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Reduced prescription of TNF-inhibitors in chronic arthritis based on therapeutic drug monitoring: A randomized controlled trial

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Objective: Dosing of tumour necrosis factor-α inhibitors (TNFis) is not personalized causing interindividual variation in serum drug levels; however, dose optimization is not widely implemented. We hypothesized that some patients areoverdosed; thus, drug prescription could be reduced by therapeutic drugmonitoring (TDM).

Method: Independent of disease activity, 239 adults treated for rheumatoid arthritis (n = 99), psoriatic arthritis 15 (n = 48), or spondyloarthritis (n = 92) were recruited for a 48-week prospective, randomized open-label trial. Standard care alone or plusTDM was applied in chronic arthritis patients treated with infliximab (IFX), (n= 81), etanercept (ETN) (n = 79), or adalimumab (ADA) (n = 79). Serum TNFitrough levels assessed at inclusion and every 4 months determined patientswithin/outside predefined therapeutic intervals, supporting change inprescription or drug switch. The primary endpoint was reduced drugprescription.

Results: Compared to standard care, TDM reduced prescribed IFX [−12% (95% confidence interval −20, −3); p = 0.001] and ETN (−15% (−29, 1); p = 0.01], and prolonged the interdosing intervals of ETN [+235% (38, 432); p = 0.02] and ADA [+28% (6, 51); p = 0.04]. Time to drug switch was accelerated ($\chi 2$ = 6.03, p = 0.01). No group differences in adverse events, disease activity, or self-reported outcomes were shown, indicating equally sustained remission.

Conclusions: TDM reduced prescription of IFX, ETN, and ADA and identified patients benefiting from accelerated drug switch, thereby minimizing treatment failure, risk of toxicity, and unnecessary adverse events.

Inflammatory joint diseases are characterized by chronic synovial inflammation and peripheral and axial joint destruction. Tumour necrosis factor-α inhibitors (TNFis) diminish the inflammatory response by targeting the potent pro-inflammatory cytokine tumour necrosis factor-α (TNF-α). The introduction of TNFis improved treatment responses and prognoses for many, including patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA), and spondyloarthritis (SpA) (1–3). However, it was acknowledged that not all patients were in remission (4–7). The first three TNFis to be marketed, which are still frequently used, are infliximab (IFX), etanercept (ETN), and adalimumab (ADA). These TNFis are typically dosed according to standard regimens, without adjusting for individual pharmacokinetic differences, causing different serum concentrations at the same prescription. Up to one-third of chronic arthritis patients change anti-rheumatic treatment every year (8, 9), with dose adjustments and drug switches based on clinical judgement, experienced adverse events, and self-reported treatment efficacy (7, 10–15).

Dosing of TNFis is currently not personalized and there is considerable interindividual variation in serum drug levels. Therapeutic drug monitoring (TDM) is an individualized treatment strategy based on repetitive assessments of serum trough levels, suggested for optimizing individual treatments and lowering costs (16). However, dose optimization is not widely implemented. The strategy supports tapering, which should be furter unravelled, since clinical studies indicate associations between treatment efficacy and IFX serum trough levels in RA (17) and inflammatory bowel disease (IBD) (18), and ETN trough levels and clinical outcomes in

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rheumatic disorders (19, 20). The clinical need for TDM in TNFi prescription is, however, still debated, and only a few randomized clinical trials (RCTs) exist. For example, the NOR-DRUM study failed to show that TDM caused a significant difference in 30 weeks in patients who initiated IFX treatment (21, 22), however TDM has proven to be more effective than treatment without TDM in sustaining disease control without disease worsening (23). Furthermore, ETN tapering was implemented without losing clinical efficacy in patients with sustained minimal disease activity treated for RA, PsA, and AS (24). In parallel, concentration–efficacy curves have been shown for ADA (19, 25–27).

This has led to suggestions of TDM based on serum trough levels, allowing reduced drug prescriptions leading to fewer potential adverse events, and benefits for the healthcare system by lowering the cost spend on medication (16). While several meta-analyses have confirmed the clinical benefit of measuring serum trough levels of TNFis in IBD, controversies in the literature exist and similar prospective data are still lacking in the treatment of RA, PsA, and SpA (1, 16, 28). This knowledge gap is reflected in the recent American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) treatment guidelines, where serum trough levels are not implemented in decision making in TNFi treatment failure (1, 7, 29). Therefore, serum trough levels within/outside therapeutic intervals may add objective value in clinical decision making. We thus hypothesized that a number of patients are overdosed and that drug prescription can be reduced by TDM. Furthermore, we hypothesized that TDM would accelerate the time to drug switch in those not benefiting from the prescribed treatment. Thus, the aim was to investigate whether TDM on top of standard care according to EULAR guidelines could reduce individual drug prescription of TNFis (assessed as reduced dosing or prolonged interdosing interval) or accelerate the time to drug switch. To ensure clinical relevance, we challenged existing treatment regimens in consecutive patients with arthritis treated at a Danish university hospital outpatient clinic.

Method

This open RCT was conducted from March 2016 to August 2018 at the Department of Rheumatology, Aarhus University Hospital, Denmark. We included patients with chronic RA treated with IFX (n = 81), ETN (n = 79), or ADA (n = 79) at the study start, according to ACR/EULAR guidelines. Inclusion criteria were age ≥ 18 years, minimum 3 months of treatment with IFX, ETN, or ADA, with a verified diagnosis of RA (n = 99) according to ACR/EULAR (30), PsA (n = 48) according to ClASsification criteria for Psoriatic ARthritis (CASPAR) criteria (31), or SpA (n = 92) according to Assessment of SpondyloArthritis international Society (ASAS) criteria (32). Exclusion criteria were according to TNFi treatment, and included malignancy, tuberculosis, pregnancy/breastfeeding, cardiovascular failure (New York Heart Association III/IV), or allergies. Thus, patients with either remission or flare were eligible for participation.

The Central Region of Denmark granted ethical approval (1-16-02-567-15) and all participants gave written informed consent. The study (EUDRA-CT2015 -004173-32) was performed in accordance with the International Council for Harmonization Good Clinical Practice and the Declaration of Helsinki.

Design

According to Danish guidelines, conventional standards of care aimed at the start of the study to treat to target using classical disease-modifying antirheumatic drugs (DMARDs) and biologics, primarily IFX, ETN, and ADA. Hence, patients treated with IFX, ETN, and ADA were block-randomized, allocated 1:1 (www.randomizer.at), and followed prospectively, while receiving either standard of care plus therapeutic drug monitoring (TDM) or standard of care (standard).

All patients underwent four doctoral examinations dispersed over approximately 4 months, where trough levels were obtained regardless of individual interdosing interval (IFX 6–8 weeks, ETN 1–2 weeks, and ADA 2–3 weeks). To ensure compliance with the protocol, they received three personal telephone calls from the study personnel approximately halfway through the treatment periods. The serum trough levels of IFX were obtained just before IFX infusion at visits 1 (V1), V3, V5, and V7, whereas the serum trough levels of ETN and ADA were obtained the day before the next self-administration of TNFi (Figure 1). Blood was obtained in silicone-coated full blood glasses with no anticoagulant and centrifuged before serum was stored at −20°C until analysis.

Intervention

Drug concentrations were analysed consecutively, by enzyme-linked immunosorbent assay (ELISA), according to Sanquin (Amsterdam, the Netherlands). Serum values were only released in the TDM group and were used for clinical decision making. In contrast, serum values from the standard group were kept blinded until the study was finalized.

In the TDM group, the clinicians used the serum trough levels to support clinical decision making for continued TNFi prescription.

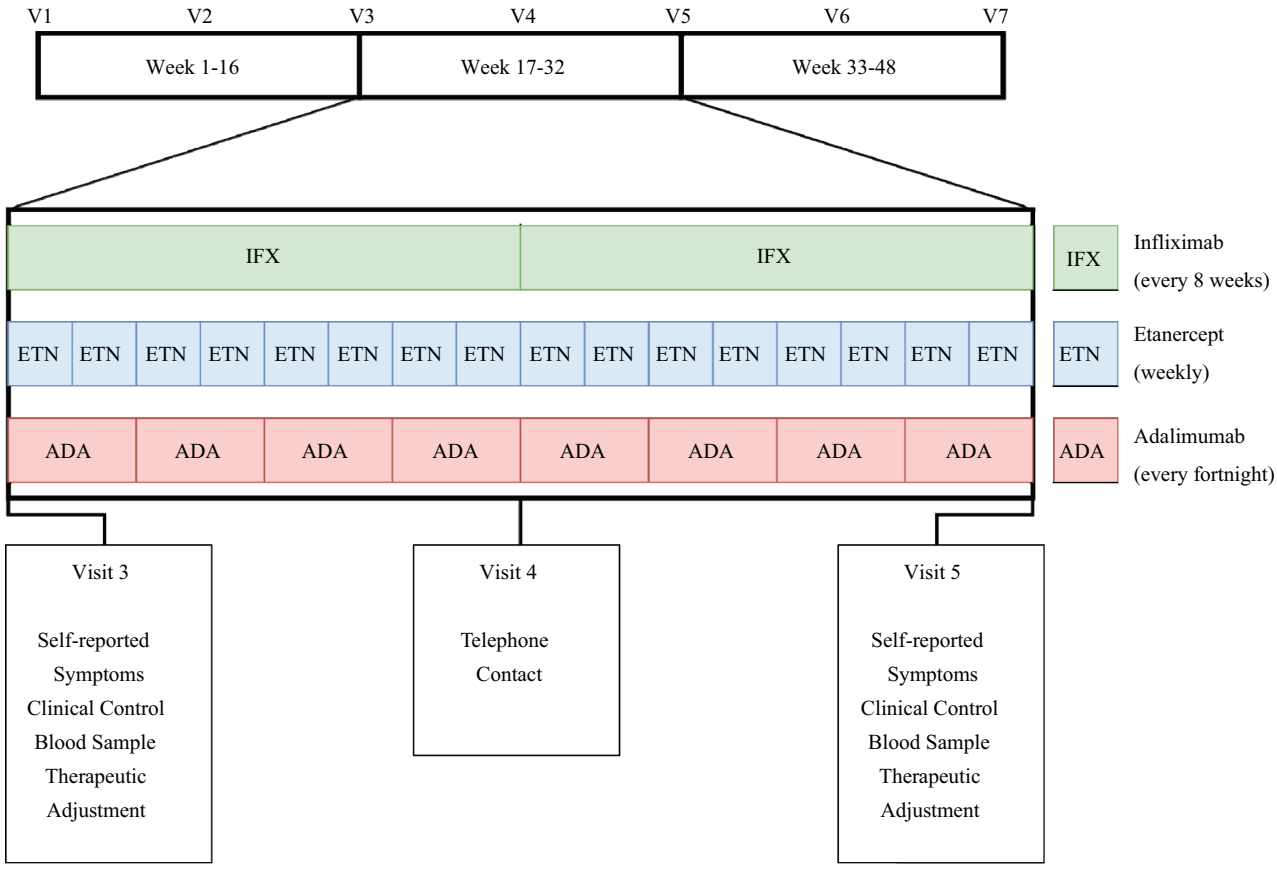

Figure 1. Schematic overview of the protocol allowing therapeutic drug monitoring (TDM) in three different tumour necrosis factor-α inhibitors: infliximab (IFX), etanercept (ETN), and adalimumab (ADA). The interdosing interval varies substantially and is determined based on the terminal half-life in plasma, ranging from 1 week (ETN) to 8 weeks (IFX). Participants were block-randomized 1:1 to the standard of care or standard of care plus TDM and followed for 48 weeks. Blood was drawn at clinical visit 1 (V1), V3, V5, and V7, and drug serum concentrations were measured to support clinical decision making. Dose adjustments were undertaken based on a series of the four measured drug concentrations (V1, V3, V5, and V7) and a clinical examination. V2, V4, and V6 were telephone contacts to ensure that participants were in remission and to answer questions related to potential dose adjustments.

Therapeutic drug monitoring

Based on previous publications, the following therapeutic intervals were used: IFX 1.5–6.5 mg/L, ETN > 1.5 mg/L, and ADA 5–8 mg/L (20, 25, 33). In the TDM group, we identified patients within/outside therapeutic intervals and used the following procedures for further treatment. (i) The prescription was sustained when the serum trough levels were within the therapeutic interval and the patient was in remission. (ii) The prescription was reduced by approximately 33% (range 28–36% depending on administration route) when serum trough levels were above the upper limit of the therapeutic interval (overdosed). For example, in IFX treatment the dose was reduced by 33% while maintaining identical interdosing intervals. As ETN comes in two doses, reduction aiming at 33% was done by either changing from 50 mg to 25 mg and shortening the interval from 7 to 6 days (35% reduction) or maintaining the dose and prolonging the interval from 7 to 9 days (28%). Dosing was maintained for ADA; however, the interdosing interval was prolonged from, for example, 14 to 18 days (29%). (iii) Treatment was paused when serum trough levels were lower than the lower limit in the therapeutic interval and patients were in clinical remission, defined by disease activity scores [Disease Activity Score based on 28-joint count–C-reactive protein (DAS28-CRP) or Ankylosing Spondylitis Disease Activity Score based on C-reactive protein (ASDAS-CRP)]. In the case of relapse during the pause, either evaluated at the first scheduled clinical visit or earlier if requested, treatment was re-established with the same TNFi regimen before pausing. (iv) Drug switch to other biologics (including treatment with other TNFis if patients were naïve to these) was established according to the Danish standard treatment algorithm (34) if serum trough levels were within or lower than the therapeutic interval and the patient had disease activity, as treatment was interpreted as non-therapeutic.

Treatment adjustments

Treatment adjustments were defined as any treatment changes, and included numbers of patients who had

their drug prescription reduced or increased, or who underwent drug switch to other biologics.

Adverse events

Any episodes of adverse events were categorized into infections, skin rash, or others. Severity was assessed clinically as mild (locally and easy to tolerate), moderate (systemic and unpleasant, interfering with normal daily activities), or severe (systemic and disabling, preventing normal daily activities). Since mild symptoms were judged to be unrelated to treatment, only moderate and severe adverse events were reported, e.g. number of hospitalized patients and numbers of total hospitalizations.

Disease activity and self-reported outcomes

At the doctoral visits V1, V3, V5, and V7, patients were monitored for disease activity by the use of the validated clinical scores DAS28-CRP and ASDAS-CRP (1, 2, 7). DAS28-CRP is a composite score used in RA and PsA incorporating the number of swollen and tender joints (out of 28), a measure of C-reactive protein (CRP), and the self-reported 'global assessment of health'. DAS28-CRP > 5.1 implies active disease, < 3.2 implies low disease activity, and < 2.6 implies remission. ASDAS-CRP is an index to assess pain in SpA, based on information regarding back pain, morning stiffness, patient-assessed global pain, number of painful joints, and CRP. Values > 3.5 are defined as 'high or very high disease activity', > 2.1 is defined as 'moderate disease activity', and < 1.3 is defined as remission.

Furthermore, clinical variables including age, gender, symptom duration, and time since diagnosis reported to the Danish National register (DANBIO) system were used, and patients were asked to electronically fill out self-reported outcomes, including the Health Assessment Questionnaire (HAQ) and global pain. The HAQ includes sections addressing dressing, arising, eating, walking, hygiene, reach, grip, and activities, with two or three questions for each section. Scoring within each section ranges from 0 (without any difficulty) to 3 (unable to do).

Outcomes

The primary outcome was a mean reduction in prescribed TNFis, assessed from baseline (V1) to end of study (V7). Secondary outcomes were (i) time to drug switch from inefficient TNFi treatment, (ii) treatment dynamics, (iii) adverse events, (iv) difference in disease activity from V1 to V7, and (v) difference in self-reported HAQ and global pain.

Justification of sample size

To detect a 10% reduction in prescribed TNFi medication in participants undergoing TNFi treatment, with a desired statistical power of 0.8 (two-tailed $\alpha = 0.05$), a total of 35 participants were required in each group, and to allow for 10% dropout, we intended to include 80 ± 1 participants in each TNFi group.

Statistical analysis

Intention-to-treat analyses were performed after the last participant had finalized study visit 7. In addition, per-protocol analysis was performed including participants who were compliant during the intervention but, for example, stopped treatment according to the protocol. Descriptive normally distributed data were shown as mean with 95% confidence interval (CI) and non-normally distributed data as median (interquartile range Q1, Q3). During the study, drug prescription was reported as treatment dose, interdosing interval, and serum trough levels; clinical outcomes, including CRP, clinical composite scores (DAS28-CRP and ASDAS-CRP), and self-reported outcome (HAQ and VAS Pain), were compared using linear mixed model analysis with repeated factor = visiting time and comparison factors 1 = visiting time and 2 = standard of care versus TDM.

Changes from baseline and delta values in drug prescription, clinical outcomes, and self-reported outcomes were compared between the groups receiving standard of care and TDM using the independent samples t-test for normally distributed data. For non-normally distributed data, the independent samples Mann–Whitney U-test or Fisher's exact test was selected according to similarities in the distribution curve between the groups.

At the study end, the actual numbers of participants who had an adjusted prescription, e.g. reduced therapeutic dose, had changed interdosing intervals, had switched to other drugs, and experienced adverse or serious adverse events, were compared between the groups using the chi-squared test. All analyses were conducted using IBM SPSS Statistics (version 26; IBM). A p-value less than 0.05 was considered statistically significant.

Results

We included 239 consecutive patients with confirmed rheumatological diagnoses, who received TNFi treatment with IFX, ETN, or ADA, and followed them prospectively for 346 ± 75 days. Baseline characteristics are provided in Table 1. CONSORT flowcharts of the treatment adjustments are available in Supplementary Figure S1(A)–(C).

Table 1. Baseline characteristics of the participants receiving treatment with infliximab, etanercept, and adalimumab.

	Infliximab			Etanercept			Adalimumab		
	TDM (n = 40)	Standard (n = 41)	p	TDM (n = 41)	Standard (n = 38)	p	TDM (n = 40)	Standard (n = 39)	p
Gender, male, (%)	19 (48)	23 (56)	0.439	10 (24)	11 (28)	0.647	22 (55)	16 (39)	0.214
Age (years)	47.1 (15)	44.3 (16)	0.617	53.0 (14)	50.6 (16)	0.91	53.2 (14)	59 [27]	0.1
Height (cm)	173 (9)	173 (10)	0.296	171 (9)	169.9 (10)	0.616	174 (9)	172 [14]	0.311
Weight (kg)	75 (14)	79 (18)	0.777	70 [27]	73 [28.5]	0.631	78.3 (16)	76.9 (20)	0.162
BMI (kg/m^2)	25 (4)	26 (4)	0.711	23.5 [7.8]	24.8 [7.1]	0.996	24.6 [4.9]	26.1 (5.8)	0.07
Disease duration (years)	5.5 [11.8]	6.0 [11]	0.85	10.0 [19]	13.5 [15]	0.76	14.5 [17]	16.4 (10.5)	0.965
Dose (mg)	376 (86)	387 (114)	0.214	49.4 (4)*	48.0 (6.8)*	0.668	40 (0)	40 (0)	n/a
Dose interval (weeks)	6.0 [2.0]	6.0 [2.0]	0.73	1.0 (0.2)*	1.0 (0.2)*	0.82	2.0 [1.0]	2.0 [1.0]	0.932
Drug concentration (mg/L) (n = 79)	5.6 [7.4]	4.2 [9.7]	0.51	1.4 [1.4]	1.6 [1.8]	0.705	5.6 (3)	6.0 (4)	0.617
MTX, n (%)	14 (33)	20 (49)	0.243	19 (46)	18 (47)	0.625	13 (31)	18 (46)	0.214
CRP (mg/L) (n = 80)	1.0 [3.0]	1.3 [3.0]	0.74	1.4 [3.0]	2.0 [3.3]	0.212	1.6 [1.0]	1.5 [5.0]	0.234
DAS28-CRP (n = 33)	2.9 (1.3)	2.1 (1.7)	0.311	2.0 [1.4]	2.2 (0.7)	0.316	1.6 [1.1]	2.1 (0.7)	0.503
ASDAS-CRP (n = 32)	1.6 [1.4]	1.8 (0.7)	0.46	2.4 (0.9)	2.0 (0.8)	0.503	1.4 [1.2]	1.3 [1.1]	0.327
VAS Pain (n = 80)	23.5 [26.3]	34.9 (24)	0.179	31.0 [38]	39.5 (40)	0.668	16.0 [32]	18.0 [39]	0.344
HAQ (n = 81)	0.38 [1.0]	0.5 [0.9]	0.34	0.8 [1.3]	0.5 [1.2]	0.743	0.1 [0.7]	0.4 [0.7]	0.619
Painful joints (n = 74)	0.0 [2.0]	1.1 (4)*	0.203	0.0 [1.0]	0.3 (0.7)*	0.743	0.1 (0.4)*	0.4 (1.0)*	0.878
Swollen joints (n = 74)	0.4 (1.2)*	0.3 (1.1)*	0.135	0.5 (1.6)*	0.2 (0.4)*	0.668	0 (0.2)*	0.3 (1.5)*	0.998

Data are shown as mean (sd) for normally distributed data, median [interquartile range] for non-normally distributed data, and frequency (%) for ordinal or nominal data.
*Data are shown as mean (sd) for the non-normally distributed data when the median, Q1, and Q3 data were identical.
n, number of patients; TDM, therapeutic drug monitoring; BMI, body mass index; MTX, methotrexate; CRP, C-reactive protein; DAS28-CRP, Disease Activity Score based on 28-joint count–C-reactive protein; ASDAS-CRP, Ankylosing Spondylitis Disease Activity Score based on C-reactive protein; VAS, visual analogue scale; HAQ, Health Assessment Questionnaire.
p-Values show the comparison between the standard of care (standard) group and standard of care plus TDM group.

Prescription of TNFis

In comparison to standard care, TDM caused a significant dose reduction in IFX [−12% (95% CI −20, −3); p < 0.001] and ETN [−15% (95% CI −29, −1); p < 0.001], and a trend towards reduction in ADA [–9% (95% CI –20, 1); p = 0.07]. Furthermore, TDM prolonged the interdosing interval in ETN [+235% (95% CI 38, 432); p = 0.03] and ADA [+28% (95% CI 6, 51); p = 0.03]. Details are presented in Table 2 and Figure 2. Of note, the TDM-induced dose reduction was not accompanied by a difference in the mean serum concentration of IFX, ETN, or ADA.

Treatment adjustments

Detailed information on the treatment adjustments is presented in the supplementary material.

In comparison to standard, during the study, TDM resulted in more frequent dose reduction in IFX treatment (19 vs 2 patients) and less frequent dose increase (5 vs 8 patients) (χ^2 = 14.9, p = 0.001). This was also the case at the end of the IFX study (13 patients vs 1 patient for dose reduction and 5 vs 8 patients for dose increase; χ^2 = 17, p < 0.001). Consistent results were obtained for ADA, where more participants were reduced (10 patients vs 1 patient) and fewer participants were increased (0 patients vs 1 patient) in comparison to the standard of care (χ^2 = 8.6, p = 0.01). More participants had prolonged interdosing intervals during (22 vs 6 patients; χ^2 = 9.32, p = 0.009) and at the end of the ADA study (10 vs 2 patients; χ^2 = 7.87, p = 0.02). Finally, TDM accelerated the switch to other biologics in comparison to standard of care (e.g. 11 vs 2 participants at V3 for all three drugs; χ^2 = 6.65, p = 0.036).

Adverse events

No difference in total experienced adverse events between the groups was shown for IFX, ETN, or ADA (χ^2 < 3.8, p > 0.15), nor were any differences found in the total number of hospitalized patients (χ^2 < 3.3, p > 0.07) or the total number of hospitalizations (χ^2 < 2.99, p > 0.08).

Clinical outcome

In the TDM group, patients diagnosed with RA and PsA, who have been prescribed ADA, experienced a reduction in the clinical composite score DAS 28-CRP in comparison to standard care (Figure 3). No other differences were shown.

Table 2. Outcomes between the standard care and therapeutic drug monitoring (TDM) groups in treatment with infliximab, etanercept, and adalimumab.

Infliximab

	Baseline		End of study		Absolute difference, baseline and study end			Relative difference, baseline and study end		
	TDM (n = 40)	Standard (n = 41)	TDM (n = 29)	Standard (n = 35)	TDM	Standard	p	TDM (%)	Standard (%)	p
Dose (mg)	376.3 (348.7, 403.8)	387.8 (351.7, 423.9)	327.8 (286.9, 368.6)	397.1 (356.1, 438.2)	0.00 [–100, 0.0]	11.4 (–0.4, 23.3)*	0.006	–11.6 (–20, –3)*	3.8 (0.6, 7.0)*	0.005
Interdosing interval (weeks)	6.00 [6.0, 8.0]	6.00 [6.0, 8.0]	6.0 [6.0, 8.0]	7.00 [6.0, 8.0]	–0.07 (–0.3, 0.1)*	0.12 (–0.05, 0.3)*	0.17	–1 (–3.2, 1.4)*	1.8 (–1, 5)*	0.163
Drug concentration (mg/L)	5.60 [2.5, 9.9]	4.20 [1.1, 10.8]	5.38 (4.1, 6.7)	4.00 [1.7, 7.9]	–0.35 [–1.0, 1.1]	–0.4 [–2.9, 0.8]	0.607	–6 [–32, 34]	17.7 [–44, 34]	0.612
CRP (mg/L)	1.00 [1.0, 4.0]	1.30 [1.0, 4.0]	1.00 [0.78, 3.15]	2.00 [1.0, 5.8]	0.00 [–0.8, 0.3]	0.10 [0.0, 1.3]	0.239	–8 [–50, 95]	3.3 [–2.5, 56]	0.402
DAS28-CRP	2.85 (2.1, 3.6)	2.05 [1.7, 3.4]	2.21 (1.62, 2.81)	2.60 (2.17, 3.03)	–0.10 (–0.8, 0.6)	0.20 [–0.03, 0.8]	0.089	1.5 (–28, 31)	8.1 [–1, 42]	0.133
ASDAS-CRP	1.60 [1.1, 2.5]	1.82 (1.4, 2.2)	1.30 [0.93, 2.45]	1.94 (1.28, 2.60)	0.10 [–0.5, 0.5]	–0.09 (–0.6, 0.4)	0.99	–9 [–33, 29]	–4 (–28, 20)	0.930
VAS Pain	23.5 [12.5, 38.8]	34.9 (27.4, 42.4)	18.0 [9.0, 43.0]	35.8 (27.5, 44.2)	–1.00 [–9.0, 10.0]	2.00 [–7.0, 11.3]	0.442	–29.4 [–50, 71]	10.1 [–17, 41]	0.270
HAQ	0.38 [0.0, 1.0]	0.50 [0.1, 1.0]	0.25 [0.0, 1.0]	0.63 [0.3, 1.0]	0.0 [0.0, 0.1]	0.0 [0.0, 0.1]	0.523	–5 (–22, 12)	0.0 [–11, 46]	0.404

Etanercept

	Baseline		End of study		Absolute difference, baseline and study end			Relative difference, baseline and study end		
	TDM (n = 41)	Standard (n = 38)	TDM (n = 28)	Standard (n = 29)	TDM	Standard	p	TDM (%)	Standard (%)	p
Dose (mg)	49.4 (48.2, 50.6)*	48.0 (45.8, 50.3)*	42.6 (35.4, 49.8)*	49.1 (47.4, 50.9)*	–7.4 (–14.6, 0.25)*	1.72 (–0.7, 4.2)*	0.026	–14.8 (–29, 1)*	6.9 (–2.9, 17) *	0.03
Interdosing interval (weeks)	1.04 (1.0, 1.1)*	1.04 (0.98, 1.1)*	3.66 (1.5, 5.8)*	1.07 (0.98, 1.2)*	2.60 (0.4, 4.8)*	0.02 (–0.01, 0.06)*	0.03**	235 (36, 432)*	2.2 (–1, 6)*	0.0**
Drug concentration (mg/L)	1.40 [1.0, 2.35]	1.60 [1.0, 2.8]	1.85 (1.47, 2.24)	1.82 (1.37, 2.27)	–0.30 [–0.6, 0.3]	0.10 [–0.4, 0.6]	0.174	–6 (–23, 11)	10 [–17, 39]	0.270
CRP (mg/L)	1.40 [1.0, 4.0]	2.00 [1.0, 4.3]	1.05 [1.0, 2.0]	2.0 [1.0, 4.0]	–0.25 [–2.1, 0.9]	–0.12 (–1.5, 1.2)	0.714	–28 [–72, 100]	0.00 [–50, 70]	0.454
DAS28-CRP	2.00 [1.5, 2.9]	2.15 (1.8, 2.5)	1.98 (1.65, 2.31)	1.7 [1.5, 2.3]	–0.06 (–0.4, 0.3)	0.09 (–0.4, 0.2)	0.89	–7 [–18, 25]	9.7 [–21, 0]	0.621
ASDAS-CRP	2.40 (1.72, 3.08)	2.03 (0.7, 3.3)	2.17 (1.29, 3.05)	2.33 (0.74, 3.92)	–0.20 [–0.6, 0.3]	0.45 (–0.2, 1.1)	0.62	–8 [–22, 14]	26.8 (–95, 148)	0.690
VAS Pain	31.0 [21.0, 58.5]	39.5 (28.9, 50.1)	40.9 (60.7, 51.2)	25.5 [6.3, 56.5]	3.35 (–5.4, 12.1)	0.65 (–8.4, 9.7)	0.67	0.00 [–50, 65]	9 [–44, 44]	0.990
HAQ	0.75 [0.13, 1.38]	0.50 [0.0, 1.2]	0.69 (0.44, 0.94)	0.63 [0.0, 1.1]	0.09 (–0.02, 0.2)	0.02 (–0.1, 0.2)	0.45	30 (3, 56)	4 [–20, 46]	0.518

(*Continued*)

Table 2. (Continued).

Adalimumab

	Baseline		End of study		Absolute difference, baseline and study end			Relative difference, baseline and study end		
	TDM (n = 40)	Standard (n = 39)	TDM (n = 32)	Standard (n = 33)	TDM	Standard	p	TDM (%)	Standard (%)	p
Dose (mg)	40 [40, 40]	40 [40, 40]	36.25 (32.0, 40.5)	40 [40, 40]	−3.75 (−8.0, 0.5)*	0 (0, 0)	0.07	−9 (−20, 1)*	0 (0, 0)	0.07
Interdosing interval (weeks)	2.0 [2.0, 3.0]	2.0 [2.0, 3.0]	2.0 [2.0, 3.0]	2.0 [2.0, 2.5]	0.00 [0.0, 0.8]	1.00 (−0.06, 0.3)*	0.03**	28.3 (5.6, 51)*	4.4 (−2, 11)*	0.0**
Drug concentration (mg/L)	5.64 (4.6, 6.7)	5.1 (3.5, 7.7]	5.52 (4.5, 6.6)	4.6 (2.1, 7.8]	−0.21 (−1.2, 0.7)	−0.87 (−1.8, 0.05)	0.32	2 [−35, 20]	−7 (−26, 12)	0.34
CRP (mg/L)	1.55 [1.0, 2.0]	1.5 [1.0, 6.0]	1.0 [0.9, 2.35]	2.0 [1.0, 6.5]	0.00 [−1.0, 0.5]	0.00 [−0.5, 2.2]	0.16	0.00 [−50, 13]	0.00 [−38, 65]	0.30
DAS28-CRP	1.55 [1.3, 2.4]	2.10 (1.8, 2.4)	1.5 [1.3, 2.1]	2.24 (1.86, 2.63)	0.00 [−0.2, 0.2]	0.10 (−0.1, 0.3)	0.41	0 (−10, 10)	9 (−2, 21)	0.34
ASDAS-CRP	1.35 [1.0, 2.2]	1.30 [0.8, 1.9]	1.35 [0.7, 2.3]	1.4 [0.9, 1.9]	−0.10 [−1.1, 1.3]	0.18 (−0.5, 0.9)	0.29	−0.9 (−37, 35)	17 [−20, 73]	0.290
VAS Pain	16.0 [3.5, 36.0]	18.0 [7.5, 46.5]	17.0 [3.0, 36.0]	22.0 [8.5, 45.0]	0.50 [−3.3, 5.3]	1.19 (−5.0, 7.4)	0.69	6 (21, 30)	0.00 [−38, 41]	0.30
HAQ	0.06 [0.0, 0.7]	0.38 [0.0, 0.8]	0.13 [0.0, 0.72]	0.38 [0.0, 1.1]	0.02 (−0.1, 0.1)*	0.00 [0.0, 0.3]	0.06	0.00 [−22, 19]	18 [0.0, 92]	0.09

Data are shown as mean (95% confidence interval) for normally distributed data, and median [Q1, Q3] for non-normally distributed data.

*Data are shown as mean (95% confidence interval) for the non-normally distributed data when the median, Q1, and Q3 data were identical. **Results from Fisher's exact test.

n, number of patients; BMI, body mass index; MTX. methotrexate; CRP, C-reactive protein; DAS28-CRP, Disease Activity Score based on 28-joint count–C-reactive protein; ASDAS-CRP, Ankylosing Spondylitis Disease Activity Score based on C-reactive protein; VAS, visual analogue scale; HAQ, Health Assessment Questionnaire.

Self-reported outcomes

In the TDM group, reductions in the self-reported HAQ and global VAS Pain were achieved for those who received IFX (p = 0.002; p = 0.004) and ADA (p = 0.03; p = 0.02) (Figure 4), indicating equally or superior sustained remission across diagnoses. Details are presented in Table 1.

Discussion

We showed consistently that TDM reduced TNFi prescription by up to 15% on dose reduction or up to 235% prolongation of the interdosing interval in chronic arthritis patients, regardless of initial disease activity. Thus, TDM resulted in overall reduced drug prescription in patients with three different rheumatic diseases treated with IFX, ETN, or ADA, treated according to existing guidelines. This confirmed our hypothesis. Furthermore, TDM added to standard care led to faster switches to other biologics in patients with suboptimal disease control. To our surprise, this was not mirrored in fewer adverse events; however, the TDM group experienced equally or superior sustained remission across diagnoses. Consequently, we suggest TDM as a relevant tool mirroring individual pharmacokinetic profiles, in the personalized treatment of patients with rheumatic diseases.

EULAR and ACR treatment guidelines for achieving maximal disease control recommend tapering of biologics to decrease the risk of serious side effects (1); however, internationally acknowledged clinical procedures for initiating tapering in patients treated with IFX, ETN, or ADA are lacking. This is the first prospective RCT in which serum trough levels were applied using TDM to support clinical decision making. The three doctoral visits ensured relevant adjustments of IFX, ETN, or ADA. Patients were monitored closely to assess any potential clinical consequences in response to tapering, thereby providing hitherto unknown data on individual TNFi responses over time. No differences in changes of serum trough levels of IFX, ETN, and ADA compared to baseline were shown between TDM and standard care. However, the absolute difference seemed lower in the TDM group and higher in the standard care

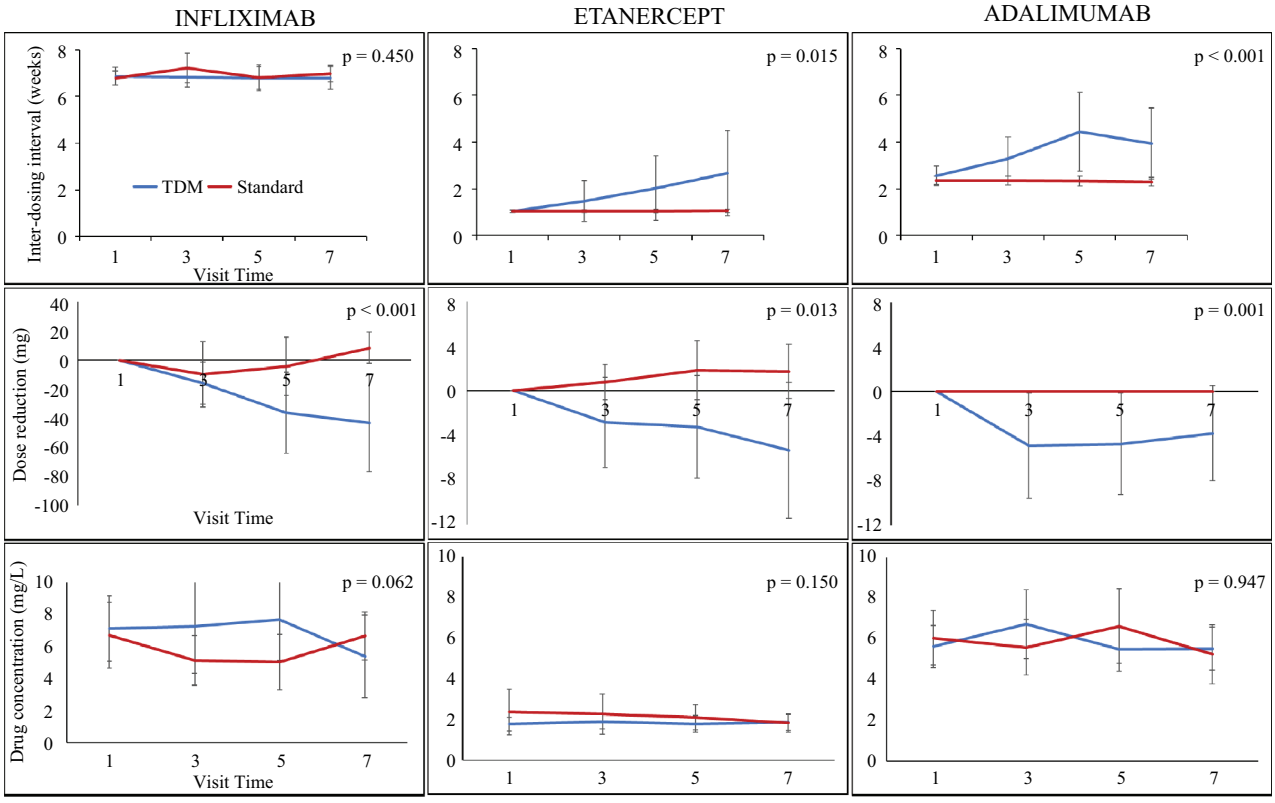

Figure 2. Differences in drug consumption during the entire study, shown as prolonged interdosing interval, drug dose reduction to the baseline, and drug concentration for the group receiving standard of care and the group receiving standard of care plus therapeutic drug monitoring (TDM) for each of the administered drugs: infliximab, etanercept, or adalimumab.

group, plausibly reflecting fewer patients with trough levels outside the therapeutic intervals.

TNFi tapering was not limited to the intravenously administrated IFX with a known high peak–trough ratio, but was also shown in patients treated with subcutaneously administered ETN and ADA, with much flatter pharmacokinetic profiles. Given the emerging and progressing field of TDM and the hope for more personalized medicine, TDM may, therefore, ultimately be applied to therapeutics in other conditions, e.g. cancer treatments with very narrow therapeutic intervals for achieving the maximal effect, for more individuals at minimal risk of serious adverse events (35).

Our TDM data revealed unrecognized individual drug concentrations below therapeutic intervals, causing accelerated drug switch. Notably, increased dosing in the standard group did not improve disease control and thus may reflect a preferred choice of increasing an already prescribed drug before choosing to switch to other biologics. We believe, however, that such hesitancy in switching to other biologics may have changed, as more new biologic therapeutics are available compared to just a couple of years ago.

Owing to the extensive use of TNFis, there is an emerging clinical need to determine relevant factors, such as the use of methotrexate, neutralizing or non-neutralizing anti-drug antibodies, that could influence the individual drug exposure (16,36). However, our data do not allow such analysis. Despite the lack of knowledge of a possible immunogenic response (with a potential effect on TNFi serum concentrations), our rather simple TDM approach allowed us to accelerate changes in drug prescriptions and switches. Such an approach is supported by Siljehult et al, who suggested that a lack of response to IFX treatment was due to the absence of IFX, rather than to the presence of anti-drug antibodies (37). Anti-drug antibodies have been shown in up to one-third of RA patients treated with IFX, ENT, or ADA, and showed an inverse correlation between anti-drug antibody concentration and serum trough levels (38). Incidence of Antidrug Antibodies in Rheumatoid Arthritis Patients From Argentina Treated With Adalimumab, Etanercept, or Infliximab in a Real-World Setting.

The concurrent relationship between trough levels and clinical outcome may, therefore, suggest that serum trough levels represent the 'net effect' of pharmacokinetic and immunogenic interaction. This would challenge the relevance of antibody measurements, adding to the ongoing discussion on the relevance of TDM in inflammatory rheumatic and musculoskeletal diseases (16).

We applied a proactive TDM strategy to encourage reduced drug prescription of IFX, ETN, or ADA in

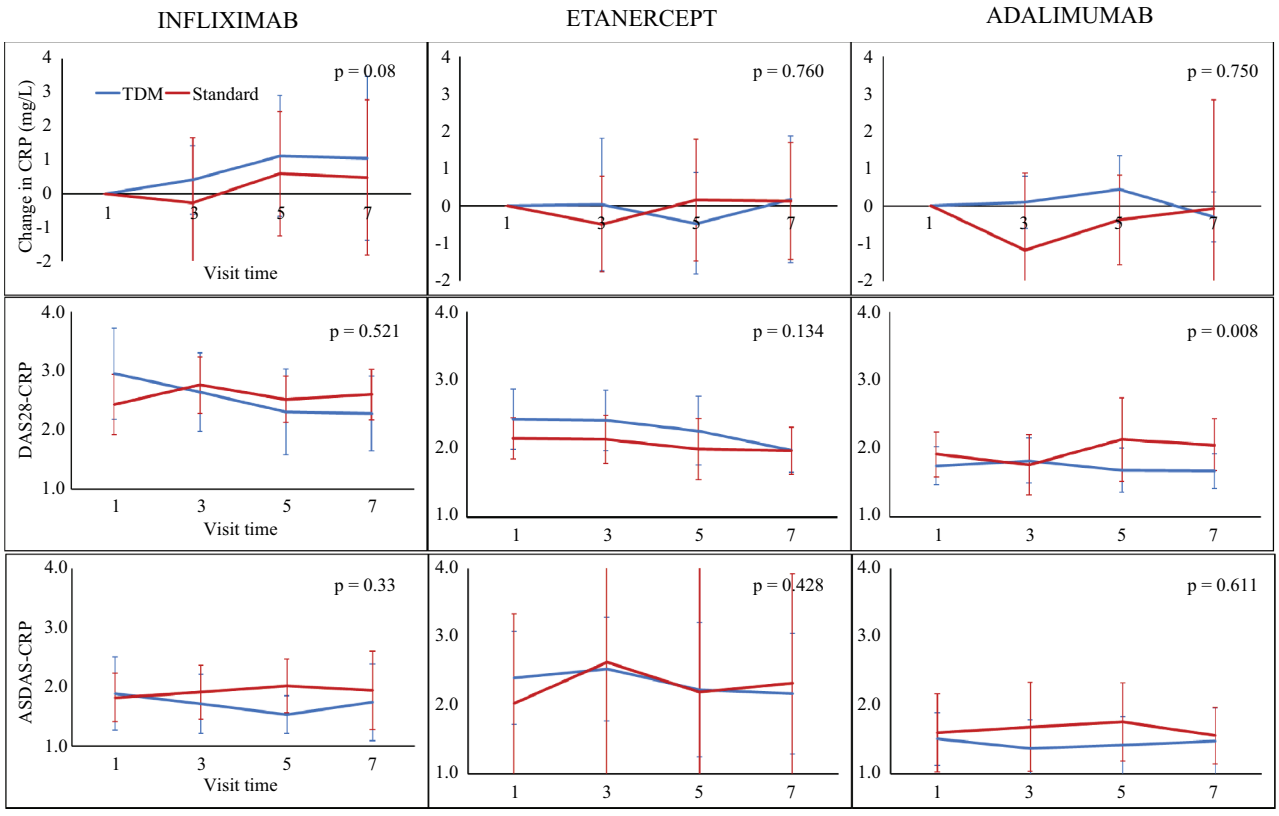

Figure 3. Differences in clinical outcomes during the entire study, shown as C-reactive protein (CRP) change to the baseline (all), Disease Activity Score based on 28-joint count–C-reactive protein (DAS28-CRP) (participants with rheumatoid arthritis and psoriatic arthritis), and Ankylosing Spondylitis Disease Activity Score based on C-reactive protein (ASDAS-CRP) (spondyloarthritis), for the group receiving standard of care and the group receiving standard of care plus therapeutic drug monitoring (TDM) for each of the administered drugs: infliximab, etanercept, or adalimumab.

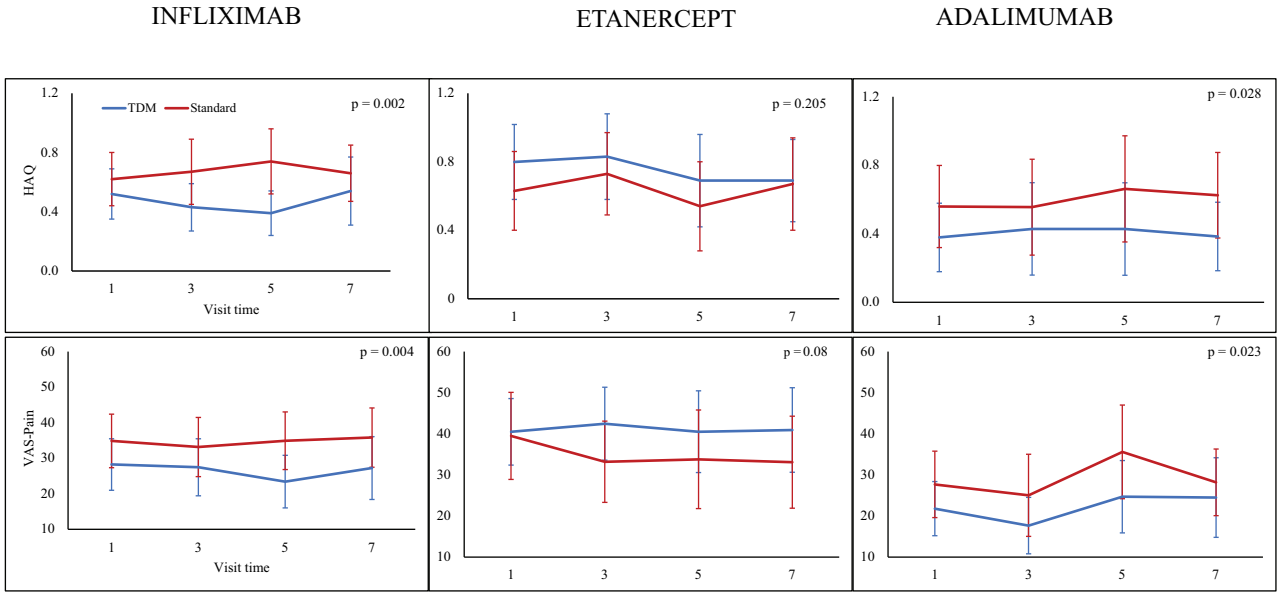

Figure 4. Differences in self-reported outcomes during the entire study, shown as Health Assessment Questionnaire (HAQ) and visual analogue scale (VAS) Pain assessed for all three diagnoses, for the group receiving standard of care and the group receiving standard of care plus therapeutic drug monitoring (TDM) for each of the administered drugs: infliximab, etanercept or adalimumab.

patients regardless of remission. We showed, consistently and across treatments, sustained disease control and superior or equivalent treatment outcome in the clinical composite scores DAS-28 and ASDAS-28, despite substantially reduced drug prescription. One could argue that tapering based on clinical evaluation of disease activity would result in the same outcome. Nevertheless, TDM allowed us to speculate that a proportion of participants with very low serum concentrations were in remission not because of their treatment, but because of the natural history of their disease. Consequently, both patients in suboptimal disease control and those in remission will potentially benefit from this proactive approach to reduce drug prescription. This supports the findings of Syversen et al, who demonstrated increased sustained disease control in patients prescribed IFX receiving TDM and concomitant determination of anti-drug antibodies (23). The same authors failed to show improvement in a heterogeneous group of patients with chronic immune-mediated inflammatory disease who had been prescribed IFX (21).

To date, implementation of tapering procedures has partly been driven by an acknowledged political wish to contain the economic burden of the treatment of chronic diseases with biologics to offer treatment to all affected patients. Thus, while the costs of IFX, ETN, and ADA have been reduced dramatically with the introduction of biosimilars, the use of TDM for biologics in more general terms may still reduce the prescribed drugs as well as the economic burden on the treatment of chronic diseases. Biochemical assays essential for TDM are currently rather costly and resource demanding, thus being a drawback for implementing TDM as a daily clinical routine. However, increased demand could encourage the development of technologies allowing measurements on fully automatic platforms, thereby reducing the analytical costs substantially. Consequently, TDM as a healthcare strategy based on objective serum trough levels of TNFis and other biologics deserves more awareness, as it contributes towards advancing the medical field in the direction of complex personalized medicine by acknowledging interpersonal pharmacokinetic variations and, thus, variations in drug exposure.

The strengths of this randomized TDM study are as follows. First, the cohort reflects a university hospital outpatient clinic, encompassing patients diagnosed with RA, PsA, and SpA, who were treated according to existing guidelines with prescribed IFX, ETN, or ADA. Secondly, reduced prescription as the primary endpoint was chosen for several reasons: (i) it is associated with less probability of toxicity, and EULAR/ACR treatment guidelines recommend tapering of biologics (1, 7, 29); (ii) drug reduction may prevent unnecessary high medicine costs (especially in newly marketed drugs); and (iii) data on administered doses and interdose interval are easy to obtain with high precision in the Danish setting, where drugs are provided by the healthcare system. Secondly, alongside the NOR-DRUM trials, this RCT is among the first prospective, randomized studies to use a TDM strategy in participants with chronic arthritis receiving IFX (21–23), and the first study to investigate patients receiving ETN or ADA. Thirdly, we showed reduced prescription of IFX, ETN, and ADA across clinical diagnosis and disease activity, embracing clinical remission as well as a flare. This contrasts with the majority of clinical outcome studies investigating 'disease activity score-steered therapy', where dose reduction was successfully implemented in patients with low disease activity (23, 24). Finally, the design reflects daily clinical routine; however, this challenges concurrent outcomes, encompassing the pragmatic protocol compared to traditional phase III clinical trials, thereby including patients in stable clinical remission with serum trough levels within the defined therapeutic intervals. Thus, our results may underestimate the full potential of the application of TDM in patients with clinical activity of disease worsening. The objective of this trial was to challenge whether TDM on top of standard care could reduce the prescription of the three TNFis. With drug switch or reduction being the only options, one could argue that it would be expected that TDM would cause an overall reduced drug prescription. However, if the majority of patients had revealed serum trough levels within the defined therapeutic intervals we would not have been able to show differences in drug prescription between the two groups at the end of the study.

The study was, however, not conducted without limitations. First, we had a heterogeneous cohort with dissimilar pathophysiology; however, as our results showed reduced prescription in response to TDM, this seems to be outweighed by the design. Secondly, the open-label study enabled consultation of the TDM result, similar to the NOR-DRUM study. However, since the TDM was based on an objective serum value and decision procedures were clear, we do not consider the potential of unconscious bias to outweigh the benefits of dose-changing abilities. Thirdly, data on the exact time for blood sampling and IFX administration allowed us to ensure the determination of true trough serum levels. This is in opposition to ETN and ADA serum levels, which could be influenced by blood sampling being less well correlated with drug administration despite careful instruction of patients. However, we do not consider this to be a major pitfall because the pharmacokinetics of the two drugs cause small fluctuations in serum levels during a dosing interval (39, 40). This approach is supported by the accurate drug accountability undertaken as part of the Danish healthcare programme, with patients being provided with ETN and ADA by the hospital pharmacies supporting patient reported information on adherence to drug prescription. Furthermore, the measured serum trough levels revealed drug compliance.

Fourthly, disappointingly, reduced TNFi consumption in the TDM group was not mirrored in reduced numbers of adverse or serious adverse events. However, this may reflect that the standard of care had already taken adverse events into account, since all patients were included following prescription of IFX, ETN, or ADA at least 3 months before study inclusion. Finally, patients with disease activity and serum trough levels below the therapeutic intervals were switched to another biologic. One could argue that the first step should be increasing drug prescription to obtain an adequate concentration of the current TNFi. However, an increase in dosing above the recommended posology was not part of the Danish guidelines (34) and therefore was not an option in these patients, who were already prescribed the maximum dose. Furthermore, the low serum trough levels could be due to neutralizing anti-drug antibodies (43), with individual and unknown correlation between increased dosing and the corresponding change in serum trough levels. Nevertheless, low serum trough levels can be due to low drug prescription or adequate drug prescription combined with neutralizing anti-drug antibodies (41). Consequently, TDM without assessment of potential neutralizing anti-drug antibodies explaining low serum trough levels required us to move directly to a drug switch. Thus, sustained prescription, decreased prescription, or change in prescribed biologic anti-inflammatory drug were the only three options in the trial design.

Conclusion

This study shows that TDM can be used to substantially reduce the prescription of IFX, ETN, and ADA in patients with chronic arthritis. TDM was more effective in identifying patients needing adjustments to their prescribed TNFi by contributing to accelerated drug switch. Furthermore, the benefit of reducing the risk of toxicity and unnecessary adverse events accompanied sustained disease control without disease worsening. Our data support TDM based solely on serum trough levels in TNFis with different pharmacokinetics as a future key player in personalized medicine for chronic rheumatoid diseases treated with biologics.

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Data availability and responsibility

The data sets generated and/or analysed during the current study are available from the corresponding author on request. The sponsor was responsible for the medicolegal aspects. The authors confirm that the principal investigator for this paper is Mogens Pfeiffer-Jensen and that he had direct clinical responsibility for patients. The authors had full access to all data in the study and final responsibility for the decision to submit for publication. The corresponding author is the guarantor of the work.

Authors' contributions

MP-J and BB conceived the design, and CB, BD, UT, and KS-P made substantial academic contributions to the final version of the protocol. MP-J and CB collected data. MP-J, JV, DL, BB, and CB organized, analysed, and interpreted the data, and BD, UT, and KS-P made substantial contributions to the final data presentation. MP-J, BB, and CB drafted the work. All co-authors revised it critically for important intellectual content and approved the final version to be published. MPJ, BB, and CB agree to be accountable for all aspects of the work, in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics statement

Ethical approval granted from the Central Region of Denmark (1-16-02-567-15). All patients signed written informed consent before entering the study.

Disclosure statement

No potential conflict of interest was reported by the authors.

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Supplementary material

Supplemental data for this article can be accessed online at https://doi.org/10.1080/03009742.2022.2121081.