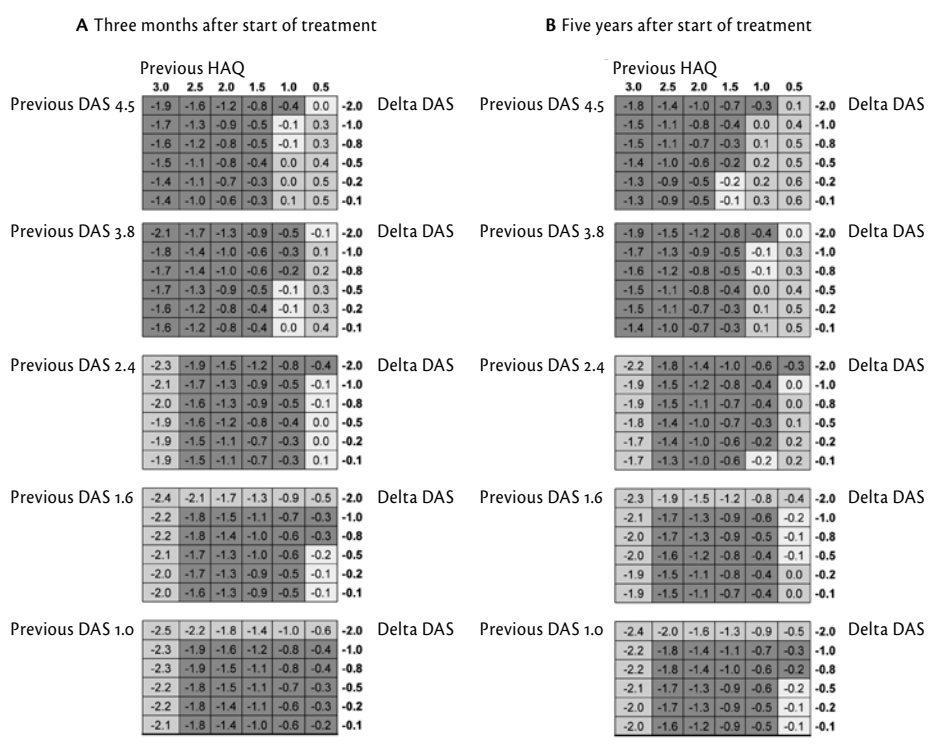

FIGURE 1 Matrix representation of predicted health assessment questionnaire (HAQ) score improvement after 3 months (A) and after 5 years of follow-up (B) based on HAQ and disease activity score (DAS) 3 months earlier, and change in DAS in the 3 preceding months. Clinically relevant HAQ decrease of ≥ 0.22 are shown in dark grey, smaller decreases in white, combinations that are unlikely to occur in real life (HAQ-DAS discrepancies) in lighter grey.

HAQ than a similar decrease resulting in a low DAS, given a similar previous HAQ. To illustrate, at DAS 4.5 and HAQ 1.5, a subsequent DAS improvement at 3 months of 1.0 was associated with a HAQ improvement of 0.5, whereas at DAS 2.4 and HAQ 1.5 the estimated HAQ improvement was 0.9.

DISCUSSION

This study shows that during 5 years of DAS-steered treatment in patients with recent-onset RA, a decrease in DAS is associated with a decrease in HAQ. The magnitude of HAQ improvement depends on the size of DAS decrease and on the absolute DAS level, but the DAS-HAQ association is independent of follow-up duration during 5 years. There appears to be no 'lowest optimum' for the DAS, since further lowering the residual disease activity, is likely to further decrease the HAQ and potentially improve the patient's functional ability, unless there is little to gain.

The matrix based on the prediction formula derived from the linear mixed model illustrates the relationship between DAS, previous DAS, delta DAS, time and HAQ, and its interactions. It shows how a change in DAS results in a change in HAQ, taking into account time since baseline and absolute HAQ level.

By showing the relationship between DAS and HAQ in a DAS-steered treated cohort, our results expand on several previous studies in non-DAS steered cohorts.[11] Welsing, et al.[12] showed that the positive relationship between DAS and HAQ could no longer be observed after 9 years, possibly due to an increasing impact of joint damage on HAQ over time. We demonstrated that the positive association between DAS and HAQ in our cohort remains stable during 5 years of follow-up and we propose that this association might remain longer since the amount of joint damage is limited.[17] Longer follow-up time would clarify this issue. We observed no deterioration of functional ability during 5 years of follow-up, in contrast to earlier studies in which the HAQ worsened after 3-6 years.[10,12]

As demonstrated by the BeSt study inclusion criteria[14], the patients included in this analysis probably have more severe RA than 'the average' new RA patient would have, especially when the new 2010 ACR/European League Against Rheumatism (EULAR) classification criteria for RA are applied.[18] Since we showed that a decrease in DAS from a lower DAS level has more impact on HAQ than a similar decrease from a higher DAS level (given a similar HAQ three months earlier), we propose that these results underline the importance of aiming at lower disease activity, including in patients with milder disease.

Although various studies illustrate that DAS-steered treatment results in better outcomes than non-DAS-steered treatment, it appears that in daily practice old routines are difficult to change. Van Hulst, et al. found that rheumatologists adjusted medication only in one of three visits where disease activity was above target (67% of visits).[19] Our results argue against reluctance in treatment adjustments and clearly emphasise the importance to actively aiming to decreasing DAS.

In conclusion, our results may encourage physicians to adjust treatment to aim at a lower DAS in order to achieve better functional ability for their patients.

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