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Original article

Effectiveness of biologic DMARDs in monotherapy versus in combination with synthetic DMARDs in rheumatoid arthritis: data from the Swiss Clinical Quality Management Registry

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Abstract

Objectives. To determine the frequency of use of biologic DMARDs (bDMARDs) in monotherapy, to describe the baseline characteristics of patients treated with bDMARDs in monotherapy and to compare the effectiveness of bDMARDs in monotherapy with that of bDMARDs in combination with synthetic DMARDs (sDMARDs).

Methods. Using data from the Swiss RA (SCQM-RA) registry, bDMARD treatment courses (TCs) were classified either as monotherapy or as combination therapy, depending on the presence of concomitant sDMARDs. Prescription of bDMARD monotherapy was analysed using logistic regression. bDMARD retention was analysed using Kaplan–Meier and Cox models with the addition of time-varying covariate effects. Evolution of the DAS28 over time was analysed with mixed-effects models for longitudinal data.

Results. A total of 4218 TCs on bDMARDs from 3111 patients were included, of which 1136 TCs (27%) were initiated as monotherapy. bDMARD monotherapy was preferentially prescribed to older, co-morbid patients with longer disease duration, lower BMI, more active disease and more previous bDMARDs. After adjusting for potential confounding factors, drug retention was significantly lower in monotherapy [hazard ratio 1.15 (95% CI: 1.03, 1.30)]. Other factors such as type of bDMARD and calendar year of prescription were associated with a stronger effect on drug retention. Response to treatment in terms of DAS28 evolution was also slightly but significantly less favourable in monotherapy ($P = 0.04$).

Conclusion. Our data suggest that bDMARD monotherapy is prescribed to more complex cases and is significantly less effective than bDMARD therapy in combination with sDMARDs, but to an extent that is clinically only marginally relevant.

Key words: rheumatoid arthritis, biologic DMARD, monotherapy, combination therapy.

CLINICAL SCINCE

Rheumatology key messages

- Monotherapy with biologic agents is commonly used in patients with RA.
- The use of biologic agents in RA varies according to disease and patient characteristics.
- In RA patients with co-morbidities the use of biologics in monotherapy is a reasonable option.

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Introduction

Biologic DMARDs (bDMARDs) have markedly changed the management and outcome of disease of patients with RA. Clinical guidelines recommend using bDMARDs in combination with MTX [or in combination with other synthetic DMARDs (sDMARDs) when MTX is not tolerated]. These recommendations are based on data from

randomized clinical trials demonstrating that TNF antagonists (aTNFs) are more effective when combined with MTX than in monotherapy [1]. The efficacy of bDMARDs with modes of action other than aTNFs used in monotherapy has been less examined. However, recent results suggest that tocilizumab has comparable efficacy in monotherapy and in combination with MTX [2].

Up to one-third of RA patients are treated with bDMARDs in monotherapy (according to data from different registries in Europe and the USA) [3–10]. This relatively high percentage may represent patients in whom sDMARDs have been discontinued during follow-up due to adverse events or as a result of low disease activity, but may also include patients in whom bDMARDs were started in monotherapy because of previous intolerance to sDMARDs or co-morbidities.

The objectives of this study were: to determine the frequency of use of bDMARDs in monotherapy at baseline or during the course of therapy; to describe the baseline characteristics of patients treated with bDMARDs in monotherapy; and to compare the effectiveness of bDMARDs in monotherapy with that of bDMARDs in combination with sDMARDs.

Methods

Patient population

Data from the nationwide Swiss Clinical Quality Management (SCQM) registry for RA was used for this study. The SCQM-RA registry is a longitudinal cohort of RA patients (established in 1997), and it has been described in detail elsewhere [11, 12]. Inclusion criteria for the SCQM-RA are a diagnosis of RA by a Board-certified rheumatologist. Ethical approval for the SCQM-RA and related studies (including this study) was obtained from the Swiss Academy of Medical Sciences review board, and all patients were required to provide written consent prior to enrolment. At inclusion, disease characteristics, concomitant treatments and co-morbidities were assessed by the rheumatologists and patients filled out self-administered questionnaires such as HAQ, SF-12 and EuroQoL. Follow-up assessments were performed at regular intervals, approximately one to four times a year (disease activity, anti-rheumatic treatments, side effects, reasons for discontinuation, co-morbidities, etc.) and included hand and foot X-rays every 1 or 2 years. The Swiss Society of Rheumatology recommends the inclusion of all the patients treated with bDMARDs. More than 300 (corresponding to 80%) of Swiss rheumatologists participate in the SCQM. Patients in SCQM-RA come from diverse clinical settings, with approximately 50% from private practice, 30% from non-academic centres and 20% from academic centres. The study population can be considered a representative sample of the Swiss RA population on bDMARDs.

The inclusion and exclusion criteria for this study were: initiation of a bDMARD and a baseline visit within a time window of 90 days prior to and up to 16 days after the start of bDMARD treatment, including information on DAS28. Exclusion criteria were: missing information on concomitant sDMARDs and overlapping bDMARD treatment courses (TCs). All TCs with bDMARDs (abatacept, adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, rituximab and tocilizumab) fulfilling the above-mentioned inclusion and exclusion criteria were extracted from the SCQM-RA database and considered eligible for the present study.

Exposure of interest

TCs were classified as either monotherapy or combination therapy, depending on the presence of concomitant sDMARDs at the start of treatment with a bDMARD. In addition, each TC was classified according to whether or not the initial therapy was maintained throughout follow-up, leading to a categorization of TCs into complete mono- or complete combination therapy, and step-up (addition of sDMARDs) or step-down (discontinuation of all sDMARDs) therapy.

Study outcomes

The primary outcome variables were bDMARD retention (time from start to discontinuation of a bDMARD) and evolution of RA disease activity in terms of DAS28 over time. For the analysis of bDMARD retention, TCs with rituximab (difficulties in defining the date of drug discontinuation) or an immediate loss of follow-up were not included. The covariates considered were: sex, age, BMI, smoking, number of previously used bDMARDs, calendar year of bDMARD treatment initiation, disease duration, seropositivity (presence of RF or ACPA), DAS28, functional disability (HAQ), lung, liver or kidney co-morbidity and type of bDMARD at baseline.

Statistical analysis

The units of interest in this study were the TCs with a bDMARD. When considered necessary or reasonable, we accounted for the presence of multiple TCs per patient using a random patient effect such as the analysis of DAS28 evolution. The prescription of initial bDMARD monotherapy in relation to patient characteristics at baseline of each TC was analysed using logistic regression analyses. bDMARD retention was analysed using methods for right censored time to event data (Kaplan–Meier and Cox models), with the addition of time-varying covariate effects (extended Cox models). DAS28 change over time was graphically displayed using cubic spline smoothing and analysed with mixed-effects models for longitudinal data. DAS28 response in terms of remission (DAS28 <2.6) and low disease activity (LDAS, DAS28 $\leqslant 3.2$) at 12 and 24 months after the start of bDMARD treatment was analysed using logistic regression analyses. For about one-quarter of the TCs (22–29%, depending on the analysis), information for at least one covariate was missing. We therefore re-analysed our main outcomes based on multiple imputation of missing covariate data. Full details on outcome variable and covariate definitions, statistical methods and software can be found as supplementary data, Methods section, available at *Rheumatology* Online.

Results

Study population

A total of 4218 TCs with bDMARDs from 3111 patients fulfilling the inclusion and exclusion criteria were present in the SCQM-RA cohort by the end of July 2013. Of the 3111 patients, 2292 (74%) contributed with one and 819 with two or more TCs. More detailed information on the inclusion of TCs for the present study can be found in supplementary Fig. S1, available at *Rheumatology* Online.

Frequency of initial or secondary bDMARD monotherapy

Overall, 1136 TCs of the 4218 (27%) were initiated as monotherapy and 3082 (73%) were initiated with sDMARD(s) co-therapy. Most combination TCs were initiated with MTX (75%), followed by LEF (26%). Table 1 presents numbers and percentages of mono- and combination therapy initiated TCs for each bDMARD. The largest percentage of TCs initiated in monotherapy (46%) was observed for certolizumab pegol and the smallest (14%) for infliximab. In 13% of TCs started in combination therapy with sDMARD(s), at least one (possibly transient) phase of monotherapy (step-down) occurred. On the other hand, in 14% of TCs started in monotherapy, at least one phase of co-therapy with sDMARD(s) (step-up) occurred. The majority of monotherapy TCs occurred as a result of initiating the biologic treatment in monotherapy, as opposed to discontinuation of sDMARD(s) during follow-up (1136 initial monotherapy TCs *vs* 388 step-down monotherapy TCs, Table 1).

Characteristics of patients who started treatment with bDMARDs in monotherapy or combination therapy

The baseline characteristics of patients at initiation of the bDMARD treatment are summarized in Table 2. Several patient and treatment characteristics as well as year of treatment initiation and type of bDMARD were associated with initial monotherapy (Table 2), suggesting that monotherapy is more often prescribed to older, co-morbid RA patients, with a lower BMI, longer disease duration, more previous bDMARDs and higher disease activity.

Effectiveness of bDMARDs started as monotherapy or in combination with sDMARDs

Biologic DMARD retention

A total of 3312 of the 4218 TCs (79%) were on bDMARDs other than rituximab and not lost to follow-up immediately. Among these, 2453 TCs (74%) had complete information for all covariates. Discontinuation of bDMARD was observed in 1545 of the 2453 TCs (63%).

The unadjusted estimates of bDMARD retention curves for mono- and combination therapy based on 3312 TCs are shown in Fig. 1. Respective estimates for unadjusted median retention under initial mono- and combination therapy were 2.08 years (95% CI 1.90, 2.55) for monotherapy and 2.30 years (95% CI 2.09, 2.58) for combination therapy. The estimated unadjusted hazard ratio (HR) for discontinuation of monotherapy *vs* combination therapy was 1.13 (95% CI 1.02, 1.24, $P = 0.018$).

The adjusted HR for discontinuation of TCs initiated in mono- *vs* combination therapy based on 2453 TCs was 1.15 (95% CI 1.03, 1.30, $P = 0.018$). All covariates except age, BMI, smoking and co-morbidity were found to significantly affect the hazard for bDMARD discontinuation (Table 3). The covariates with the largest impact were the type of bDMARD and the year of treatment initiation. We explored potential interactions between initial co-therapy and type of bDMARD, between initial co-therapy and co-morbidity and between bDMARD and smoking, but none were significant (results not shown). For DAS28 and seropositivity we had evidence for a non-proportional hazard, that is, an HR that is not constant over time.

Table 1 Summary of type of co-therapies based on all 4218 eligible TCs contributed by 3111 patients

	TCs, *n* (%)	Initial combo, *n* (%)	Initial mono, *n* (%)	Complete combo, *n* (%)	Step-down, *n* (%)	Complete mono, *n* (%)	Step-up, *n* (%)
ABA	272 (6[a])	192 (71[b])	80 (29[b])	175 (91[c])	17 (9[c])	75 (94[d])	5 (6[d])
ADA	1298 (31[a])	967 (74[b])	331 (26[b])	846 (87[c])	121 (13[c])	276 (83[d])	55 (17[d])
CER	48 (1[a])	26 (54[b])	22 (46[b])	24 (92[c])	2 (8[c])	19 (86[d])	3 (14[d])
ETA	1193 (28[a])	777 (65[b])	416 (35[b])	648 (83[c])	129 (17[c])	353 (85[d])	63 (15[d])
GOL	174 (4[a])	145 (83[b])	29 (17[b])	139 (96[c])	6 (4[c])	27 (93[d])	2 (7[d])
INF	651 (15[a])	559 (86[b])	92 (14[b])	515 (92[c])	44 (8[c])	72 (78[d])	20 (22[d])
RIT	324 (8[a])	249 (77[b])	75 (23[b])	216 (87[c])	33 (13[c])	64 (85[d])	11 (15[d])
TOC	258 (6[a])	167 (65[b])	91 (35[b])	131 (78[c])	36 (22[c])	86 (95[d])	5 (5[d])
Total	4218	3082 (73 [b])	1136 (27[b])	2694 (87[c])	388 (13[c])	972 (86[d])	164 (14[d])

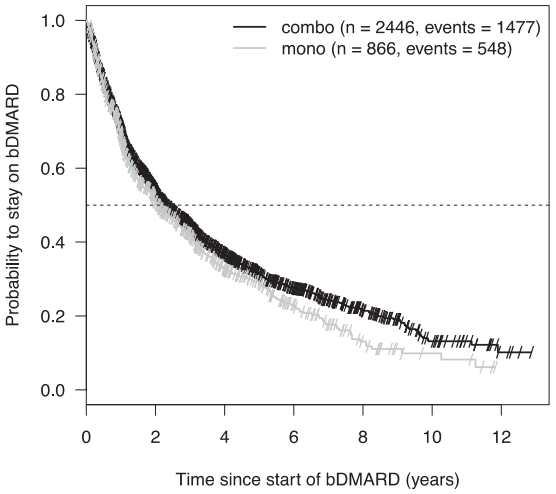
Reading example: 31% of all bDMARD TCs were with adalimumab (ADA); 26% of ADA TCs were initiated in monotherapy. The great majority of TCs initiated in combination therapy or monotherapy remained as such during the entire treatment course (87% and 86%, respectively). Calculation of percentages (may not add to 100 due to rounding): [a]with respect to total number of TCs; [b]with respect to number of TCs per bDMARD (or in total); [c]with respect to number of initial combination therapies per bDMARD (or in total); [d]with respect to number of initial monotherapies per bDMARD (or in total). bDMARD: biologic DMARD; TCs: treatment courses; initial combo: initial combination therapy; initial mono: initial monotherapy; complete combo: complete combination therapy; complete mono: complete monotherapy; ABA: abatacept; ADA: adalimumab; CER: certolizumab pegol; ETA: etanercept; GOL: golimumab; INF: infliximab; RIT: rituximab; TOC: tocilizumab.

Table 2 Summary of covariates based on all 4218 eligible TCs

	All ($n = 4218$)	Mono ($n = 1136$)	Combination ($n = 3082$)	P	OR (95% CI) for initial monotherapy ($n = 2974$)
Age, years	55 (13.4) 46–64	56 (13.5) 47–65	54 (13.4) 46–64	0.0023[a]	1.17 (1.01, 1.35) (per 20 years more)
BMI, kg/m^2 ($n = 4084$)	25.5 (4.9) 21.9–28.3	25.1 (4.8) 21.7–27.7	25.6 (5.0) 22.0–28.5	0.0028[a]	0.82 (0.73, 0.92) (per 6 kg/m^2 more)
Number of previous bDMARDs, %				0.0002	
1	21	22	21		1.37 (1.1, 1.72) (*vs* 0)
2+	13	17	12		1.64 (1.22, 2.19) (*vs* 0)
Disease duration, years ($n = 4079$)	10.9 (9.7) 3.6–15.8	12.8 (10.5) 4.8–18.0	10.2 (9.3) 3.1–14.5	<0.0001[a]	1.24 (1.13, 1.36) (per 10 years more)
DAS28	4.3 (1.4) 3.3–5.3	4.5 (1.4) 3.5–5.5	4.3 (1.4) 3.3–5.3	0.0012[a]	1.22 (1.07, 1.39) (per 2 U more)
HAQ ($n = 3705$)	1.1 (0.7) 0.5–1.6	1.2 (0.7) 0.6–1.8	1.1 (0.7) 0.5–1.6	0.0002[a]	0.98 (0.85, 1.12) (per 1 U more)
Sex: female, %	78	79	78	0.43	0.99 (0.8, 1.24) (male *vs* female)
Smoking, % yes ($n = 3504$)	53	53	54	0.84	0.89 (0.75, 1.07) (no *vs* yes)
Seropositivity, % yes ($n = 4135$)	77	75	78	0.13	1.2 (0.97, 1.49) (no *vs* yes)
Co-morbidity, % no	95	93	95	0.01	1.48 (1.0004, 2.19) (yes *vs* no)
Year of initiation, %				0.0005	
2004–09	50	45	52		0.55 (0.43, 0.71) (*vs* 1999–2003)
2010–13	31	31	31		0.6 (0.44, 0.81) (*vs* 1999–2003)
bDMARD, %				0.0005	
Adalimumab	ADA: 31, CER: 1, ETA: 28, GOL: 4, INF: 15, RIT: 8, TOC: 6	ADA: 29, CER: 2, ETA: 37, GO: 3, INF: 8, RIT: 7, TOC: 8	ADA: 31, CER: 1, ETA: 25, GOL: 5, INF: 18, RIT: 8, TOC: 5		1.18 (0.80, 1.74) (*vs* ABA)
Certolizumab pegol					2.83 (1.30, 6.17) (*vs* ABA)
Etanercept					1.64 (1.11, 2.44) (*vs* ABA)
Golimumab					0.51 (0.26, 0.99) (*vs* ABA)
Infliximab					0.63 (0.40, 0.98) (*vs* ABA)
Rituximab					0.76 (0.48, 1.20) (*vs* ABA)
Tocilizumab					1.32 (0.83, 2.10) (*vs* ABA)

Sample size (n) equals the number of eligible treatment courses (TCs) unless indicated otherwise. Mean (S.D.) and interquartile range are presented for discrete or continuous covariates and percentages for categorical covariates. P-values provided are from Kruskal–Wallis tests for discrete or continuous covariates ([a]) and from Fisher's exact tests for categorical covariates. The last column presents estimated odds ratios (ORs) for initial monotherapy and 95% Wald confidence intervals (CIs) based on a multiple logistic regression considering all covariates and including all TCs with complete covariate information [not accounting for multiple TCs per patient (see supplementary data, Results section for more details, available at *Rheumatology* Online)]. ORs for discrete or continuous covariates are presented for a difference corresponding approximately to the interquartile range. For sex, seropositivity and smoking, the values for all TCs of the same patient are identical. Previous bDMARDs: previously used biologic DMARDs; ABA: abatacept.

Fig. 1 Retention of biologic DMARDs used in monotherapy or in combination with synthetic DMARDs



Kaplan–Meier plot of unadjusted retention of biologic DMARDs (bDMARDs) for initial mono- (grey) and combination (black) therapy based on 3312 treatment courses ($P = 0.018$, log-rank test, not accounting for multiple treatment courses per patient). Small diagonal lines indicate censored retention times. Treatment courses with rituximab or immediate loss to follow-up were excluded.

For these two covariates, Table 3 presents more than one HR estimate to illustrate its behaviour over time.

DAS28 over time

All 4218 TCs were used to investigate the course of DAS28 over time. A smoothed plot of the raw time course of DAS28 (Fig. 2) suggests that DAS28 levels were slightly higher at baseline (0.1–0.2 U) in monotherapy than in combination TCs and improved slightly less after the start of bDMARD treatment. The multiple covariate-adjusted mixed-effects model, analysing a total of 3280 TCs (78%) with complete covariate information confirmed the crude model (supplementary Table S1, available at *Rheumatology* Online). Indeed, there was a significant but small difference in the long-term slope in favour of combination therapy ($P = 0.04$) as well as a clear indication of a difference between therapy types with respect to the DAS28 time course overall ($P = 0.001$, likelihood ratio test for the joint effect of co-therapy on initial drop and long-term slope). The estimated difference in DAS28 between monotherapy and combination TCs after 1, 2 and 4 years was 0.11, 0.15 and 0.23 DAS28 units, respectively.

Other covariates were also associated with significant differences in the course of DAS28 over time. A greater improvement in DAS28 over time in the initial 2 months was observed in TCs started in more recent calendar years and in TCs with tocilizumab. On the other hand, the initial improvement was less pronounced in patients with longer disease duration, more previous bDMARDs and on infliximab. Male *vs* female sex and more previous

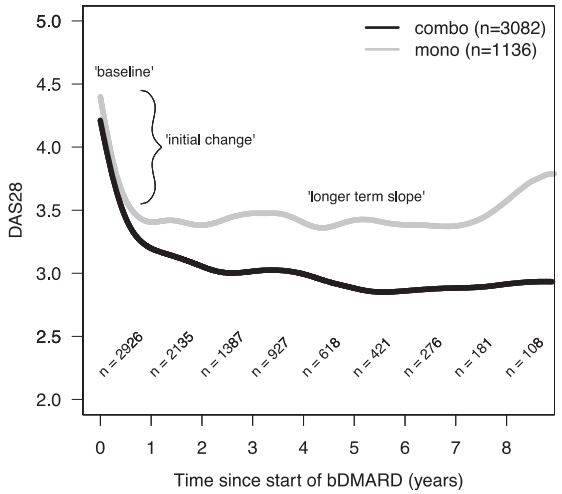
Table 3 Results from extended, covariate-adjusted Cox proportional hazards analysis of bDMARD retention ($n = 2453$ TCs)

	HR (95% CI)	*P*-value
Mono- *vs* combination therapy	1.15 (1.03, 1.30)	0.018
Age, per 20 years more	0.97 (0.90, 1.06)	0.52
BMI, per 6 kg/m^2 more	1.004 (0.94, 1.07)	0.92
No. of previous bDMARDs		
1 *vs* 0	1.24 (1.09, 1.41)	0.0014
2+ *vs* 0	1.20 (0.997, 1.46)	0.054
Disease duration, per 10 years more	0.91 (0.85, 0.96)	0.0019
DAS28, per 2 U more		
<1 year since treatment start	1.27 (1.13, 1.42)	<0.0001[a]
⩾1 year since treatment start	1.01 (0.91, 1.12)	0.0021[b]
HAQ, per 1 U more	1.10 (1.02, 1.19)	0.016
Sex, male *vs* female	0.84 (0.74, 0.96)	0.010
Smoking, no *vs* yes	0.92 (0.83, 1.02)	0.12
Seropositivity, no *vs* yes		
At start	1.27 (1.08, 1.51)	0.0052[c]
At 2 years	1.01 (0.87, 1.16)	0.0043[d]
At 4 years	0.80 (0.63, 1.02)	
Co-morbidity, yes *vs* no	1.29 (0.995, 1.68)	0.054
Year of initiation		
2004–09 *vs* 1999–2003	1.35 (1.18, 1.55)	<0.0001
2010–2013 *vs* 19992003	2.05 (1.68, 2.50)	<0.0001
bDMARD		
Adalimumab *vs* ABA	0.73 (0.56, 0.93)	0.012
Certolizumab pegol *vs* ABA	0.40 (0.18, 0.87)	0.020
Etanercept *vs* ABA	0.74 (0.56, 0.94)	0.015
Golimumab *vs* ABA	1.03 (0.72, 1.49)	0.85
Infliximab *vs* ABA	0.82 (0.64, 1.06)	0.14
Tocilizumab *vs* ABA	0.62 (0.46, 0.85)	0.0031

Shown are estimated hazard ratios (HRs), 95% Wald CIs and associated *P*-values for all covariates based on a model not accounting for multiple TCs per patient. For discrete or continuous covariates ratios are shown for a difference corresponding approximately to the interquartile range. For DAS28 and seropositivity, several HRs are shown to illustrate their behaviour over time. [a]*P*-value for the effect of DAS28 in the first year. [b]*P*-value for the change in the effect of DAS28 when going from <1 year to ⩾1 year. [c]*P*-value for the effect of seropositivity at start of treatment. [d]*P*-value for the change in the effect of seropositivity with time since start of treatment. Of the 2453 TCs, 1860 TCs [76%, including 1155 observed discontinuations (62%)] were initiated in combination therapy and 593 [including 390 observed discontinuations (66%)] in monotherapy. bDMARDs: biologic DMARDs; ABA: abatacept.

bDMARDs were associated with a slightly better long-term course of DAS28 (supplementary Table S1, available at *Rheumatology* Online). The results from a robustness analysis by excluding TCs with high residuals (in total 2% of TCs) were similar (data not shown).The results from the analyses based on multiple imputation of missing covariates were qualitatively similar to those from the

FIG. 2 Evolution of DAS28 in treatment courses with bDMARDs in monotherapy or in combination with sDMARDs



Smoothed unadjusted time course of DAS28 for initial mono- (grey) and combination (black) therapy based on 4218 treatment courses (TCs) and 13 370 observations. Smoothing was done using cubic splines. A total of 2926 TCs had one or more follow-up visits after start of biologic treatment and 1292 contributed only with a baseline observation. The number of TCs still under observation is listed above the time axis. Baseline, initial change and longer-term slope indicate the different phases of the DAS28 time course that were modelled in the longitudinal mixed-effects analysis. The unadjusted difference in the course of DAS28 over time between initial mono- and combination therapy based on such a longitudinal mixed-effects regression model was significant ($P < 0.0001$, likelihood ratio test, accounting for multiple TCs per patient).

complete-case analyses especially with respect to our main interest, the effect of type of therapy on bDMARD retention and evolution of DAS28 (details not shown).

DAS28 response rates

All 1859 TCs with at least one follow-up visit around 12 months (in the time window of 9–15 months) after bDMARD treatment initiation were used for the analysis of DAS28 response rates. Of these TCs, 76% had complete baseline covariate data and were used in a multiple adjusted analysis. Remission and LDAS at 12 months were less frequently achieved in monotherapy compared with combination TCs: remission 32% *vs* 35%, LDAS 51% *vs* 54%, respectively, but this did not reach statistical significance [remission: unadjusted odds ratio (OR) 0.87 (95% CI 0.70, 1.10), multiple-adjusted (m.a.) OR 0.91 (95% CI 0.67, 1.23), LDAS: unadjusted OR 0.89 (95% CI 0.72, 1.10), m.a. OR 0.81 (95% CI 0.61, 1.09)]. After 24 months of treatment (in the time window 21–27 months, $n = 797$ TCs with complete covariate information), remission was numerically lower [m.a. OR 0.82 (95% CI 0.54, 1.23)] and LDAS was significantly lower in TCs started in monotherapy compared with combination therapy [m.a. OR 0.62 (95% CI 0.42, 0.92), $P = 0.02$)]. ORs were very similar in analyses where TCs discontinued before the follow-up visit at 12 or 24 months after the start of treatment were imputed as non-responders (data not shown).

Discussion

We found that bDMARDs were initially prescribed as monotherapy in 27% of TCs (14–46% depending on bDMARD). In addition, in 13% (4–22% depending on bDMARD) of TCs started in combination therapy, at least one transient phase of monotherapy occurred. Initial monotherapy with bDMARDs was more often prescribed to older RA patients with kidney, lung or liver co-morbidities, a lower BMI, longer disease duration, higher number of previous bDMARDs and higher disease activity. Patients treated initially in monotherapy may, thus, represent a subgroup of patients that is more difficult to manage. We observed that bDMARDs are more effective when started in combination with sDMARDs, both in terms of clinical response and based on bDMARD retention. However, although statistically significant, the differences between the two groups were relatively modest. Other factors seem to play a more important role, such as the year of treatment initiation of the bDMARD or the type of bDMARD, both for clinical response and drug retention.

Studies based on different registries have observed that bDMARDs are prescribed in monotherapy in up to one-third of RA patients [3–10]. An observational study by Soliman *et al*. [4] found that the use of aTNFs in monotherapy was associated with older age and longer disease duration, higher number of prior bDMARDs, higher DAS28 and HAQ, and higher percentage of co-morbidities at baseline. Taken together, these results and our data indicate that the prevalence of bDMARD monotherapy is relatively stable in different countries and that bDMARDs in monotherapy are preferentially prescribed to patients with more difficult disease management.

We observed that retention was decreased when the bDMARD was started in monotherapy as compared with combination therapy. It is likely that this difference is due to a relative lack of efficacy rather than to adverse events. Indeed, DAS28 response for initial monotherapies was slightly but significantly decreased as compared with initial combination therapies. aTNFs were used in 3364 (80%) of the 4218 TCs and had, therefore, a large influence on our results. Soliman *et al*. [4] found that drug retention is reduced when aTNFs are prescribed in monotherapy as compared with in combination with MTX. These data are also consistent with several clinical trials showing that aTNFs are consistently more efficacious in combination with MTX than in monotherapy (reviewed in [13, 14]). Of note, these studies included either MTX-naïve patients or patients with inadequate response to MTX. In contrast, the ADORE study [15] showed similar clinical responses with etanercept alone and with

etanercept in combination with MTX in patients with active disease despite MTX therapy. Another exception is based on aTNF data of the RABBIT registry, where no significant differences in remission rates between mono- and combination therapy were found [5].

The efficacy of monotherapy with bDMARDs other than aTNFs has also been investigated earlier. In a randomized clinical trial the combination of rituximab and MTX, but not rituximab alone, was superior to MTX, as assessed by the number of patients achieving ACR50 response. Of note, DAS28 changes, as well as the rate of good and moderate EULAR responders, were superior in both the rituximab alone and the rituximab combination group as compared with MTX alone [16]. The results from a large cohort of patients included in various European registries did not find any difference between rituximab monotherapy and the combination of rituximab and MTX regarding DAS28 response [17]. In the Accompany study, which included both MTX-naïve and patients previously treated with MTX with active disease, the clinical response was similar when abatacept was used in monotherapy or in combination with MTX [18]. The efficacy of tocilizumab in monotherapy was extensively studied in both MTX-naive patients and MTX inadequate responders [19–21]. The Act-Ray study showed that in patients with active disease despite MTX therapy, switching to tocilizumab monotherapy or adding tocilizumab to MTX resulted mostly in comparable clinical and radiological outcomes [2]. Tocilizumab in monotherapy was superior to adalimumab in monotherapy in patients with inadequate response to MTX [22]. Taken together, these results suggest that, according to their mode of action, the effectiveness of bDMARDs in monotherapy may not significantly differ from that of bDMARDs in combination with sDMARDs.

We found that the difference in DAS28 responses between monotherapy-initiated TCs and combination-therapy–initiated TCs increased over time. The development of anti-drug antibodies, in particular against monoclonal anti-TNF antibodies, may explain this observation. Progressive resistance to infliximab and adalimumab are associated with the occurrence of anti-drug antibodies. Importantly, co-therapy with MTX attenuates the development of these antibodies [23, 24].

Year of TC initiation had a strong influence on bDMARD retention. We arbitrarily divided the past 14 years into three periods according to the availability of different bDMARDs in Switzerland. Our results suggest that rheumatologists are more likely to change the bDMARD treatment in case of inadequate response if more treatment choices are available.

Our study included a relatively large group of patients followed longitudinally for several years recruited from both academic and non-academic institutions (50%) and smaller rheumatology practices (50%), which is representative of the general consultation situation in Switzerland. It may, however, suffer from potential limitations inherent in the analysis of observational data. Confounding by indication may result in biased estimates for the initial co-therapy effect. We counteracted this in our covariate-adjusted analysis, but we cannot exclude the presence of residual confounding by other unmeasured confounders. One class of such potential unmeasured confounders are characteristics of the previous TC. Apart from the number of distinct biologics received prior to the current TC, we have not considered any other information relating to previous TCs. Missing data is another potential concern. We lost 22–29% of our data due to incomplete covariate information. We have re-run some of our analyses based on multiple imputation of missing covariates and obtained fairly similar results to our complete-case analysis. We prefer the complete-case analysis over the multiple imputation approach for several reasons. A complete-case analysis is unbeatable in its simplicity and non-error-prone implementation. Furthermore, after careful consideration of the likely missingness mechanisms at work, we concluded that a complete-case analysis is more likely to give unbiased results than an analysis based on multiple imputation [25–27]. Although our study included all the available bDMARDs, it was mostly driven by the most frequent bDMARDs (adalimumab and etanercept), thus limiting the possibility of examining the effectiveness of different bDMARDs in monotherapy. International collaboration between registries will be useful for examining this question in more detail for other bDMARDs. Some studies reported that a substantial percentage of patients are non-adherent to sDMARDs and that this is associated with decreased treatment effectiveness [28, 29]. The extent of non-adherence to sDMARD therapy by patients in our registry is not known, but we would expect that the extent of non-adherence does affect the comparison of monotherapy and combination initiated bDMARDs.

Conclusion

Our study observed that just over a quarter of TCs with bDMARDs were initiated as monotherapy, preferentially in patients with more unfavourable disease characteristics and co-morbidities. Overall, the effectiveness of bDMARDs initiated as monotherapy was found to have been slightly lower than that of bDMARDs initiated with sDMARDs, but to an extent that seems only marginally clinically relevant.

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Supplementary Data

Supplementary data are available at *Rheumatology* Online.

References

1 Smolen JS, Landewe R, Breedveld FC *et al*. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. Ann Rheum Dis 2014;73:492–509.

2 Dougados M, Kissel K, Sheeran T *et al*. Adding tocilizumab or switching to tocilizumab monotherapy in methotrexate inadequate responders: 24-week symptomatic and structural results of a 2-year randomised controlled strategy trial in rheumatoid arthritis (ACT-RAY). Ann Rheum Dis 2013;72:43–50.

3 Heiberg MS, Koldingsnes W, Mikkelsen K *et al*. The comparative one-year performance of anti-tumor necrosis factor alpha drugs in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis: results from a longitudinal, observational, multicenter study. Arthritis Rheum 2008;59:234–40.

4 Soliman MM, Ashcroft DM, Watson KD *et al*. Impact of concomitant use of DMARDs on the persistence with anti-TNF therapies in patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register. Ann Rheum Dis 2011;70:583–9.

5 Listing J, Strangfeld A, Rau R *et al*. Clinical and functional remission: even though biologics are superior to conventional DMARDs overall success rates remain low—results from RABBIT, the German biologics register. Arthritis Res Ther 2006;8:R66.

6 Askling J, Fored CM, Brandt L *et al*. Time-dependent increase in risk of hospitalisation with infection among Swedish RA patients treated with TNF antagonists. Ann Rheum Dis 2007;66:1339–44.

7 Mariette X, Gottenberg JE, Ravaud P, Combe B. Registries in rheumatoid arthritis and autoimmune diseases: data from the French registries. Rheumatology 2011;50:222–9.

8 Yazici Y, Shi N, John A. Utilization of biologic agents in rheumatoid arthritis in the United States: analysis of prescribing patterns in 16,752 newly diagnosed patients and patients new to biologic therapy. Bull NYU Hosp Jt Dis 2008;66:77–85.

9 Lee SJ, Chang H, Yazici Y *et al*. Utilization trends of tumor necrosis factor inhibitors among patients with rheumatoid arthritis in a United States observational cohort study. J Rheumatol 2009;36:1611–7.

10 Sarzi-Puttini P, Antivalle M, Marchesoni A *et al*. Efficacy and safety of anti-TNF agents in the Lombardy rheumatoid arthritis network (LORHEN). Reumatismo 2008;60:290–5.

11 Uitz E, Fransen J, Langenegger T, Stucki G. Clinical quality management in rheumatoid arthritis: putting theory into practice. Swiss Clinical Quality Management in Rheumatoid Arthritis. Rheumatology 2000;39:542–9.

12 Ciubotariu E, Gabay C, Finckh A, Physicians of the Swiss Clinical Quality Management Program for Rheumatoid A. Joint damage progression in patients with rheumatoid arthritis in clinical remission Do biologics perform better than synthetic antirheumatic drugs? J Rheumatol 2014;41:1576–82.

13 Emery P, Sebba A, Huizinga TW. Biologic and oral disease-modifying antirheumatic drug monotherapy in rheumatoid arthritis. Ann Rheum Dis 2013;72:1897–904.

14 Gabay C, Hasler P, Kyburz D *et al*. Biological agents in monotherapy for the treatment of rheumatoid arthritis. Swiss Med Wkly 2014;144:w13950.

15 van Riel PL, Taggart AJ, Sany J *et al*. Efficacy and safety of combination etanercept and methotrexate versus etanercept alone in patients with rheumatoid arthritis with an inadequate response to methotrexate: the ADORE study. Ann Rheum Dis 2006;65:1478–83.

16 Edwards JC, Szczepanski L, Szechinski J *et al*. Efficacy of B-cell-targeted therapy with rituximab in patients with rheumatoid arthritis. N Engl J Med 2004;350:2572–81.

17 Chatzidionysiou K, Lie E, Nasonov E *et al*. Effectiveness of disease-modifying antirheumatic drug co-therapy with methotrexate and leflunomide in rituximab-treated rheumatoid arthritis patients: results of a 1-year follow-up study from the CERERRA collaboration. Ann Rheum Dis 2012;71:374–7.

18 Nash P, Nayiager S, Genovese MC *et al*. Immunogenicity, safety, and efficacy of abatacept administered subcutaneously with or without background methotrexate in patients with rheumatoid arthritis: results from a phase III, international, multicenter, parallel-arm, open-label study. Arthritis Care Res 2013;65:718–28.

19 Nishimoto N, Hashimoto J, Miyasaka N *et al*. Study of active controlled monotherapy used for rheumatoid arthritis, an IL-6 inhibitor (SAMURAI): evidence of clinical and radiographic benefit from an x ray reader-blinded randomised controlled trial of tocilizumab. Ann Rheum Dis 2007;66:1162–7.

20 Nishimoto N, Miyasaka N, Yamamoto K *et al*. Study of active controlled tocilizumab monotherapy for rheumatoid arthritis patients with an inadequate response to methotrexate (SATORI): significant reduction in disease activity and serum vascular endothelial growth factor by IL-6 receptor inhibition therapy. Mod Rheumatol 2009;19:12–9.

21 Jones G, Sebba A, Gu J *et al*. Comparison of tocilizumab monotherapy versus methotrexate monotherapy in patients with moderate to severe rheumatoid arthritis: the AMBITION study. Ann Rheum Dis 2010;69:88–96.

22 Gabay C, Emery P, van Vollenhoven R *et al*. Tocilizumab monotherapy versus adalimumab monotherapy for

treatment of rheumatoid arthritis (ADACTA): a randomised, double-blind, controlled phase 4 trial. Lancet 2013;381:1541–50.

23 Jani M, Barton A, Warren RB, Griffiths CE, Chinoy H. The role of DMARDs in reducing the immunogenicity of TNF inhibitors in chronic inflammatory diseases. Rheumatology 2014;53:213–22.

24 Garces S, Demengeot J, Benito-Garcia E. The immunogenicity of anti-TNF therapy in immune-mediated inflammatory diseases: a systematic review of the literature with a meta-analysis. Ann Rheum Dis 2013;72:1947–55.

25 White IR, Carlin JB. Bias and efficiency of multiple imputation compared with complete-case analysis for missing covariate values. Stat Med 2010;29:2920–31.

26 Allison PD. Multiple imputation for missing data: a cautionary tale. Socio Meth Res 2000;28:301–9.

27 Little RJA, Rubin DB. Statistical analysis with missing data. 2nd edn. Oxford: Wiley, 2002.

28 Cannon GW, Mikuls TR, Hayden CL *et al*. Merging veterans affairs rheumatoid arthritis registry and pharmacy data to assess methotrexate adherence and disease activity in clinical practice. Arthritis Care Res 2011;63:1680–90.

29 Waimann CA, Marengo MF, de Achaval S *et al*. Electronic monitoring of oral therapies in ethnically diverse and economically disadvantaged patients with rheumatoid arthritis: consequences of low adherence. Arthritis Rheum 2013;65:1421–9.