RHEUMATOLOGY

Rheumatology 2018;57:vii42–vii53
doi:10.1093/rheumatology/key195

Switch or swap strategy in rheumatoid arthritis patients failing TNF inhibitors? Results of a modified Italian Expert Consensus

Monica Todoerti[1], Ennio Giulio Favalli[2], Florenzo Iannone[3], Ignazio Olivieri[4,†], Maurizio Benucci[5], Alberto Cauli[6], Alessandro Mathieu[6], Leonardo Santo[7], Giovanni Minisola[8], Giovanni Lapadula[3], Romano Bucci[9], Elisa Gremese[10] and Roberto Caporali[1]

Abstract

Objective. To establish evidence-based and experts' opinion filtered statements on the optimal treatment choice between cycling (switch) and changing mode of action strategies (swap) in RA patients failing TNF inhibitors (TNFis).

Methods. The relevant question (switch *vs* swap) was rephrased into a research question according to the population, intervention, comparison and outcome (PICO) strategy, considering all the available scientific evidence published from the 2013 EULAR set of recommendations up to mid-January 2016. Final statements derived from the retrieved scientific evidence and experts' consensus, with eventual rephrasing through a Delphi method during a national consensus of Italian rheumatologists.

Results. From a total of 365 records, 12 studies were finally included. The final statements argued that, until head-to-head comparison data are available, switch and swap can be still considered suitable strategies in RA patients failing first TNFi, even though some data seem to lend more support to a different mode of action-targeted strategy.

Conclusion. After failure of first TNFi course, switch and swap can be currently considered as alternative suitable approaches in RA patients.

Key words: rheumatoid arthritis, biologic therapy, TNF-inhibitor failures, tocilizumab, abatacept, rituximab

REVIEW

Rheumatology key messages

- RA patients failing first TNFi might benefit from both a cycling and a swapping strategy.
- After failure of first TNFi course, swapping seropositive RA patients to rituximab seems more efficacious.
- Cost-effectiveness evaluation in head-to-head trials should clarify the best option for RA patients after TNFi failure.

Introduction

Biologic DMARDs (bDMARDs) have dramatically improved the management of RA patients failing conventional therapies. Several bDMARDs have been approved both as first and as second line therapies, with a general and actual trend by rheumatologists of commencing TNF inhibitors (TNFis) as primary choice, due to the more robust data on their long-term efficacy and safety compared with other more recently introduced bDMARDs with different mode of action (MoA). However, almost 30% of patients do not respond (or respond suboptimally) to TNFi, failing to maintain an initially good response over time or experiencing adverse events (AEs) leading to treatment discontinuation [1]. Existing recommendations (Table 1), in line with published scientific data integrated with experts' opinions,

[1]Division of Rheumatology, University of Pavia, IRCCS Policlinico San Matteo Foundation, Pavia, [2]Department of Rheumatology, Gaetano Pini Institute, Milan, [3]Department of Emergency and Organ Transplantation (DETO), University of Bari, Section of Rheumatology, Bari, [4]Rheumatology Department of Lucania, San Carlo Hospital of Potenza and Madonna delle Grazie Hospital of Matera. Basilicata Ricerca Biomedica (BRB) Foundation, Potenza, [5]Rheumatology Unit, S. Giovanni di Dio Hospital, Florence, [6]Rheumatology Unit, University Clinic and AOU of Cagliari, Cagliari, [7]Rheumatology Service ASL BT – DSS4 Barletta, [8]Fondazione Ospedale San Camillo – Roma, [9]Reumatologia Ospedaliera, Dipartimento Internistico, A.O.U. 'OO.RR' – Foggia and [10]Institute of Rheumatology, Fondazione Policlinico Universitario Agostino Gemelli, Catholic University of the Sacred Heart, Rome, Italy

Submitted 11 August 2017; revised version accepted 4 June 2018

[†]Deceased.

Correspondence to: Monica Todoerti, Division of Rheumatology, University of Pavia, IRCCS Policlinico San Matteo Foundation, Pavia, Piazzale Golgi 19, Pavia, Italy.
E-mail: monica.todoerti@gmail.com

Table 1 Overview across existing recommendations on the cycling *vs* swapping topic in RA

Caporali *et al.* [2] Italian Recommendations	In patients with inefficacy or adverse events to the first TNF antagonist agent, a treatment either with a second TNF antagonist or with another biologic with a different MoA is recommended.
	Switching from a second to a third TNF antagonist is not recommended.
	In patients failing to respond to a second TNF antagonist, other biologics with different MoA should be considered.
	In patients failing to respond to three (or more) biologic drugs, an attempt with another biologic drug might be helpful.
Smolen *et al.* [3] EULAR Recommendations	If a first biologic has failed, patients should be treated with another biologic. If a first TNF-α inhibitor has failed, patients may receive another TNF-α inhibitor or a biologic with another mode of action.
	TNF-α inhibitors (i.e. adalimumab, certolizumab pegol, etanercept, golimumab, infliximab and biosimilars), abatacept, tocilizumab and, under certain circumstances, rituximab are essentially considered to have similar efficacy and safety. If the first biologic fails, any other biologic may be used.
Singh *et al.* [4] ACR Recommendations	If disease activity remains moderate or high, despite use of a single TNF-α inhibitor, use a non-TNF biologic over another TNF-α inhibitor.
	If disease activity remains moderate or high despite use of multiple (>2) sequential TNF-α inhibitors, first use a non-TNF biologic over another TNF-α inhibitor or tofacitinib.
Smolen *et al.* [5] EULAR Recommendations	If a bDMARD or tsDMARD has failed, treatment with another bDMARD or a tsDMARD should be considered; if one TNF inhibitor therapy has failed, patients may receive another TNF inhibitor or an agent with another mode of action.

bDMARD: biologic DMARD; MoA: mode of action; tsDMARD: targeted synthetic DMARD.

offer evidence-based flow-charts in cases of failure of one or more TNFis in RA patients [2–5]. All these sets of recommendations agree in suggesting a different MoA bDMARD when two or more TNFis have failed, recognizing that efficacy might decline when cycling to a third or fourth TNFi. On the contrary, in the case of failure of the first TNFi, no strong evidence seems to support one strategy over another, so that the therapeutic choice is left to the experience of the treating physician, who should take into consideration also patient and disease characteristics. In this setting, switching to a second anti-TNF agent (cycling strategy) or adopting an alternative class of targeted agents with a different MoA (swapping strategy) might both be considered as alternative available strategies, but the optimal treatment approach has yet to be defined. In the 2013 and 2016 set of European recommendations from the EULAR, the corresponding topic similarly states that 'if a bDMARD or tsDMARD [targeted synthetic DMARD] has failed, treatment with another bDMARD or a tsDMARD should be considered; if one TNF inhibitor therapy has failed, patients may receive another TNF inhibitor or an agent with another mode of action' [3, 5]. Once again, no standardized approach was defined, still suggesting that TNFi cycling might offer further gain in clinical control when a first TNFi failed to obtain the target. Anyway, from available scientific evidence, some considerations about this topic should be derived for the decision making process: as demonstrated in real life settings, clinical response tends to decline with the increasing number of previous TNFis adopted and, in addition, the reason for discontinuation of the first TNFi seems to affect the response to the second one [6]. Moving from this background and dealing with this relevant definitive gap in the existing treatment recommendations, we retrieved available literature evidence on the clinical performance (efficacy and safety) of cycling *vs* swapping strategies in RA patients failing TNFi therapy, in order to eventually derive more definitive conclusions.

Methods

The literature review was conducted through PubMed and EMBASE databases to identify all English-language articles fitting the pre-specified topic of cycling (Intervention, I) *vs* swapping strategies (Comparison, C) with respect to efficacy and safety (Outcomes, O) in adult RA patients (Population, P) failing a TNF inhibitor (as first or subsequent line of treatment), regardless of the underlying reason (inefficacy, primary or secondary, or AEs). The literature review was extended from the 2013 update of the EULAR RA recommendations (8 April 2013) up to 15 January 2016, using appropriate key words and Medical Subjects Headings for disease (RA) and bDMARD names (infliximab/IFX, etanercept/ETA, adalimumab/ADA, golimumab/GOL, certolizumab pegol/CZP, abatacept/ABA, rituximab/RTX, tocilizumab/TCZ). The research was performed either by crossing each single TNFi with every non-TNF bDMARD or by considering all TNFi agents as a class *vs* non-anti-TNFs single agents. The EMBASE search was carried on through population, intervention, comparison and outcome and also advanced strategies. Additionally, the bibliography of relevant articles was hand-searched for identification of other potentially suitable studies. The research was designed and performed by one author (M.T.). All available scientific evidence (Table 2) coming from meta-analyses, randomized controlled trials (RCTs), national registries of biologics and national healthcare databases has been considered for data extraction, whenever considering clinical efficacy endpoints as primary outcomes; safety issues were

Table 2 Search strategy and results

Database	Search-strategy	Retrieved results	Selected number (Authors)
EMBASE	#1 AND limits	178	6 (Rotar Z, Harrold LR, Emery P, Manders SKM, Sakai R, Backhaus M)
PubMed			
	#2 AND limits	36	1 (Hirabara S)
	#3 AND limits	79	1 (Navarro-Coy NC)
	#4 AND limits	26	1 (Hirabara S)
	#5 AND limits	45	5 (Emery P, Kobayakawa T, Hirabara S, Favalli EG, Kim HL)
Hand-made search		1	1 (Harrold LR)

evaluated as secondary outcomes. Narrative reviews, editorials, scientific conference abstracts and case reports have been excluded from this work. The hierarchy of study types was indicated by levels of evidence as suggested by the Oxford Centre for Evidence-based Medicine (http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/).

Preliminary statements based on available results have been presented in line with their level of evidence, discussed, eventually reformulated and voted through a Delphi method during a national consensus of a panel of Italian rheumatologists. In this article, all the steps dealing with the swap *vs* switch strategy will be presented. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines for preparing the article (http://www.prisma-statement.org/).

Results

General results

Globally, 12 out of 365 full-text articles dealing with cycling *vs* swapping strategies in adult RA patients failing at least one TNFi were selected for final evaluation [7–18]. Three studies had been conducted in Japanese populations: one of them, from the REAL Registry, considered only safety issues between tocilizumab (TCZ) and TNFi in patients failing previous unspecified bDMARDs (in 71 and 11% of patients, respectively, in the two groups) [11, 13, 15]. This study was subsequently deleted from the final analysis for incomplete and unavailable relevant informative data [11]. One report from Navarro-Coy was a study-protocol with no available results at the date this article was submitted [14]. Supplementary Fig. S1 shows the corresponding article flow-chart.

Background data pro-cycling

Several uncontrolled studies suggested benefit in switching between TNFis [6, 19–26, 28]. The rationale for switching between different TNFis was strengthened by a large, randomized, industry-led efficacy study comparing golimumab (GOL) with placebo (GO-AFTER trial) [29]. This phase III study involved 461 patients, who had previously received and either failed or were intolerant to one or more TNFis, that were randomized to placebo or subcutaneous GOL 50 or 100 mg every 4 weeks. Significantly higher ACR20 response rates at week 14 were observed in the 50 and 100 mg GOL groups compared with the placebo group (35 and 38% *vs* 18%, respectively) [29]. One of the first trials addressing the issue of switching between TNFis was the open-label multicentre Research in Active RA focusing on the effectiveness of adalimumab (ADA) among both TNFi-naïve and TNFi-experienced patients. Of the 6610 patients enrolled, 5711 had never been treated with a TNFi, while 899 had received prior treatment with etanercept (ETA) and/or infliximab (IFX) (591 patients IFX only, 188 ETA only), with 120 patients already failing either IFX or ETA. After 12 weeks of open label treatment with ADA, statistically significant and clinically important improvements from baseline occurred in all measures of RA activity in prior TNFi-treated patients as well as in naïve patients: ACR20 response was achieved by 60% of TNFi-experienced patients and 70% of TNFi-naïve patients, thus suggesting the efficacy of cycling in this real life setting. ADA effectiveness varied by the reason for discontinuation of the prior TNFi, with the highest response rate in patients who had been intolerant to prior TNFi and with the lowest effectiveness in those patients stopping TNFi for primary non-response. Moreover, ADA was effective when used as the third TNFi too, with 46% among 120 difficult-to-treat patients achieving an ACR20 response. More recently, similar results came from the Realistic study, which investigated the efficacy and safety of certolizumab pegol (CZP) in a broad population of RA patients, resembling those commonly seen in clinical practice, that is subjects with active, inadequately controlled disease, irrespective of disease duration and using a broad range of previous and current medications, including previous TNFi treatment [30]. Of 1063 enrolled patients, 37.6% had previously been treated with TNFi. Globally, primary and secondary endpoints were more frequently achieved in patients in the active arm (CZP), with ACR20 response rate at week 12 being 51.1% compared with 25.9% for placebo ($P < 0.001$) and ACR50 and ACR70 response rates 26.6 and 12.9% for the CZP group compared with 9.9 and 2.8% for placebo, respectively ($P < 0.001$ for each comparison). CZP efficacy was consistent across the subgroups, even when stratified by previous TNFi use, concomitant use of MTX and disease duration. Specifically, ACR20 response rates were numerically higher in patients without previous TNFi use than in

those with previous TNFi use, although the treatment interactions were not significant. Similar proportions of CZP patients previously receiving one or two TNFis achieved ACR20 response rates at week 12 (46.7 *vs* 48.2%, respectively), regardless of whether they received ADA (45.0%), ETA (52.4%) or IFX (46.4%). In addition to these data, more recently (out of the time frame of our systematic search) the first head-to-head trial in TNFi-experienced RA patients has been published, showing a good efficacy of cycling to a second TNFi even after primary insufficient response to the first one. The EXXELERATE study is the first prospective, single blind (double blinded to week 12 and investigator blinded thereafter) trial assessing in RA patients on MTX background firstly the efficacy of CZP compared with ADA with a primary superiority end point at 12 weeks and 2 years, secondly the comparative efficacy of cycling (from CZP to ADA and viceversa) in primary non-responders at week 12 without a wash-out period [31]. The results in the predefined analyses showed no superiority of CZP at the short-term and long-term endpoints, along with a comparable safety profile over 2 years. Importantly, in this study, among patients with a primary inadequate response to the first TNFi, a similar proportion of subjects responded after cycling to a second TNFi: 58% of patients switching to CZP and 62% of patients switching to ADA became responders 12 weeks later, thus providing additional clinical evidence of the efficacy and safety of an immediate switch to a second TNFi in a primary TNFi inadequate responder population. Such uncontrolled and controlled data from real life and clinical trials settings confirm that cycling strategy is a suitable approach in patients failing one or more TNFis, with a general trend of better clinical gain in first-switcher patients rather than in subjects not responding to two or more TNFis.

Background data pro-swap

Several observational studies in RA patients report comparative data about cycling and swapping [mainly regarding rituximab (RTX)] strategies from a real life setting. Trends of better effectiveness in favour of RTX come from the majority of them, demonstrating significantly better clinical and functional results compared with the adoption of a second or third TNFi [32–35]. From the Danish DANBIO register, comparative data on drug survival, disease activity and clinical response between ABA and TCZ in RA patients failing at least one TNFi (>90% patients) have been reported: a good or moderate EULAR response was achieved in ⩾70% of patients treated with both non-TNFi agents for 24 weeks in routine care, but without any comparison with a second course of TNFi [36]. At the time of preparing this article, a first head-to-head observational trial comparing the efficacy of swapping strategy compared with cycling in TNFi inadequate responders showed that a non-TNF biologic agent was more effective in achieving a good or moderate disease activity at 24 weeks than a second TNFi [37]. In this trial, a total of 300 RA patients with an insufficient response to TNFi were included in a 52-week multicentre, pragmatic, open-label RCT, and randomized to receive a second TNFi (different from the first) or a different MoA bDMARD (23% ABA, 28% RTX and 48% TCZ). At week 24, 69% in the non-TNF group and 52% in the second TNFi group achieved a good or moderate EULAR response with an odds ratio (OR) of 2.06 (95% CI: 1.27, 3.37; $P = 0.004$) in favour of swapping strategy. With several limits in mind (lack of blinding of participants, some bDMARDs such as GOL not allowed, unpowered for individual drug differences, bDMARD monotherapy in at least 40% of cases), these results seem to support the choice of a non-TNF biologic agent after a first TNFi failure.

Results pro-swap

In line with the pre-specified limits of the performed systematic review, data supporting a swapping strategy are limited in terms of both quality and quantity (Table 3). The vast majority of data comes from open label retrospective or prospective observational trials. In an Italian retrospective monocentric analysis, among 201 RA non-responder patients to the first TNFi (mainly due to non-toxic causes, but with no specification of primary *vs* secondary non-response), survival on therapy with a second line bDMARD was significantly higher in the swapping than in the cycling group [16]. After adjustment and matching for propensity score, probability of treatment retention in the swapping 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. No significant differences emerged when comparing the retention rates of different MoA drugs in the swapping group, even if limitation due to the paucity of patients in each single therapeutic group might have affected the power of the results. In the multicentre prospective real-life analysis SWITCH-RA by Emery and coauthors, among 728 RA patients stopping the first TNFi (204 for primary inefficacy, 332 for secondary inefficacy, 168 due to AEs, 13 for other reasons), the 6-month effectiveness was significantly better when swapping to RTX rather than cycling to a second TNFi: change in DAS28 was substantially greater in patients starting RTX than a second course of TNFi, especially in patients failing the first TNFi due to inefficacy [9]. On the contrary, in cases of failure of the first TNFi for AEs, switching to a second TNFi or swapping to RTX seem to provide similar medium-term clinical benefits. Stratified analysis according to serotype (double seropositive patients for RF and ACPA) results in different performance of swapping *vs* switching strategy according to the different subsets of patients: seropositive patients failing the first TNFi due to inefficacy could benefit more from RTX than from a second TNFi course; seropositive patients failing the first TNFi for AEs could gain similar benefits form RTX or TNFi; seronegative patients failing the first TNFi, regardless of the reason, could gain similar benefits from RTX or a second TNFi. Regarding safety issues, the overall incidence of AEs and serious AEs was similar in the two groups. Similarly to most non-interventional studies, this open-label, observational study had the limitation of substantial missing data. Because the number and timing

Table 3 List of selected studies

References	Study design	Population	Intervention	Comparison	Outcomes	Results
Kim *et al.* [17]	Meta-analysis: One RCT on GOL (GOAFTER) One RCT on RTX (REFLEX) Two RCTs on ABA (ATTAIN and sub-analysis) Two RCTs on TCZ (RADIATE and sub-analysis)	Inclusion criteria: Trial design = double-blind RCTs Population = inadequate responders to ⩾TNFi	GOL TCZ ABA RTX	Indirect comparison among agents	ACR20/50/70 and HAQ at 6 months	TCZ has the highest ACR20 response (62%) > RTX > ABA > GOL TCZ has the highest ACR50 response (32%) > RTX > ABA > GOL RTX has the highest ACR70 response (17%) > TCZ (14%) The magnitude of HAQ improvement, was highest for ABA > TCZ > RTX and lowest for GOL
Favalli *et al.* [16]	Retrospective study	201 RA failures to the first TNFi[a] (1999–2013): 73 for AEs, 128 for non-toxic causes[b]	119 switchers (cycling): 67 to ETA, 8 IFX, 31 ADA, 1 GOL, 12 CZP	82 swappers: 26 ABA, 40 RTX, 15 TCZ	Survival on therapy (using Kaplan–Meyer method) adjusted for propensity score and stratified by reason of first TNFi failure	Retention on therapy significantly higher in swap *vs* switch (HR = 2.25; $P < 0.0001$), either for inefficacy or AEs to the first TNFi No significant differences for MoAs in the swap groups: trend of better retention for RTX No significant differences for type of TNFi switching
Hirabara *et al.* [13]	Retrospective study	89 RA patients, switching from first course of monoclonal TNFi (IFX/ADA) due to inadequate efficacy (No specification about primary *vs* secondary inefficacy)	26 ETA (more IFX failures)	25 ABA (more ADA failures) 38 TCZ (more IFX failures)	Retention rate over 52 weeks Clinical efficacy	Retention rates for ABA, TCZ, ETA at 52 weeks were similar: 72, 89.5 and 84.6%, respectively Continuation rates due to AEs: ABA 88%, TCZ 97%, ETA 90.5% (not significant) Continuation rate due to inefficacy: ABA 82.6%, TCZ 91.9%, ETA 95.7% (not significant) Globally, all drugs exhibited similarly good retention rates, but discontinuation of TCZ for AEs was low and discontinuation of ETA for inefficacy was low No significant difference in CDAI at 52 weeks No safety data are given

(continued)

Table 3 Continued

References	Study design	Population	Intervention	Comparison	Outcomes	Results
Manders *et al.* [10]	Pragmatic multicentre randomized trial	144 RA patients failing previous first TNFi treatment (due to ineffectiveness or AEs[c]) 139 pts included in the analyses	51 treated with a different TNFi with respect to the first one 50 included in the analyses: 21 ADA, 19 ETA, 5 IFX, 3 GOL, 2 CZP	43 i.v. ABA (43 included in the analyses) 50 in RTX (46 included in the analyses) TCZ was not yet licensed at the start of the study	Effectiveness (DAS28, HAQ, SF-36) over 12 months Cost-effectiveness (medication costs and QUALYs over 12-month period) Caveats: more RF+ patients in RTX; 30% bDMARD monotherapy	No significant differences with respect to DAS28, HAQ, SF-36 over time (corrected for confounders) No significant difference in drug survival between ABA and different TNFi No major differences in AEs RTX significantly more cost-effective than ABA and TNFi: advantage primarily due to the difference in drug costs Treating patients with a second TNFi was more cost-effective than treating with ABA
Emery *et al.* [9]	Prospective analysis (multicentre, real life study): SWITCH-RA study	1111 RA (full population) with inadequate response to first TNFi: 827 due to inefficacy, 263 to AE, 21 other 'Effectiveness population'[d]: 728 RA: 547 inefficacy (I: 204; II: 332), 168 AE, 13 other	507 on second TNFi Effectiveness pop: 323 second TNFi	604 RTX Effectiveness pop: 405 RTX	Effectiveness over 6 months after the start of the second bDMARD (ΔDAS28 0–6 months) stratified for: reason of first TNFi failure (Of note, non-specification for primary and secondary inefficacy) RF+/− Safety at 6 months	Mean ΔDAS28 significantly greater in RTX over second TNFi (−1.5 *vs* −1.1), especially in patients failing 1st TNFi due to inefficacy (−1.7 *vs* −1.3) No significant difference in case of 1st TNFi failure due to AEs (−0.7 in both groups) Subanalysis: RF^+ patients experienced significantly greater DAS28 reduction in RTX *vs* second TNFi (−1.6 *vs* −1.2), especially in case of first TNFi failure due to inefficacy rather than AEs. In RF− patients, no significant difference in clinical response between RTX and second TNFi regardless of the reason of first TNFi failure Safety: overall AEs and SAEs were similar between groups, but more serious infections were reported with RTX
Backhaus *et al.* [12]	Retrospective multicentre study	1603 csDMARDs and/or bDMARDs IR (TNFis) RA patients	TNFi as mono/combo therapy with csDMARDs	TCZ as mono/combo therapy with csDMARDs	DAS28 remission at 12 weeks EULAR response at 12 weeks	In patients with inadequate response to csDMARDs and/or TNFi, TCZ as mono- or combo-

(continued)

Table 3 Continued

References	Study design	Population	Intervention	Comparison	Outcomes	Results
					Results stratified by groups: csDMARDs IR starting TCZ/TNFi as combo-therapy; cs/bDMARDs starting TCZ/TNFi as mono-therapy; TNFi IR starting TCZ/TNFi + csDMARDs (as combo)	therapy results more efficacious in the short time (12 weeks) than TNFis for most outcomes
Harrold *et al.* [18]	Retrospective analysis on the CORRONA-based observational study	Patient failures to ⩾1 anti-TNF No specification about reason for TNFi failure Matched by PS (age, sex, race, insurance, disease characteristics, comorbidities, past/current drugs)	The PS-matched groups included: 746 anti-TNF users at 6 months and 493 anti-TNF users at 12 months Globally 531 anti-TNF users contributed to both 6 and 12 months cohorts	The PS-matched groups included: 431 ABA at 6 months and 311 ABA at 12 months Globally 272 ABA users contributed to 6- and 12-months cohorts	Effectiveness (using PS) at 6–12 months: change in CDAI, ACR20–50–70, HAQ, CDAI remission	In adjusted analyses, similar results for: weighted mean change in CDAI at 6 and 12 months; mACR20 responses at 6 and 12 months; mACR50 and mACR70 at 6 and 12 months; change in mHAQ at 6 and 12 months; CDAI remission rates at 6 and 12 months No safety results comparison given
Harrold *et al.* [8]	Retrospective analysis on the CORRONA-based observational study	Patient failures to ⩾1 anti-TNF No specification about reason for TNFi failure	Trimmed population: 737 anti-TNF Stratified[f] matched[e] population: 205 pts in each group (55% for each group received more than two TNFi)	Trimmed population: 737 anti-TNF Stratified[f] matched[e] population: 205 pts in each group (55% for each group received more than two TNFi)	Effectiveness (CDAI LDA/remission, ACR20/50/70, HAQ) and safety at 1 year	In the stratified-matched population, OR for LDA or remission was higher (OR = 1.54; 95% CI: 1.00, 2.36) for RTX *vs* anti-TNF RTX users more likely to achieve ACR20 (OR = 2.15; 95% CI: 1.35, 3.42) and HAQ improvement No significant differences in ACR50/70 No significant differences for safety (infections, cancer, CDV events)
Rotar *et al.* [7]	Retrospective analysis from the Slovenian Registry (BioRx.si) Of note, in Slovenia bDMARDs have been available since 2002. ABA not available.	238 RA patients failing their first TNFi due to ineffectiveness or AEs	130 on second TNFi: 34% ADA, 40% ETA, 9% IFX, 15% CZP, 1.5% GOL	108 non-TNFi (combined as a group): 31.5% in RTX, 68.5% in TCZ	Retention on therapy, adjusted for confounders	46% treatment failures in second-TNFi group *vs* 14.8% in non-TNFi group More discontinuation in TNFi group due to

(continued)

Table 3 Continued

References	Study design	Population	Intervention	Comparison	Outcomes	Results
	TNFi is prescribed as the first biologic unless contraindicated					primary/secondary IE than in non-TNFi group Significantly higher retention on therapy in non-TNFi group *vs* TNFi group Results more pronounced in case of switching of the first line TNFi due to primary ineffectiveness (such difference was not significant)
Kobayakawa *et al.* [15]	Retrospective analysis from the multicentre cohort from the Tsurumai Biologics Communication Registry	169 patients failing their first TNFi (IFX, ETA and ADA)	IFX → ETN (33/74; 44.6%) IFX → ADA (26/74; 35.1%) ADA → IFX (1/12; 8.3%) ADA → ETN (7/12; 58.3%) ETA → IFX (8/83; 9.6%) ETA → ADA (46/83; 55.4%)	IFX → TCZ (15/74; 20.3%) ADA → TCZ (4/12; 33.3%) ETA → TCZ (29/83; 34.9%)	Retention on therapy at 52 weeks	Drug retention rate of second ADA/IFX significantly lower (59.3%) *vs* second ETA (90.0%) or TCZ (94.7%) HRs for discontinuation of the second biologic agent at 52 weeks *vs* ETA (reference): 4.58 (95% CI: 1.45, 12.98) for second ADA/IFX; 0.51 (95% CI: 0.15, 7.23) for second TCZ

[a]48 ETA, 78 ADA, 66 IFX, 5 GOL, 4 CZP. [b]No specification between primary *vs* secondary inefficacy. [c]Reasons not clearly specified in each single treatment group. [d]Patients with both baseline and 6 months DAS28 data. [e]Matched by PS (age, sex, race, insurance, disease characteristics, comorbidities, past/current drugs). [f]Stratified by previous number TNFis. ABA: abatacept; ADA: adalimumab; AE: adverse event; bDMARD: biologic DMARD; csDMARD: conventional synthetic DMARD; CDAI: Clinical Disease Activity Index; CDV: cardio-vascular; CZP: certolizumab pegol; ETA: etanercept; HR: hazard ratio; GOL: golimumab; IFX: infliximab; IR: insufficient responder; LDA: low disease activity; OR: odds ratio; PS: propensity score; RCT: randomized controlled trial; RTX: rituximab; SAE: serious adverse events; TCZ: tocilizumab; TNFi: TNF inhibitor.

of visits were left to the investigators' discretion, limited data were available to implement most of the imputation methods appropriate to handle the withdrawal. However, the overall results are broadly in agreement with recent reports from national European registries [38–40].

Considering TCZ, in the multicentre retrospective analysis by Backhaus, TCZ both as mono- or combo-therapy with csDMARDs was significantly better than TNFi as mono-combo-therapy in 1603 patients failing a csDMARD or a previous course of TNFi in terms of achievement of DAS28 remission at 12 weeks (pre-specified primary outcome of the study). In the specific subset of previous TNFi failing patients, the pre-defined target of clinical remission was obtained in 41% in TCZ + csDMARDs *vs* 19% in the second TNFi + csDMARDs ($P < 0.001$). Globally, TCZ monotherapy was more efficacious than TNFi monotherapy in patients failing a previous csDMARD or a first TNFi, considered as a global population (DAS28 remission 37.2% *vs* 30.2%, respectively, $P < 0.001$). Similar results in favour of TCZ *vs* another TNFi (cycling strategy) were obtained with other outcomes not including acute phase reactants, such as mean Clinical Disease Activity Index (CDAI) difference from baseline to 3 months, and with patient-reported outcomes, such as Visual Analogue Scale for Patient's Global Assessment (VAS-PGA), VAS-pain and morning stiffness, thus avoiding eventual over-results due to TCZ effects on serum inflammatory biomarkers. As a limit of this study, the authors stated that long-term results are obviously required to confirm such short-term data, which represent the cut-off time point to assess primary response to bDMARDs in accordance with EULAR guidelines [3]. Anyway, in accordance with this, it seems that in the short term TCZ might offer higher clinical efficacy compared with TNFi after previous TNFi failure, with no current information about the maintenance of the benefits over time.

Additional data regarding RTX and ABA in TNFi failure patients come from two retrospective reports from the CORRONA registry by Harrold *et al*.: in the stratified-matched population (failures of at least one TNFi), ABA offered no advantage (mean CDAI modification, ACR20/50/70 responses, HAQ improvement) over a further TNFi both at 6 and 12 months of follow-up, while RTX users had significantly higher probability of achieving low disease activity, ACR20 response and HAQ improvement [8, 18].

Overall, available data seem to confirm that changing mode of action might be a better option, especially in seropositive patients failing a first TNFi due to inefficacy (results in favour of RTX *vs* another TNFi) or in patients requiring bDMARD monotherapy (results in favour of TCZ monotherapy *vs* another TNFi monotherapy).

Results pro-similar performance cycling *vs* swapping

In the absence, within the pre-specified time frame of the review, of direct head-to-head trials comparing bDMARDs with different MoA in TNFi failure patients, indirect meta-analysis has emerged as an accepted and valid methodology for comparing drugs with each other using a common comparator (placebo or a synthetic DMARD). The best quality data indirectly comparing switching *vs* swapping strategies in TNFi failures come from a network meta-analysis (Tables 3 and 4), which pooled results from four randomized placebo-controlled trials involving quite homogeneous target populations: the GO-AFTER trial, the RADIATE trial, the REFLEX trial and the ATTAIN trial [17]. All these studies, even if with different proportions, included long-standing RA patients failing one or more TNFis (ADA, IFX, ETA) due to inefficacy or AE, mostly used in combination with csDMARDs. Globally, the proportion of patients who achieved ACR20 was highest for TCZ (62.4%; 95% CI: 49.9, 74.0%), followed by RTX (47.0%; 95% CI: 37.7, 56.6%), ABA (43.7%; 95% CI: 32.9, 55.4%) and GOL (32.1%; 95% CI: 22.3, 44.0%), and lowest for placebo (15.5%; 95% CI: 12.8, 18.5%). Similarly, the ACR50 was higher for TCZ and lower for placebo; RTX had the highest proportion of patients achieving ACR70. According to the clinical evidence to date, these findings suggest that non-TNF biologic agents such as RTX, ABA and TCZ are more effective than TNFi for the treatment of RA patients failing a first TNFi. However, no definite conclusions can be drawn in this setting due to many limitations: short follow-up period, lack of safety analysis along with efficacy data, absence of studies involving cycling to a TNFi different from GOL, lack of sub-analysis stratified by number of previous TNFis. A previous indirect meta-analysis by Schoels involving the same trials underlined the similarity in the ACR50 and 70 response rates for all agents (ABA, GOL, RTX and TCZ), suggesting that all biologic drugs have comparable efficacy in TNFi-failing RA patients, when considering relevant clinical response [41]. In addition, in line with this first report, GOL presented significantly fewer AEs with respect to indirect comparators. Moreover, in sub-analysis stratified by the number of previous TNFi failures, indirect comparison of response rates between GOL and TCZ found very similar rates after one, two or three TNFis, although there was a trend toward significance after three TNFis: the small number of patients in this subgroup represents an important limit of this part of the study. Besides these two meta-analyses, a study by Manders and colleagues [10] published in 2015 tried to compare the effectiveness and cost-effectiveness of three biologic treatments with different MoA in RA patients in which TNFi therapy has failed. In this pragmatic multicentre randomized trial, 139 RA patients failing a first TNFi (due to ineffectiveness or AEs) were allocated to a second TNFi agent (50 patients) or to i.v. ABA or RTX (43 and 46 patients, respectively); TCZ was not yet licensed at the time of the study and thus not analysed. There were no significant differences between the three groups with respect to multiple RA outcomes at 1 year of follow-up (primary outcome: DAS28 and secondary outcomes: HAQ and SF-36); however, the analysis revealed that RTX therapy was significantly more cost-effective than both ABA and TNFi. In other words, all treatment options were similarly clinically effective; however, when costs were factored into the treatment decision, RTX was the best option available for patients whose first TNFi treatment failed. However, generalization of these cost-effective analyses to other countries should

Table 4 Final statements

Final statement	Level of evidence	Level of agreement (%)
In case of failure to one or more TNFis (regardless of the reason), switching to another TNFi or swapping to a different MoA agent (+ csDMARDs) could provide similar relevant clinical (ACR50/ACR70) control.	1A	91
Treatment with RTX after TNFi failure might be associated with higher prevalence of infusion reactions respect to i.v. TCZ and ABA.	1A	75
The use of GOL after previous TNFi failure might be associated with less occurrence of AEs with respect to non-anti-TNF bDMARD agents.	1A	86
In seropositive patients (RF and ACPA^{+}) failing a first TNFi due to inefficacy, swapping to RTX could provide more clinical benefits than switching to a second TNFi. In seropositive patients, failing a first TNFi due to AEs, similar benefits could be obtained with either RTX or a second TNFi.	2 B	95
Seronegative (RF and ACPA^{-}) patients failing the first TNFi (regardless of the reason) could gain similar benefits using either a second TNFi or RTX.	2 B	91
Clinical response at 12 weeks in patients with inadequate response to TNFi has been reported to be higher for TCZ (as mono- or combo-therapy) than TNFis.	2 B	97

ABA: abatacept; AE: adverse event; bDMARD: biologic DMARD; csDMARD: conventional synthetic DMARD; GOL: golimumab; MoA: mode of action; RTX: rituximab; TNFi: TNF inhibitor; TCZ: tocilizumab.

be considered carefully, due to possible differences in pharmaco-economic issues. No differences resulted in the performance of a second course of bDMARD in line with cycling (toward ETA) or swapping (to TCZ or ABA) in 89 Japanese RA patients stopping a first TNFi mAb (ADA or IFX) due to inadequate response: similar retention rate and mean CDAI values were observed among patient groups [13]. In another Japanese study, retention rates of a second biologic treatment were compared by the type of first TNFi and second biologic agents: 169 RA patients who failed a first course of TNFi therapy from the Tsurumai Biologics Communication Registry (ADA/IFX, ETA) received a different TNFi or TCZ as a second biologic agent [15]. Adjusting for confounders, drug retention rate of the second biologic agent after switching from IFX/ADA was significantly higher with ETA (90.0%) and TCZ (94.7%) than with ADA/IFX (59.3%); drug retention rate of the second biologic agent after switching from ETA was significantly higher with TCZ (75.9%) than with ADA/IFX (46.3%). In other words, switching from anti-TNF mAb (ADA/IFX) to soluble anti-TNF receptor (ETA) leads to better results than vice versa: as the authors stated, this might be due mainly to the well-known lesser immunogenicity of ETA, thus inducing lower incidence of anti-drug antibodies. Another reason of higher probability of failure after switching from ETA to ADA/IFX rather than vice versa might rely on its additional targeting against lymphotoxin-α (TNF-β), besides TNF-α. Differences in ADAs detection between Japanese and Caucasian patients, possibly related to different MTX dosage adoption and/or different ethnic background, might in part suggest caution when interpreting such results.

Conclusions

No standardized and homogeneous approach has been proposed by existing recommendations for RA patients failing a first TNFi. Several bDMARDs with different MoA are now available for the treatment of this subset of patients, with no proven direct comparison (at the time this systematic review was performed) between alternative options (cycling *vs* swapping strategies). Moving from this gap in our knowledge, we performed a systematic review trying to update evidence-based information supporting the decision-making process. According to scientific data on this relevant topic published within the pre-defined temporal limits, thus combined and enriched by a national consensus of expert rheumatologists, preliminary statements regarding cycling *vs* swapping strategies in RA patients failing the first course of TNFis might be formulated as indicated in Table 4. Thus, up to now, mainly from indirect comparison from RCTs and real life experiences, both strategies might be adopted in cases of first TNFi failure, with some evidence suggesting better performance of swapping over switching.

Reasearch agenda

Since our work was submitted, further evidence had been published on such a relevant topic involving emerging and progressively marketed drugs, such as biosimilars and targeted systemic DMARDs, namely tofacitinib and baricitinib. Specifically, in a systematic review by Singh and coauthors, results have been reported from a network meta-analysis involving 12 trials dealing with subsequent therapies in RA patients failing previous TNFi [42]. Patients were stratified by biologic type (anti-TNF *vs* non-anti-TNF biologic agents), DMARD background (bDMARD monotherapy *vs* MTX combo-therapy) and bDMARD dose (standard *vs* high dose). Considering clinical outcomes, on background MTX and compared with non-TNF agents, TNF biologics were not associated with any statistically significant or clinically meaningful difference in the odds of both clinical remission (OR = 0.75, 95% CI: 0.04, 26.4) and ACR50 response (OR = 0.51, 95% CI: 0.18, 1.54) [42]. Similarly, non-statistically significant differences were seen when comparing tofacitinib to non-TNF (for

ACR50 response OR = 0.65, 95% CI: 0.23, 1.86) or TNFi (for ACR50 response OR = 1.26, 95% CI: 0.36, 4.40). No studies examined radiographic progression outcome, so that indirect comparisons on structural endpoints should not be evaluated. Considering safety issues, no significant advantage was reported for one agent over another. Moreover, in a real life setting, Li *et al*. [43] demonstrated that only ADA could be as efficacious as non-TNF bDMARD after ETA failure in a large multinational RA population. Nevertheless, TNFis as a class were overall less effective than a second non-TNF-α biologic (EULAR good response rate 56.0 *vs* 64.4%, $P < 0.05$ and CDAI score change −6.3 *vs* −7.3, $P = 0.06$, respectively). Such a relevant issue could be finally resolved by the future results of the SWITCH trial, whose protocol design has been already published and that includes also global cost-effectiveness evaluation among secondary outcomes [14].

Supplement: This work was carried out with the unconditioned support of Edizioni Internazionali srl, Pavia, Italy.

Funding: No specific funding was received from any bodies in the public, commercial or not-for-profit sectors to carry out the work described in this manuscript.

Disclosure statement: The authors have declared no conflicts of interest.

Supplementary data

Supplementary data are available at *Rheumatology* online.

References

1 Marchesoni A, Zaccara E, Gorla R *et al*. TNF-alpha antagonist survival rate in a cohort of rheumatoid arthritis patients observed under conditions of standard clinical practice. Ann N Y Acad Sci 2009;1173:837–46.

2 Caporali R, Conti F, Alivernini S *et al*. Recommendations for the use of biologic therapy in rheumatoid arthritis: update from the Italian Society for Rheumatology I. Efficacy. Clin Exp Rheumatol 2011;29 (3 Suppl 66):S7–14.

3 Smolen JS, Landewé 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.

4 Singh JA, Saag KG, Bridges SL Jr *et al*. 2015 American College of Rheumatology Guideline for the treatment of rheumatoid arthritis. Arthritis Care Res 2016;68:1–25.

5 Smolen JS, Landewé R, Bijlsma J *et al*. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. Ann Rheum Dis 2017;76:960–77.

6 Hyrich KL, Lunt M, Watson KD, Symmons DPM, Silman AJ; British Society for Rheumatology Biologics Register. Outcomes after switching from one anti-tumor necrosis factor alpha agent to a second anti-tumor necrosis factor alpha agent in patients with rheumatoid arthritis: results from a large UK National Cohort Study. Arthritis Rheum 2007;56:13–20.

7 Rotar Ž, Tomsic M. Survival of the second biologic after the first tumor necrosis factor alpha inhibitor's failure in the treatment of rheumatoid arthritis: prospective observational data from Biorx. Si registry. Arthritis Rheum 2013;65 (Suppl 10):S1149–50.

8 Harrold LR, Reed GW, Shewade A *et al*. Effectiveness of rituximab for the treatment of rheumatoid arthritis in patients with prior exposure to anti-TNF: results from the CORRONA registry. J Rheumatol 2015;42:1090–8.

9 Emery P, Gottenberg JE, Rubbert-Roth A *et al*. Rituximab versus an alternative TNF inhibitor in patients with rheumatoid arthritis who failed to respond to a single previous TNF inhibitor: SWITCH-RA, a global, observational, comparative effectiveness study. Ann Rheum Dis 2015;74:979–84.

10 Manders SHM, Kievit W, Adang E *et al*. Cost-effectiveness of abatacept, rituximab, and TNFi treatment after previous failure with TNFi treatment in rheumatoid arthritis: a pragmatic multi-centre randomised trial. Arthritis Res Ther 2015;17:1–12.

11 Sakai R, Cho SK, Nanki T *et al*. Head-to-head comparison of the safety of tocilizumab and tumor necrosis factor inhibitors in rheumatoid arthritis patients (RA) in clinical practice: results from the registry of Japanese RA patients on biologics for long-term safety (REAL) registry. Arthritis Res Ther 2015;17:74.

12 Backhaus M, Kaufmann J, Richter C. Comparison of tocilizumab and tumour necrosis factor inhibitors in rheumatoid arthritis: a retrospective analysis of 1603 patients managed in routine clinical practice. Clin Rheumatol 2015;34:673–81.

13 Hirabara S, Takahashi N, Fukaya N *et al*. Clinical efficacy of abatacept, tocilizumab, and etanercept in Japanese rheumatoid arthritis patients with inadequate response to anti-TNF monoclonal antibodies. Clin Rheumatol 2014;33:1247–54.

14 Navarro Coy NC, Brown S, Bosworth A *et al*. The 'Switch' study protocol: a randomised-controlled trial of switching to an alternative tumour-necrosis factor (TNF)-inhibitor drug or abatacept or rituximab in patients with rheumatoid arthritis who have failed an initial TNF-inhibitor drug. BMC Musculoskelet Disord 2014;15:452.

15 Kobayakawa T, Kojima T, Takahashi N *et al*. Drug retention rates of second biologic agents after switching from tumor necrosis factor inhibitors for rheumatoid arthritis in Japanese patients on low-dose methotrexate or without methotrexate. Modern Rheumatol 2015;25:251–6.

16 Favalli EG, Biggioggero M, Marchesoni A, Meroni PL. Survival on treatment with second-line biologic therapy: a cohort study comparing cycling and swap strategies. Rheumatology 2014;53:1664–8.

17 Kim HL, Lee MY, Park SY *et al*. Comparative effectiveness of cycling of tumor necrosis factor-α (TNF-α) inhibitors versus switching to non-TNF biologics in rheumatoid arthritis patients with inadequate response to TNF-α inhibitor using a Bayesian approach. Arch Pharmacal Res 2014;37:662–70.

18 Harrold LR, Reed GW, Kremer JM *et al*. The comparative effectiveness of abatacept versus anti-tumour necrosis factor switching for rheumatoid arthritis patients

previously treated with an anti-tumour necrosis factor. Ann Rheum Dis 2015;74:430–6.

19 Buch MH, Bingham SJ, Bejarano V *et al*. Therapy of patients with rheumatoid arthritis: outcome of infliximab failures switched to etanercept. Arthritis Rheum 2007;57:448–53.

20 Buch MH, Emery P. Nonresponse to tumor necrosis factor antagonists—is there any point in re-treatment? Nat Clin Pract Rheumatol 2006;2:288–9.

21 Buch MH, Seto Y, Bingham SJ *et al*. C-reactive protein as a predictor of infliximab treatment outcome in patients with rheumatoid arthritis: defining subtypes of non-response and subsequent response to etanercept. Arthritis Rheum 2005;52:42–8.

22 Gomez-Reino JJ, Carmona L; BIOBADASER Group. Switching TNF antagonists in patients with chronic arthritis: an observational study of 488 patients over a four-year period. Arthritis Res Ther 2006;8:R29.

23 Wick MC, Ernestam S, Lindblad S *et al*. Adalimumab (Humira®) restores clinical response in patients with secondary loss of efficacy from infliximab (Remicade®) or etanercept (Enbrel®): results from the STURE registry at Karolinska University Hospital. Scand J Rheumatol 2005;34:353–8.

24 Van Vollenhoven R. Switching between biological agents. Clin Exp Rheumatol 2004;22:S115–21.

25 Hansen KE, Hildebrand JP, Genovese MC *et al*. The efficacy of switching from etanercept to infliximab in patients with rheumatoid arthritis. J Rheumatol 2004;31:1098–102.

26 van Vollenhoven R, Harju A, Brannemark S, Klareskog L. Treatment with infliximab (Remicade) when etanercept (Enbrel) has failed or vice versa: data from the STURE registry showing that switching tumour necrosis factor alpha blockers can make sense. Ann Rheum Dis 2003;62:1195–8.

27 Hjardem E, Ostergaard M, Podenphant J *et al*. Do rheumatoid arthritis patients in clinical practice benefit from switching from infliximab to a second tumor necrosis factor alpha inhibitor? Ann Rheum Dis 2007;66:1184–9.

28 Nikas SN, Voulgari PV, Alamanos Y *et al*. Efficacy and safety of switching from infliximab to adalimumab: a comparative controlled study. Ann Rheum Dis 2006;65:257–60.

29 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 multicentre, randomised, double-blind, placebo-controlled, phase III trial. Lancet 2009;374:210–21.

30 Weinblatt ME, Fleischmann R, Huizinga TW *et al*. Efficacy and safety of certolizumab pegol in a broad population of patients with active rheumatoid arthritis: results from the REALISTIC phase IIIb study. Rheumatology 2012;51:2204–14.

31 Smolen JS, Burmester GR, Combe B *et al*. Head-to-head comparison of certolizumab pegol versus adalimumab in rheumatoid arthritis: 2-year efficacy and safety results from the randomised EXXELERATE study. Lancet 2016;388:2763–74.

32 Kekow J, Mueller-Ladner U, Schulze-Koops H. Rituximab is more effective than second anti-TNF therapy in rheumatoid arthritis patients and previous TNFα blocker failure. Biologics 2012;6:191–9.

33 Chatzidionysiou K, van Vollenhoven RF. Rituximab versus anti-TNF in patients who previously failed one TNF inhibitor in an observational cohort. Scand J Rehabil Med 2013;42:190–5.

34 Blom M, Kievit W, Donders AR *et al*. Effectiveness of a third tumor necrosis factor-α-blocking agent compared with rituximab after failure of 2 TNF-blocking agents in rheumatoid arthritis. J Rheumatol 2011;38:2355–61.

35 Gomez-Reino JJ, Maneiro JR, Ruiz J *et al*. Comparative effectiveness of switching to alternative tumour necrosis factor (TNF) antagonists versus switching to rituximab in patients with rheumatoid arthritis who failed previous TNF antagonists: the MIRAR Study. Ann Rheum Dis 2012;71:1861–4.

36 Leffers HC, Ostergaard M, Glintborg B *et al*. Efficacy of abatacept and tocilizumab in patients with rheumatoid arthritis treated in clinical practice: results from the nationwide Danish DANBIO registry. Ann Rheum Dis 2011;70:1216–22.

37 Gottenberg JE, Brocq O, Perdriger A *et al*. Non-TNF-targeted biologic vs a second anti-TNF drug to treat rheumatoid arthritis in patients with insufficient response to a first anti-TNF drug: a randomized clinical trial. J Am Med Assoc 2016;316:1172–80.

38 Finckh A, Ciurea A, Brulhart L *et al*. Which subgroup of patients with rheumatoid arthritis benefits from switching to rituximab versus alternative anti-tumour necrosis factor (TNF) agents after previous failure of an anti-TNF agent? Ann Rheum Dis 2010;69:387–93.

39 Finckh A, Ciurea A, Brulhart L *et al*. B cell depletion may be more effective than switching to an alternative anti-tumor necrosis factor agent in rheumatoid arthritis patients with inadequate response to anti-tumor necrosis factor agents. Arthritis Rheum 2007;56:1417–23.

40 Soliman MM1, Hyrich KL, Lunt M *et al*. Rituximab or a second anti-tumor necrosis factor therapy for rheumatoid arthritis patients who have failed their first anti-tumor necrosis factor therapy? Comparative analysis from the British Society for Rheumatology Biologics Register. Arthritis Care Res 2012;64:1108–15.

41 Schoels M, Aletaha D, Smolen JS, Wong JB. Comparative effectiveness and safety of biological treatment options after tumour necrosis factor α inhibitor failure in rheumatoid arthritis: systematic review and indirect pairwise meta-analysis. Ann Rheum Dis 2012;71:1303–8.

42 Singh JA, Hossain A, Tanjong Ghogomu E *et al*. Biologics or tofacitinib for people with rheumatoid arthritis unsuccessfully treated with biologics: a systematic review and network meta-analysis. Cochrane Database Syst Rev 2017;(3):CD012591. doi: 10.1002/14651858.CD012591.

43 Li N, Betts KA, Messali AJ, Skup M, Garg V. Real-world effectiveness of biologic disease-modifying antirheumatic drugs for the treatment of rheumatoid arthritis after etanercept discontinuation in the United Kingdom, France, and Germany. Clinical Therapeutics 2017;39:1618–27.