Worldwide treatment opportunities of rheumatoid arthritis

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CHAPTER 7

Further Treatment Intensification in Undifferentiated and Rheumatoid Arthritis Patients Already in Low Disease Activity has Limited Benefit towards Physical Functioning

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ABSTRACT

Background: It is recommended to optimize treatment as long as a predefined treatment target is not met. But should we aim at remission if patients are in low disease activity? The aim of this study was to assess if in rheumatoid or undifferentiated arthritis (RA, UA) patients with Disease Activity Score (DAS)≤2.4 (LDA) treatment intensification results in better functional ability.
Methods: In the IMPROVED study 610 patients with early RA or UA were treated with methotrexate + tapered high dose prednisone. After 4 months, patients with DAS≥1.6 were randomized to two treatment strategies. Patients with DAS<1.6 tapered treatment. Over 5 years, patients with DAS≥1.6 required treatment intensification, but protocol violations occurred, which allowed to test the effect of treatment intensification regardless of subsequent DAS. A linear mixed model was performed to test in patients in LDA the relationship between treatment intensification and functional ability (Health Assessment Questionnaire, HAQ) over time.
Results: The number of patients in LDA per visit ranged from 88 to 146. Per visit, 27% to 74% of the patients in LDA had a treatment intensification. We found a statistically significant effect of treatment intensification on ΔHAQ, corrected for baseline HAQ, age, gender and treatment strategy (β=-0.085, 95%CI -0.13;-0.044). When ΔDAS was added, the effect of treatment intensification was partly explained by ΔDAS and the association with HAQ was no longer statistically significant (β=-0.022, 95%CI -0.060;0.016). When the interaction between treatment intensification and time in follow-up was added, a statistically significant interaction was found (β=0.0098, 95%CI 0.0010;0.019), indicating lesser improvement in HAQ after treatment intensification if follow-up time increased.
Conclusions: For early RA and UA patients already in LDA, further treatment intensification aiming at DAS remission does not result in meaningful functional improvement.

BACKGROUND

In the past decades, the treatment of rheumatoid arthritis (RA) has considerably changed. Earlier treatment with disease modifying anti-rheumatic drugs (DMARDs) has resulted in a milder disease course, with better functional ability – as measured for example by the Health Assessment Questionnaire (HAQ)[1]– and less joint damage progression.[2, 3] One of the main aims of RA treatment is to achieve or maintain good physical functioning. In order to achieve this, it is recommended to start treatment early and regularly monitor disease activity and optimize treatment as long as a predefined treatment target has not yet been achieved ('treat-to-target' approach).[4] International recommendations state that at least low disease activity (e.g. DAS ≤ 2.4) (LDA), but preferably remission (e.g. DAS ≤ 1.6, or more stringent definitions), are the best treatment targets when treating RA patients.[5] Previous research has shown that a patient's functional ability is related to the level of DAS and, after prolonged disease activity, also to joint damage.[6-9] Moreover, a stronger decrease in DAS is associated with a stronger decrease in HAQ, even if DAS is already low.[10] However, it may be a patient characteristic rather than a further treatment intensification that determines how low a DAS and HAQ can be achieved. It has never been proved that intensifying drug therapy in patients who are already in LDA will result in further improvement in functional ability that is clinically meaningful. As treatment intensification may not always be effective in further lowering disease activity, and may come with potential side effects and costs, it is worthwhile to test the effect on functional ability of the effort itself, independent of the subsequent observed DAS outcome. Here we have assessed whether aiming for remission – and modifying or intensifying treatment accordingly – in patients who are already in LDA, results in further clinically relevant improvements in functional ability, irrespective of a subsequent change in DAS.

METHODS

Study design

The present study was an observational secondary analysis of data from the IMPROVED study. For this study, visits of patients in LDA (DAS >1.6 but ≤2.4) were selected at each time point of the original study and the effect of treatment intensification versus no treatment intensification on the change in HAQ observed at the next visit was analysed. The IMPROVED study is a multicentre, randomized, single-blind, two-step clinical trial in patients with recent-onset RA and UA. Patients were recruited between March 2007 and September 2010 from 12 hospitals in the western part of The Netherlands. Recent-onset RA was diagnosed according to the 2010 ACR/EULAR classification criteria, with

symptom duration ≤2 years.[11] UA was defined as arthritis in at least one joint and at least one other painful joint, clinically suspected by the rheumatologist to be early RA, but not fulfilling the 2010 criteria. The study protocol was approved by the Medical Ethics Committee of each participating centre and all patients gave written informed consent. A detailed description of the study has been reported previously.[12]
Patients were 'treated-to-target', aimed at DAS-remission (DAS <1.6), with assessment of disease activity every 4 months, during 5 years. Treatment was tapered and discontinued if DAS-remission was achieved and henceforth maintained. Treatment was restarted, changed or intensified (henceforth called 'treatment intensification') if DAS remission was not achieved or lost. The protocol required that all patients started induction therapy with methotrexate 25 mg/week for 4 months and a tapered high dose of prednisone, starting with 60 mg/day and tapered to 7.5 mg/day in 7 weeks. For patients in early DAS-remission (DAS <1.6 after 4 months), prednisone was tapered to 0, and if DAS-remission persisted after 8 months, methotrexate was also tapered to 0. If DAS was ≥1.6 after 8 months prednisone was restarted at 7.5 mg/day. In case of DAS≥1.6 after restarting prednisone, patients were randomized ("delayed randomization") to arm 1 or arm 2. Patients not in early DAS-remission were randomized either to methotrexate 25 mg/week + hydroxychloroquine 400 mg/day + sulfasalazine 2000 mg/day + prednisone 7.5 mg/day (arm 1) or a combination of adalimumab 40 mg/2 weeks + MTX 25 mg/week (arm 2). When patients did not achieve DAS-remission at 8 months, those in arm 1 were switched to adalimumab + methotrexate and for those in arm 2, the dosage of adalimumab was increased to 40 mg/week. For patients in both arms who achieved DAS-remission within 8 months, treatment was tapered to methotrexate monotherapy. If patients in both groups did not achieve DAS-remission with ADA 40 mg/week, further treatment was left to the opinion of the treating rheumatologist.
During the follow-up of the IMPROVED study, several protocol violations occurred and were monitored every four months. If treatment was not intensified in patients who were in LDA, this was registered as a protocol violation. In the current article, subsequent changes in functional ability for patients in LDA (DAS >1.6 but ≤2.4) were compared, who did or did not have a protocol violation (no treatment intensification versus treatment intensification), which allowed us to investigate the effect of treatment intensification on HAQ change.

Statistical analysis

Functional ability was measured every 4 months using the Dutch version of the Health Assessment Questionnaire (HAQ).[13] A change in HAQ score ≥0.22 in a patient is considered clinically relevant.[14] At each time point, all visits where patients were in LDA (DAS ≤2.4 but >1.6) were selected. Thus, the number of included visits could differ per patient. Visits of patients in LDA with treatment intensification (according to protocol)

and without treatment intensification (protocol violation) were compared. Differences in HAQ and DAS at each visit compared to the next visit were calculated (ΔHAQ and ΔDAS, i.e. Y{t+1} – Y{t}), and a negative ΔHAQ or ΔDAS implies improvement. Linear mixed model analyses with random intercept were performed to test the relationship between treatment intensification and ΔHAQ over time, taking into account the correlation of visits within a patient. Models were fitted using restricted maximum likelihood. For each model it was tested whether allowing a random slope improved the fit of the model. If not, it was tested which covariance matrix for within-cluster residuals gave the best fit of the model. Three models were fitted and each model was adjusted for the possible confounders follow-up time, baseline HAQ, age, gender and treatment arm. In the second model, additionally, the effect of ΔDAS on the model was tested. In the third model the interaction effect between change in treatment and follow-up time was added. All analyses were performed using STATA SE version 14 (StataCorp LP).

RESULTS

Over a period of 5 years, both DAS and HAQ showed statistically significant improvement across all patients included in the original study [mean (SD) baseline HAQ 1.2 (0.7), ΔHAQ -0.59, 95% CI -0.61, -0.57; mean (SD) baseline DAS 3.2 (0.9), ΔDAS -1.77, 95% CI -1.79; -1.75]. In 69% of the patients the change in HAQ was clinically meaningful (≥0.22).
The number of patients in low disease activity ranged from 88 to 146 per visit, of which 26% to 73% did not get treatment intensification, with an increase in such protocol violations towards the end of study (online supplementary file 1). In total, 482 patients were in low disease activity at one or more visits where there was information available regarding medication use as well as a follow up visit, resulting in a total number of 1532 visits available for analyses. The average patient and disease characteristics over all included visits where patients were in LDA are provided in table 1. Patients with a treatment intensification more often fulfilled the ACR/EULAR 2010 criteria and were more often male and rheumatoid factor and anti-citrullinated protein antibodies positive, although most differences were small.
For patients in LDA, after treatment intensification the mean (SD) change in DAS at the next visit was -0.48 (0.71), resulting in remission in 59% of the visits. In cases where there was no treatment intensification this was -0.15 (0.67) , resulting in remission in 38% of the visits. The mean (SD) change in HAQ at the next visit for patients in LDA was -0.083 (0.37) after treatment intensification, resulting in a clinically meaningful change in HAQ in 24% of the visits, and -0.0011 (0.35) without treatment intensification, resulting in a clinically meaningful change in HAQ in 25% of the visits.
Results of the linear mixed model analyses to assess the effect of treatment

Table 1. Average patient and disease characteristics over all included visits where DAS ≤2.4 but >1.6.

		No treatment intensification	Treatment intensification
Age, *mean (SD)*		52.6 (12.6)	51.0 (12.4)
Gender, n (*% female)*		46 (78.9)	39 (68.4)
Treatment arm	early remission	46.2	57.2
	MTX + SSZ + HCQ + prednisone	20.9	19.9
	MTX + adalimumab	19.1	16.0
	Out of protocol	13.8	6.7
Symptom duration in weeks, *median (IQR*)		20 (9; 35)	19 (9; 32)
Diagnosis RA, *% meeting 2010 criteria*		46 (79.2)	47 (84.5)
Anti-citrullinated protein antibodies, *% positive*		34 (57.6)	35 (61.9)
Rheumatoid factor, *% positive*		33 (58.9)	34 (63.0)
Health Assessment Questionnaire (0-3)[a], *mean (SD)*		0.78 (0.56)	0.63 (0.48)
Disease Activity Score, *mean (SD)*		1.95 (0.23)	1.99 (0.23)
Tender joint count, *median (IQR)*		2 (2; 4)	3 (2; 4)
Swollen joint count, *median (IQR)*		0 (0; 1)	1 (0; 2)
VAS general health (0-100)[b], *mean (SD)*		31.0 (19.6)	31.7 (20.3)
Erythrocyte Sedimentation Rate, *median (IQR)*		15.7 (13.0)	13.9 (11.2)

The average number of patients per visit with low disease activity without a treatment intensification was 56 (range 24-103) and the average number of patients per visit with low disease activity with treatment intensification was 61 (range 30-77). RA: rheumatoid arthritis, VAS: visual analogue scale, SD: standard deviation, IQR: interquartile range. MTX = methotrexate, SSZ = sulfasalazine, HCQ = hydroxychloroquine. [a]0 no functional limitations, [b]100 best score, [c]0 no radiographic damage.

intensifications on ΔHAQ are shown in table 2. All models had a random intercept and an independent covariance matrix. We found a small but statistically significant effect of treatment intensification on ΔHAQ, corrected for baseline HAQ, time in follow-up, age, gender and treatment arm [model 1, β (95% CI) -0.085 (-0.13; -0.044)]. The unadjusted model showed a larger effect [β (95% CI) -0.12 (-0.15; -0.08)]. This points to a weak association between treatment intensification and an improvement in HAQ: patients with a treatment intensification had a 0.085 additional improvement in ΔHAQ over time compared to patients without treatment intensification. When ΔDAS was added (model 2), the association between treatment intensification and delta HAQ became weaker and was no longer statistically significant [β (95% CI) -0.022 (-0.060; 0.016)]. Patients with treatment intensification now only had a 0.022 additional improvement in ΔHAQ over time compared to patients without treatment intensification. When the interaction between treatment intensification and time in follow-up was subsequently added (model 3),

Table 2. Linear Mixed Model analysis to assess the effect of treatment intensification on change in HAQ.

	β	95% CI	P
Model 1 (n patients = 479, n visits = 1528)			
Treatment intensification	-0.085	-0.13; -0.044	<0.001
Follow-up time[a]	0.0057	0.00094; 0.010	0.019
Model 2 (n patients = 476, n visits = 1509)			
Treatment intensification	-0.022	-0.060; 0.016	0.246
Follow-up time[a]	0.0022	-0.0021; 0.0066	0.313
DAS change	0.23	0.21; 0.26	<0.001
Model 3 (n patients = 476, n visits = 1509)			
Treatment intensification	-0.10	-0.18; -0.021	0.013
Follow-up time[a]	-0.0034	-0.010; 0.0033	0.323
Treatment intensification * follow-up time	0.0098	0.0010; 0.019	0.029
DAS change	0.23	0.21; 0.26	<0.001

HAQ = health assessment questionnaire, SE = standard error, CI = confidence interval.

[a]Follow-up time is added to the model as visit number, with time between visits being 4 months. All models were adjusted for baseline HAQ, gender, age and treatment arm.

a statistically significant interaction was found [β (95% CI) 0.0098 (0.0010; 0.019)], suggesting that the association between treatment intensification and HAQ-improvement, already weak in the early phases, only becomes weaker over time. Again, the unadjusted model showed a larger effect [β (95% CI) treatment intensification -0.24 (-0.32; -0.15); time -0.005 (-0.012; 0.0027); treatment intensification*time 0.017 (0.0075; 0.027)].

DISCUSSION

In this observational secondary analysis of data from a randomized clinical trial it was assessed whether intensifying drug therapy in patients who are in low disease activity, but not in remission, results in a clinically meaningful improvement in physical functioning, as measured by the HAQ. It was found that intensifying treatment in RA or UA patients in low disease activity resulted in a statistically significant improvement in ΔHAQ over time. However, the effect was rather small and appears clinically irrelevant. The improvement in ΔHAQ was partly explained by ΔDAS, and the effect of treatment intensification or change on ΔHAQ decreased by increasing follow-up time.

It is currently recommended that treatment efforts in patients with rheumatoid arthritis should be aimed at remission or low disease activity.[15] It remains the question if patients

would further benefit from aiming at remission if they are already in low disease activity. Several studies already confirmed the relationship between ΔDAS and ΔHAQ, also with longer follow-up time,[6-8, 10] however, those studies aimed for low disease activity and/or assessed the relationship between ΔDAS and ΔHAQ in a cross-sectional manner. Previous research also showed that patients with sustained clinical remission (≥24 weeks) had a continuous improvement in HAQ values and that remission implies better physical functioning than low disease activity.[16-18] However, finding that some patients achieved remission and had lower HAQ than the patients who did not achieve remission may have been coincidental and not the result of a therapeutic intervention, as none of these studies assessed prospectively whether further aiming for remission by intensifying treatment in patients who had already achieved low disease activity, results in further clinically relevant improvement in HAQ. The IMPROVED study provided the opportunity to test this, since the study protocol formally required treatment intensification as long as DAS was not <1.6. But rheumatologists did not always comply with this formal requirement, thus allowing us to compare outcomes after treatment intensification vs. lack thereof in patients with DAS<2.4 but still >1.6. In addition, we could investigate if such an association was dependent of the time of follow up.

Our results suggest that the minimally positive effect of a treatment intensification on ΔHAQ is mainly present at the start of treatment and that it decreases by increasing treatment duration. This observation is in line with earlier findings and current guidelines that RA patients should be treated early in the disease process.[19-21] It also suggests that in early RA and UA patients, initial treatment should consist of (a combination of) highly effective drugs, in order to decrease disease activity rapidly and thus maximally improve physical functioning. Persistently aiming for remission in patients already in low disease activity may lead to inappropriate treatment intensifications and increased use of antirheumatic drugs (overtreatment), without additional benefits. This was recently found in studies were clinical remission and imaging remission were compared as treatment target.[22, 23]

A limitation of this study was that we only looked at treatment intensifications in general, and did not specify the type of treatment changes. Different treatments may have different effects on physical functioning. A second limitation of our analysis is that patients with low disease activity in whom treatment was intensified may differ from those in whom treatment was not intensified with respect to characteristics that are relevant to the outcome of interest, but that we have not measured (intangible confounders). Previous studies also showed that ΔHAQ is not only associated with ΔDAS, but also that an increase in joint damage may lead to worse physical functioning, especially with longer follow-up time.[6-9] Since in the remission steered IMPROVED study the majority of the patients hardly had any radiographic damage, joint damage was not further considered in this analysis.[24]

CONCLUSIONS

In conclusion, treatment intensification in early RA or UA patients who have already achieved LDA is associated with a statistically significant decrease in HAQ, but not with a clinically meaningful improvement in functional ability during 5 years of DAS remission steered treatment. Therefore not remission or LDA, but good functional ability may be the optimal treatment target at which to steer treatment adjustments. Thus, it might be sufficient to accept achieved LDA rather than continue treatment intensifications aiming at remission. Further treatment intensifications may not lead to a clinically relevant improvement in HAQ, but it may have downsides such as side effects and costs.

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PART 2

Worldwide differences in RA