Towards improved treatment of undifferentiated and rheumatoid arthritis

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Sustained drug-free remission in rheumatoid arthritis after DAS-driven or non-DAS-driven therapy

A comparison of two cohort studies

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Abstract

Objectives

To compare the prevalence of and predictors for sustained drug-free remission in two cohorts of patients with recent-onset rheumatoid arthritis (RA) treated with disease activity score (DAS)-driven therapy or non-DAS-driven therapy.

Methods

Sustained drug-free remission was assessed after 5 years follow-up in 508 patients treated with DAS-driven therapy (DAS≤2.4) in a randomized treatment cohort, and in 424 patients who received non-DAS-driven therapy in a prospective inception cohort. The design of the DAS-driven cohort required systematic joint assessments with DAS-driven restart of therapy. The prevalence was also assessed in patients with or without antibodies to citrullinated proteins (ACPA). Predictors for remission were identified by univariable and multivariable logistic regression in each cohort separately, including a sensitivity analysis on patients receiving initial monotherapy.

Results

Patients in the DAS-driven cohort had more active disease at baseline, but the prevalence of sustained drug-free remission was similar after DAS-driven therapy (9.8%) and non-DAS-driven therapy (10.6%). ACPA-positive patients had a higher chance of achieving drug-free remission after DAS-driven than after non-DAS-driven therapy (OR 2.68, 95%CI 0.97-7.43). The absence of ACPA and short symptom duration were independent predictors for sustained drug-free remission in both cohorts. Initial treatment choice and inclusion period were not predictive. The sensitivity analysis yielded comparable results.

Conclusions

In a comparison of a DAS-driven and a non-DAS-driven therapy cohort, the occurrence and predictors of sustained drug-free remission appeared similar. The DAS-driven cohort had a more unfavorable prognosis. DAS-driven therapy may improve the chance of sustained drug-free remission in patients with recent-onset active RA.

INTRODUCTION

In rheumatoid arthritis (RA), an early start of treatment, use of combination therapy with corticosteroids or tumor necrosis factor (TNF)-blockers, and a strategy of tight control have significantly improved the clinical and radiographic outcomes of patients.[1-6] Continued tight control aimed at a predefined goal of minimal disease activity has resulted in suppressed inflammation, improved functional status and high remission percentages, irrespective of the initial choice of therapy.[7;8] Recently an international task force has reviewed and summarized all the evidence on tight control of RA and has formulated recommendations to enhance the implementation of 'treating to target' in clinical practice.[9;10]

According to these recommendations, the primary target of RA treatment should be a state of clinical remission, defined as the absence of signs and symptoms of inflammatory disease activity, assessed by a validated (composite) measure such as the disease activity score (DAS).[10;11] Ideally, clinical remission is maintained even after discontinuation of treatment, resulting in what could be called 'cure'. In the BeSt study, which combined an early start of treatment with DAS-driven therapy adjustments in four different therapeutic strategies, patients who achieved clinical remission (DAS<1.6), by protocol tapered and discontinued their disease-modifying antirheumatic drugs (DMARDs). After four years, 8-18% of the patients in the four strategy groups were in drug-free remission with a mean duration of one year.[7]

Does DAS-driven therapy result in more drug-free remission than routine non-DAS-driven treatment? It is known that a proportion of patients treated according to routine care, have been able to discontinue their antirheumatic medication.[12-14] DAS-driven therapy might have a benefit by increasing the proportion of patients who achieve and maintain sustained drug-free remission, by inducing remission earlier in the disease course, in patients with more severe disease, or all of these alternatives.

To investigate this, we set out to compare the prevalence and predictors of sustained drug-free remission in two cohorts of recent-onset RA patients, originated from the same region, and treated with either DAS-driven or non-DAS-driven therapy.

MATERIALS AND METHODS

Patients

Two cohorts of patients were compared:

1. the BeSt study (DAS-driven therapy cohort): 508 patients with recent-onset RA according to the 1987 American College of Rheumatology (ACR) criteria[15], a symptom duration <2 years and active disease at baseline (≥6/66 swollen joints, ≥6/68 tender joints, and either an erythrocyte sedimentation rate (ESR) ≥28 mm/hr or a global health score ≥20 mm on a visual analogue scale (VAS) of 0-100 mm), who were randomized to four different DAS-driven treatment strategies. The inclusion period was 2000-2002.[16]

2. the Leiden Early Arthritis Clinic (EAC) (non-DAS-driven therapy cohort): 424 patients with recent-onset RA according to the 1987 ACR criteria from an inception cohort of consecutive arthritis patients with a symptom duration <2 years. The inclusion period was 1993-2002.[17] In contrast to a previous report on the EAC[12], patients who also participated in the BeSt study were excluded.

Treatment

In the BeSt study, patients were randomized to one of four treatment groups: initial methotrexate monotherapy subsequently replaced by or extended with other DMARDs (group 1 and 2), initial combination therapy including conventional DMARDs and prednisone (group 3) or initial combination therapy including infliximab (group 4). Every three months, treatment was adjusted following a strict protocol, aiming at a DAS≤2.4. If the DAS was ≤2.4 for at least 6 consecutive months, medication was tapered to monotherapy in maintenance dose. Subsequently, from the third year of the study, if the DAS was <1.6 for at least an additional 6 consecutive months, the last DMARD was tapered and discontinued. If the DAS increased to >1.6, the last DMARD was immediately restarted. Details of the treatment protocol can be found elsewhere.[7,16]
Patients in the EAC were treated according to the clinical judgment of their rheumatologist, via non-DAS-based efficacy evaluations.[17] The treatment strategy differed according to the inclusion period. Patients included from 1993 to 1996 were initially treated with analgesics and subsequently with chloroquine. Between 1996 and 1998, patients were initially treated with chloroquine or sulfasalazine, while after 1998 the initial treatment strategy consisted of either sulfasalazine or methotrexate.[12] The initial treatment of the patients described in the current manuscript consisted of non-steroidal antiinflammatory drugs (NSAIDs) in 27% or DMARDs (with or without NSAIDs) in 73% of patients. Of all patients, 37% started with DMARD combination therapy, and 15% initially used (also) corticosteroids. Tapering and discontinuation of the medication was not protocolized.

Definition of remission

In the DAS-driven cohort, sustained drug-free remission was defined as a continued DAS<1.6 after discontinuation of DMARDs. In 85% of the patients in drug-free remission the swollen joint count (SJC) was zero, as based on systematically performed 66/68 joint counts during the three-monthly follow-up visits. In the non-DAS-driven cohort patients, the DAS was not routinely performed, but a full joint count was registered yearly. In the non-DAS-driven cohort, drug-free remission was defined according to the rheumatologist and required the absence of swollen joints after cessation of therapy. In both cohorts, drug-free remission was required to have lasted at least one year and was still sustained at the 5-year follow-up time point. In the non-DAS-driven cohort, patients thus defined as being in drug-free remission were discharged from the outpatient clinic after on average 2.5 years of drug-free remission. After that there was no systematic follow-up, but if patients had a recurrence of their arthritis after discharge, they were instructed to return to the Leiden University Medical Center. During the period under investigation, one patient was re-referred with a relapse and was therefore included in

the non-remission group. Seventy-two patients (14%) in the DAS-driven cohort dropped out or were lost to follow-up, and 31 patients (7.3%) in the non-DAS-driven cohort were lost to follow-up before the 5-year endpoint due to withdrawal, death or moving. An intention to treat analysis with last observation carried forward approach was used.

Statistical analysis

The prevalence of sustained drug-free remission was assessed in both treatment cohorts (DAS-driven and non-DAS-driven). Since ACPA has been previously reported as predictive factor for drug-free remission and since the growing concept is that ACPA-positive and ACPA-negative RA are two distinct diseases[12,18], crosstabs stratified for ACPA were made and odds ratios (OR) with 95% confidence intervals (CI) for DAS-driven versus non-DAS-driven therapy were calculated. Baseline predictors for sustained drug-free remission were identified via univariable logistic regression analysis in both cohorts separately. Predictors which had previously been reported and with a p-value<0.10 in univariable analysis were taken along in a multivariable analysis with a backward selection procedure (removal criterion: p>0.10), yielding independent predictors for sustained drug-free remission. Subsequently, sensitivity analyses were performed to assess whether and in which direction the early use of combination therapy in the DAS-driven cohort or the earlier inclusion period (associated with treatment choice) in the non-DAS-driven cohort had influenced the analyses. The sensitivity analysis was performed on the patients who received initial DMARD monotherapy, being the patients from arm 1 and 2 in the DAS-driven cohort, and patients included after 1998 in the non-DAS-driven cohort.

RESULTS

Cohort characteristics and prevalence of sustained drug-free remission

At baseline, based on inclusion criteria of the BeSt study, patients in the DAS-driven therapy cohort had a longer symptom duration, more active disease characterized by worse function measured by the health assessment questionnaire (HAQ) and a higher SJC, and were more often RF- or ACPA-positive than patients in the non-DAS-driven cohort (table 1). After 5 years of follow-up, the prevalence of sustained drug-free remission was 50/508 = 9.8% in the DAS-driven therapy cohort and 45/424 = 10.6% in the non-DAS-driven cohort (table 2). Stratified for ACPA, the prevalence of sustained drug-free remission was approximately 20% in ACPA-negative RA patients, irrespective of the therapy cohort. The prevalence of drug-free remission was markedly lower in ACPA-positive patients (2-5%). ACPA-positive patients treated with DAS-driven therapy had a higher chance of achieving drug-free remission compared with non-DAS-driven therapy (OR 2.68, 95%CI 0.97-7.43). In the DAS-driven cohort, the discontinuation of antirheumatic therapy was prohibited by treatment protocol before two-and-a-half years of follow-up. The mean time to drug-free remission was 3.1 years in the DAS-driven cohort and 2.6 years in the non-DAS-driven therapy cohort.

Table 1. Baseline characteristics of 508 recent-onset RA patients in the DAS-driven therapy cohort (BeSt) and 424 recent-onset RA patients in the non-DAS-driven cohort (EAC).

Baseline characteristics	DAS-driven therapy (n=508)	Non-DAS-driven therapy (n=424)	p-value
Age, mean ± SD years	54 (13.7)	56 (16.1)	0.06
Female gender, no. (%)	346 (68%)	288 (68%)	0.90
Symptom duration, median (IQR) weeks	23 (14-53)	20 (11-39)	<0.001
BMI, mean ± SD	25.6 (4.0)	25.5 (3.6)	0.62
DAS, mean ± SD	4.4 (0.86)	NA	-
HAQ, mean ± SD	1.4 (0.67)	1.1 (0.72)	<0.001
SJC, median (IQR)	14 (10-19)	8 (5-12)	<0.001
CRP, median (IQR) mg/L	21 (9-55)	19 (9-44)	0.41
ESR, median (IQR) mm/hr	37 (19-56)	37 (21-59)	0.24
RF-positive, no. (%)	329 (65%)	237 (56%)	0.008
ACPA-positive, no. (%)	294 (62%)	238 (56%)	0.10
SE, no. (%)	281 (67%)	270 (67%)	0.98

For dichotomous variables, the number and the percentage of patients are listed, relative to the total number of patients for whom information about the characteristic under investigation was available. P-values are listed for the comparison between the two cohorts, using t-test for normally distributed variables, Mann-Whitney for non-Gaussian distributions and Chi-square for dichotomous variables. ACPA=anti-citrullinated protein antibodies; SD=standard deviation; IQR=interquatile range; DAS= disease activity score; SJC=swollen joint count; CRP=C-reactive protein; ESR=erythrocyte sedimentation rate; HAQ=health assessment questionnaire; RF=rheumatoid factor; SE=shared epitope; BMI=body mass index; NA=not applicable.

Predictive factors

In the DAS-driven cohort, male gender, lower DAS and HAQ at baseline and the absence of RF, ACPA and shared epitope (SE) alleles were significantly univariately associated with sustained drug-free remission (table 3). The allocated initial treatment (mono- versus combination therapy), was not predictive (data not shown). The multivariate model revealed male gender, short symptom duration, the absence of ACPA and lower baseline DAS as independent predictors for sustained drug-free remission (table 4 I). If the DAS was replaced with the HAQ, HAQ was also an independent predictor with borderline significance (OR 0.61, 0.37-1.006, p=0.053). RF was a significant independent predictor if put in the model instead of ACPA (OR 0.33, 0.18-0.60, p=<0.001), but was not significant if included in addition to ACPA.

Also in the non-DAS-driven cohort, absence of RF, ACPA and SE were significant univariate predictors (table 3). In addition, shorter symptom duration and non-smoking were identified as predictors. The inclusion period as surrogate variable for the initial treatment, was not predictive for sustained drug-free remission (data not shown). The

Table 2. Prevalence of sustained drug-free remission in the DAS-driven and the non-DAS-driven therapy cohort, in the total group and stratified for ACPA-positive and ACPA-negative patients.

		Drug-free remission	No drug-free remission	OR (95% CI)
Total	DAS-driven therapy	50 (9.8%)	458 (90.2%)	0.92 (0.60-1.41)
	non-DAS-driven therapy	45 (10.6%)	378 (89.4%)	
ACPA-positive	DAS-driven therapy	16 (5.4%)	278 (94.6%)	2.68 (0.97-7.43)
	non-DAS-driven therapy	5 (2.1%)	233 (97.9%)	
ACPA-negative	DAS-driven therapy	34 (18.6%)	149 (81.4%)	0.83 (0.50-1.38)
	non-DAS-driven therapy	40 (21.6%)	145 (78.4%)	

Odds ratios (OR) with 95% confidence intervals (CI) represent the chance for drug-free remission with DAS-driven versus non-DAS-driven therapy. ACPA=anti-citrullinated protein antibodies; DAS=disease activity score.

multivariable model revealed a lower symptom duration and the absence of ACPA as independent predictors for sustained drug-free remission in this cohort (table 4 II). Again, RF was only a significant independent predictor if put in the model instead of ACPA (OR 0.25, 0.12-0.51, p=<0.001).
Looking at the effect of ACPA-positivity, the odds ratio (OR) for sustained drug-free remission was two times higher with DAS-driven therapy (OR 0.20) than with non-DAS-driven therapy (OR 0.09), suggesting that the negative effect of having ACPA on achieving sustained drug-free remission may be counterbalanced to some extent by a benefit of DAS-driven therapy.

Sensitivity analysis

The analyses in the total cohorts did not reveal treatment allocation in the DAS-driven cohort nor the inclusion period in the non-DAS-driven cohort as factors associated with achieving drug-free remission. Nevertheless, to investigate if the differences in initial treatment and the inclusion period within and between the cohorts influenced our results, we performed a sensitivity analysis on the patients who received comparable initial DMARD monotherapy in a similar time period. The prevalence of sustained drug-free remission was 25/247 (10.1%) in the patients treated with initial methotrexate monotherapy in the DAS-driven cohort and 19/199 (9.5%) in the patients included after 1998 in the non-DAS-driven cohort, treated with either initial methotrexate or sulfasalazine monotherapy. In the DAS-driven cohort, independent multivariate predictors for drug-free remission remained male gender (OR 2.1, 0.84-5.35, p=0.112), absence of ACPA (OR 0.23, 0.09-0.59, p=0.002) and short symptom duration (OR 0.98, 0.96-0.99, p=0.038). In the non-DAS-driven cohort, only absence of ACPA remained a significant independent predictor (OR 0.09, 0.02-0.41, p=0.002).

Table 3. Characteristics of patients who did or did not achieve sustained drug-free remission after 5 years in the DAS-driven therapy cohort (BeSt) and non-DAS-driven therapy cohort (EAC).

Potential predictors for remission	DAS-driven therapy			Non-DAS-driven therapy		
	Remission (n=50)	No remission (n=458)	OR (95%CI)	Remission (n=45)	No remission (n=379)	OR (95%CI)
Age, mean ± SD years	55 (16)	54 (14)	1.01 (0.98;1.03)	60 (17)	56 (16)	1.02 (0.998;1.04)
Male gender, no. (%)	23 (46%)	139 (30%)	2.27 (1.26;4.09)*	16 (36%)	120 (32%)	1.19 (0.62;2.28)
Symptom duration, median (IQR) weeks	19 (11-34)	24 (14-55)	0.99 (0.98;1.00)	13 (6-28)	21 (11-41)	0.98 (0.96;0.99)*
Smoking, no. (%)	14 (28%)	163 (36%)	0.69 (0.36;1.33)	14 (31%)	170 (49%)	0.48 (0.25;0.93)*
BMI, mean ± SD	25 (3)	26 (4)	0.96 (0.88;1.04)	25 (3)	26 (4)	0.95 (0.83;1.08)
DAS, mean ± SD	4.19 (0.88)	4.45 (0.86)	0.70 (0.49;1.00)*	NA	NA	NA
HAQ, mean ± SD	1.22 (0.66)	1.42 (0.67)	0.63 (0.40;0.98)*	1.17 (0.73)	1.04 (0.72)	1.26 (0.78;2.03)
SJC, median (IQR)	15 (10-18)	13 (10-19)	1.01 (0.97;1.06)	8 (4-11)	8 (5-12)	0.99 (0.94;1.04)
Total SHS, median (IQR)	3 (1.0-6.4)	4 (1.5-9.0)	0.98 (0.94;1.02)	3 (1.0-11.0)	6 (2.0-12.0)	0.97 (0.93;1.01)
Erosive >=1, no. (%)	31 (65%)	326 (72%)	0.70 (0.37;1.31)	31 (72%)	300 (83%)	0.52 (0.99;1.01)
CRP, median (IQR) mg/L	16 (6-36)	22 (9-56)	1.00 (0.99;1.01)	15 (8-32)	20 (9-44)	1.00 (0.99;1.01)
ESR, median (IQR) mm/hr	29 (15-44)	37 (20-57)	0.99 (0.98;1.00)	34 (17-54)	37 (22-60)	1.00 (0.99;1.01)
RF-positive, no. (%)	22 (44%)	307 (67%)	0.39 (0.21;0.70)*	11 (24%)	226 (60%)	0.22 (0.11;0.44)*
ACPA-positive, no. (%)	16 (32%)	281 (65%)	0.25 (0.14;0.47)*	5 (11%)	233 (62%)	0.08 (0.03;0.20)*
SE, no. (%)	23 (50%)	258 (69%)	0.46 (0.25;0.85)*	20 (44%)	250 (69%)	0.35 (0.19;0.66)*

Odds ratios (OR) and 95% confidence intervals (CI) are presented from the univariable logistic regression analyses. *=statistically significant, For abbreviations see table 1.

Table 4. Independent predictors for sustained drug-free remission in the DAS-driven cohort (I) and the non-DAS-driven cohort (II).

Predictor	OR (95% CI)	p-value
I DAS-driven cohort		
Male gender	2.39 (1.26-4.53)	0.008
Symptom duration (weeks)	0.99 (0.98-1.002)	0.099
ACPA-positivity	0.20 (0.10-0.39)	<0.001
DAS	0.63 (0.43-0.94)	0.022
II Non-DAS-driven cohort		
Symptom duration (weeks)	0.99 (0.97-1.003)	0.108
ACPA-positivity	0.09 (0.04-0.24)	<0.001

For abbreviations see table 1.

DISCUSSION

Although it is clear that tight-control strategies such as DAS-driven therapy result in better clinical and radiographic outcomes, and recommendations for 'treating RA to target' have recently been formulated, it has not yet been investigated whether DAS-driven therapy also results in more drug-free remission than non-DAS-driven routine treatment evaluations.[9,10] In this study, we found that in two cohorts of patients with recent-onset RA, treated with either DAS-driven or non-DAS-driven therapy, the occurrence of sustained drug-free remission was fairly similar, as were predictors of sustained drug-free remission: a short symptom duration and the absence of ACPA.

Since there were significant differences between the two cohorts at baseline, the comparison is not straightforward. A randomized controlled trial would be the ideal setting to investigate the effect of DAS-driven versus non-DAS-driven therapy on achieving sustained drug-free remission. However, as DAS-driven therapy leads to better functional and radiological outcomes than non-DAS-driven therapy [4,6,8] such a design may be considered unethical. In addition, large patient numbers per group would be required, since sustained drug-free remission does not occur often. Therefore, we resorted to a retrospective comparison of two existing large cohorts.

Patients in the DAS-driven cohort, which started as the BeSt trial[16], had more severe disease and therefore poorer prognosis, based on the inclusion criteria of the trial, whereas the non-DAS-driven cohort also included less severe patients[17]. In addition, the definition of sustained drug-free remission and frequency of follow-up differed slightly between both cohorts, although in practice this will not have had a major impact on the results. In the DAS-driven cohort, remission required a sustained DAS<1.6 at three-monthly intervals and as soon as the DAS rose above 1.6, medication was restarted. In 15% of patients in remission based on a DAS <1.6, residual joint swelling (based on a 66/68 joint count) was still present. In the non-DAS driven cohort remission was based on the rheumatologist's opinion, including absence of swollen joints at yearly evaluati-

ons. Restart of therapy nor duration or frequency of follow-up were protocolized. The inclusion period, which partly differed between the two cohorts, may have represented different practices in timing and choice of prescribing anti-rheumatic drugs, which may have influenced our results.[19] Part of the patients in the non-DAS-driven cohort who were included at an earlier point in time, were not promptly treated with DMARDs, and a delay of DMARD therapy is associated with worse disease outcome.[2,5] Initial combination therapy, used in a subpopulation of the DAS-driven cohort, is associated with early and better suppression of disease activity, but was seldomly prescribed in the non-DAS-driven cohort. It is difficult to separate the effect of using more (novel) DMARDs from the effect of DAS-driven strategy, as a tight control strategy with frequent DAS-measurements inherently leads to rapid changes in medication. However, in our sensitivity analysis we partly disentangled these effects by excluding all the patients with initial combination therapy, as well as the patients included before 1999, which did not result in a change in the observed remission rates. Furthermore, neither the specific treatment arm in the BeSt study, nor the inclusion period and corresponding medication in the EAC, were associated with drug-free remission, confirming previous reports.[7,12]

With, or despite, the differences between the two cohorts, the rate of sustained drug-free remission did not differ between the DAS-driven and non-DAS-driven cohort. ACPA-negative patients achieved sustained drug-free remission more easily than ACPA-positive patients, whether DAS-driven or not, but ACPA-positive patients, despite having in general a worse prognosis, had a higher chance for achieving drug-free remission in the DAS-driven cohort than in the non-DAS-driven cohort.[20] We tentatively propose that this may indicate that with DAS-driven therapy sustained drug-free remission can be easier achieved, even in patients with more unfavorable prognostic characteristics.

The absolute number of patients with sustained drug-free remission in both our cohorts is still low and an important question is if and how we can attain more sustained drug-free remission in the future. Is sustained drug-free remission intrinsically possible only for certain patients, or should we be able to induce it in all patients? The similar rates of sustained drug-free remission in both cohorts as well as the higher sustained drug-free remission rate among ACPA-negative patients support the former, but the fact that with DAS-driven treatment drug-free remission was attainable also in more poor prognosis ACPA-positive patients support the latter. In addition, the finding of short symptom duration as a predictor of sustained drug-free remission may indicate a 'window of opportunity'. The studied DAS-driven cohort aimed at a DAS ≤ 2.4, a cut-off which allows for some residual inflammation. Thus, actively aiming at even lower levels of disease activity, as well as starting treatment earlier and including the use of drug combinations and biologicals might result in more patients achieving early and sustained drug-free remission in patients with RA.

In summary, in a comparison of a DAS-driven and a non-DAS-driven therapy cohort, the occurrence and predictors of sustained drug-free remission appeared similar, but the DAS-driven cohort had more patients with an unfavorable prognosis. We propose that DAS-driven therapy may improve the chance of achieving sustained drug-free remission in patients with recent-onset active RA.

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