Implementation of protocolized tight control and biological dose optimization in daily clinical practice: results of a pilot study

N Lesuis1, LM Verhoef1, LM Nieboer1, GA Bruyn2, P Baudoin2, RF van Vollenhoven3, MEJL Hulscher4, FHJ van den Hoogen1,5, AA den Broeder1

1Department of Rheumatology, Sint Maartenskliniek, Nijmegen, The Netherlands, 2Department of Rheumatology, MC Zuiderzee, Lelystad, The Netherlands, 3Unit for Clinical Therapy Research, Inflammatory Diseases (ClinTRID), Karolinska Institute, Stockholm, Sweden, 4IQ healthcare, Radboud Institute for Health Sciences, Radboud University Medical Centre, Nijmegen, The Netherlands, and 5Department of Rheumatology, Radboud University Medical Centre, Nijmegen, The Netherlands

Objectives: To assess the effects of education, guideline development, and individualized treatment advice on rheumatologist adherence to tight control-based treatment and biological dose optimization in rheumatoid arthritis (RA), psoriatic arthritis (PsA), and spondyloarthropathy (SpA) patients.

Method: This pilot study, among two rheumatologists and two specialized nurses in a general hospital, combined education, feedback, local guideline development, and individualized treatment advice. Outcomes (baseline and 1 year post-intervention) were the percentage of patients with a Disease Activity Score in 28 joints (DAS28) or Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) measured during the visit, mean DAS28/BASDAI, and the percentage of patients using a reduced biological dose. DAS28 outcomes only applied to RA and PsA patients, BASDAI outcomes only applied to SpA patients whereas outcomes on biological dose applied to all patients.

Results: A total of 232 patients (67% RA, 15% PsA, 18% SpA; 58% female, mean age 56 ± 15 years) were included in the study. The percentage of DAS28 and BASDAI measurements performed increased after the intervention [DAS28 15–51%, odds ratio (OR) 3.3, 95% confidence interval (CI) 2.1–5.5; BASDAI 23–50%, OR 2.2, 95% CI 1.0–5.5], with mean DAS28 and BASDAI scores remaining similar (DAS28: mean difference 0.1, 95% CI −0.3 to 0.5; BASDAI: mean difference 0.03, 95% CI −1.8 to 1.9). Use of a reduced biological dose increased from 10% to 61% (OR 3.9, 95% CI 2.4–6.5).

Conclusions: A multicomponent intervention strategy aimed at rheumatologists can lead to improved adherence to tight control-based treatment and a reduction in the use of biologicals in RA, SpA, and PsA patients.

Treatment of rheumatoid arthritis (RA) is based on tight control principles: setting a target, frequent assessment of disease activity, and a structured protocol to make treatment changes. This strategy leads to lower disease activity and less functional damage compared to usual care (1, 2). Unfortunately, the dissemination of tight control-based guidelines has insufficient influence on the daily practice of rheumatologists (3). For example, treatment is not always changed on time in case of active disease or patients are not receiving the correct disease-modifying anti-rheumatic drugs (DMARDs) (3).

According to the 2014 treat-to-target recommendations: ‘maintenance of the treatment target does not in itself imply maintenance of treatment’. This refers to biological DMARD (bDMARD) dose optimization, that is dose reduction or cessation of bDMARDs (4). In recent years, several studies have shown that this strategy can be successful in patients while preserving low disease activity (5, 6). The high costs and dose-related side-effects of bDMARDs make dose optimization a desirable goal for implementation in daily practice. Nevertheless, actual adherence does not seem to be optimal (7).

To date, tight control based-treatment and biological dose optimization have mainly been studied in RA. However, there is evidence that the same principles might be applied for patients with psoriatic arthritis (PsA) and spondyloarthropathy (SpA) (8, 9) and treat-to-target recommendations have been published recently (10).

In view of all the existing evidence, we conducted a pilot study to improve adherence to tight control-based treatment and bDMARD optimization using a multicomponent intervention strategy.

Method

This pilot study was conducted in a general hospital in The Netherlands with two rheumatologists and two...
specialized nurses between May and October 2014. Although the intervention was aimed at clinicians, outcomes were measured in patients. All adult patients with an ICD-9 code of 714.0 (RA), 696 (PsA), and 720 (SpA) who were using a bDMARD at study start and had visited their rheumatologist during the pre- and post-intervention periods were eligible for inclusion.

The intervention strategy consisted of: (i) an educational meeting combined with feedback and local guideline development (bDMARD dose optimization and tight control-based treatment of RA, PsA, and SpA), (ii) individualized treatment advice for all bDMARD users, written in their electronic health record (EHR), and (iii) feedback after 3 and 6 months. An example of the PowerPoint slides used during the educational meeting can be found in the Supplementary Material. This strategy was developed and provided by a rheumatologist–epidemiologist, a rheumatology PhD student, and an administrative assistant (AdB, NL, and LN, respectively) from the Sint Maartenskliniek, a specialized rheumatology clinic in The Netherlands, with experience in using tight control-based guidelines and dose optimization. The choice of the different steps was based on Cochrane reviews on effective interventions (11, 12) and previous experience of the authors. The various steps of the intervention took place between May and October 2014.

The outcome measures used in this study are outlined in Table 1. All outcomes were compared between the pre- and post-intervention periods. As the intervention took place between May and October 2014, the patients’ visits most closely situated before and after this time period were used as pre- and post-intervention visits, respectively. For all patients, a single visit in each period was used for data collection (data as recorded in the EHR).

The study hospital approved this study. The rheumatologists were informed beforehand about this study and asked if they would participate. As this was a quality assessment performed in the hospital where two authors of this study worked, no written informed consent was obtained from the patients. In addition, data collection was performed within the study hospital and directly afterwards all patient data were anonymized. Depending on the type of variable, descriptive statistics are presented as percentages with the accompanying absolute numbers or as means with standard deviations. Outcome comparisons between the two time periods were made using appropriate statistics (t-test or McNemar; two-sided, $\alpha = 0.05$). As bDMARD dose optimization, according to local guidelines, should only be conducted in patients with low disease activity (DAS28 < 3.2/BASDAI < 4 or, if not available, the judgement of the rheumatologist) and bDMARD use of minimally 6 months, a post-hoc sensitivity analysis was carried out on the percentage of patients using a reduced bDMARD dose, only including patients fulfilling both criteria. All analyses were performed using STATA version 13.

### Results

The four rheumatologists and nurses who participated in this study undertook all of the intervention steps. At study start, 258 RA, SpA, and PsA patients were using a bDMARD. Of those patients, 24 were lost to follow-up (eight had moved to another city; 16 had not visited the study clinic during the post-intervention period). The remaining 232 patients were included in the final analysis (Table 2).

### Table 1. Outcome measures.

| Outcome measure                                                                 | Patient population                      |
|-------------------------------------------------------------------------------|----------------------------------------|
| Percentage of patients with a disease activity measure                        | RA and PsA patients                     |
| DAS28                                                                          | SpA patients                            |
| BASDAI                                                                        |                                        |
| Mean score of the disease activity measures                                   | RA and PsA patients                     |
| DAS28                                                                          | SpA patients                            |
| BASDAI                                                                        |                                        |
| Percentage of patients using a reduced dose of their bDMARD                   | All patients using a bDMARD             |
| Percentage of patients using a concomitant cDMARD                             | All RA patients using a bDMARD          |

DAS28, Disease Activity Score in 28 joints; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; bDMARD, biological disease-modifying anti-rheumatic drug; cDMARD, conventional disease-modifying anti-rheumatic drug.

### Table 2. Description of the patient population (n = 232).

| Variable                          | Count (n) |
|-----------------------------------|-----------|
| Female, % (n)                     | 58 (131)  |
| Age (years), mean ± sd            | 56 ± 16   |
| Disease duration (years), mean ± sd| 9 ± 8    |
| Diagnosis, % (n)                  |           |
| RA                                | 67 (153)  |
| PsA                               | 15 (34)   |
| SpA                               | 18 (40)   |
| Type of bDMARD, % (n)             |           |
| Adalimumab                        | 42 (98)   |
| Etanercept                        | 22 (50)   |
| Tocilizumab                       | 13 (30)   |
| Other                             | 23 (54)   |

RA, Rheumatoid arthritis; PsA, psoriatic arthritis; SpA, spondyloarthropathy; bDMARD, biological disease-modifying anti-rheumatic drug; sd, standard deviation.
After the intervention, more disease activity measurements (DAS28 and BASDAI) were performed and more patients were using a concomitant DMARD (Table 3). Similarly, after the intervention, more patients were using a reduced biological dose while the disease activity remained stable (Table 3 and Supplementary Tables S1 and S2). Of note, after the intervention, 20 of the 232 included patients (9%) stopped taking bDMARDs. Nine of them stopped for reasons other than dose optimization (pregnancy, infection, ineffectiveness), leaving 11 patients who successfully stopped their bDMARD after dose optimization (5%).

Finally, the results of the sensitivity analysis on reduced bDMARD use, including only patients with data on disease activity and duration of bDMARD use (71% available), were no different from those of the primary analysis.

Discussion

To our knowledge, this is the first study within rheumatology describing an improvement strategy on tight control-based bDMARD dose optimization combining education, feedback, and individualized treatment advice. Our results suggest that the implementation of relatively new treatment principles in daily practice is feasible, resulting in increased adherence to tight control-based treatment and a sizable reduction in bDMARD use.

The main strengths of this study are the short time between the publication of positive trial results on bDMARD dose reduction and the conduct of this pilot study, the combined focus on tight control and dose optimization (with tight control being a necessary prerequisite for safe and patient-friendly tapering), and the inclusion of RA, PsA, and SpA patients to aid generalizability. The main limitation of our study is its small scale, indicating the need to replicate our trial in a larger sample of rheumatology describing an improvement strategy on tight control-based bDMARD dose optimization combining education, feedback, and individualized treatment advice. Our results suggest that the implementation of relatively new treatment principles in daily practice is feasible, resulting in increased adherence to tight control-based treatment and a sizable reduction in bDMARD use.

The main strengths of this study are the short time between the publication of positive trial results on bDMARD dose reduction and the conduct of this pilot study, the combined focus on tight control and dose optimization (with tight control being a necessary prerequisite for safe and patient-friendly tapering), and the inclusion of RA, PsA, and SpA patients to aid generalizability. The main limitation of our study is its small scale, indicating the need to replicate our trial in a larger sample of rheumatologists. In addition, our uncontrolled study design means we are not aware of any external factors during the study that could have influenced our results.

Within rheumatology, only few intervention studies on tight control implementation exist. One Canadian study also used education and feedback to improve daily practice (13), and found that education and feedback resulted in more disease activity measures being collected by the rheumatologists (DAS28 measurement increased from 43% to 57%). These results are in line with our study, although the increase in number of DAS28 measurements was higher in our study and the mean DAS28 lower (2.1 vs. 3.05) (13).

Of note, with our intervention strategy we were able to replicate the results from the only two randomized controlled trials on bDMARD dose optimization: the DRESS and STRASS studies (5, 14). For example, in the DRESS study, 43% of the RA patients could taper their adalimumab or etanercept dose and 20% could stop their bDMARD (5). In our pilot study even more patients used a reduced bDMARD dose (61%); however, fewer patients completely stopped their bDMARDs (9%). This might be explained by a shorter follow-up in our study (12 months vs. 18 months) and the inclusion of SpA patients, in whom stopping is probably less successful (15). Nevertheless, our study shows that replication of trial results in daily practice is possible, if sufficient attention is paid to optimal implementation of the required changes.

In other settings the separate components of our strategy have previously been shown to be effective (11, 12), but we cannot discriminate between the effects of the different components of our intervention strategy. To gain some insight into this issue, a short interview with the participating rheumatologists and nurses was conducted after the study. During this evaluation it was suggested that the individual treatment advice in the EHR of included patients was crucial because it acted as a reminder. In addition, the educational session and the development of local guidelines were seen as necessary prerequisites to changing results as other events in the same time period might have contributed to the observed results. However, we are not aware of any external factors during the study that could have influenced our results.

Table 3. Outcomes on DAS28, BASDAI, and bDMARD use.

| Outcome                                                                 | Pre-intervention (n = 232) | Post-intervention (n = 232) | MD or OR (95% CI) | p-value |
|------------------------------------------------------------------------|----------------------------|----------------------------|-------------------|---------|
| DAS28 performed*, % (n)                                               | 15 (29)                    | 51 (97)                    | OR 3.3 (2.1 to 5.2) | < 0.01  |
| BASDAI performed†, % (n)                                              | 23 (9)                     | 50 (20)                    | OR 2.2 (1.0 to 5.5) | 0.04    |
| DAS28*, mean ± sd                                                     | 2.2 ± 0.9                  | 2.1 ± 0.9                  | MD 0.1 (–0.3 to 0.5) | 0.51    |
| BASDAI†, mean ± sd                                                    | 4.4 ± 2.5                  | 4.3 ± 2.1                  | MD 0.03 (–1.8 to 1.9) | 0.97    |
| Patients using a reduced bDMARD dose†, % (n)                         | 10 (21)                    | 61 (124)                   | OR 3.9 (2.4 to 6.5) | < 0.01  |
| Patients using a concomitant cDMARD‡, % (n)                          | 42 (63)                    | 52 (72)                    | OR 1.1 (0.7 to 1.5) | 0.79    |

DAS28, Disease Activity Score in 28 joints; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; bDMARD, biological disease-modifying anti-rheumatic drug; cDMARD, conventional disease-modifying anti-rheumatic drug; MD, mean difference; OR, odds ratio; CI, confidence interval.

†Outcome assessed in patients with rheumatoid arthritis (RA) and psoriatic arthritis (PsA). †Outcome only assessed in patients with spondyloarthritis (SpA). ‡Outcome assessed in all bDMARD users. §Outcome only assessed in RA patients using a bDMARD.
behaviour. Finally, the feedback acted as a trigger to improve their practice and the close contact with the research team was evaluated positively.

Despite the use of our strategy in only one centre, our study has important practical implications as it shows that implementation of tight control and bDMARD dose optimization in daily practice is feasible. The enthusiasm of the rheumatologists and nurses at the study centre has strengthened our view that rheumatologists are able to apply new treatment strategies if they receive assistance in this regard. In our opinion, this study emphasizes the fact that implementation research is important in the field of rheumatology to bridge the gap between theory and practice. Therefore, we are planning a randomized controlled trial to assess the effectiveness of our intervention strategy in a multicentre study aimed at tight control-based bDMARD dose optimization: the RAIN-BOW (Rheumatoid Arthritis ImplemeNtation of Biological dose Optimization in the real World) study.

Acknowledgements

We thank M. de Waal and R. de Kort for their enthusiastic participation during the implementation of all changes, their hospitality and invaluable practical help with the data collection.

References

1. Schipper LG, van Hulst LTC, Grol R, van Riel PLCM, Hulscher MEJL, Fransen J. Meta-analysis of tight control strategies in rheumatoid arthritis: protocolized treatment has additional value with respect to the clinical outcome. Rheumatology (Oxford) 2010;49:2154–64.
2. Escalas C, Dalichampt M, Combe B, Fautrel B, Guillemin F, Durieux P, et al. Effect of adherence to European treatment recommendations on early arthritis outcome: data from the ESPOIR cohort. Ann Rheum Dis 2012;71:1803–8.
3. Harrold LR, Harrington JT, Curtis JR, Furst DE, Bentley MJ, Shan Y, et al. Prescribing practices in a US cohort of rheumatoid arthritis patients before and after publication of the American College of Rheumatology treatment recommendations. Arthritis Rheum 2012;64:630–8.
4. Smolen JS, Breedveld FC, Burmester GR, Bykerk V, Dougados M, Emery P, et al. Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force. Ann Rheum Dis 2016;75:3–15.

Supporting Information

Additional Supporting Information may be found in the online version of this article.

Supplementary Material: PowerPoint slides used during the educational meetings.
Supplementary Table S1. Outcomes on bDMARD use per patient category.
Supplementary Table S2. Outcomes on bDMARD use per bDMARD.

Please note that the editors are not responsible for the content or functionality of any supplementary material supplied by the authors. Any queries should be directed to the corresponding author.