Clinical Rheumatology (2018) 37:1689–1694
https://doi.org/10.1007/s10067-017-3958-1

BRIEF REPORT

High burden of adverse events is associated with reduced remission rates in early rheumatoid arthritis

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Received: 25 September 2017 / Revised: 9 December 2017 / Accepted: 14 December 2017 / Published online: 26 December 2017

Abstract

Adverse events (AEs) are common during disease-modifying antirheumatic drug (DMARD) treatment, but their influence on treatment results is unclear. We studied AEs in relation to disease activity in early rheumatoid arthritis (RA). Ninety-nine patients started intensive treatment with three conventional synthetic DMARDs (csDMARDs) and oral prednisolone, and were randomized to a 6-month induction treatment with infliximab or placebo. All AEs during the first 12 months of treatment were recorded. We scored each AE based on severity (scale 1–4) and defined the burden of AEs as the sum of these scores. Patients were divided into tertiles according to the burden of AEs. As outcomes, we assessed 28-joint disease activity score (DAS28) levels and remission rates at 12 and 24 months. Three hundred thirty-one AEs in 99 patients were reported, and 27 (8%) were categorized as severe or serious. Mean burden of AEs per patient was 5.4 ± 4.3. Seventy-nine AEs (24%) led to temporary ($n = 52$) or permanent ($n = 27$) csDMARD discontinuation. Of discontinuations, 1, 21, and 57 were detected in the first, second, and third tertiles, respectively. DAS28 remission rates decreased across tertiles at 12 months (94, 94, and 76%; p for linearity 0.029) and at 24 months (90, 86, and 70%; p for linearity 0.021). Mean DAS28 levels increased across tertiles at 12 months (1.5 ± 1.0, 1.7 ± 0.9, and 1.9 ± 1.2; p for linearity 0.021) and at 24 months (1.4 ± 0.8, 1.6 ± 1.0, and 1.9 ± 1.1; p for linearity 0.007). High burden of AEs is associated with higher disease activity and lower likelihood of remission in early RA.

Keywords Adverse events · Clinical trials · DMARDs · Remission · Rheumatoid arthritis

Introduction

Early suppression of disease activity with active and conscientious use of disease-modifying antirheumatic drugs (DMARDs) is essential for achieving good outcomes in rheumatoid arthritis (RA) [1, 2]. However, DMARDs, like all drugs, may cause adverse events that lead to discontinuation of the medication or reduced drug adherence.

In RA, the two leading causes for drug discontinuation are inefficacy and adverse events [3–5]. Adverse events are

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carefully monitored in all clinical trials, but previous studies have not examined their impact on treatment outcomes in early RA. In this study, we perform a post hoc analysis of clinical trial data with intensively treated early RA patients to determine if the cumulative burden of adverse events during the first year of treatment is associated with disease activity and remission rates at 1 and 2 years after study initiation.

Materials and methods

Patients

Ninety-nine patients with early, active, and untreated RA fulfilling the American College of Rheumatology (ACR) 1987 classification criteria were recruited into the NEO-RACo (New Finnish Rheumatoid Arthritis Combination treatment strategy) trial that began in 2003. In this multicenter study, all patients were treated with a combination of methotrexate (up to 25 mg/week, administered orally or in case of adverse events subcutaneously), sulfasalazine (2 g/day), hydroxychloroquine (35 mg/kg/week), and oral low-dose prednisolone (7.5 mg/day) for 2 years. In addition, the patients were randomized to receive infliximab or placebo infusions at weeks 4, 6, 10, 18, and 26. The patients were assessed clinically 11 times during the first year, and thereafter every 3 months. The treatment was targeted to a modified ACR remission throughout the study. Medication had to be modified if remission was not achieved. The patients were required to use a combination of three conventional synthetic DMARDs (csDMARDs) at all times.

If an adverse event led to temporary or permanent drug discontinuation, csDMARD treatment was restarted as soon as possible. If drug discontinuation was permanent, the csDMARDs were substituted as follows: methotrexate with azathioprine, sulfasalazine with ciclosporin, and hydroxychloroquine with auranofin. Patient selection criteria of the trial, treatment protocol, and 2-year outcomes have been presented in detail previously [6].

Burden of adverse events and outcomes

We analyzed all adverse events during the first 12 months of the study. The treating physicians categorized the events based on their severity: (1) mild—barely notable with no measures required; (2) moderate—possible dose changes in study medication; (3) severe—possible temporary or permanent discontinuation of study medication; and (4) serious—any event leading to death, hospitalization, or causing permanent or significant injury. Each adverse event was taken into account only once. If the same adverse event was reported on multiple study visits, we used the most severe category reported. The investigators recategorized the adverse event only if the patient had been hospitalized, but the treating physician had not classified the event as serious. We defined the cumulative burden of adverse events as the sum of scores (from 1 for mild to 4 for serious events) of all individual events. We assessed the 28-joint disease activity score (DAS28) and DAS28 remission rates (DAS28 < 2.6) at 12 and 24 months as outcomes.

Statistical analysis

The data is presented as means with standard deviations (SD) or as counts with percentages. For analysis, we divided the patients into tertiles according to the burden of adverse events. We used Cochran-Armitage test and analysis of variance (ANOVA) for evaluating the statistical significance of the hypothesis of linearity. In the case of violation of the assumptions (e.g., non-normality), a bootstrap-type test was used. We used generalizing estimating equations (GEE) models with appropriate distribution and link function for analyzing repeated measures data. Age, sex, rheumatoid factor, baseline disease activity, and treatment arm were used as covariates. The normality of the variables was evaluated using the Shapiro-Francia W test. STATA 14.1, StataCorp LP (College Station, TX, USA), statistical software was used for the analyses.

Results

Ninety-nine patients were included in the study. Three hundred thirty-one adverse events were reported during the first 12 months. The mean burden of adverse events per patient was 5.4 ± 4.3. The patients were divided into tertiles according to the burden of adverse events. The baseline clinical and demographic characteristics of the patients by tertiles are shown in Table 1. Of the baseline characteristics, erythrocyte sedimentation rate ($p = 0.03$) and tender joint count ($p = 0.001$) differed across the tertiles. The range of the burden of adverse events in the first, second, and third tertiles was 0–2, 3–6, and 7–18, respectively. Thirteen patients in the first tertile reported no adverse events.

Seventy-nine (24%) of 331 adverse events led to csDMARD discontinuation. Of the discontinuations, 52 (66%) were temporary and 27 (34%) permanent. The number of temporary and permanent csDMARD discontinuations and the number of severe and serious adverse events were the highest in the third tertile (Table 2). Of the 27 permanent csDMARD discontinuations, four involved methotrexate, ten sulfasalazine, and 13 hydroxychloroquine. In addition, one patient in the infliximab arm and two patients in the placebo arm discontinued the 6-month induction treatment with infliximab or placebo due to an adverse event.

The treating physician classified 22 (7%) of the adverse events as definitely connected to study medication. In 88 (27%) cases, the connection between study medication and

Table 1 Baseline characteristics of the patients by tertiles of the burden of adverse events

Characteristic	Tertile of adverse event burden			*p* value
	I (*n* = 31)	II (*n* = 35)	III (*n* = 33)	
Demographics				
Female, *n* (%)	20 (65)	22 (63)	24 (73)	0.48
Age years, mean (SD)	48 (9)	47 (10)	44 (12)	0.15
Duration of symptoms (months), mean (SD)	4 (3)	4 (2)	4 (2)	0.99
Rheumatoid factor present, *n* (%)	25 (81)	27 (77)	23 (70)	0.31
Measures of disease activity				
DAS28, mean (SD)	5.7 (1.1)	5.2 (1.2)	5.7 (1.2)	0.99
ESR, (mm/h), mean (SD)	41 (22)	30 (22)	29 (20)	0.03
Swollen joints (66 joint count), mean (SD)	16.5 (5.6)	13.3 (5.7)	16.0 (7.7)	0.81
Tender joints (68 joint count), mean (SD)	17.6 (7.7)	17.2 (8.3)	24.8 (12.9)	0.005
Patient's global assessment (VAS), mean (SD)	46 (24)	49 (29)	52 (24)	0.26
Pain assessment (VAS), mean (SD)	48 (29)	57 (30)	55 (21)	0.29
Physician's global assessment (VAS), mean (SD)	52 (20)	47 (21)	55 (21)	0.60
Physical function (HAQ), mean (SD)	0.9 (0.6)	1.0 (0.7)	1.1 (0.7)	0.23
Infliximab treatment, *n* (%)	19 (61)	15 (43)	16 (48)	0.32

p values are for linearity. The range of the burden of adverse events by tertiles I, II, and III was 0–2, 3–6, and 7–18

DAS28, 28-joint Disease Activity Score; *ESR*, erythrocyte sedimentation rate; *VAS*, Visual Analog Scale; *HAQ*, Health Assessment Questionnaire

an adverse event was probable; in 99 (30%) cases, possible; and in 85 (26%) cases, unlikely. Thirty (9%) adverse events were classified as unrelated to study medication, and data were missing for seven events (2%).

At 12 months, the DAS28 remission rates decreased across the tertiles according to burden of adverse events, being 94, 94, and 76% in the first, second, and third tertiles, respectively (*p* for linearity 0.029; Fig. 1). Similarly, remission rates by tertiles at 24 months were 90, 86, and 70% (*p* for linearity 0.021). Mean DAS28 scores (±SD) in the first, second, and third tertiles were 1.5 ± 1.0, 1.7 ± 0.9, and 1.9 ± 1.2 at 12 months (*p* for linearity 0.021), and, respectively, 1.4 ± 0.8, 1.6 ± 1.1, and 1.9 ± 1.1 at 24 months (*p* for linearity 0.007; Fig. 1). Mean DAS28 change from baseline was − 4.2, − 3.5, and − 3.8 in the first, second, and third tertiles at 12 months, and, respectively, − 4.3, − 3.8, and − 3.8 at 24 months.

Discussion

The influence of adverse events on RA remission rates has not been explored earlier. In the current study, we found that higher burden of adverse events during the first year of RA treatment was associated with lower DAS28 remission rates and higher disease activity at 1 and 2 years of follow-up in

Table 2 CsDMARD discontinuations and severity of adverse events by tertiles of burden of adverse events

	Tertile of AE burden		
	I (*n* = 31)	II (*n* = 35)	III (*n* = 33)
Adverse events			
Number, *n* (%[a])	21 (6)	111 (34)	199 (60)
Led to csDMARD discontinuation and switch, *n* (%[a])	0 (0)	5 (2)	22 (7)
Led to temporary csDMARD discontinuation, *n* (%[a])	1 (0)	16 (5)	35 (11)
Adverse event severity			
Severe	0	2	9
Serious	0	4	12
Moderate	6	39	96
Mild	15	66	82

[a] Percentage of all adverse events (*n* = 331)

AE, adverse event; *csDMARD*, conventional synthetic disease-modifying antirheumatic drug

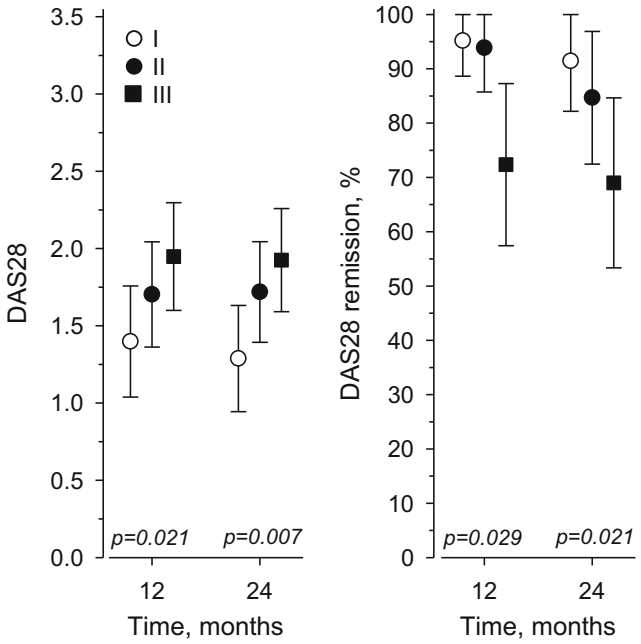

Fig. 1 Disease activity score assessing 28-joint (DAS28) scores and remission rates (DAS28 < 2.6) by tertiles of the 12-month burden of adverse events at 12 and 24 months. *p* values are for linearity. Adjusted for age, sex, rheumatoid factor, baseline disease activity, and treatment arm (infliximab or placebo)

intensively treated early RA patients. Although 92% of the adverse events were mild or moderate, one in four led to temporary or permanent csDMARD discontinuation. Despite these discontinuations, differences in clinical outcomes were small. DAS28 reduction from baseline by tertiles ranged from 3.5 to 4.2 at 12 months, and, respectively, from 3.5 to 4.3 at 24 months. Most patients, 70–90% depending on the tertile, achieved DAS28 remission at 24 months.

When interpreting our results, it should be taken into account that the protocol of the current trial, commenced in 2003, is not in line with the latest international RA management recommendations, which suggest tapering glucocorticoids as soon as clinically feasible [7]. However, as demonstrated by the high remission rates, the used strategy leads to excellent results. Further, triple combination of csDMARDs is still recommended as the initial treatment for RA in Finland, where excellent results have been achieved also in routine clinical practice [8, 9].

We found no previous studies that have specifically assessed the impact of experienced adverse events on RA outcomes. However, we identified one recent study that focused on medication persistence in RA patients [10]. In this study, Contreras-Yanes et al. showed that the length of DMARD discontinuation periods during the first 4 years of RA treatment was associated with higher disease activity and increased disability during the fifth year in a cohort of Mexican early RA patients. The exact timing of the non-persistence during the follow-up had no impact on the outcomes, which is slightly surprising, as it is known that RA generally reacts more amenably to early treatment [11]. As we did not study treatment persistence, it is challenging to compare these results directly with ours. Nonetheless, based on the relatively high csDMARD discontinuation rates, non-persistence caused by adverse events was most likely the primary reason for lower remission rates in the third tertile of adverse event burden in our study. Additionally, cumulating adverse events may have influenced csDMARD adherence negatively leading to further reduced medication persistence. The impact of drug discontinuations is accentuated by the fact that it may take from 2 to 3 months to reach the peak effect of a new csDMARD. Thus, patients with adverse events leading to drug switches might be undertreated for several months, which decreases the probability remission. Further, in routine clinical practice, the impact of drug discontinuations is likely more pronounced due to less intensive treatment, particularly if monotherapy is used, lower adherence, and longer control intervals.

We found only minor differences in the baseline characteristics of patients categorized by the burden of adverse events. Patients who experienced the most adverse events during the first 12 months had higher tender joint count and lower erythrocyte sedimentation rate (ESR) compared with the two other groups. The discordance of these measures is interesting and could be caused by higher disease activity or by higher prevalence of non-inflammatory joint pain in the third tertile. The latter seems more likely based on previous studies, which have shown that RA patients suffering from non-inflammatory pain, like fibromyalgia, have higher DAS28 scores and lower likelihood of remission due to disproportionately high subjective disease activity measures compared to patients with RA alone [12–14].

Few studies have assessed the underlying causes for DMARD treatment failure in early RA. According to these studies, mental health seems to be one of the key factors associated with both treatment failure and drug discontinuation [15, 16]. Mental health problems can also affect patient-reported outcomes; depressive symptoms and anxiety have been shown to increase DAS28 by inflating tender joint count and patient global assessment values [17]. Further, some patients may also be more prone to adverse events due to their psychological characteristics, like anxiety or depression, and negative expectations concerning medications [18]. In our study, the use of a triple combination of csDMARDs was mandatory, and therefore adverse events led to changes, and not to cessation or failure, of the drug regimen. However, impaired mental health may have been one of the drivers of increased adverse event reporting in our study. Unfortunately, we were not able to test this hypothesis due to lack of data on patients' psychiatric morbidity.

Despite its strengths such as the clinical trial design reducing the possibility of bias, and the short follow-up intervals, which enabled obtaining comprehensive adverse event data, our study also has some limitations. First, the patients were of working age and very intensively treated and followed. Therefore, our results may not be generalizable to other settings and

populations. Second, because of the small study sample, the number of csDMARD switches remained low. This prevented us from assessing the effects of permanent discontinuation of individual csDMARDs, such as methotrexate. Third, we had no data on the prevalence of non-inflammatory joint pain and fibromyalgia, or psychiatric morbidity in the study population. We can therefore only speculate that these factors might be associated with a higher burden of adverse events. Additionally, nocebo effect, i.e., negative treatment effects caused by patient's negative expectations, could explain a part of the differences in experienced adverse events. However, exploring the influence of this phenomenon is beyond the scope of the current study. Finally, we developed a novel method for measuring the influence of adverse events. Due to the limited sample size, our results should be confirmed in larger trials.

We conclude that in early RA patients treated with a triple combination of csDMARDs, the higher burden of adverse events during the first year of treatment is associated with reduced remission rates and higher disease activity thereafter. These reduced remission rates are most likely explained by reduced DMARD exposure over time caused by adverse events. In the current study, one third of patients experienced almost two thirds of adverse events. Future studies should elucidate factors influencing patients' adverse event reporting.

Acknowledgements The authors would like to thank all participating patients, other members of the NEO-RACo study group (Eeva Alasaarela, Harri Blåfield, Kari K. Eklund, Mikko Hakola, Pekka Hannonen, Kirsti Ilva, Heikki Julkunen, Oili Kaipiainen-Seppänen, Markku Kauppi, Aulikki Kononoff, Maija-Liisa Krogerus, Kari Laiho, Riitta Luosujärvi, Reijo Luukkainen, Timo Möttönen, Helena Niinisalo, Ritva Peltomaa, Jari Pöllänen, Tea Uusitalo, Toini Uutela, Heikki Valleala, Kaisa Vuori, Leena Laasonen, Eeva Moilanen, Riina Nieminen, and Katriina Vuolteenaho), and the study nurses for their contribution.

Compliance with ethical standards

Conflict of interest Laura Kuusalo has received honoraria and consulting fees (less than $10,000 each) from Bristol-Myers Squibb and Pfizer. Kari Puolakka has received honoraria and consulting fees (less than $10,000 each) from Abbvie, Bristol-Myers Squibb, MSD, Pfizer, Roche, and UCB. Hannu Kautiainen has received honoraria (less than $10,000 each) from AbbVie and Pfizer. Anna Karjalainen has received honoraria (less than $10,000 each) from MSD, Novartis, Roche, and UCB. Timo Malmi has received an honorarium (less than $10000) from Pfizer. Leena Paimela has received honoraria and consulting fees (less than $10,000 each) from Abbvie, Bristol-Myers Squibb, Pfizer, and Roche. Marjatta Leirisalo-Repo has received honoraria and consulting fees (less than $10,000 each) from AbbVie, Boehringer Ingelheim, Bristol-Myers Squibb, Lilly, Pfizer, Regeneron, and Roche. Vappu Rantalaiho has received an honorarium (less than $10000) from Bristol-Myers Squibb.

Ethical standards The study protocol was approved by the ethics committee of the Hospital District of Helsinki and Uusimaa. The patients provided written informed consent. The study was conducted according to the Declaration of Helsinki and has been registered at http://www.clinicaltrials.gov (NCT00908089).

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