Review

Clinical relevance of switching to a second tumour necrosis factor-alpha inhibitor after discontinuation of a first tumour necrosis factor-alpha inhibitor in rheumatoid arthritis: A systematic literature review and meta-analysis

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ABSTRACT
Objective. *To assess the clinical relevance of switching to a second tumour necrosis factor (TNF)-alpha inhibitor after discontinuation of a first TNF-alpha inhibitor in patients with rheumatoid arthritis.*

Methods. *A systematic literature search of MEDLINE, EMBASE and Cochrane database and Congress abstracts up to March 2009 retrieved all studies assessing the efficacy of switching to a second TNF-alpha inhibitor. Key words were rheumatoid arthritis AND failure OR switching AND TNF-alpha inhibitors OR adalimumab OR etanercept OR infliximab. Efficacy was evaluated by American College of Rheumatology (ACR), European League Against Rheumatism (EULAR) response criteria and drug survival. A meta-analysis of the percentage of responders was carried out. Statistical heterogeneity was tested by the Q-test.*

Results. *In the 32 relevant studies (4,441 patients) selected, the pooled percentage of ACR 20 responders (12 studies; 1,570 patients) was 55.1% (95% confidence interval, CI 48.2–62) and that of EULAR responders (15 studies; 2,665 patients) was 74.9% (95% CI 72.3–77.5). In the 19 studies analysing the efficacy by the reason to switch, the pooled percentage of ACR20 responders was 54.3% (95% CI 45.8–62.5) for switch because of lack of efficacy and 62.5% (95% CI 57.3–67.6) because of adverse events. The percentage of EULAR response was similar in both groups.*

Conclusion. *This meta-analysis suggests that switching to a second TNF-alpha inhibitor is clinically relevant in RA. Response to a second TNF-alpha inhibitor appears to be slightly better if the first TNF-alpha inhibitor was discontinued because of adverse events.*

Introduction

The development of tumour necrosis factor (TNF)-alpha inhibitors has been a major advance in the treatment of rheumatoid arthritis (RA). These drugs have improved signs and symptoms and prevented structural progression of RA in randomised controlled clinical trials (1-3). Since introduction of intensive treatment strategy including tight control of disease activity, achieving low disease activity and remission is now a realistic objective in RA management (4-5).

TNF-alpha blockers are currently recommended as the first-line biologics to use for patients with active RA (6-7) However, nearly 30% of patients with RA fail to respond or do not tolerate a first TNF-alpha inhibitor, and in real life, around 50% of them discontinue this therapy within 2 years (1-3, 8-9). Switching to another TNF-alpha inhibitor can be considered for these patients, and effectiveness was suggested for patients with treatment failure or who could not tolerate a first TNF-alpha inhibitor when concomitant conventional disease-modifying antirheumatic drugs (DMARDs) were used at the optimal dosage (4, 8-9).

However, several other biologics with different mechanisms of action are now available for RA management (10) These biologics, including rituximab, abatacept and, more recently, tocilizumab, have shown their effectiveness in randomised controlled clinical trials for patients with active RA showing an inadequate response to TNF-alpha inhibitors (11-13).

An important question in clinical practice today is the best therapeutic strategy for patients with an inadequate response to a first TNF-alpha inhibitor. For these patients, the next choice can be a second TNF-alpha inhibitor or another biologic. To help in the decision process, the efficacy of a second TNF-alpha inhibitor must be evaluated because we lack results of randomised clinical trial investigating the 3 major approved drugs in this patient population.

We aimed to assess the current evidence in support of switching between TNF-alpha inhibitors (adalimumab, etanercept, infliximab) in terms of treatment response for patients with inadequate response or intolerance to an initial TNF-alpha inhibitor. The secondary objective was to determine the efficacy of the switch according to the reason for discontinuation of the first TNF-alpha inhibitor and to the nature of the first or second TNF-alpha inhibitor. In this purpose, a systematic literature review with meta-analysis was performed.

Methods

This systematic literature review with meta-analysis was performed according to the Cochrane guidelines (14).

Inclusion criteria

We included all reports of studies of the clinical efficacy of one of the 3 available TNF-alpha inhibitors (adalimumab, etanercept, infliximab) used as second-line strategy after inadequate response to only one TNF-alpha blocker and used a composite response criterion (Disease Activity Score in 28 joints (DAS28) or American College of Rheumatology (ACR) criteria) or drug survival in RA patients.

Only studies published in English or French and investigating RA patients fulfilling the ACR criteria (15) were included. Randomised controlled trials, prospective or retrospective studies, or data from registries were included. Reviews, articles on other inflammatory arthritis and articles of studies not differentiating between second- and third-line TNF-alpha inhibitor results were excluded. Reports of studies analysing only third-line TNF-alpha inhibitors, or analysing a combination therapy associated rituximab and etanercept were also excluded.

Data sources

A systematic literature search was conducted in MEDLINE, EMBASE, and Cochrane databases up to March 2009, and abstracts from ACR, European League Against Rheumatism (EULAR) 2007 and 2008 congresses. This search was supplemented by hand-searching the reference lists of relevant articles. Search terms were rheumatoid arthritis AND (failure OR switching) AND (TNF-alpha inhibitors OR adalimumab OR etanercept OR infliximab) (text word). If more than one report for a study was found, the most recently report was retained.

Data extraction

Data extraction was performed by one reviewer (A.R) on the full texts, not blinded to author and journal, using a predefined extraction sheet available from the authors. Information extracted included first author, journal, study design, number of patients who switched, characteristics of patients (mean age, sex, mean duration of disease, rheumatoid factor positivity), reasons for switching and the nature of the first and second TNF-alpha inhibitors. The outcome measures extracted were percentage of responders according to ACR 20, 50 and/or 70 criteria and EULAR criteria, as well as drug survival at 3, 6 and 12 months after switching, as available.
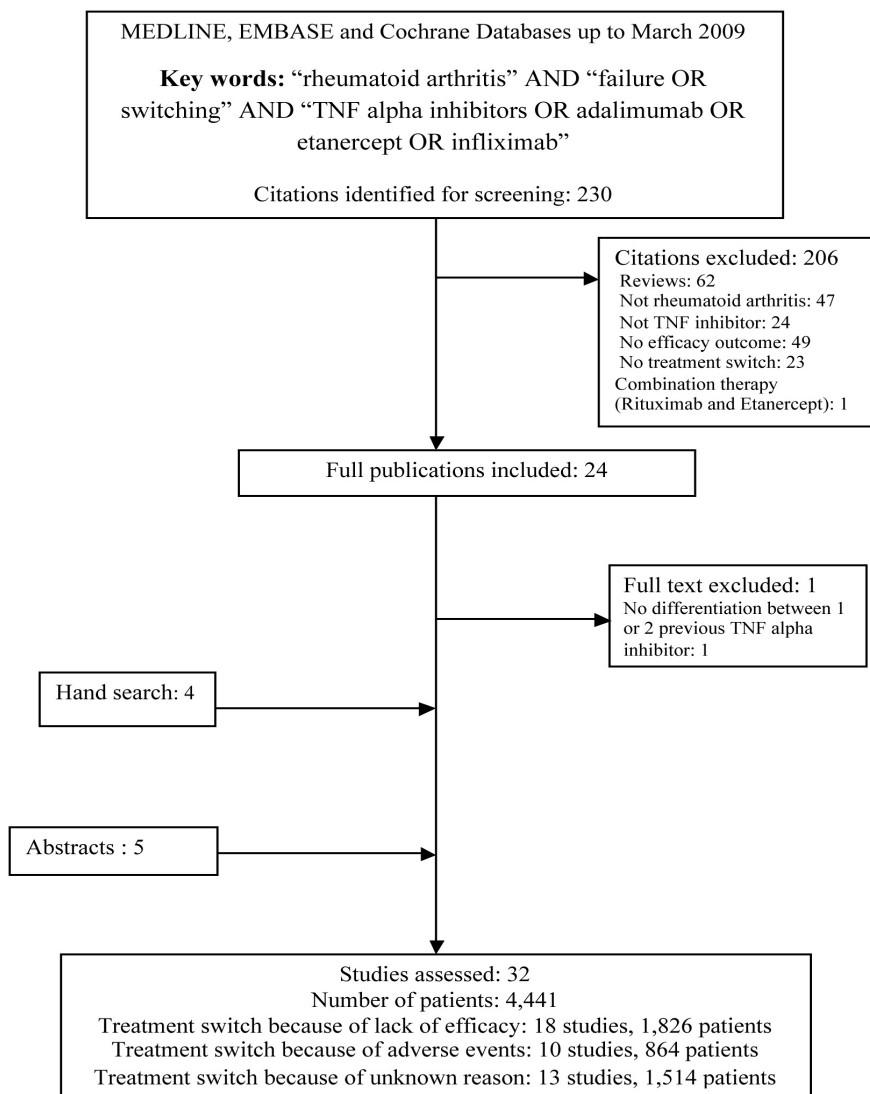

Fig. 1. Flowchart of study inclusion process.

Data analysis

A meta-analysis of the percentage of responders according to the ACR 20, 50 and 70 and EULAR criteria was carried out, for each time point (3, 6 and 12 months) and pooled for all time point, using the method of the inverse of the variance after arcsine transformation. Prevalence was calculated for each study as the ratio of patients with response according to ACR and/or EULAR criteria to the eligible RA population. Each individual prevalence was first transformed into a quantity by use of the Freeman-Tukey variance-stabilising transformation (16). A weighted mean of the transformed proportions was computed by a DerSimonian-Laird random effects model (17). The combined prevalence was calculated as the back-transform of this weighted mean. Statistical heterogeneity was tested by the Q-test (chi-square) (18). All meta-analyses involved use of a fixed-effects model or random-effects model in case of significant heterogeneity. Sensitivity was analysed by the reason for the switch and the nature of the first and second. TNF-alpha inhibitor. For this sensitivity analysis, we excluded data for patients with unknown cause of discontinuation of the first TNF-alpha inhibitor. Reports of studies that described the cause of discontinuation of the first TNF-alpha inhibitor without statistical analysis were also excluded.

Results

Of the 230 articles retrieved by the literature research, 207 articles were excluded (Fig. 1) and 9 additional references were found by hand-searching or were 2007 ACR and 2008 EULAR congress abstracts. Finally, 32 studies were included (19-50): 27 full publications and 5 meeting abstracts, for 4,441 RA patients.

Study and patient characteristics

Most of articles (n=26, 81%) described prospective cohort studies (Table I). Only 1 report was of a randomised open-label trial with single-blind evaluation (39). Twenty-two studies (68%) were of short duration (≤6 months). Studies

Table I. Patient characteristics from reports of 32 studies of the efficacy of a switch to a second TNF-alpha after a first TNF alpha inhibitor in rheumatoid arthritis.

References	Second TNF-alpha inhibitor	Number of patients	Mean age, years (SD)	Number of females	Mean disease duration, years (SD)	Mean baseline DAS 28 (SD)	Follow-up, months
(19)	IFX/ETN	8/6	59.5	12	17	NA	12
(20)	NA	29	NA	26	NA	NA	12
(21)	IFX/ETN	18/13	53.2 / 48.7	14/11	15.2 (2.2)/14.5 (3.5)	5.2 (0.9)	6
(22)	ETN/ADA	10/8	57	16	18	NA	12
(23)	NA	15	46.4	14	13.2 (2)	6 (1.2)	6
(24)	IFX	20	48	12	9.2	NA	6
(25)	ETN	25	50	21	10.8	NA	3
(26)	NA	194	NA	NA	NA	NA	12
(27)	NA	70	NA	60	NA	NA	3
(28)	ADA	19	55	16	13	3.9 (0.3)	3
(29)	NA	93	67.6	NA	12.6 (7.5)	NA	12
(30)	ETN	808	54.4	NA	NA	6.1 (1.2)	6
(31)	NA	178	43	133	14.5 (7.7)	6.3 (0.9)	12
(32)	ETN	12	59	11	11 (6.2)	5.6 (1.1)	6
(33)	ETN	21	NA	NA	NA	NA	6
(34)	ETN	12/22	63/52	10/14	NA	6.5/6.3	3
(35)	ADA	21	NA	NA	NA	NA	6
(36)	ETN/IFX	24/14	53.6/55.8	21/10	12.2 (9.6)/15.7 (8.9)	5.6 (1.1)/5.9 (1.2)	3
(37)	ADA/ADA	27/9	50/47.1	NA	NA	5.5 (0.3)/6 (0.2)	6
(38)	ADA/ADA	15/9	56.7	22	16.6 (7)	5.7 (0.8)/5.4 (0.7)	12
(39)	IFX	13	45.1	10	9.6 (11.3)	6.2 (1.2)	6
(40)	ADA/ADA	591/188	53/54	472/150	12 (8)/13 (9)	6.2 (1.1)/6.5 (1.2)	3
(41)	ETN/ETN	34/38	57.2/57.2	NA	NA	6.4 (0.2)/6.3 (0.1)	3
(42)	ADA/ADA/ADA	15/21/5	55	36	12.2 (9.2)/11.8 (7)/9.2 (2.5)	5.9 (0.7)/6.2 (1)/6.5 (0.9)	12
(43)	NA	337	56	276	14 (10)	5.5 (1.3)	3
(44)	ETN	18	52	15	NA	6.7 (1)	6
(45)	NA	235	NA	177	NA	NA	3
(46)	NA	503/353	54/54	398/285	13 (9)/14 (9)	6.8 (1)/6.8 (1)	6
(47)	ETN	37	49	30	8.3 (6)	NA	6
(48)	ETN /ETN	20/6	51/56	15/6	8/12	5.4 (1.4)/5 (1.4)	12
(49)	NA	126	NA	NA	NA	NA	3
(50)	ETN	201	57	160	9.1	6.6	3

SD: standard deviation; NA: not available; IFX: infliximab; ETN: etanercept; ADA: adalimumab; DAS 28: Disease Activity Score on 28 joints.
Data were separated according to the nature of switch and when the same TNF-alpha inhibitor was repeated for the second TNF-alpha inhibitor, data were separated according to the reason for switch.

Table II. Number of studies and patients according to the nature of the switch in treatment with TNF-alpha inhibitor.

Nature of treatment switch	Number of studies	Number of patients
IFX to ETN	15	1364
IFX to ADA	7	788
ETN to ADA	4	210
ETN to IFX	6	77
ADA to ETN	1	17
ADA to IFX	1	5

ADA: adalimumab; ETN: etanercept; IFX: infliximab.

conducted in European countries predominated (n=25, 78%). The switch from infliximab to etanercept was the most frequent: 15 studies (46.8%) for 1364 patients (Table II).

The mean age of patients and mean disease duration were 53.6±10.7 and 12.5±7.1 years respectively for all studies. Eighty percent of the patients were female (2453/3070 available data). In total, 70.3% of patients were positive for rheumatoid factor (793/1128 available data). The mean DAS 28 score collected in 19 studies before the treatment switch was 5.9±0.9. The mean follow-up after the switch was 6.9±3.6 months.

In the 26 studies describing the reason for the switch, 81.3% of patients (n=2672) switched to a second TNF-alpha inhibitor because of lack of efficacy, whereas 34.7% (n=932) switched because of adverse events. Of these 26 studies, 19 reported an analysis of the efficacy of the second TNF-alpha blocker according to the reason for the switch. Eighteen studies (32-46;48-50) included an analysis of the efficacy of the switch in terms of lack of efficacy (1,826 patients), whereas 10 studies (36, 38, 40, 42, 43, 45-49) included an analysis of the switch in terms of adverse events (864 patients).

Nine of these studies included an analysis of the efficacy of the switch because of lack of efficacy of the first inhibitor only (32-35, 37, 39, 41, 43, 50) and 1 in terms of adverse events only (47). The characteristics of these patients were similar to the whole population.

In these 19 studies, the mean age and mean disease duration were 53.9±11.4 and 11.6±7.8 years, respectively and 86% of the patients (2046/2380 available data) were female. The mean DAS 28 score was 6.0±0.9. The mean follow-up in the studies including an analysis of the switch in terms of lack of efficacy and adverse events was 6.0±3.5 and 7.2±4.2 months, respectively.

Efficacy of switching to a second TNF-alpha inhibitor – Composite criteria response rate

In all 32 studies, many studies described more than one composite criterion to evaluate the efficacy of a second TNF-alpha inhibitor and three reported the efficacy with all composite criteria.

The results for each criterion were pooled for all time point (3, 6 and 12 month), due to low number of studies at each time point. Data for ACR and EULAR responses are reported in Table III. The pooled percentage of responders according to ACR 20 criteria (12 studies; 1,570 patients) was 55.1% (95% CI 48.2–62), and that according to EULAR criteria (15 studies; 2,665 patients), including good and moderate EULAR response, 74.9% (95% CI 72.3–77.5). The pooled percentage of responders according to ACR 50 criteria

Table III. Meta-analysis of the percentage of responders according to ACR and EULAR criteria, as well as survival at 1 year, for all studies and for studies that analysed the switch to the second TNF-alpha inhibitor in terms of lack of efficacy or adverse events.

Results for all 32 studies

Criteria of response	Studies	Patients	% Responders	95% CI	Q	p heterogeneity
ACR 20	12	1570	55.1*	48.2-62	36.8	0.005
ACR 50	10	1538	31.5*	29-34.1	17.4	0.294
ACR 70	9	1525	13.8*	10.1-18.1	25.6	0.028
EULAR	15	2665	74.9*	72.3-77.5	37.2	0.113
Drug survival at 1 year	10	655	61.8	50.8-72.3	63.3	< 0.0001

Results of studies that analysed the switch to a second TNF-alpha inhibitor in terms of lack of efficacy

Criteria of response	Studies	Patients	% Responders	95% CI	Q	p heterogeneity
ACR 20	9	1003	54.3*	45.8-62.5	50.6	< 0.0001
ACR 50	8	967	30.6*	24.5-37	31.6	0.002
ACR 70	7	954	11.9*	9.7-14.1	14.8	0.251
EULAR	12	1183	71.5*	64.4-78.1	32	0.057
Drug survival at 1 year	3	90	60.4	38.4-80.5	6.1	0.045

Results of studies that analysed the switch to a second TNF-alpha inhibitor in terms of adverse events

Criteria of response	Studies	Patients	% Responders	95% CI	Q	p heterogeneity
ACR 20	4	335	62.5*	57.3-67.6	2.8	0.581
ACR 50	5	372	43.1*	29.9-56.8	21.7	0.0005
ACR 70	5	372	20*	8.6-34.7	35.3	< 0.0001
EULAR	6	451	69.5*	50.4-85.7	87.2	< 0.0001
Drug survival at 1 year	2	15	58.9	35.4-80.4	0.3	0.534

*pooled data at 3-, 6- and 12-month follow-up. 95% CI: 95% confidence interval.
ACR: American College of Rheumatology; EULAR: European League Against Rheumatism.

REVIEW

Clinical relevance of switching to a second TNF inhibitor / A. Rémy et al.

(10 studies; 1,538 patients) was 31.5% (95% CI 29–34.1), and that according to ACR 70 criteria (9 studies; 1,525 patients), 13.8% (95% CI 10.1–18.1).

– Survival rate
The second TNF-alpha inhibitor was maintained in 80.4% patients (95% CI 65.8–91.7) in all selected studies at 3 months, increased with a 6-month survival rate of 84.6% (95% CI 76.2–91.5), then decreased with a 12-month survival rate of 61.8% (95% CI 50.8–72.3).

Efficacy of treatment switch
according to the nature of the
first TNF-alpha inhibitor
The different switching procedures did not consistently differ on analysis of efficacy (Table IV). The proportion of studies differed according to the nature of the treatment switch.
A meta-analysis of the drug survival could not be performed because of the low number of available studies and because of the statistical heterogeneity of the results of these studies.

– Efficacy of switching
from infliximab
For studies of patients who switched from infliximab to etanercept, the percentages of responders according to ACR 20 and EULAR criteria were 45.6% (95% CI 40.3–51.1) and 59.3%

(95% CI 52.7–65.7), respectively, which was lower than that for patients who switched from infliximab to adalimumab (63.9% (95% CI 60.2–67.4) and 74% (95% CI 62.1–84.3), respectively. However the ACR 50 and 70 responses were similar, whether the switch was to etanercept or adalimumab (Table IV).

– Efficacy of switching
from etanercept
We pooled the data related to the switch from etanercept to infliximab and to adalimumab because of the low number of available studies. The percentages of responders according to ACR 20 and EULAR criteria were 58.6% (95% CI 52.2–64.9) and 76.7% (95% CI 34.1–99.6), respectively. The ACR 50 and ACR 70 response could not be compared because of insufficient data.
Other switching procedures were not analysed as they were reported in a too low number of studies (Table II).

Results of a second TNF-alpha
inhibitor according to the reason
for switching (Table III)
– Composite criteria response rate
Switching to a second TNF-alpha inhibitor because of adverse events seemed to be more efficient than switching because of lack of efficacy, according to ACR criteria. However, the pooled percentage of responders (at 3, 6 and 12

months) according to EULAR criteria was similar for both groups (Table III). However, at 3 months, the percentage of responders according to ACR 20 and EULAR criteria was higher for the patients who switched treatment because of adverse events (62.4% (95% CI 57–67.7) and 69.4% (95% CI 46.7–88), respectively) than for patients who switched because of lack of efficacy (52.6% (95% CI 43.9–61.1) and 66.3% (95% CI 55.8–76.1), respectively). ACR 50 and 70 responses showed similar trends.
Meta-analysis of results at 6 and 12 month cannot be performed due to low number of available studies.

– Survival rate
At 3 months, survival with the second TNF-alpha inhibitor was slightly higher when the first TNF-alpha inhibitor was discontinued for inefficacy than for adverse events: 83% (95% CI 70–92.9) *vs*. 78.4% (95% CI 50.2–96.6).
Survival with the second TNF-alpha inhibitor at 12 months was similar for patients for whom the first TNF-alpha inhibitor failed and patients who discontinued the first TNF-alpha inhibitor because of side effects: 60.4% (95% CI 38.4–80.5) *vs*. 58.9% (95% CI 35.4–80.4).
Only one study analysed the survival with the second TNF-alpha inhibitor at 6 month in both groups.

Table IV. Meta-analysis of the percentage of responders according to ACR and EULAR criteria for studies that analysed the treatment switch by nature of the first TNF-alpha inhibitor.

Results of studies that analysed the switch from infliximab to etanercept or to adalimumab

		Switch from infliximab to etanercept					Switch from infliximab to adalimumab			
Criteria	Studies	Patients	% Responders (95% CI)	Q	p heterogeneity	Studies	Patients	% Responders (95% CI)	Q	p heterogeneity
ACR 20	4	320	45.6% (40.3-51.1)*	9.6	0.085	4	683	63.9% (60.2-67.4)*	6.6	0.353
ACR 50	5	357	37.9% (21.1-56.3)*	49.8	<0.0001	3	656	34% (30.5-37.7)*	4.3	0.494
ACR 70	5	357	18.2% (8-31.4)*	31.3	<0.0001	3	656	13.9% (11.4-16.6)*	9.29	0.097
EULAR	8	1193	59.3% (52.7-65.7)*	25	0.008	5	728	74% (62.1-84.3)*	20.4	0.004

Results of studies that analysed the switch from etanercept to monoclonal antibodies

Criteria	Studies	Patients	% of responders	95% CI	Q	p heterogeneity
ACR 20	4	228	58.6*	52.2-64.9	1.9	0.586
EULAR	4	211	76.7*	34.1-99.6	33	<0.0001

*pooled data at 3, 6 and 12 months. 95% CI=95% confidence interval.
ACR: American College of Rheumatology; EULAR: European League Against Rheumatism.

Heterogeneity

Heterogeneity was significant in all 32 studies and in the 19 studies that analysed the switch to a second TNF-alpha inhibitor by reason for the switch. Because of this significant heterogeneity, results were based on random effects model. Results of the Q-test were shown in Table III and 4 for all meta-analyses performed.

However, the results of studies analysing the switch from infliximab to etanercept were more statistically heterogeneous than were those of studies analysing the switch from infliximab to adalimumab. The results of studies that analysed the switch from etanercept showed low statistical heterogeneity according to the number of studies analysed, except for EULAR criterion (Table IV).

Discussion

This systematic review and meta-analysis of observational studies in RA suggests that switching to a second TNF-alpha inhibitor after discontinuation of a first TNF-alpha inhibitor is clinically pertinent. The rate of response appeared slightly higher when the first TNF-alpha inhibitor was discontinued due to adverse events. The nature of the first or the second TNF-alpha inhibitor had no clear influence on the efficacy of the treatment switch.

Several reviews have been published on therapeutic strategies after failure of TNF-alpha treatment and on the switch to a second TNF-alpha inhibitor. Some of these publications had already suggested that failure with a first TNF-alpha inhibitor does not preclude the efficacy of a second TNF-alpha inhibitor and that the response to a subsequent TNF-alpha inhibitor seemed to be influenced by the reason for discontinuing the previous TNF-alpha inhibitor. (4, 6-10).

Our systematic review has some limitations. First, it was a meta-analysis of observational data, not randomised trial results, which does not preclude bias. However, in this area, randomised trials answering the research question are unlikely to be performed. In this case, meta-analysis is the best way to analyse the published data. Another limitation

is the statistical heterogeneity of the results of the 32 studies. Only one study was a randomised single-blind but open-label. The majority of the studies had small sample sizes, short trial durations and lack of a control group. The outcome measures and the follow-up of the studies were not standardised. Some detailed information, especially at baseline was missing, including dosing regimens, washout period, and concomitant use of steroids or DMARDs. Nevertheless several studies had shown results with composite criteria at the same time, (*i.e.* 3, 6 or 12 months) to allow for performing this meta-analysis (19-50).

This systematic review adds strong support to the clinical efficacy of a second TNF-alpha blocker after discontinuation of a first one. These data are on line with the results of recent randomised clinical trial of golimumab *versus* placebo in patients previously treated with other TNF-alpha inhibitors (51). This study was not included in our analysis because the article did not allow for differentiating patients who received therapy with one or several TNF-alpha blockers before inclusion.

The clinical efficacy of a second TNF-alpha blocker, in this meta-analysis, showing around 50% of patients with ACR 20 response appears to be in the same range of efficacy than the switch to golimumab (51) and to biologics with other mode of action, such as rituximab (11, 52), abatacept (12) or tocilizumab (13), showed by randomised controlled trials, in patients with inadequate response to TNF-alpha blocker. These data and absence of relevant head to head comparison between the different biologics make the choice between a second TNF-alpha blocker and other biologics currently difficult in clinical practice. A recent review tries to assess treatment strategy for RA patients failing previous TNF-alpha blocker according to the reason of switch but no international recommendations exist as regards to the sequence of the various biologics after a first TNF-alpha blocker has been stopped (9). However the strong and consistent structural effect as well as the long-term safety data with TNF-alpha blockers and absence

of demonstrated clinical superiority of other drugs may explain why the strategy of switching to a second TNF-alpha blocker rather than with biologics with other mode of action is currently the preferred choice of numerous rheumatologists and is also recommended by some national guidelines (4).

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REVIEW

Clinical relevance of switching to a second TNF inhibitor / A. Rémy et al.

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