

EXTENDED REPORT

Discontinuation of tumour necrosis factor inhibitors in patients with rheumatoid arthritis in low-disease activity: persistent benefits. Data from the Corrona registry

Arthur Kavanaugh,¹ Susan J Lee,^{1,2} Jeffrey R Curtis,³ Jeffrey D Greenberg,^{4,5} Joel M Kremer,^{5,6} Lilian Soto,⁷ Carol J Etzel,^{5,8} Vanessa Cox,⁵ Kazuki Yoshida,^{9,10} George W Reed,^{5,11} Daniel H Solomon⁹

Handling editor Tore K Kvien

► Additional material is published online only. To view please visit the journal online (<http://dx.doi.org/10.1136/annrheumdis-2014-206435>)

For numbered affiliations see end of article.

Correspondence to

Professor Arthur Kavanaugh, Center for Innovative Therapy, Division of Rheumatology, Allergy and Immunology, 9500 Gilman Drive, La Jolla, CA 92093-0943, USA; akavanaugh@ucsd.edu

Received 7 August 2014
Revised 14 November 2014
Accepted 15 November 2014

ABSTRACT

Background There is increasing interest in discontinuing biological therapies for patients with rheumatoid arthritis (RA) achieving good clinical responses, provided patients maintain clinical benefit.

Methods We assessed patients with RA from the Corrona registry who discontinued treatment with their first tumour necrosis factor inhibitor (TNFi) while in low-disease activity (LDA) or lower levels of disease activity. Patients were followed until they lost clinical benefit, defined as increased disease activity or change in RA medications. Duration of maintenance of clinical benefit was estimated using the Kaplan–Meier method. Cox proportional hazard models were assessed to identify factors related to maintenance of benefit.

Results We identified 717 eligible patients with RA from 35 656 in the Corrona registry. At discontinuation, patients had a median RA duration of 8 years, mean clinical disease activity score of 4.3 ± 0.11 ; 41.8% were using TNFi as monotherapy. 73.4% of patients maintained benefit for >12 months after discontinuing therapy and 42.2% did so through 24 months. Factors predictive of maintaining clinical benefit in multivariate analysis included lower disease activity, less pain and better functional status at the time of TNFi discontinuation. Among 301 patients initiating their first TNFi within the registry, faster responders (ie, those who achieved LDA in 4 months or less) did better than slower responders (HR 1.54 (95% CI 1.17 to 2.04)). RA disease duration did not affect maintenance of clinical benefit.

Conclusions Discontinuation of a first course of TNFi may be associated with persistent clinical benefit. Half of patients maintained response through 20 months. Several patient characteristics may help predict persistent benefit.

INTRODUCTION

Biological therapies have helped advance the care of patients with rheumatoid arthritis (RA).¹ Clinical success achieved with biological agents, particularly inhibitors of tumour necrosis factor (TNF), has led to alterations in the overall treatment approach to RA and the goals of therapy. Thus, at present, low-disease activity (LDA) or remission is considered the most appropriate objective for treatment.² This

has been reflected in treatment recommendations by international rheumatology societies.^{3,4}

An area of increasing interest is whether patients with RA who have achieved good clinical responses may discontinue biological therapies while maintaining clinical benefit. The potential benefits of such an approach could include lower costs, reduced safety concerns and conforming with patient preferences.^{5–23} To date, this concept has been addressed mainly in clinical trials using heterogeneous methods.⁵ In these studies, tapering or discontinuing TNFi therapy has been successful for subsets of patients over variable periods of time.

The objective of this study was to determine how long patients with RA in clinical practice who had achieved LDA while receiving their first TNF inhibitor (TNFi) could maintain clinical benefit after discontinuing that agent. We used data from a large US-based patient registry to understand the success of TNFi discontinuation in typical practice. Such analyses help fill evidence gaps sometimes left with data from clinical trials by virtue of factors such as greater patient diversity and heterogeneity, longer follow-up and better generalisability to actual clinical practice.

MATERIALS AND METHODS

Study cohort

The Corrona RA registry is an independent, prospective observational cohort.²⁴ Patients with RA are enrolled by clinical rheumatologists at 104 academic and private practice sites across the USA. Using standardised questionnaires, patients with RA and rheumatologists provide data on demographics, disease activity and severity, comorbid conditions, concomitant medications, laboratory and imaging data, adverse effects and other information. At the time of these analyses (through September 2013), Corrona included data on 35 636 patients with RA with data provided every 3–6 months (mean follow-up 3.3 years).

We assessed all patients with RA who discontinued their first TNFi and had no prior use of a non-TNFi biologic. All background non-biological disease-modifying antirheumatic drugs (DMARDs) were permitted as co-therapy. Analysis was restricted to the first TNFi because data suggest

To cite: Kavanaugh A, Lee SJ, Curtis JR, et al. *Ann Rheum Dis* Published Online First: [please include Day Month Year] doi:10.1136/annrheumdis-2014-206435

subsequent courses of TNFi therapy may have lesser efficacy.⁴ To be included in the analysis, patients with RA had to have LDA or lower levels of disease activity, defined by a clinical disease activity index (CDAI) ≤ 10 , at the time their TNFi was discontinued, had no switch to or addition of any biological or non-biological DMARD at time of discontinuation and had at least one follow-up visit after discontinuation. These criteria yielded a population of 717 patients. From those 717, we separately assessed a subset of 301 patients who had initiated their first TNFi while in Corrona to evaluate factors including time on drug, speed of response and time in LDA. The remaining 416/717 patients began data collection within the registry while already receiving their first TNFi.

Outcome

Failure to maintain clinical benefit was defined as (1) increase of the CDAI score to >10 , (2) initiation or reinitiation of any biological agent, (3) addition of any non-biological DMARD or increase in dose, or (4) addition of prednisone or increase in dose. Patients without these were censored at the time of their last recorded Corrona visit.

Covariates

Covariates of interest measured at the time of TNFi discontinuation included age, sex, race, education level, insurance coverage, duration of RA, smoking status (never, former or current smoker), body mass index (BMI), rheumatoid factor (RF) and cyclic citrullinated peptide (CCP) seropositivity (neither, either, both), radiographically erosive disease; concomitant non-biological DMARD use (methotrexate (MTX) or another nbDMARD), over-the-counter drug use (non-steroidal anti-inflammatory drugs, folic acid, fish oil or borage oil) and prednisone use. Collected were disease activity measures at discontinuation: CDAI (and its components: 28 tender and swollen joint counts, patient and physician global assessment scores), patient pain, modified Health Assessment Questionnaire (mHAQ), disease activity score 28 (DAS28)-erythrocyte sedimentation rate (ESR), ESR and C-reactive protein (mg/L). Among the subset of 301 patients who initiated their first TNFi while in Corrona, time on TNFi, time in LDA prior to TNFi discontinuation and time from TNFi initiation to LDA, stratified by early responders (≤ 4 months) versus late responders (>4 months), were assessed.

Statistical analyses

All Corrona data are actively maintained by Corrona personnel, including statisticians (CE, VC, GR), who performed all the analyses. Summary statistics were used for demographics, drug therapy and disease-related characteristics at discontinuation of TNFi and again when they lost clinical response or were censored.

Kaplan–Meier method was used to estimate median time to loss of clinical benefit and the proportion of patients remaining with clinical benefit at 6-month intervals from 6 to 36 months after drug discontinuation. Cox proportional hazards model method was used to identify factors related to maintaining clinical benefit. Factors significant at the 20% α level ($p < 0.20$) in univariable Cox modelling were evaluated together in a multivariable Cox model. Age, CDAI and other disease activity variables at discontinuation were dichotomised at the median of their distributions. Duration of RA disease was assessed in several ways: median at time of TNF discontinuation: >8 vs ≤ 8 years (reference), >1 vs ≤ 1 (reference) and >2 vs ≤ 2 years (reference). HRs are shown for high (above median) versus low

(below median, reference). BMI was categorised as normal: <24.5 and overweight/obese: >25 units. RF and CCP-positive status were modelled separately and combined. Since disease activity variables were significantly correlated ($R > 0.20$, $p < 0.001$) with CDAI at discontinuation, CDAI, patient pain and mHAQ were evaluated in separate multivariable models. Although DAS and erosive disease were significant in univariable analyses, they were not included in the multivariable analyses due to a lower rate of data collection for these two variables that reduced the analysable sample size.

Survival models based on interval censoring were evaluated, but results were similar to the Cox models based on right censoring, so only the Cox model based on right censoring is presented. The proportional hazard assumption was evaluated by visual inspection of the regression of scaled Schoenfeld residuals on time but there was no evidence that it was violated. A physician random effect (frailty model) was evaluated to account for patients clustering within the same physician in order to model unexplained heterogeneity.²⁵ In the Cox model using the full set of $N=717$ patients, the resulting $p=0.333$ for the physician random effect; it was concluded that there was no evidence of within-physician correlation observed (HRs of variables in the final Cox model were consistent with and without inclusion of physician random effect).

We performed the above analyses in the subset of patients who initiated their first TNFi within Corrona. In addition to the above variables, we evaluated CDAI at TNF initiation dichotomised as ≤ 10 (LDA) vs >10 , time on TNF (dichotomised at median=9 months), time in LDA (in months) prior to TNFi discontinuation (dichotomised at median=5.7 months) and time from TNFi initiation to LDA (in months), stratified by early responders (≤ 4 months) versus late responders (>4 months).

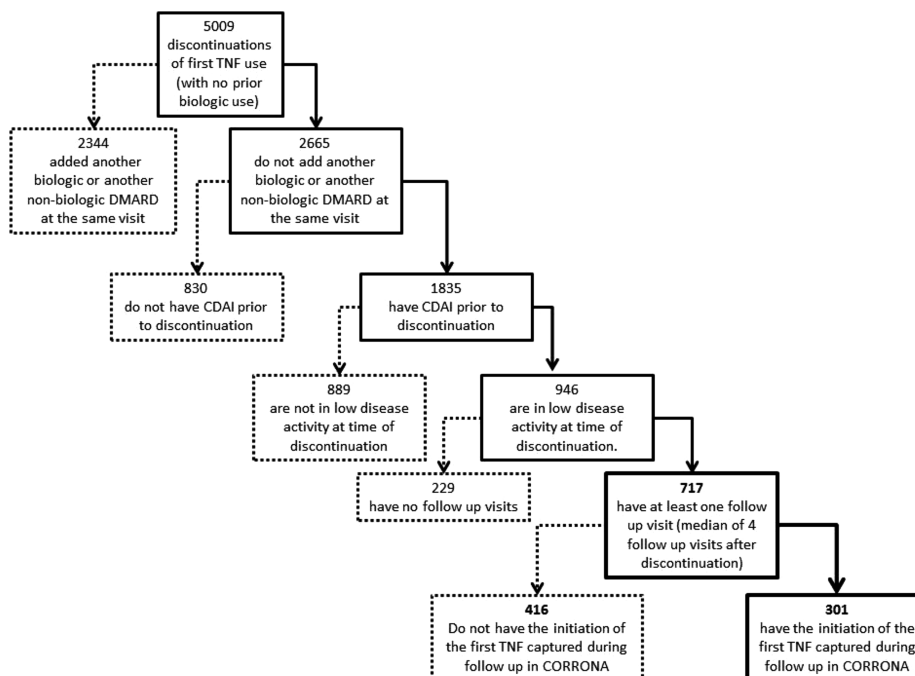
RESULTS

Figure 1 summarises how the final set of 717 patients with RA in Corrona who met the inclusion criteria was derived. Of these, 301 (42%) patients had the initiation of their first TNFi captured while they were in the Corrona registry; the remaining 416 were prevalent TNFi users. Table 1 summarises the baseline characteristics of the population at the time of TNFi discontinuation.

Over the years of follow-up, 601 of 717 patients (83.8%) eventually lost clinical benefit; 116 (16.8%) were censored. Among the subset of 301 patients that initiated their first TNFi while under observation in the Corrona registry, 243 (80.7%) lost clinical benefit during follow-up and 58 (19.3%) were censored. Disease activity measures at the time of TNFi discontinuation and at the end of study (loss of clinical benefit or last visit) are shown in table 2.

Reasons for loss of clinical benefit are shown in table 3. A patient could have multiple events that defined loss of clinical response. Among the list of events that defined loss clinical benefit, the largest reason was initiation of a biological agent, followed by an increase in disease activity with the CDAI score increasing to >10 .

The time course of loss of clinical benefit is shown in figure 2. The median time until failure to maintain clinical response among all patients was 20.1 months (18.6–21.7). Patients with initiation of their first TNFi in Corrona had a similar median time to loss of clinical response of 20.2 months (17.4–23.3). Kaplan–Meier estimates for the proportion of patients remaining with benefit (percentage, 95% CI) over 6-month intervals were 6 months, 98.7 (97.6 to 99.3); 12 months, 73.4 (70.0 to 76.5); 18 months, 55.6 (52.8 to 59.2); 24 months, 42.2 (38.6 to 46.0); and 36 months, 27.6 (24.2 to 31.0) (figure 2). Time course was

Figure 1 Persistency feasibility flow chart.

similar among the 301 patients initiating their first TNFi within Corrona (data not shown).

A number of potential factors that could have affected maintenance of clinical benefit were assessed—smoking status, BMI, seropositivity, DAS, CDAI at discontinuation, patient pain at discontinuation and mHAQ at discontinuation. Factors that were significant at the 20% level in univariable Cox modelling were evaluated together in a multivariable Cox model. Age and gender included in multivariable models as covariates although they were not significant at the 20% level. Seropositivity was also statistically significant and related to loss of clinical benefit among all patients (data not shown); however, inclusion of this variable in the multivariable model also reduced the analysable sample size. In the final multivariable models, it was observed that clinical disease activity index (CDAI), patient pain and mHAQ at discontinuation were statistically significant with HR of 1.28 (95% CI 1.09 to 1.50) for CDAI, HR 1.24 (95% CI 1.05 to 1.47) for patient pain and HR 1.21 (95% CI 1.02 to 1.42) for mHAQ (table 4). Concomitant MTX or prednisone use at the time did not impact the results.

Among patients initiating their first TNFi within Corrona, the time to achieve clinical response correlated with loss of clinical benefit. Thus, patients who achieved LDA within 4 months of therapy, typically the time of the earliest follow-up visit in the Corrona registry, did better than those who responded slower—HR 1.43 (95% CI 1.07 to 1.91) with adjustment for age, gender, race, smoking status and BMI (data not shown). Time on TNFi was not significant—HR 1.0 (95% CI 0.99 to 1.01) (data not shown). Time in LDA was not a significant ($p > 0.05$) predictor of loss of clinical benefit; however, because this may have been affected by patients starting TNFi while already in LDA, a separate analysis was performed for the 133/301 patients whose CDAI was > 10 at the time of TNFi initiation. In that subset of patients, less time in LDA was associated with loss of clinical benefit (HR for time in months as a continuous variable—0.98 95% CI (0.97 to 0.99)). Of note, RA disease duration, assessed in multiple ways, did not impact duration of clinical benefit maintenance (data not shown).

DISCUSSION

An area of increasing interest in RA is whether patients who have achieved good clinical responses may discontinue biological therapies while maintaining clinical benefit. Interest in this approach relates to several factors. Because the acquisition costs of biological therapies exceed those of older agents, there could be substantial economic benefit if these agents could be stopped while maintaining desirable clinical outcomes. Also, although biological agents are generally safe, any immunomodulatory therapy may potentially be associated with untoward effects, such as increased risk of infection. Discontinuing therapy would reduce those concerns. In addition, patients with chronic diseases such as RA often express to their physicians a preference to not use medications chronically. Indeed, patients' choices regarding medication use, based on factors such as beliefs about medications and disease, critically impact how therapies are actually used.^{26 27}

To date, the question of whether TNFi can be discontinued has been addressed mainly in a number of clinical trials.^{5–23} This is an area of intense interest, with many studies ongoing. Of note, the methods used across these studies has been heterogeneous, and important differences among them makes synthesis of data complex.⁵ Important differences include tapering plan (decreased dose, increased interval, discontinue), target prior to tapering (LDA, remission and how these are defined), length of time at target prior to tapering, duration of RA, prior and concomitant treatments, depth of response prior to tapering and definitions of failure.²⁸ In most studies, some patients have been able to discontinue treatment for some time, although the numbers and duration have been variable. Moreover, as many of these reports were clinical trials, there is the possibility that the patients enrolled in studies may have important differences from the general RA population. Also, follow-up times have generally been a year or less. Thus, it is difficult to extrapolate data from these studies to typical practice. We used registry data from the large Corrona registry to address this question.

In this study, we found that patients with RA who were in LDA and stopped their first TNFi could maintain clinical benefit after

Clinical and epidemiological research

Table 1 Baseline population characteristics (at the time of TNFi discontinuation)

Characteristic	All patients N=717	Patients initiating TNFi in Corrona N=301 (42% of 717)
Age in years, median (IQR)	60 (50–69)	62 (52–69)
Women: N (%)	536 (74.8)	231 (76.7)
Caucasian: N (%)	641 (89.4)	245 (81.4)
Education: N (%)		
Completed college, n (%)	419 (61.4)	175 (60.6)
Insurance*: N (%)		
None	14 (2.0)	4 (1.3)
Medicaid	25 (3.6)	12 (4.0)
Medicare	257 (36.7)	104 (34.8)
Private	520 (74.2)	227 (75.9)
Duration of RA in years, median (IQR)	8 (4–15)	8 (4–14.5)
Smoking status: N (%)		
Never	363 (50.6)	141 (46.8)
Former	263 (36.7)	120 (39.9)
Current	91 (12.7)	40 (14.4)
BMI	27.3 (23.8–31.6)	27.5 (23.7–32.0)
Time on first TNF; months, median (IQR)	NA	9 (4.1–23.2)
Medication use		
TNFi monotherapy	300 (41.8%)	159 (52.8%)
Concomitant MTX	320 (44.7%)	99 (32.9%)
Concomitant DMARD (other than MTX)	59 (8.2%)	23 (7.6%)
Concomitant MTX+DMARD	38 (5.3)	20 (6.6%)
Number of non-biological DMARDS, median (IQR)	2 (2–3)	2 (2–3)
Recent prednisone (within 3 months)	188 (27.2%)	68 (29.3%)

*Sum may not add to total N as some patients have dual insurance coverage. BMI, body mass index; DMARD, disease-modifying antirheumatic drugs; MTX, methotrexate; RA, rheumatoid arthritis; TNFi, tumour necrosis factor inhibitor.

Table 3 Reasons for study exit

	All patients N=717	Subset of patients initiating their first TNFi while in Corrona registry N=301
Censored (still with persistent clinical benefit)	116 (16.2)	58 (19.3)
CDAI >10	302 (42.1)	135 (44.9)
Treatment change at same visit	133/302 (44.0)	57/135 (42.2)
No treatment change at same visit	169/302 (56.0)	78/135 (57.7)
Addition of	0 (0)	0 (0)
MTX only	48 (6.7)	23 (7.6)
Any non-biological DMARD (excluding MTX)	76 (10.6)	28 (9.3)
Non-biological DMARD and MTX any DMARD	124 (17.3)	51 (16.9)
Initiation of any biological	380 (53.0)	141 (46.8)
Prednisone		
Start	63 (8.8)	27 (9.0)
Dose increase	28 (3.9)	12 (4.0)

Sums may not add to total N=717 (301) as 406 (57) patients had more than one end of benefit defining event (ex. CDAI >10 and biological start) at same visit. CDAI, clinical disease activity score; DMARD, disease-modifying antirheumatic drugs; MTX, methotrexate; TNFi, tumour necrosis factor inhibitor.

discontinuing that agent. Although the majority of patients did eventually lose clinical benefit, according to the strict definitions we used, it is notable that the median persistence of benefit was over 20 months. Several factors were predictive of maintaining benefit, including seropositivity, as well as functional status and disease activity at the time of discontinuation. These have been noted in some other clinical trials assessing biological discontinuation. Interestingly, although it was looked at in several ways,

Table 2 Disease activity table at baseline* and end of study

	At baseline*	At time of loss of benefit or last follow-up (censored)		
		All patients n=717	Censored n=116	Loss of benefit n=601
Patient global median (IQR)	15 (5–35)	18.5 (5–40)	10 (2–25)	20 (5–50)
Physician global median (IQR)	8 (3–18)	10 (4–24)	5 (0–9)	15 (5–25)
Pain median (IQR)	15 (5–35)	20 (5–44)	10 (5–25)	20 (5–50)
mHAQ median (IQR)	0 (0–0.38)	0 (0–0.38)	0 (0–0.25)	0.13 (0–0.50)
CDAI median (IQR)	4 (1.5–6.8)	6.9 (2.5–13.5)	2.5 (0.6–5.0)	9.3 (3.1–15.1)
DAS28 median (IQR) (available for 217 patients)	2.31 (1.73–3.03)	2.38 (1.79–3.54)	1.89 (1.55–2.19)	2.72 (1.83–3.74)
Erosive diseases ever: n/N (%)	304/549 (55.4)	314/555 (56.6)	45/85 (52.9)	269/470 (57.2)
Seropositivity: n/N (%)	351/442 (79.4)	360/455 (79.1)	51/75 (68.0)	309/380 (81.3)
RF-positive ever: n/N (%)	310/408 (76.0)	320/422 (75.8)	48/71 (67.6)	272/351 (77.5)
CCP-positive ever: n/N (%)	143/216 (66.2)	152/229 (66.4)	24/45 (53.3)	128/184 (69.6)

*Defined as the time of TNFi discontinuation. Seropositivity=combined positive status for RF and CCP. A patient is defined as seropositive if RF-positive or CCP-positive or both. Erosive disease, RF-positive, CCP-positive testing is not required on all Corrona RA; therefore, these counts are available on a reduced set of patients with RA: n/N (%), where n is the observed frequency of positive among N patients with available data. CCP, cyclic citrullinated peptide; CDAI, clinical disease activity score; DAS28, disease activity score 28; mHAQ, modified Health Assessment Questionnaire; RA, rheumatoid arthritis; RF, rheumatoid factor; TNFi, tumour necrosis factor inhibitor.

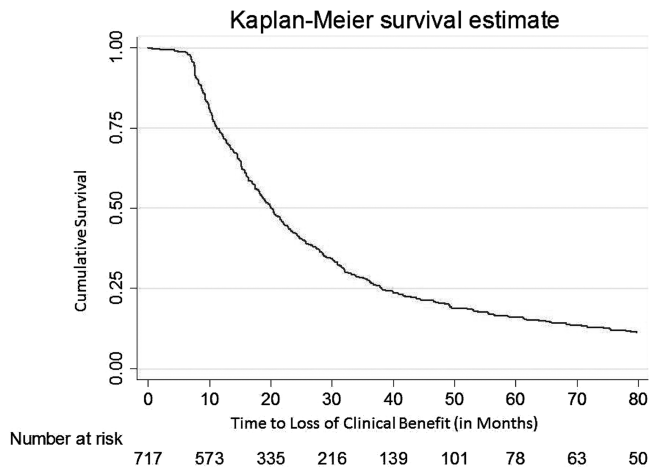


Figure 2 Kaplan–Meier survival estimate.

early disease did not emerge as a factor influencing maintenance of clinical benefit. This may be surprising as patients with early RA generally achieve higher outcomes such as LDA and remission to a greater extent than those with more established disease. However, we did observe that patients who achieved LDA more rapidly maintained clinical benefit longer than those achieving LDA more slowly. This suggests that factors impacting speed of achievement of remission or LDA may correlate better with persistent clinical benefit after discontinuing therapy than the achievement itself. However, the small number of patients available for these analyses is an important caveat.

There are a number of strengths to our analysis. By using the large Corrona database, we were able to accrue over 700 patients who were relatively homogeneous in important aspects, including use of their first TNFi. These patients are also recruited from rheumatology clinics and may perhaps be more representative of the overall RA population than patients from clinical trials. Also, we used a very conservative assessment of loss of benefit, with any change in treatment indicating treatment failure. Indeed, this might also be a limitation of the analysis as the rules used may be too conservative. In this analysis, patients who took low-dose steroids for a week for a small flare of disease would be considered to have lost clinical benefit even if they then stayed in LDA for years still off therapy. Similarly, patients whose CDAI went from 9 to 11 but then returned to 9 with no change in therapy would also be considered a failure. Another factor that may ultimately have made our analyses too conservative is that there is no control group. It could perhaps be expected that some patients in LDA who continued their first TNFi also would have ‘failed’ according to the conservative rules used. In future

analyses, inclusion of a control group could be considered, although the need to accurately match patients for several key variables would make this logistically challenging.

There are several other potential limitations to our study. We do not know the specific reasons that TNFi therapy was discontinued by our patients and their physicians. No reason is available for the vast majority (>85%) of instances, and even among those noted, 47% were listed as ‘other’, thereby not allowing comprehension of the complexities of such decisions. Knowing the granular details involved in the patient and physician choice to discontinue therapy might provide important information relating to the success of this strategy. That would allow better extrapolation of these results. In addition, whereas we focused on discontinuation of therapy, it is possible that decrease in the dose of therapy may be a more successful strategy than discontinuing therapy. This was not addressed in this analysis, but will no doubt be investigated in future analyses. Another potential limitation is that the analysis was restricted to TNFi; the idea of tapering or stopping other biological agents or DMARDs (eg, MTX) in RA is also of interest.^{29 30} On the other hand, by grouping TNFi, potential differences among the agents as regards sustained clinical benefit after discontinuation were not explored. TNFi were grouped in order to minimise reduction of the populations, and hence power of the analysis, that such assessment would require, and with the idea that clinical results achieved across all available agents have typically been comparable. In this analysis, we focused on LDA; it may be that the course of patients achieving higher levels of response, for example, remission, would differ in some ways from what we observed. This issue is an area of intense discussion in clinical trial design.⁵ While restricting studies or analyses to patients in remission has a theoretical appeal, the trade-off is that smaller numbers of patients will achieve the higher target, and hence the studies need to be substantially larger or the analyses will be more restricted. In common with most registries, Corrona collects data at 3-month to 6-month intervals; it is possible that collection at additional time points may have provided further information. Another potential limitation to our study is that the strict definitions and requirements for the population assessed also resulted in a small percentage of the overall database being analysed (700/>35 000). As the interest in this topic has been increasing exponentially only in the past few years, it may well be that similar registry analyses performed in the near future might capture larger numbers of patients for assessment as the practice of tapering therapy increases in clinical practice. Finally, in this analysis we do not systematically address the disease course for patients who fail to maintain clinical benefit to see, for example, how they respond to reinstitution of therapy.

Table 4 Multivariable Cox proportional hazard analysis to evaluate factors (at time of TNFi discontinuation) related to loss of clinical benefit among all 717 patients

	MV model with CDAI	MV model with patient pain	MV model with mHAQ
Age (<60 is reference)	0.98 (0.84 to 1.16)	1.01 (0.86 to 1.18)	0.98 (0.83 to 1.15)
Female sex	1.03 (0.85 to 1.25)	1.05 (0.86 to 1.26)	1.04 (0.86 to 1.26)
Caucasian (vs non-Caucasian)	0.80 (0.65 to 0.99)	0.78 (0.63 to 0.96)	0.78 (0.64 to 0.97)
Ever smoker (current/former vs never)	1.18 (1.00 to 1.40)	1.18 (1.00 to 1.40)	1.20 (1.02 to 1.42)
BMI (overweight/obese vs normal)	1.24 (1.04 to 1.48)	1.22 (1.02 to 1.46)	1.23 (1.03 to 1.46)
CDAI at discontinuation (per unit change)	1.28 (1.08 to 1.50)	–	–
Patient pain at disc	–	1.24 (1.06 to 1.46)	–
mHAQ at disc	–	–	1.21 (1.03 to 1.42)

BMI, body mass index; CDAI, clinical disease activity score; mHAQ, modified Health Assessment Questionnaire.

Clinical and epidemiological research

These data show that discontinuation of a first course of TNFi may be associated with persistent benefit for a sizeable proportion of patients. Certain patient characteristics at TNFi discontinuation may help predict persistent benefit. Further analyses such as this may shed further light on this important emerging issue and allow physicians and patients to optimise their use of RA medications.

Author affiliations

- ¹University of California San Diego, San Diego, La Jolla, California, USA
²San Diego Veterans Affairs Medical Center, San Diego, La Jolla, California, USA
³University of Alabama at Birmingham, Birmingham, USA
⁴NYU School of Medicine, New York, New York, USA
⁵Corrona, LLC, Southborough, Massachusetts, USA
⁶Albany Medical College, Albany, New York, USA
⁷Universidad de Chile, Santiago, Chile
⁸Department of Epidemiology, UT MD Anderson Cancer Center, Houston, Texas, USA
⁹Brigham and Women's Hospital, Boston, Massachusetts, USA
¹⁰Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts, USA
¹¹UMASS Medical School, Worcester, Massachusetts, USA

Contributors SJL contributed to study design, data analysis, data interpretation and paper writing. JRC contributed to figures, study design, data analysis, data interpretation and writing. JDG and CJE contributed to study design, data analysis, data interpretation and manuscript editing. JMK contributed to study design, data interpretation and manuscript editing. LS contributed to study design and data interpretation. VC contributed to data analysis and interpretation, review of manuscript and editing of manuscript. KY contributed to interpretation of data and drafting of manuscript. GWR contributed to study design, analysis plan, data interpretation and critical review of manuscript. DHS contributed to study design, analysis, interpretation and manuscript editing. AK contributed to study design, data analysis plan, data interpretation and writing.

Funding This study is sponsored by Corrona. In the last two years, AbbVie, Amgen, AstraZeneca, Genentech, Horizon Pharmaceuticals, Eli Lilly, Novartis, Pfizer, Vertex and UCB have supported Corrona through contracted subscriptions.

Competing interests DHS receives salary support from research grants to Brigham and Women's Hospital from Amgen, Lilly, Pfizer and Corrona. JRC receives support from the NIH (AR064172) and the Agency for Healthcare Research and Quality (R01HS018517). JMK receives salary support from Corrona and owns shares in Corrona. JDG is an employee and shareholder in Corrona and has received consulting fees from AstraZeneca, Pfizer, Celgene and Novartis. CJE, GWR and VC are full-time employees at Corrona. AK has received research support from Amgen, AbbVie, UCB. KY receives tuition support jointly from Japan Student Services Organization (JASSO) and Harvard School of Public Health (partially supported by training grants from Pfizer, Takeda, Bayer and PhRMA).

Ethics approval This study has been approved by the New England Institutional Review Board.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- Furst DE, Keystone EC, Ko AK, *et al.* Updated consensus statement on biological agents for the treatment of rheumatic diseases, 2012. *Ann Rheum Dis* 2013;72(Suppl):ii2–34.
- Smolen JS, Aletaha D, Bijlsma JWJ, *et al.* Treating rheumatoid arthritis to target: recommendations of an international task force. *Ann Rheum Dis* 2010;69:631–7.
- Singh JA, Furst DE, Bharat A, *et al.* 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. *Arthritis Care Res (Hoboken)* 2012;64:625–39.
- 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.
- Yoshida K, Sung YK, Kavanaugh A, *et al.* Biologic discontinuation studies: a systematic review of methods. *Ann Rheum Dis* 2014;73:595–9.
- Quinn MA, Conaghan PG, O'Connor PJ, *et al.* Very early treatment with infliximab in addition to methotrexate in early, poor-prognosis rheumatoid arthritis reduces magnetic resonance imaging evidence of synovitis and damage, with sustained benefit after infliximab withdrawal: results from a twelve-month randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2005;52:27–35.
- Nawata M, Saito K, Nakayama S, *et al.* Discontinuation of infliximab in rheumatoid arthritis patients in clinical remission. *Mod Rheumatol* 2008;18:460–4.
- Brocq O, Millasseau E, Albert C, *et al.* Effect of discontinuing TNFalpha antagonist therapy in patients with remission of rheumatoid arthritis. *Joint Bone Spine* 2009;76:350–5.
- Tanaka Y, Takeuchi T, Mimori T, *et al.* Discontinuation of infliximab after attaining low disease activity in patients with rheumatoid arthritis: RRR (remission induction by Remicade in RA) study. *Ann Rheum Dis* 2010;69:1286–91.
- Van den Broek M, Klarenbeek NB, Dirven L, *et al.* Discontinuation of infliximab and potential predictors of persistent low disease activity in patients with early rheumatoid arthritis and disease activity score-steered therapy: subanalysis of the BeSt study. *Ann Rheum Dis* 2011;70:1389–94.
- Van der Maas A, Kievit W, van den Bemt B, *et al.* Down-titration and discontinuation of infliximab in rheumatoid arthritis patients with stable low disease activity and stable treatment: an observational cohort study. *Ann Rheum Dis* 2012;71:1849–54.
- Haraigai M, Takeuchi T, Tanaka Y, *et al.* Discontinuation of adalimumab treatment in rheumatoid arthritis patients after achieving low disease activity. *Mod Rheumatol* 2012;22:814–22.
- Tanaka Y. Intensive treatment and treatment holiday of TNF-inhibitors in rheumatoid arthritis. *Curr Opin Rheumatol* 2012;24:319–26.
- Smolen JS, Nash P, Durez P, *et al.* Maintenance, reduction, or withdrawal of etanercept after treatment with etanercept and methotrexate in patients with moderate rheumatoid arthritis (PRESERVE): a randomised controlled trial. *Lancet* 2013;381:918–29.
- Detert J, Bastian H, Listing J, *et al.* Induction therapy with adalimumab plus methotrexate for 24 weeks followed by methotrexate monotherapy up to week 48 versus methotrexate therapy alone for DMARD-naive patients with early rheumatoid arthritis: HIT HARD, an investigator-initiated study. *Ann Rheum Dis* 2013;72:844–50.
- Nishimoto N, Amano K, Hirabayashi Y, *et al.* Drug free REMission/low disease activity after cessation of tocilizumab (Actemra) Monotherapy (DREAM) study. *Mod Rheumatol* 2014;24:17–25.
- Smolen JS, Fleischmann R, van Vollenhoven R, *et al.* Adjustment of therapy in rheumatoid arthritis on the basis of achievement of stable low disease activity with adalimumab plus methotrexate or methotrexate alone: the randomized controlled OPTIMA trial. *Lancet* 2014;383:321–32.
- Tanaka Y, Hirata S, Kubo S, *et al.* Discontinuation of adalimumab after achieving remission in patients with established rheumatoid arthritis: 1-year outcome of the HONOR study. *Ann Rheum Dis* 2013. Published Online First: 28 November 2013. doi:10.1136/annrheumdis-2013-204016
- Van Vollenhoven R, Østergaard M, Leirsalo-Repo M, *et al.* In rheumatoid arthritis patients with stable low disease activity on methotrexate plus etanercept, continuation of etanercept 50 mg weekly or 25 mg weekly are both clinically superior to discontinuation: results from a randomized, 3-armed, double-blind clinical trial [abstract]. *Arthritis Rheum* 2012;64(Suppl 10):4171.
- Fautrel B, Gandjbakhch F, Foltz V, *et al.* Targeting the lowest efficacious dose for rheumatoid arthritis patients in remission: clinical and structural impact of a step-down strategy trial based on progressive spacing of tnf-blocker injections (STRASS trial) [Abstract]. *Ann Rheum Dis* 2013;72(Suppl 3):72.
- Emery P, Hammoudeh M, Fitzgerald O, *et al.* Sustained remission with etanercept tapering in rheumatoid arthritis. *N Engl J Med* 2014;371:1781–92.
- Chatzidionysiou K, Tresson C, Teleman A, *et al.* A multicenter, randomized, controlled, open-label pilot study of the feasibility of discontinuation of adalimumab in rheumatoid arthritis patients in stable clinical remission [abstract]. *Arthritis Rheum* 2012;64(Suppl 10):S336.
- Smolen JS, Emery P, Ferraccioli G, *et al.* Maintenance of remission in rheumatoid arthritis patients with low-moderate disease activity following withdrawal of certolizumab pegol treatment: week 52 results from the certain study [abstract]. *Ann Rheum Dis* 2012;71(Suppl 3):361.
- Kremer JM. The Corrona database. *Clin Exp Rheumatol* 2005;23:S172–7.
- Hougaard P. Survival models for heterogeneous populations derived from stable distributions. *Biometrika* 1986;73:387–96.
- Horne R, Weinman J. Patients' beliefs about prescribed medications and their role in adherence to treatment in chronic physical illness. *J Psychosom Res* 1999;47:555–67.
- Wolfe F, Michaud K. Resistance of rheumatoid arthritis patients to changing therapy; discordance between disease activity and patients treatment choices. *Arthritis Rheum* 2007;56:2135–42.
- Kavanaugh A, Smolen JS. The when and how of biologic agent withdrawal in rheumatoid arthritis: learning from large randomised controlled trials. *Clin Exp Rheumatol* 2013;31(Suppl 78):S19–21.
- Takeuchi T, Matsubara T, Ohta S, *et al.* Abatacept biologic-free remission study in established rheumatoid arthritis patients ORION study [Abstract]. *Ann Rheum Dis* 2013;72(Suppl 3):613.
- Aguiar-Lozano L, Castillo-Ortiz JD, Vargas-Serafin C, *et al.* Sustained clinical remission and rate of relapse after tocilizumab withdrawal in patients with rheumatoid arthritis. *J Rheumatol* 2013;40:1069–73.



Discontinuation of tumour necrosis factor inhibitors in patients with rheumatoid arthritis in low-disease activity: persistent benefits. Data from the Corrona registry

Arthur Kavanaugh, Susan J Lee, Jeffrey R Curtis, Jeffrey D Greenberg, Joel M Kremer, Lillian Soto, Carol J Etzel, Vanessa Cox, Kazuki Yoshida, George W Reed and Daniel H Solomon

Ann Rheum Dis published online December 3, 2014

Updated information and services can be found at:
<http://ard.bmj.com/content/early/2014/12/03/annrheumdis-2014-206435>

References

These include:

This article cites 29 articles, 11 of which you can access for free at:
<http://ard.bmj.com/content/early/2014/12/03/annrheumdis-2014-206435#BIBL>

Email alerting service

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections

Articles on similar topics can be found in the following collections

[Connective tissue disease](#) (3910)
[Degenerative joint disease](#) (4260)
[Immunology \(including allergy\)](#) (4690)
[Musculoskeletal syndromes](#) (4552)
[Rheumatoid arthritis](#) (2989)
[Pain \(neurology\)](#) (814)

Notes

To request permissions go to:
<http://group.bmj.com/group/rights-licensing/permissions>

To order reprints go to:
<http://journals.bmj.com/cgi/reprintform>

To subscribe to BMJ go to:
<http://group.bmj.com/subscribe/>