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Evaluating adherence to a treat-to-target protocol in recent-onset rheumatoid arthritis: reasons for compliance and hesitation

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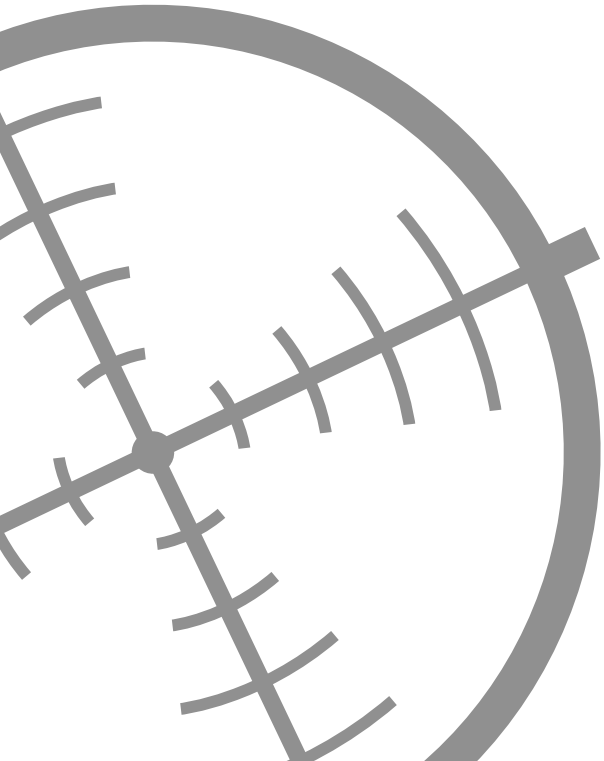

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ABSTRACT

Objective

To evaluate rheumatologists' adherence to a low disease activity score (DAS) steered treat-to-target (T2T) strategy in treatment of patients with rheumatoid arthritis (RA) and to assess associated conditions.

Methods

Data of the BeSt study were used, a multicenter T2T strategy trial with ten year follow-up. During three-monthly visits the physician answered questions about satisfaction with level of RA suppression, agreement with the study protocol and with the DAS. Associations between the answers and non-adherence were evaluated.

Results

Protocol adherence decreased over time from 100% to 60% per visit with an average over time of 79%. Rheumatologists mostly agreed with DAS (80 – 90% of visits over time), were satisfied with the treatment steps (75 – 90%) and with the level of RA suppression (85 – 90%). The odds for protocol violation were higher when the rheumatologist disagreed with the DAS (OR 2.3, 95% CI 2.0 – 2.7 when they felt the DAS overestimated actual disease activity, OR 2.5, 95% CI 2.0 – 3.1 when DAS was felt to underestimate) or with the next required treatment step (OR 3.0, 95% CI 2.5 – 3.5), and when the physician was dissatisfied with disease suppression (OR 1.3, 95% CI 1.1 – 1.6).

Conclusions

Rheumatologists generally agreed with and followed a ten year follow-up DAS steered T2T strategy. Disagreement with the DAS, the required treatment or dissatisfaction with the level of disease suppression were risk factors for non-adherence. These results indicate the feasibility of continued protocol driven T2T therapy. For daily practice, adherence to T2T therapy might be improved by adopting the structure components of a clinical trial.

INTRODUCTION

Targeted treatment has proven to effectively suppress disease activity in patients with early rheumatoid arthritis (RA).[1–4] These days treat-to-target therapy is a well-known concept in trials,[1,3–6] and is also recommended in daily practice.[7–9] Questionnaire based research showed that the majority of rheumatologists agreed with this recommendation.[10] Other studies suggest that actual implementation of a treat-to-target approach in daily practice remains challenging.[11–14] One of the reasons may be that rheumatologists are reluctant to base treatment decisions on a composite score such as the disease activity score (DAS),[15] arguing that it is too sensitive for non-inflammatory pain[16] or may be falsely elevated when erythrocyte sedimentation rate (ESR), or C-reactive protein (CRP) is elevated due to non-rheumatic inflammation.[17]

In the BeSt study, treat-to-target therapy is a central theme of the initial study design, which is embedded in the daily practice of the rheumatologists in 20 participating hospitals, and maintained over ten year follow-up. In the current post hoc-analysis, we set out to determine to what extent the rheumatologists adhered to the treat-to-target protocol and to identify factors influencing this adherence, such as satisfaction with the level of disease activity, agreement with the DAS, agreement with the next treatment step and apparently contradictory DAS components.

PATIENTS AND METHODS

Study design

In the BeSt study (Dutch acronym for treatment strategies), a clinical trial with 2 academic and 18 peripheral participating hospitals, 508 patients with early RA according to the 1987 criteria were included.[18] Over time, approximately 60 rheumatologists participated and treated patients according to the study protocol. The protocol was approved by the medical ethics committees of all twenty participating hospitals in the western part of the Netherlands. All patients gave written informed consent.

Patients were randomly allocated to four treatment strategy arms: 1. sequential monotherapy, 2. step-up combination therapy, 3. initial combination therapy with prednisone, 4. initial combination therapy with infliximab. In all patients during 10 year follow up, disease activity was measured three-monthly by trained nurses using the DAS (53/44 joint count and including a patient's opinion of global health, filled in on a 0 – 100 mm visual analogue scale (VASgh)).[15] If the DAS was >2.4, the rheumatologist was required to intensify treatment according to the study protocol. If the DAS was ≤2.4 for ≥6 months, medication was tapered to a maintenance dose. Next, if the DAS was <1.6 for ≥6 months, the last disease-modifying antirheumatic drug (DMARD) was discontinued. Every three months, possible next treatment steps were detailed in advance in the medical records by the trial physicians. In case of disagreement with the DAS and the required treatment step, rheumatologists could request an extra study

visit and DAS calculation one month later. This extra DAS measurement then determined the treatment decision. In a random sample of these extra visits the effect of this option was explored.

Study endpoints

All treatment continuations, adjustments, tapering and discontinuations at regular and extra study visits were recorded by the trial physicians and whether treatment was per protocol or not. Protocol adherence was defined as dose escalation or changing/adding medication according to the protocol in case of DAS >2.4, tapering or discontinuation of medication according to the protocol in case of sustained DAS ≤2.4 or <1.6 and unchanged treatment continuation in case of short-term DAS ≤2.4 or <1.6. Consequently, protocol violation was defined as any treatment adjustment that was not according to the DAS measurement, or a choice of medication that was not according to the protocol, and can thus represent undertreatment (not intensifying medication when disease activity is high) or overtreatment (not tapering when disease activity is low). When medication was not adjusted according to the protocol due to an adverse event, this was not considered as a protocol violation.

At every visit, rheumatologists were asked to provide a VAS physician (VASphys) to indicate a global assessment of disease activity. With some changes over time, they also were asked to fill in a brief questionnaire about satisfaction with the effect of treatment, agreement with the required treatment step, and agreement with the DAS representing actual disease activity (Table 1).

We formulated hypothetical conditions that might influence the rheumatologist to disagree with the DAS or deviate from the protocol. These entailed possible discrepancies between observed clinical synovitis and reported pain or inflammatory signs in the laboratory analysis, the rheumatologist's VAS for actual disease activity and the patient's VAS of general health (Table 2).

Table 1. Questionnaire for the rheumatologists about their opinion on the treatment by protocol, effectiveness of treatment and DAS.

1. Are you satisfied with the next treatment step?
□ Yes, I would have taken the same (or a comparable) step
□ No, I would have treated the patient as follows: …
2. Are you satisfied with the effect of the treatment on the rheumatoid arthritis in this patient?
□ Yes
□ No, the disease is not sufficiently suppressed
3. Do you think the DAS adequately represents the disease activity in this patient?
□ Yes, the situation is well represented by the DAS
□ No, the patient is doing better than the DAS represents
□ No, the patient is doing worse than the DAS represents

Ad 1: this question was asked every visit from the 2nd until the 26th visit in the 6th year of follow-up. Ad 2: asked every visit from the 2nd until the last visit at 10 years of follow-up. Ad 3: asked every visit from the 10th visit in year 3 until the last visit at 10 years of follow-up.
DAS, disease activity score.

Table 2. Hypothetical conditions on which an association with disagreement with DAS and protocol violation was checked.

No. 1	SJC ≤1 and TJC ≥2
No. 2	SJC ≤1 and ESR ≥28
No. 3	SJC ≤1 and VASgh ≥20 mm
No. 4	VASgh ≥20 mm higher than VASphys
No. 5	VASphys ≥20 mm higher than VASgh

SJC, swollen joint count; TJC, tender joint count; VASgh, visual analogue scale of general health by patient; VASphys, visual analogue scale of global disease activity by physician.

Statistical analysis

As long-term outcomes were similar in the four randomization arms, all arms were combined for these analyses. The exception to this was a non-parametric test to compare protocol violations per patient year among the treatment strategies. Descriptive statistics were used to count the frequency of answers to the questionnaires and protocol adherence per time point. Trends over time were tested with a generalized linear model, adjusting for sphericity as appropriate. The percentage of protocol adherence was calculated and compared between several subgroups of participating centers, based on the following characteristics: per center, per region, per type of hospital (academic, peripheral, teaching hospitals), number of rheumatologists, number of included patients. To allow for the missing data, which are probably not completely at random, and for repeated measurements within one patient, we performed generalized linear mixed models (GLMM) to assess: (a) the association between protocol violations and the physician's answers to the questionnaire in Table 1; (b) the association between protocol violations and the presence of specific conditions listed in Table 2; (c) the association between the rheumatologist's disagreement with DAS and the presence of the conditions as described in Table 2; (d) the association between the rheumatologist's disagreement with DAS and DAS categories; (e) the association between satisfactory disease suppression and DAS categories. An ARMA correlation matrix was used, assuming a decrease of association between more distant measurements over time, because this structure fitted the data best. First, a GLMM with protocol violation (yes/no) as dependent variable and the answers to the questionnaire (Table 1) as independent variable was performed (a). The conditions as formulated in Table 2 were entered as independent variable in the GLMM to calculate an odds ratio (OR) for protocol violation (yes/no) (b) as well as an OR for disagreeing with the DAS (yes/no) (c). Next, two GLMM were performed to calculate an OR for remission (DAS <1.6, yes/no) in case of disagreement (yes/no) with DAS because rheumatologists felt the DAS underestimated actual disease activity and an OR for high disease activity (DAS >2.4, yes/no) in case of disagreement (yes/no) with DAS because it was felt to overestimate actual disease activity (d). Finally, a GLMM with DAS category (remission: DAS <1.6, low disease activity: DAS 1.6 – 2.4, high disease activity: DAS >2.4) as independent variable and being satisfied with the effect of the treatment (yes/no) as dependent variable was performed (e).

RESULTS

Protocol adherence and violations

The frequency of treatment decisions according to the protocol and the frequency of non-adherence are depicted in Figure 1A. The peaks in the Figure correspond to the yearly visits, when attendance was highest. The frequency of protocol adherence decreased over time, from 100% during the first visit up to circa 60% of the completed visits in the 9th and 10th year ($p<0.001$ for decrease over time). The average adherence during ten year follow-up was 79%. Of 2742/3044 times (90%) when the protocol was not followed, a DAS was available. In 891/2742 situations (33%) DAS was <1.6, in 847/2742 situation (31%) DAS was between 1.6 and 2.4, and in 1004/2742 situations (37%) DAS was >2.4.

Non-adherence to the treatment protocol was more likely when the rheumatologist disagreed with the next treatment step (OR 2.97, 95% confidence interval (CI) 2.53 – 3.48), was not satisfied with the level of disease suppression (OR 1.34, 95% CI 1.14 – 1.57) or disagreed with the DAS (OR 2.31, 95% CI 1.96 – 2.72 in case the DAS was felt to overestimate actual disease activity; OR 2.50, 95% CI 1.99 – 3.13 in case the DAS was felt to underestimate actual disease activity) (Table 3). Still, of the 1196 times a rheumatologist answered that he or she did not agree with the next treatment step in the protocol, 898 times (75%) the protocol was followed. Also, in 643/976 situations (66%) when the rheumatologist was not satisfied with the effect of the current treatment, and in 1023/1558 situations (66%) when the DAS was felt to misrepresent actual disease activity, the protocol was still followed.

There was an increased risk of non-adherence to the protocol when there was a discrepancy in the VAS of the patient and that of the physician: in case the patient's VAS was ≥20 mm higher than the physician's VAS (condition 4, Table 2) (OR 1.24, 95% CI 1.10 – 1.40) as well as in case the physician's estimation of disease activity that was higher than the patient's estimation of general health (condition 5, OR 1.66, 95% CI 1.27 – 2.16). A joint score with

Table 3. GLMM with protocol violation as dependent variable and physicians' answers as independent variables. Questions were: (1) Are you satisfied with the next treatment step? (2) Are you satisfied with the effect of the treatment on the rheumatoid arthritis in this patient? (3) Do you think the DAS adequately represents the disease activity in this patient?

	Protocol Violation (n=3044)	
	OR	**95% CI**
Agreement with next treatment step in protocol (n=7064)	ref	*ref*
Disagreement with next treatment step in protocol (n=1203)	2.97	2.53 – 3.48
Satisfied with effect of current treatment on RA (n=7151)	ref	*ref*
Not satisfied with effect of current treatment on RA (n=983)	1.34	1.14 – 1.57
DAS represents actual level of disease activity well (n=10132)	ref	*ref*
DAS overestimates disease activity (n=1108)	2.31	1.96 – 2.72
DAS underestimates disease activity (n=466)	2.50	1.99 – 3.13

95% CI, 95% confidence interval; DAS, disease activity score; GLMM, generalized linear mixed model; OR, odds ratio; RA, rheumatoid arthritis.

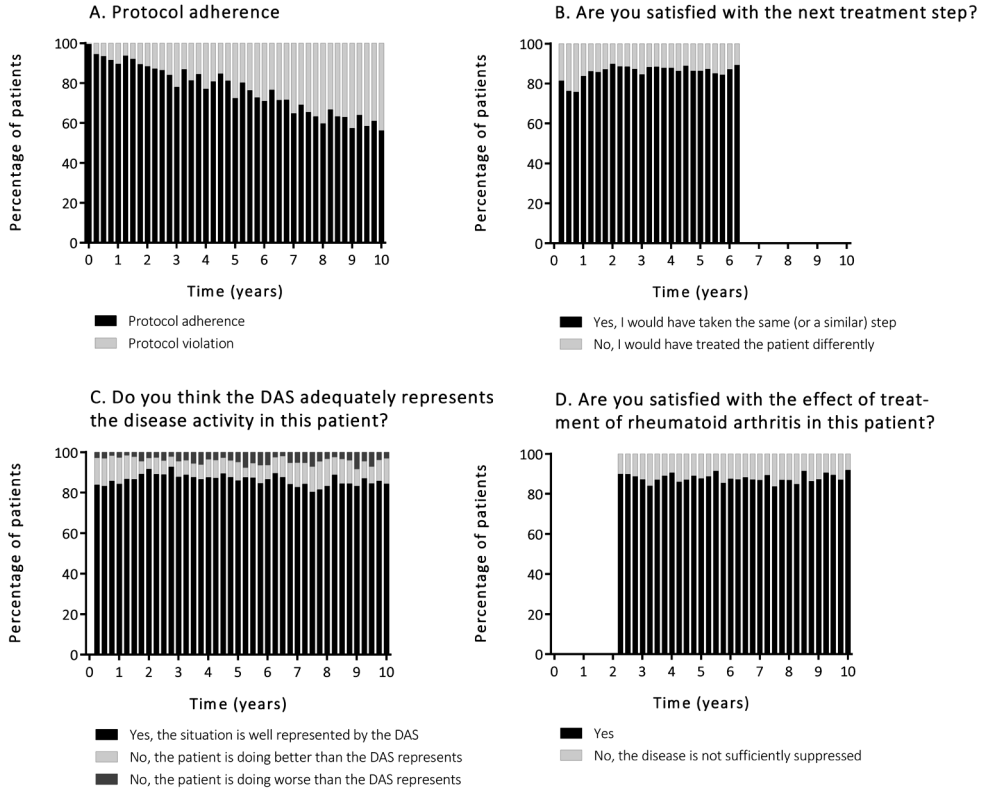

Figure 1. Frequencies of protocol adherence and physicians' answers to the questionnaire.
Note: These graphs show the available data only. Missing data and the number of drop outs increased over time up to 40% at year 10 for protocol adherence/ violation, 60% at year 10 for (dis)agreement with the DAS, 60% at year 10 for (dis)satisfaction with the effect of protocol and 80% for (dis)agreement with the effect of treatment. (A) protocol adherence was checked every visit; (B) question was asked every visit from the 2nd until the 26th visit in the 6th year of follow-up; (C) question was asked every visit from the 2nd until the last visit at 10 years of follow-up; (D) question was asked every visit from the 10th visit in year 3 until the last visit at 10 years of follow-up.
DAS, disease activity score.

≥2 painful joints but a swollen joint count ≤1 (condition 1) was not associated with more protocol violations (OR 0.96, 95% CI 0.85 – 1.09), nor was a high ESR but a swollen joint count ≤1 (condition 2, OR 1.05, 95% CI 0.87 – 1.25), nor a high patient's VAS for general health (>20 mm) with a swollen joint count ≤1 (condition 3, OR 0.94, 95% CI 0.83 – 1.06).
Similar protocol adherence was observed among the treatment strategies. Median (IQR) protocol deviation per patient year was 0.4 (0.1 – 0.9) in arm 1, 0.4 (0.1 – 1.0) in arm 2, 0.6 (0.2 – 1.0) in arm 3 and 0.6 (0.2 – 1.2) in arm 4 (p=0.119). Although we found some differences in adherence percentages between the individual centers, none of the centers showed significantly better or worse adherence than the others. Comparing the percentages

based on center characteristics did not reveal apparent features that seemed to influence adherence. For example, in the academic hospitals in 80% the protocol was followed, compared to 79% in peripheral hospitals (other data not shown).

Extra study visits were incorporated in the study protocol as optional one month after the regular visit if the rheumatologist felt that a DAS would reach ≤2.4 in the next month without a treatment adjustment at the regular visit. In total, 240 extra visits were scheduled for this purpose, 78 during the first year, when rheumatologists also recorded most often that the patient was doing better than the DAS suggested (Figure 1C), and 162 in the subsequent 9 years. In 31/78 extra visits in year 1 (40%) the DAS had decreased to ≤2.4, in 35/78 extra visits (45%) the DAS remained >2.4 and treatment was adjusted according to protocol, whereas in 12/78 extra visits (15%) there was a protocol violation. During year 2 to 10, fewer extra visits were scheduled because the rheumatologists believed that the DAS would further decrease without a treatment adjustment. They followed the study protocol in 79/162 extra visits (49%) where a DAS ≤2.4 was achieved and in 48/162 extra visits (30%) where the DAS remained >2.4. In 35/162 extra visits (22%), they deviated from the protocol.

Agreement with DAS

The frequency of rheumatologists' agreement with the DAS is illustrated in Figure 1C. In about 80 to 90% of the patients per visit, the rheumatologists felt that DAS adequately represented disease activity. When rheumatologists reported that the DAS did not adequately represent disease activity, they more often felt that the current DAS overestimated than underestimated the actual disease activity (Figure 1C). This links with our finding that non-adherence occurred more often when DAS was ≤2.4 than when it was >2.4.

First, we investigated the potential association between disagreement with DAS and the constructed conditions (Table 2) indicating possible discrepancies between joint inflammation and DAS measurement. We tested this both for disagreement with DAS due to overestimation (separately for conditions 1 to 4), and for disagreement due to underestimation according to the rheumatologist (condition 5). If the patient's VAS for general health was 20 mm or more higher than the physician's VAS, rheumatologists were more likely to report that the DAS overestimated actual disease activity (condition 4, OR 3.32, 95% CI 2.88 – 3.83). A tender joint count ≥2 but a swollen joint count ≤1 was not associated with rheumatologists reporting that the DAS overestimated disease activity (condition 1, OR 1.11, 95% CI 0.96 – 1.28), nor a high ESR with low swollen joint count (condition 2, OR 1.03, 95% CI 0.82 – 1.28). A high VAS with a low swollen joint count seemed to decrease the risk of disagreeing with the DAS because of overestimation (condition 3, OR 0.85, 95% CI 0.74 – 0.99). A physician's VAS at least 20 mm higher than the patient's VAS was associated with rheumatologists reporting that the DAS underestimated actual disease activity (condition 5, OR 8.54, 95% CI 6.48 – 11.25) (see also Table 4).

Second, we examined whether there was an association between disagreement with the DAS and the height of the DAS. As can be expected, if the DAS was >2.4 it was more often felt to overestimate actual disease activity compared to when the DAS was <2.4 (OR 9.21, 95% CI

7.95 – 10.67), and if the DAS was <1.6, it was more often felt to underestimate actual disease activity compared to when the DAS was ≥1.6 (OR 2.23, 95% CI 1.82 – 2.74) (see also Table 4).

Satisfaction with treatment

In 85 to 90% of the visits, the rheumatologist was satisfied about the level of RA suppression as a result of the current treatment (Figure 1D). The probability of rheumatologists reporting to be satisfied with the effect of current medication increased with lower DAS (OR 63.54, 95% CI 48.85 – 82.65 if the DAS was <1.6, OR 7.67, 95% CI 6.47 – 9.08 if the DAS was >1.6 but ≤2.4, DAS >2.4 used as reference category) (see also Table 4).

The question about rheumatologist's agreement with the next treatment step according to the protocol was filled in for 85% of the visits in year 1 and 2. Over time, the response decreased to 55% of the visits still replied in year 5. In year 6 the question was abandoned. During year 1, 75 to 80% the rheumatologists were satisfied with the required treatment steps. In subsequent years, satisfaction slightly increased to 85 to 90% of filled in visits (p=0.732 for trend over time) (Figure 1B).

Table 4. GLMM with the DAS category and the presence of conditions as independent variables and several physicians' answers as dependent variable (first "Yes, I am satisfied with the effect of the treatment on the rheumatoid arthritis in this patient", then "the DAS does not adequately represents disease activity, the patients is doing better than the DAS represents", and at last "the DAS does not adequately represents disease activity, the patients is doing worse than the DAS represents").

		Satisfied with effect of treatment (n=7151)	
	n	**OR**	**95% CI**
DAS >2.4	3640	*ref*	*ref*
DAS ≥1.6- 2.4	4522	7.67	6.47 – 9.08
DAS <1.6	5788	63.54	48.85 – 82.65
		DAS overestimates actual disease activity (n=1108)	
	n	**OR**	**95% CI**
DAS ≤2.4	10310	*ref*	*ref*
DAS >2.4	3640	9.21	7.95 – 10.67
Any condition absent		*ref*	*ref*
Condition 1 present	2920	1.11	0.96- 1.28
Condition 2 present	1126	1.03	0.82- 1.28
Condition 3 present	3474	0.85	0.734- 0.99
Condition 4 present	4076	3.32	2.88- 3.83
		DAS underestimates actual disease activity (n=466)	
	n	**OR**	**95% CI**
DAS ≥1.6	8162	*ref*	*ref*
DAS <1.6	5788	2.23	1.82 – 2.74
Condition 5 absent	12014	*ref*	*ref*
Condition 5 present	544	8.54	6.48 – 11.25

95% CI, 95% confidence interval; DAS, disease activity score; GLMM, generalized linear mixed model; OR, odds ratio; ref, reference category.

DISCUSSION

We found a continued high willingness among rheumatologists to follow the treat-to-target therapy protocol of the BeSt study as it was embedded in their daily practice. In 60 to 95% of the visits the required treatment step was taken, even in most situations when rheumatologists reported to disagree with it. Still, reported disagreement with how the DAS represents actual disease activity, with the medication required in the next treatment step or with the extent to which disease activity was suppressed; all were found to be risk factors for non-adherence. In addition, when patients' and rheumatologists' estimation of disease activity differed considerably, rheumatologists more often deviated from the protocol.

These observations may be valuable for the implementation of targeted treatment in daily practice based on measurement of disease activity using a composite score such as the DAS, as is recommended in the management of RA patients.[7,8] Previous studies suggest that in daily practice the implementation of these recommendations is not yet completed, due to a number of reasons. First, the DAS could be felt to be too time consuming.[14,19] To ensure unbiased assessment of treatment outcomes, in the BeSt study, the DAS was calculated by a trained nurse who remained blind for treatment strategy, and rheumatologists were required to adjust medication based on that DAS. This may have avoided the 'time consuming' objections, but a previous study showed that being provided with a DAS does not necessarily promote targeted treatment.[11] Second, rheumatologists may feel that the provided DAS is too sensitive to non-rheumatic pain and inflammation to accurately represent actual disease activity.[16] Patients and physicians sometimes differ in their perspective of disease activity.[20,21] In the DREAM registry, where protocol adherence was on average 69%, the main reason for protocol deviation also was perceived discordance between DAS and disease activity.[22] We found that rheumatologists in the BeSt study more often disagreed with the DAS if there was a difference of ≥20 mm between the patient's and physician's VAS, but not when there was a discrepancy between swollen joint count and tender joint count, or a combination of an elevated ESR and low swollen joint count. This might indicate that rheumatologists are more prone to distrust a subjective score such as a VAS than an objective measure such as the ESR. With this interpretation, we should keep in mind that the patient's VAS has part in the determinant, and also in the level of the DAS, and could therefore influence physician's disagreement with the DAS.

Furthermore, we found that rheumatologists who disagreed with the DAS more often reported that it overestimated, not underestimated, actual disease activity. Non-adherence occurred more often when the DAS was ≤2.4. In addition, although the odds for protocol violation increased (with OR >2) when the rheumatologist disagreed with the DAS or with the next required treatment step, the risk of protocol violation only slightly increased (with OR 1.3) when rheumatologists reported to be dissatisfied with the effect of the current medication. Prevalence of protocol deviation was slightly lower in arm1 and 2 compared to arm 3 and 4 (0.4 versus 0.6 per patient year, no statically significant difference). This might indicate that rheumatologists were more often reluctant to taper medication than to intensify treatment

as required by the study protocol, but we cannot prove this hypothesis with our data.
Protocol adherence may have been stimulated by the fact that the treatment protocol was designed by the participating rheumatologists. Our results also suggest a learning curve, as after the first study year both agreement with DAS and with the treatment per protocol increased. This may have been encouraged by younger rheumatologists joining the BeSt study group, who through their training were more accustomed to the use of the DAS and following a treat-to-target strategy. However, subsequent treatment steps in the BeSt protocol were based on availability and preference of use of medications dating from study onset in 2000. In particular in the later years of the study, rheumatologists may sometimes have preferred to make other treatment choices with newer (biologic) drugs. Unfortunately, the question regarding agreement with the study protocol was omitted from year 6 of follow-up onwards. Based on our observations, it is our estimation that, even if rheumatologists deviated from the treatment protocol with their choice of drugs, they still adhered to the treat-to-target strategy. As specification of the type of protocol violation is not available in our database, it is impossible to assess the exact percentage of adherence to the treat-to-target strategy. Therefore, it could also be possible that the strategy of targeted treatment was abandoned more often over time, in particular in patients with persistent DAS >2.4 (with or without clinically active disease) or recurrent intolerances to medication, but we cannot substantiate this.
It is likely that the success of the treat-to-target design of the study, resulting in most patients achieving low disease activity and up to 50% even achieving DAS-remission,[5] has stimulated the rheumatologists to continue to follow the protocol. Also, rheumatologists might have been more willing to follow the treatment protocol because through the questionnaire they could vent their potential disagreements. To further promote protocol adherence, before each study visit the trial physicians provided the required treatment step in the medical records, for every possible DAS category. The option to schedule an extra study visit was provided if the rheumatologist wanted to postpone a treatment decision because it was felt that the DAS would further decrease to ≤2.4 within a month. These extra DAS evaluations were requested particularly in year 1 of the study. Since more than 80% of these extra visits resulted in the protocol being followed, this option appears to have been rather effective in averting protocol violations.
The rheumatologists were asked to fill in the questionnaires during daily practice and missing data could perhaps be attributed to a lack of time and 'questionnaire fatigue'. Over time, this motive also led to some questions being omitted or altered. Despite this, the BeSt study with ten year follow-up provided a large dataset for an analysis on day to day adherence to a treat-to-target treatment protocol in RA. Obviously, daily practice outside a trial often presents a different situation. It is known that outside a trial patients may be reluctant to treatment adjustments,[23,24] and the same may be true for rheumatologists.
Our results show a great willingness among rheumatologists to adhere to a DAS based treat-to-target protocol and consensus derived predefined treatment steps. We suggest that if

rheumatologists would adopt elements and structure of a clinical trial into daily practice, implementation of the targeted treatment recommendations might be improved.

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