Concise report

Survival on treatment with second-line biologic therapy: a cohort study comparing cycling and swap strategies

Ennio Giulio Favalli1, Martina Biggioggero1,2, Antonio Marchesoni1 and Pier Luigi Meroni1,2

Abstract

Objective. The aim of this study was to evaluate the survival on treatment with second-line biologic therapy in RA patient non-responders to TNF inhibitors (TNFis) by comparing treatments with a second anti-TNF (cycling strategy) or with agents with a different mechanism of action (MoA; swap strategy).

Methods. RA patients treated with biologics since 1999 who stopped a first-line TNFi and started a second-line biotherapy were included in this cohort study. After adjusting for propensity scores, drug retention rates were calculated using the Kaplan–Meier method. The log-rank test was used to compare survival curves and the Cox regression model was used to compare risk for discontinuation between the two groups.

Results. Two hundred and one patients discontinued the first TNFi, switching to a second anti-TNF [n = 119 (59.2%)] or to abatacept [n = 26 (31.7%)], rituximab [n = 40 (48.8%)] or tocilizumab [n = 15 (18.3%)]. Drug survival was significantly higher in the swap group than in the cycling group (P < 0.0001). After adjustment for propensity scores, probability of treatment retention in the swap group was significantly higher (hazard ratio = 2.258, 95% CI 1.507, 3.385), even after stratification according to the reason for the first TNFi discontinuation (P = 0.005). No significant differences emerged when comparing the retention rates of different MoAs (P = 0.51) in the swap group.

Conclusion. In the clinical practice setting, the best option for managing TNFi non-responders seems to be swapping to a different MoA, with no differences between abatacept, rituximab and tocilizumab, irrespective of the reason for first TNFi discontinuation.

Key words: anti-TNF, rheumatoid arthritis, biologic agents, treatment, cycling, swap, drug survival, mechanism of action.

Introduction

The development of biologic agents has dramatically improved the management of RA. According to more recent international recommendations [1], TNF inhibitor (TNFi) therapies have been routinely used as first-line biotherapy for the treatment of RA patients who have failed traditional non-biologic DMARDs. However, ~30% of patients do not respond (or respond suboptimally) to anti-TNF agents, fail to maintain an initially good response over time or experience adverse events leading to treatment discontinuation [2]. Management of the first TNFi failure may involve switching to a second anti-TNF agent (cycling strategy) or the use of an alternative class of targeted agents with a different mechanism of action (MoA) (swap strategy), but to date the optimal treatment approach has yet to be defined.

In fact, data on the efficacy of the cycling strategy from a few randomized controlled trials (RCTs) [3, 4] and national registries [5, 6] are still controversial. Moreover, RCTs involving TNFi insufficient responders (TNFi-IRs)...
have demonstrated the efficacy of several biologic agents vs placebo [4, 7–9], but no head-to-head RCT comparing the strategy of cycling between TNF inhibitors vs using an agent with a different MoA has yet been conducted. The aim of this study was to analyse, in the clinical practice setting, the survival on treatment with second-line biologic therapy in TNFi-IRs comparing cycling and swap strategies.

**Patients and methods**

**Study population**

Data from all RA patients treated with biologics between October 1999 and August 2013 in our rheumatology unit were collected in a local registry. The registry was approved by the Gaetano Pini Institute Ethics Committee and patients aged >18 years were enrolled after giving their written informed consent, in accordance with the following inclusion criteria: (i) a diagnosis of RA fulfilling the 1987 ACR revised criteria [10]; (ii) failure to respond to at least one course of combination therapy with full-dose DMARDs, one of which should always be MTX unless contraindicated; and (iii) active disease as defined by a 28-joint DAS (DAS28) >3.5. The database includes demographic features (age and gender), baseline clinical parameters (DAS28, Simplified Disease Activity Index, Clinical Disease Activity Index, RF and ACPA positivity, CRP level and HAQ score) and therapeutic data (concomitant MTX use). The data were retrospectively analysed beginning when the first biologic agent other than TNFi (rituximab) became available (i.e. January 2007) and continued through August 2013. This choice offered the possibility of minimizing differences in exposure to different biologics. All RA patients who failed their first TNFi therapy for any reason since January 2007 and were then treated with a second anti-TNF agent (cycling strategy) or with a different MoA (abatacept, rituximab or tocilizumab; swap strategy) were eligible for inclusion in the study. During this study period, patients were treated in strict accordance with RA treat-to-target recommendations [1]. The reasons for discontinuing first-line TNFi therapy were classified into two major categories: adverse events and non-toxic causes (including inefficacy, desire for pregnancy and patient preference). Subanalyses were conducted by stratifying the study population according to the reason for TNFi replacement, to different MoA in the swap group and to the different TNFi pattern of the switch (antibody–antibody vs antibody–soluble receptor and soluble receptor–antibody) in the cycling group. Drug survival was retrospectively calculated as the number of days during which a given patient maintained treatment until the first missed dose. All observations were censored at the last registered visit before 1 September 2013.

**Statistical analysis**

The rate of drug discontinuation in the two groups was estimated by the Kaplan–Meier method and compared using the log-rank (Mantel–Cox) test. Given that patients were treated in routine clinical practice and therefore were not randomized to the therapy they switched to, differences in baseline population characteristics between the two treatment groups were analysed using the t-test and the chi-squared test for comparing continuous and dichotomous variables, respectively. Moreover, propensity scores were evaluated for each patient using logistic regression with treatment (cycling or swap) as the dependent variable and the following baseline characteristics as independent variables: age, gender, extra-articular manifestations, RF positivity, ACPA positivity, DAS28 score, CRP, HAQ score and concomitant MTX use. In order to adjust for the differences in baseline characteristics of the two groups of patients, subjects in the swap and cycling groups were matched without replacement on the logit of the propensity score using callipers of width equal to 0.2 of the standard deviation of the logit of the propensity score [11]. The relative balance in measured baseline characteristics after matching was compared using the standardized difference method. The risks for drug discontinuation have been evaluated using Cox regression model and are presented as the hazard ratio (HR) and 95% CI; a P-value ≤ 0.05 was considered statistically significant. Data were analysed with SPSS statistical software, version 15.0 (SPSS, Chicago, IL, USA).

**Results**

**Baseline characteristics**

The study population was selected from 771 patients treated with first-line biotherapy between 1999 and 2013 in our rheumatology department (Fig. 1). Two hundred and one patients who discontinued the first TNF blocker [etanercept (n = 48; 47%), adalimumab (n = 78; 38.8%), infliximab (n = 66; 32.8%), golimumab (n = 5; 2.5%), certolizumab pegol (n = 4; 2%)] because of adverse events (n = 73; 36.3%) or non-toxic causes (n = 128; 63.7%) were enrolled in the study. Since January 2007, 119 (59.2%) patients have switched to a second TNFi [etanercept, 67 (56.3%); infliximab, 8 (6.7%); adalimumab, 31 (26.1%); golimumab, 1 (0.8%); certolizumab pegol, 12 (10.1%)] and 82 patients swapped to abatacept [26 (31.7%), rituximab [40 (48.8%)] or tocilizumab [15 (18.3%)]. The demographics and clinical characteristics of the two groups are reported in supplementary Table S1, available at *Rheumatology* Online. Briefly, no significant differences emerged in the comparison between the two groups, except for higher disease activity scores in the swap group compared with the cycling group. However, since a combination of non-statistically significant differences can still influence the comparison between the two groups, adjustment for propensity scores was applied.

**Drug survival analyses**

After adjustment for propensity scores, drug survival was significantly greater in the swap group than in the cycling group (P < 0.0001; Fig. 2A). The probability of treatment retention in the swap group was significantly higher.
HR = 2.258, 95% CI 1.507, 3.385) compared with the cycling group. These findings were confirmed after stratification of both groups according to the reason for first TNFi discontinuation (adverse events or non-toxic causes). In both the subgroups drug survival of the cycling strategy was significantly lower ($P$ = 0.005 for both; Fig. 2B and C), with a higher adjusted risk of drug discontinuation (HR = 2.642, 95% CI 1.330, 5.248 and HR = 2.051, 95% CI 1.234, 3.408, respectively, for the safety and inefficacy subgroups). Stratifying the swap group according to different MoAs, no significant differences emerged when comparing the retention rates of abatacept, rituximab and tocilizumab ($P$ = 0.51; Fig. 2D).

Finally, no statistically significant differences in drug retention rate ($P$ = 0.67; see supplementary Fig. S1, available at Rheumatology Online) and risk of discontinuation (HR = 1.144, 95% CI 0.607, 2.155) were detected when comparing the two different TNFi patterns of switch (antibody–antibody vs antibody–soluble receptor and soluble receptor–antibody) in the patients treated with the cycling strategy.

**Discussion**

To our knowledge this is the first study comparing the long-term drug survival of different biologic agents used as second-line biotherapy in RA patients who failed a first-line anti-TNF treatment. Overall, our results show that the probability of retaining a second TNFi is significantly lower than that of retaining a differently targeted biologic agent. Of further interest, the probability of survival was not influenced by the reason for drug replacement or by the MoA.

The performance of cycling and swap strategies in TNFi-IRs have been evaluated in previous studies. The efficacy vs placebo of golimumab, rituximab, abatacept and tocilizumab as second-line biotherapy has been demonstrated in four RCTs [4, 7–9] and recently was indirectly compared in a meta-analysis [12]. The main conclusion was that the swap strategy provides more significant improvement with good safety. Lacking head-to-head trials, comparative data come only from one observational trial [13] and two analyses from national registries [14, 15]. As a whole, the reports suggest that swapping to rituximab may be of more benefit than switching to an alternative TNFi therapy, without reporting data on drug survival.

A recent observational study [16] investigating the effects of different anti-cytokine therapies in a real-life setting found similar ($P$ = 0.354, log-rank test) retention rates between tocilizumab (72.6% at 6 months, 60.5% at 12 months) and combined TNFi (81.8% at 6 months, 76.7% at 12 months) used as second-line biotherapy. However, the sample size was small, involving only 44 patients. The much larger series of patients (201) enrolled in our current analysis may be responsible for the different finding.

Since it has been suggested that the cause of TNFi discontinuation may influence the performance of the cycling strategy [17], we performed drug survival subanalyses stratifying the study population according to the cause for first-line biotherapy withdrawal. Consistent with data from other authors [5, 18], our results show that the efficacy of the second anti-TNF is not influenced by the reason for stopping the first one. Moreover, the difference in drug survival between the cycling and swap strategies remained statistically significant in TNFi-IRs for both safety and non-toxic issues.

In order to better investigate the swap strategy, we stratified swap patients according to the biologic agent used, but we failed to demonstrate any statistically significant differences in drug survival when comparing abatacept, rituximab and tocilizumab ($P$ = 0.51; Fig. 2D).
Moreover, incomplete efficacy data prevented a comparative efficacy analysis between swapped and cycled patients. Nonetheless, survival on treatment can be considered a very good surrogate indicator of both drug effectiveness and safety profile in the clinical practice setting. In order to minimize these potential biases, we limited our data analysis to the period after the first biologic agent other than anti-TNF became available. Moreover, we adjusted the analysis for propensity scores that considered differences in the baseline characteristics of the patients.

In summary, this study demonstrated that the best option for treating TNFi-IRs seems to be swapping to a different MoA, with no differences between abatacept, rituximab and tocilizumab, irrespective of the reason for the first TNFi discontinuation. Additional analyses in a larger population may be useful to confirm our findings and to better clarify which MoAs would be preferable as second-line biotherapy according to patient characteristics.

**Disclosure statement:** E.G.F. has received lecture fees from BMS, Roche, MSD, UCB, Pfizer and AbbVie. P.L.M. received lecture fees from BMS, Roche, MSD, UCB, Pfizer and AbbVie. A.M. has received honoraria from Pfizer, AbbVie, MSD, Roche and UCB. The other author has declared no conflicts of interest.

**Supplementary data**

Supplementary data are available at Rheumatology Online.

**References**


4. Smolen JS, Kay J, Doyle MK et al. Golimumab in patients with active rheumatoid arthritis after treatment with tumour necrosis factor alpha inhibitors (GO-AFTER study): a


