# HOW GOOD IS TO SWITCH BETWEEN BIOLOGICS? A SYSTEMATIC REVIEW OF THE LITERATURE.

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## Abstract

Despite the biological rationale for switching between TNF-antagonists, there is not a definitive answer from a clinical point of view.
**Methods**: We performed a systematic review. The strategy for the literature search included synonyms for the active drugs, trade names, and different synonyms for biologic therapies, plus the words "switch" or "switching", limited to studies in humans. The time limit was March 1st 2007. From 256 initial hits in Medline and Embase, plus 13 abstracts from rheumatology meetings, we finally included 33 studies.
**Results and discussion**: The most frequently studied switches are those between etanercept and infliximab. The mean number of patients studied per type of switch was 126. There are, apart from retrospective observational studies and cases series, 5 prospective cohorts from biologic registries, 1 randomised open-label clinical trial and 1 phase IV clinical trial, all seven of which are of moderate to good quality. The results are promising but not excellent. Any switch, especially those between monoclonal antibodies, have an effect size that is usually lower than that of a first biologic. When the switch is due to an adverse event with the first TNF-antagonist, however, the response rate of the second one is high. Perhaps the best alternative when a first TNF-antagonist fails is to start a different type of biologic, and leave the switch to another TNF-antagonist in the case of adverse event to the previous one.

**Keywords:** Switch; Biologic; TNF-antagonist; Arthritis; Systematic Review.

## Resumo

Apesar da fundamentação biológica para a troca (*switch*) entre antagonistas do TNF, não existe uma resposta definitiva do ponto de vista clínico.
**Métodos**: Realizámos uma revisão sistematizada. A estratégia para a pesquisa bibliográfica incluiu sinónimos para os fármacos activos, nomes comerciais e diferentes sinónimos para terapêuticas biológicas, mais as palavras "switch" ou "switching", limitando a pesquisa a estudos em humanos. O limite temporal foi 1 de Março de 2007. Dos 256 artigos detectados na Medline e Embase e dos 13 resumos de congressos de reumatologia, incluimos 33 estudos.
**Resultados e discussão**: Os *switches* mais frequentemente estudados foram entre etanercept e infliximab. O número médio de doentes estudado por tipo de *switch* foi de 126. Existem, para além de estudos retrospectivos observacionais, 5 coortes prospectivas dos registos de biológicos, 1 estudo aberto aleatorizado e um estudo de fase IV, todos os sete de qualidade moderada a boa. Qualquer que seja o *switch*, mas especialmente os efectuados entre anticorpos monoclonais, o benefício é geralmente inferior ao do primeiro agente biológico. Contudo, quando o *switch* se deve a um efeito adverso ao primeiro antagonista do TNF, a porporção de resposta ao segundo é alta. Provavelmente, a melhor alternativa perante a falência a um primeiro antagonista do TNF é iniciar um diferente tipo de agente biológico, reservando o *switch* para outro antagonista do TNF para os casos de efeito adverso com o primeiro fármaco.

**Palavras-chave:** Switch; Biológicos; Anti-TNF; Artrite; Revisão Sistematizada.

## Introduction

When, less than a decade ago, biotechnology products entered the scene of the inflammatory rheumatic diseases, little was foreseen of what was to come. Rheumatologists became, with the thoughtful use of the so-called biologics, the speakers in front of Health authorities for other specialists willing to use this new kind of compounds. Part of this

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paradigm shift, came along with the high price of the biologics. From using drugs that had almost no cost to the health system, rheumatologists started millionaire treatments, and hospital managers looked at us as children with new toys, refraining us from using biologics loosely. Some managers even banned the use of more than one biologic in the same centre, alluding to the same mechanism of action, as at least three of the new agents blocked tumour necrosis factor alpha (TNF-α) action. Some rheumatologists were also sceptical: How sure could we be that exchanging between molecules with so similar mechanism of action would be a useful and safe measure? Is it reasonably, for patients who have failed one TNF-α antagonist, to give them a trial with another similar agent? Or is this measure a simple waste of time and money? Is it safe to change from certain biologics to others? How about switching biologics in other diseases apart from rheumatoid arthritis?

Switching is a common practice. In a survey to United States rheumatologists in 2005, 91% reported using a TNF-α antagonist with other disease modifying anti-rheumatic drug (DMARD) in patients with severe rheumatoid arthritis who had responded inadequately to methotrexate.[1] Additionally, over 94% of the rheumatologists reported switching patients from one TNF-α antagonist to another due to inadequate response or side effects. A few opinion articles have been published on this issue,[2-5] and some practical guidelines, like those from the French Society for Rheumatology, recommend the use of any one of the biologics in patients with inadequate response to a previous one.[6]

Other alternatives to switching between TNF-α antagonists exist. These include combining them with DMARDs other than methotrexate. Also new biologics have been made available, or are under research, in the last two years. These biologics' mechanisms of action involve targeting B cells with an anti-CD20 antibody (rituximab), blockade of T cell co-stimulation by a CTLA-4 Ig fusion protein (abatacept), blockade of interleukin (IL)-6 signalling with an antibody to the IL-6 receptor (MRA), and neutralizing IL-15 by a monoclonal antibody.

## Rationale for Interchange

It is not uncommon to switch between biologics in other diseases and treatments. In all cases, patients who require a biologic agent are often difficult to manage, and the comorbidities that are prevalent in these patients further complicate management and agent selection. Although effectiveness may not appear notably different between the various agents available, and since there is no *a priori* mean to determine the effect of a given biologic agent on an individual patient, therapeutic interchange is inadvisable once a patient has been stabilized.[7]

To explain differences among anti-TNF-α agents and to provide a rationale for trying several anti--TNF-α agents in the same patient, data on pharmacokinetics and mechanisms of action suggest a number of hypotheses. First, the half-life is 3 days for etanercept, 10 days for infliximab, and 13 days for adalimumab. These half-life differences may translate into differences in the duration of TNF-α neutralization. Also, the two monoclonal antibodies, infliximab and adalimumab, exhibit very strong affinity for TNF-α, which may increase the percentage of neutralized TNF-α molecules. In addition, the complexes formed when monomeric and trimeric soluble and membrane-associated TNF-α bind to the anti-TNF-α agent are far more stable with the monoclonal antibodies infliximab and adalimumab than with the soluble receptor etanercept. Finally, the monoclonal antibodies are highly specific of TNF-α, whereas etanercept also binds to lymphotoxin a. This last effect may play a role in disorders associated with high lymphotoxin levels, such as juvenile idiopathic arthritis. Also, although the available TNF-α inhibitors have similar efficacy in rheumatoid arthritis, they differ in their effectiveness in other rheumatic diseases. Etanercept, in contrast to the monoclonal antibodies, is not effective in the treatment of granulomatosis disorders such as Crohn's disease, Wegener's granulomatosis, and sarcoidosis. Taken together, the data provide a strong rationale for switching TNF-α inhibitors in the event of failure.

## Methods for a Systematic Review on Switching

Despite the biological rationale for switching, there is not a definitive answer from a clinical point of view. Therefore, we performed a systematic review on this matter. The strategy for the literature search included synonyms for the active drugs, trade names, and different synonyms for biologic therapies, plus the words "*switch*" or "*switching*", limited to studies in humans. The time limit was March 1st 2007. With such a strategy, we captured 177 cites in Medline (through PubMed) and 203 cites in

Embase (through Ovid), of which 123 were duplicates and were discarded. We decided to include any study in which a measure of efficacy, effectiveness, or safety of switching between biologics had been assessed. We decided not to exclude studies because of the design, except for narrative reviews, neither we excluded studies based on the population studied, provided that the study was focused in inflammatory arthritis, or on sample size. We additionally discarded, by reading the 256 titles, all articles that were clearly unrelated to the issue, thus yielding a total of 31 articles. We read the abstracts of these 31 articles and selected 23 for detailed review. Additionally, we searched the abstracts presented at the American College of Rheumatology, EULAR, and the Spanish Society of Rheumatology meetings for the last 5 years, and obtained 13 useful abstracts, of which all those that corresponded to subsequently published studies were discarded from detailed analysis. We collected systematically data on the design, the patient population studied, the number and type of switches and the results in the included studies.

## Studies on Switching

Tables I trough IV show the synthesis of the data collected from the 33 finally included studies, by type of switching. The first studies on switching were published in 2002, and most of them came from North America and from Europe. The most frequently studied switches are those between etanercept and infliximab. Up to five studies have addressed the effectiveness of switching between monoclonal antibodies. Many studies contribute to information on different types of switching, and some provide information on over four different types of analyses. The number of patients by analysis varies greatly, from 1 to 956, with a mean n per switch of 126 patients studied, although the majority of studies includes less than 30 patients.

The classification of the studies based on the design showed that they were mainly observational prospective (n=13) or retrospective (n=2) studies, and case series or reports (n=11), of moderate to poor quality. There were, however, some prospective cohorts from biologic registries (n=5) and a randomised open-label multicentre clinical trial and a phase IV clinical trial, all seven of which were of moderate to good quality.

The patients included in the studies are mainly those in which a switch may be indicated. The majority are rheumatoid arthritis patients (total studied n=3,487) but some studies have included also spondyloarthritis (total n=41), and juvenile idiopathic arthritis patients (total n=16). The study from Gómez-Reino et al, includes an admixture of patients, representing all rheumatic diseases for which a biologic can be used (n=488).[8] Taking the means of the studies of rheumatoid arthritis, most patients included are women (83%, range: 60-100), the average age is 52 (range: 32-68), and the disease duration is 12 years (range: 3-27). Regarding activity and function, the mean DAS is high, 5.6 (range: 2.4-6.8), as well as the mean HAQ, 1.7 (range: 1.5-1.9). Still some studies lack a description of the patients at baseline, and in most of them the duration of a previous treatment with a biologic is not reported.

Most studies utilize TNF antagonists at their recommended doses, although some of the studies that have involved infliximab treated patients, accepted dose escalation or reducing dose intervals. Studies on spondyloarthropathies used higher doses in general as compared to rheumatoid arthritis ones. Other studies do not provide information regarding the dose or regimes utilized.

The results are promising but not excellent. Any switch, specially those between monoclonal antibodies, have an effect size that is usually lower than that of a first biologic. Studies on switches between DMARDs show the same picture, patients who fail more than one option are not always easy to rescue with a new one.[9] Perhaps the exception is when the switch is due to an adverse event with the first biologic, in which case the response rate is high. Moreover, the patient will not necessarily have the same adverse event with the second or third biologic.[10]

## Switching Biologics in Diseases other than Rheumatoid Arthritis

There is not much information on other diseases apart from rheumatoid arthritis. The best evidence comes from a 54-week, open-label, prospective, follow-up study to evaluate the efficacy and tolerability of etanercept administered at 50 mg once weekly in patients with active ankylosing spondylitis who were resistant or intolerant to previous therapy with infliximab.[11] At week 24, ASAS20 was achieved by 18 (78%) out of 23 patients, ASAS50 by 12 (52%) out of 23. At week 54, ASAS20 was reached

**Table I. Characteristics of Studies Included in the Systematic Review in which an Analysis of the Switch from Soluble Receptor (Etanercept) to TNF Monoclonal Antibodies (Infliximab or Adalimumab) was Included. Sorted by Number of Patients Studied.**

| Study | Patients | Intervention | Results |
|---|---|---|---|
| Gomez-Reino, 2006[8]<br>Spain<br>Prospective cohort from a biologic registry (BIOBADASER) | 52 pts with chronic arthritis on ETN who switched to IFX (in 82% of the cases due to inefficacy).<br>Full description not provided. | Doses not provided. | a) Effectiveness (drug survival): First year survival of the switch to IFX was 0.28 (95% CI: 0.15-0.42).<br>b) Safety. The reason for discontinuing IFX was AEs in 54% of cases. |
| Hansen KE, 2004[18]<br>United States<br>Observational comparative retrospective multicentre study.<br>Duration not provided.<br>Supported by Aventis | 93 RA pts with IFX + LEF<br>a) 20 pts had switched from ETN to IFX (17 due to LOE, 3 to AEs) (Group Switchers): 60% women. Mean age 48. Mean disease duration 9 years<br>b) 73 had not previously used ETN (control group): 75% women. Mean age 48. Mean disease duration 10 years | IFX mean number of infusions and doses:<br>Group "switchers": 5.7 infusions, 4.4 mg/kg<br>Control: 5 infusions, 3.19 mg/kg | a) Efficacy. Comparison between groups (Switchers vs control):<br>• Reduction in SJC: 64% vs 62% (p=0.56)<br>• Reduction in prednisone dose: 53% vs 33% (p=0.07)<br>• ESR: increased 100% vs decrease in 38% (p=0.04)<br>• Decrease in C-RP: 28% vs 51% (p=0.46)<br>b) Safety<br>• No analytical disorders.<br>• Infections: 15% vs 9.6% (p=0.69)<br>• Infusion reactions: 4 in control group (p=0.58) |
| Keystone EC, 2004[19] Canada<br>Study RADIUS, observational prospective.<br>Duration 6 months | 72 RA pts who switched from ETN to IFX due to LOE<br>Mean RA duration 9 years. | Doses or regimens not provided. | c) Efficacy after 6 months<br>• HAQ -0.13<br>• SJC -4.14<br>• Patient global assessment -0.84<br>• Physician global assessment: +2.37<br>d) Safety. Not enough information provided. |
| Shergy WJ, 2002[20]<br>United States<br>Case series.<br>Duration not provided. | 40 RA pts who had switched from ETN to IFX due to LOE.<br>65% women. Mean age 61.<br>Mean disease duration 10 years. | ETN: 25 mg/ twice per week sc<br>IFX: mean 3.5 mg/kg | a) Efficacy after 14 weeks<br>• 38% reduction in prednisone dose<br>• 66% improvement in SJC<br>• 20% reduction in ESR<br>• 1 pt discontinued due to no response.<br>b) Safety. 5 pts discontinued (3 due to AEs, 1 due to the cost of treatment, 1 due to lung cancer) |
| Yazici Y, 2004[21]<br>United States<br>Observational prospective study.<br>Study duration: 1 year 3 months | 37 RA pts treated with IFX who had switched from ETN to IFX due to LOE.<br>77% women. Mean age 61.<br>Mean disease duration 13 years. | No dose specification. | a) Efficacy. 16 pts (43%) are not included in the analysis owing to insufficient data. No improvement was seen in HAQ, pain and morning stiffness.<br>b) Safety. Being ETN naive or have failed previously to it does not make any difference in safety. |

*(continue)*

**Table I.**

| Study | Patients | Intervention | Results |
|---|---|---|---|
| Furst, 2007[22]<br>United States<br>Randomized, open--label, multicenter, clinical trial (OPPOSITE study) for 16 weeks | 28 RA pts switching from ETN to IFX due to an inadequate response to ETN.<br>90% women. Mean age 50.<br>Median disease duration 9 years for IFX-treated pts, and 12 years for ETN-treated ones. Mean DAS28 6.3 | Pts were randomized 1:1 to:<br>a) discontinue ETN and receive IFX 3 mg/kg at weeks 0, 2, 6, 14, and 22<br>b) continue ETN 25 mg twice weekly.<br>All pts remained on background MTX. | a) Efficacy (Single blind assessor). At week 16:<br>IFX: ACR20 62%, ACR59 31%, DAS28 -31%<br>ETN: ACR20 29%, ACR59 14%, DAS28 -16%<br>b) Safety. Both drugs were well tolerated; 54% of IFX-treated patients and 50% of ETN-treated patients reported AEs. |
| Ang HT, 2003[23]<br>United States<br>Case series<br>Duration not provided.<br>Supported by NIH | 24 RA pts who had switched from ETN to IFX (12 due to inadequate response, 10 to AEs).<br>Full description not provided. | IFX doses or regimens not provided. | a) Efficacy. No correlation (by phi coefficient) in joint counts or acute phase reactants between ETN or IFX.<br>b) Safety. No correlation between the occurrence of drug hypersensitivity reactions or infectious complications. The occurrence of anemia with the use of one TNF-$\alpha$ antagonist was correlated with a similar occurrence with the use of the other antagonist (exact p value 0.007) |
| van Vollenhoven A, 2003[24]<br>Sweden<br>Observational prospective study.<br>Duration not provided. | 18 pts (14 RA, 2 JIA, 2 SpA) who switched from ETN to IFX (14 due to LOE, 2 to AEs, 2 to unknown causes).<br>83% women. Mean age 53.<br>Mean disease duration 15 years | ETN: 25 mg/ twice per week sc<br>IFX: 3 mg/kg at weeks 0, 2, 6 and then every 8 weeks | a) Efficacy. Before and after:<br>- DAS28: 5.2 to 3.6 ($p<0.02$)<br>b) Safety. Not compared. |
| Cohen G, 2005[15]<br>France<br>Case series<br>Study duration:<br>36 weeks | 14 RA pts who had switched from ETN to IFX (13 due to LOE, 1 to AEs)<br>71% women. Mean age 55<br>Mean disease duration 15 years.<br>Mean baseline DAS28 5.9 | IFX: 3 mg/kg at weeks 0, 2, 6 and then every 8 weeks | a) Efficacy:<br>• Global physician's assessment at 3 months: 12 satisfactory, 2 insufficient<br>• EULAR response at 3 months: 4 good, 4 moderate, 5 no response<br>• At the end of follow-up 9 pts were still on IFX and 1 had discontinued it due to LOE.<br>b) Safety: 3 pts had discontinued due to AEs and 1 to pregnancy |
| Delaunay, 2005[12]<br>France<br>Case series<br>Duration 10 months. | 15 SpA pts (7 AS, 6 undifferentiated SpA, 2 PsA) who switched from IFX to ETN due to inadequate response or AEs. | Doses not provided. | a) Efficacy (Clinical response):<br>• 3/7 in AS. In 2 of the 4 non responders global self-evaluation indicated an improvement. |

*(continue)*

**Table I.**

| Study | Patients | Intervention | Results |
|---|---|---|---|
| | 73% women; Mean age 43; Mean disease duration 15 years | | • All 8 patients with undifferentiated axial SpA or PsA met response criteria after 3 months.<br>• BASDAI score went from 71 ± 36 to 41 ± 73.<br>b) Safety: none experienced intolerance to this agent. |
| Katsicas, 2005[25]<br>Argentina<br>Prospective longitudinal single center study.<br>Median follow-up period was 19 (2-113) weeks. | 6 pts with JIA who switched from ETN to IFX due to LOE. | IFX: 3-10 mg/kg iv + MTX 7.5-10 mg/week. | a) Effectiveness:<br>• 3 pts met ACR paediatric 30 criteria at 2 weeks (2 pts) and 10 weeks after IFX.<br>• Improvement lasted for 4, 12, and 84 weeks.<br>• Fever/rash was not modified by the treatment.<br>b) Safety: IFX was discontinued due to moderate side effects in 4 pts. No serious AE were observed. |
| Moreno E, 2002[26]<br>Spain<br>Case report | 1 RA pt who switched from ETN to IFX due to an AE.<br>68 years, 12 years of disease duration. | Doses not provided. | The patient reached ACR50.<br>No adverse reaction. |
| Burmester GR, 2005[27]<br>United States<br>Study ReAct, multicentre, observational prospective.<br>Duration 12 weeks | 114 RA pts who switched from ETN to ADA due to any cause.<br>Mean age 54; disease duration 11 years; DAS28 6.0; HAQ 1.62. | ADA: 40 mg/ 2 weeks sc | a) Efficacy at 12 weeks<br>• ACR20: 52%<br>• ACR50: 30%<br>• ACR70: 11%<br>• Decrease in SJC: -7<br>• Decrease in HAQ: -0.36<br>• Decrease in DAS28: -1.9<br>b) Safety. Not provided |
| Gomez-Reino, 2006[8]<br>Spain. Prospective cohort from a biologic registry (BIOBADASER) | 14 pts with chronic arthritis on ETN who switched to ADA.<br>Full description not provided. | Doses not provided. | a) Effectiveness (drug survival):<br>First year survival of the switch to ADA was 0.75 (95% CI:0.31-0.93).<br>b) Safety. Not provided. |
| Wick MC, 2005[28]<br>Sweden<br>Case series.<br>Study duration:<br>6 months | 9 RA pts who switched from ETN to ADA due to LOE.<br>Mean age 47. Mean DAS28 5.7. | ETN: 25 mg/ twice per week sc<br>ADA: 40 mg/ 2 weeks sc | a) Efficacy (before and after)<br>• At 3 months: mean DAS28 4.8 ($p<0.005$)<br>• At 6 months: mean of DAS28 4.1 ($p<0.001$)<br>• 78% of pts reached ACR20 at 6 months<br>b) Safety. Not provided. |
| Brocq O, 2004[29]<br>France<br>Case series<br>Duration not provided. | 8 RA pts who switched from ETN to ADA<br>89% women. Mean age 57.<br>Mean disease duration 18 years. | Doses not provided. | a) Efficacy (ad hoc outcome):<br>5 responded and 3 did not.<br>b) Safety. Not provided. |

Abbreviations: pt, patient; ETN, etanercept; IFX, infliximab; MTX, methotrexate; ADA, adalimumab; LEF, leflunomide; RA, rheumatoid arthritis; JIA, juvenile idiopathic arthritis; SpA, spondyloarthritis; AS, ankylosing spondylitis; PsA, psoriatic arthritis; DMARD, disease modifying anti-arthritis drug; SJC, swollen joints count; LOE, lack of efficacy; AE, adverse event.

**Table II. Characteristics of Studies Included in the Systematic Review in Which an Analysis of the Switch from Antibodies (Infliximab or Adalimumab) to Soluble Receptor (Etanercept) was Included. Sorted by Number of Patients Studied.**

| Study | Patients | Intervention | Results |
|---|---|---|---|
| Gomez-Reino, 2006[8]<br>Spain. Prospective cohort from a biologic registry (BIOBADASER) | 356 pts with chronic arthritis on IFX who switched to ETN (in 57% of the cases due to inefficacy).<br>Full description not provided. | Doses not provided. | a) Effectiveness (drug survival): The first year survival of the switch to ETN was 0.78 (95% CI: 0.71-0.83).<br>b) Safety. The reason for discontinuing IFX was AEs in 42% of cases. |
| Bingham CO, 2005[30]<br>Canada. Study EMBARK. Phase IV clinical trial.<br>Duration 8 weeks. | 84 RA pts who switched from IFX to ETN due to LOE.<br>Mean age 55. Mean disease duration 7. Mean DAS28 6.7. | Doses not provided. | a) Efficacy at 8 weeks: 21% improvement in DAS28. No changes in acute phase reactants.<br>b) Safety. Not provided. |
| Keystone EC, 2004[19]<br>Canada. Study RADIUS, observational prospective<br>Duration 6 months | 83 RA pts who switched from IFX to ETN due to LOE:<br>Mean RA duration 3 years | Doses or regimens not provided. | a) Efficacy at 6 months (change from baseline)<br>• HAQ: -0.41<br>• SJC: -5.29<br>• Patient global assessment: -2.15<br>• Physician global assessment: -3.2<br>b) Safety. Not enough information. |
| Iannone, 2007[31]<br>Italy. Retrospective observational study.<br>Study assessment for 24 weeks. | 37 RA pts who had switched from IFX to ETN due to AE (mostly infusion reactions) and who had previously responded to IFX.<br>DAS-44 of 2.4, IFX should have been stopped not before 14 weeks. Pts were excluded if no clinical response to IFX.<br>81% women. Mean age 49.<br>Mean RA duration 8 years. | IFX: 3 mg/kg iv at 0, 2 and 8 weeks, and every 8 weeks + MTX.<br>ETN: 25 mg twice weekly sc | a) Efficacy after 24 weeks (period IFX vs period ETN):<br>• DAS-44: 2.7 vs 1.9<br>• HAQ: 0.75 vs 0.75<br>• ESR: 21 vs 14<br>• C-RP: 0.5 vs 0.3<br>b) Safety. Not provided. |
| Haraoui B, 2004[32]<br>Canada. Observational prospective study for 12 weeks.<br>Supported by Inmunex and Wyeth | 25 RA pts who switched from IFX to ETN (19 due to LOE, 3 to AEs)<br>84% women. Mean age 50.<br>Mean disease duration 10 years.<br>Mean SJC 8.6, mean HAQ 1.53 | IFX: mean dose 4.4 mg/kg every 7 weeks<br>ETN: 25 mg/ twice per week sc | a) Efficacy at 12 weeks:<br>• ACR20: 64%<br>• ACR50: 23%<br>• ACR70: 5%<br>• Mean HAQ: 1.08<br>b) Safety. No serious AEs. |
| Cohen G, 2005[15]<br>France. Observational retrospective study.<br>Study duration: 36 weeks | 24 RA pts who switched from IFX to ETN (16 to LOE, 8 to AEs)<br>Description not provided. | ETN: 25 mg/ twice per week sc<br>IFX: 3 mg/kg at weeks 0, 2, 6 and then every 8 weeks. If no response, dose was increased to 5 mg/kg or dose interval reduced to every 6 weeks. | a) Efficacy at 3 months:<br>• Physician global assessment: satisfactory in 18, insufficient in 6<br>• EULAR response: good 11, moderate 3, no response 5<br>b) After 3 years 14 pts were still on ETN, and 10 had discontinued (7 due to LOE, 7 to AEs) |

*(continue)*

**Table II.**

| Study | Patients | Intervention | Results |
|---|---|---|---|
| Cantini F, 2006[11]<br>Italy. Observational prospective study of 54 weeks | 23 AS pts who switched from IFX to ETN due to LOE or AE.<br>20% women. Mean age 43.<br>mean disease duration 10 years. | ETN: 50 mg per week sc. | a) Efficacy:<br>• At week 24: ASAS20 78%, ASAS50 52%, ASAS70 39%<br>• At week 54: ASAS20 74%, ASAS50 61%, ASAS70 39%<br>b) Safety. No serious AEs. |
| Buch MH, 2003[33]<br>UK. Observational prospective study.<br>Study duration:<br>12 weeks | 17 RA pts who switched from IFX to ETN due to LOE.<br>Description not provided. | Doses or regimens not provided. | c) Efficacy after 12 weeks of treatment with ETN (EULAR response)<br>• good: 13%<br>• moderate: 33%<br>• No response: 47%<br>• Worsening in DAS28: 6%<br>d) Safety. Not provided. |
| Favalli EG, 2004[13]<br>Italy. Case series. Study duration: 6 months | 14 pts (8 RA, 7 JIA) who switched from IFX to ETN due to LOE.<br>93% women. Mean age 46.<br>Mean disease duration 13 years. Mean DAS28 >3.7.<br>No response to previous DMARDs. | ETN: 25 mg/ twice per week sc.<br>IFX doses or regimens not provided. | a) Efficacy at 6 months (change from baseline):<br>RA / JIA<br>ESR, mm/hour: -16.5 / -23.4<br>CRP, mg/dl: -1.5 / -1.9<br>Swollen joint count: -5.0 / -5.4<br>DAS28: -1.4 / -1.6<br>HAQ: -0.3 / -0.4<br>b) Safety. Urticaria developed in 2 pts, but did not prevent them from continuing ETN. |
| Sanmartí R, 2004[34]<br>Spain. Observational prospective study<br>Study duration:<br>6 months | 14 RA pts who switched from IFX to ETN due to LOE.<br>93% women. Mean age 53.<br>Mean disease duration 11 years.<br>Mean DAS28 6.01 | ETN: 25 mg/ twice per week sc<br>IFX: 3 mg/kg at weeks 0, 2, 6 and then every 8 weeks.<br>If no response, dose was increased to 5 mg/kg or dose interval reduced to every 6 weeks. | a) Efficacy (before and after):<br>• Mean of DAS28: 4.3 (p=0.02)<br>• Mean patient global assessment: 41.7 (p=0.02)<br>• Mean Physician global assessment: 41.3 (p>0.05)<br>• Mean C-RP:1.6 (p=0.02)<br>b) Safety. No serious AEs. |
| van Vollenhoven, 2003[24]<br>Sweden. Observational prospective study<br>Duration not provided. | 13 pts (11 RA, 1 JIA, 1 SpA) who switched from IFX to ETN (11 due to AEs, and 2 unknown)<br>92% women. Mean age 48.<br>Mean disease duration 14 years. | ETN: 25 mg/ twice per week sc<br>IFX: 3 mg/kg at weeks 0, 2, 6 and then every 8 weeks | a) Efficacy (before and after):<br>• DAS28: better after ETN (p<0.02)<br>• SJC: no differences (p>0.05)<br>b) Safety not provided. |
| Albadalejo C, 2003[35]<br>Spain. Observational prospective study.<br>Duration not provided. | 11 RA pts who switched from IFX to ETN (6 to lack of response, 5 to AEs).<br>91% women. Mean age 49.<br>Mean disease duration 10 years | ETN: 25 mg/ twice per week sc<br>IFX: 3 mg/kg at weeks 0, 2, 6 and then every 8 weeks. If no response dose was increased to 5 mg/kg | a) Efficacy:<br>• 50% improvement in SJC: 6 pts (55%)<br>• 50% improvement in ESR: 4 pts (37%)<br>• 50% improvement in C-RP: 7 pts (64%) |

*(continue)*

**Table II.**

| Study | Patients | Intervention | Results |
|---|---|---|---|
| | | | • Good DAS28 response: 2 pts (18%)<br>• Moderate DAS28 response: 7 pts (64%)<br>b) Safety. No important AEs. |
| Brocq O, 2002[29]<br>France. Case series<br>Study duration: 2 years 6 months | 8 RA pts who switched from IFX to ETN (6 due to AEs, 2 to no response).<br>89% women. Mean age 57.<br>Mean disease duration 18 years. | Doses not provided. | a) Efficacy (ad hoc outcome variable): 5 responded and 2 did not. 1 pt abandoned treatment.<br>b) Safety. Not provided. |
| Ang HT, 2003[23]<br>United States<br>Case series.<br>Duration not provided.<br>Supported by NIH | 5 RA pts who switched from IFX to ETN (2 due to inadequate response, 3 to AEs).<br>Description not provided. | Doses not provided. | a) Efficacy. No correlation (by phi coefficient) in joint counts or acute phase reactants between ETN or IFX.<br>b) Safety. No correlation between the occurrence of drug hypersensitivity reactions, infectious complications, or anemia. |
| Arenere M, 2005[36]<br>Spain. Case series.<br>Study duration:<br>6 months | 5 RA pts who switched from IFX to ETN due to LOE.<br>All women. Mean age 51. | Doses not provided. | a) Efficacy at 6 months: DAS28 decreased from 5.1 to 3.2<br>b) Safety. Not provided. |
| Cantini F, 2005[37]<br>Italy. Observational prospective study<br>Study duration:<br>24 weeks | 22 RA pts who switched from IFX or ADA to ETN due to LOE.<br>82% women; median age: 56 years; median disease duration: 6 years. | ETN: 50 mg/ sem sc<br>IFX doses or regimens not provided. | a) Efficacy: inefficacy in 15/22 (68%):<br>• ACR20 response in 12/21 (57%) patients<br>• ACR50 in 5/21 (24%)<br>• ACR70 in 2/21 (9.5%)<br>• Mean DAS28 declined from 5.30 to 2.87 ($p<0.001$) at 24-week visit.<br>b) Safety: AEs in 7/22 (32%) patients. 1 patient withdrew the study due to a serious AE (shoulder septic arthritis after 8 weeks of therapy). Minor AEs, such as injection site bleeding, cutaneous erythema, dizziness, and transient headache were recorded in 7/21 (33%) patients. |

Abbreviations: pt, patient; ETN, etanercept; IFX, infliximab; MTX, methotrexate; ADA, adalimumab; LEF, leflunomide; RA, rheumatoid arthritis; JIA, juvenile idiopathic arthritis; SpA, spondyloarthritis; AS, ankylosing spondylitis; PsA, psoriatic arthritis; DMARD, disease modifying anti-arthritis drug; SJC, swollen joints count; LOE, lack of efficacy; AE, adverse event.

**Table III. Characteristics of Studies Included in the Systematic Review in which an Analysis of the Switch between Monoclonal Antibodies of TNF (Infliximab and Adalimumab) was Included. Sorted by Number of Patients Studied.**

| Study | Patients | Intervention | Results |
|---|---|---|---|
| Burmester GR, 2005[27] United States. Study ReAct, multicentre, observational prospective. Duration 12 weeks | 358 RA pts who switched from IFX to ADA due to any cause. Mean age 54; disease duration 11 years; DAS28 6.0; HAQ 1.62. | ADA: 40 mg/ 2 weeks sc | a) Efficacy at 12 weeks (change from baseline):<br>• ACR20: 63%<br>• ACR50: 35%<br>• ACR70: 12%<br>• SJC: -6<br>• HAQ: -0.49<br>• DAS28: -2<br>b) Safety. Not enough information. |
| Nikas SN, 2006[38] Greece. Observational prospective study. Study duration: 12 months | a) 24/49 RA pts who switched from IFX to ADA due to LOE o AEs: 92% women. Mean age 56. Mean disease duration 16 years. Mean DAS28 5.6<br>b) 25/49 pts (control) without previous IFX: 88% women. Mean age 59. Mean RA duration 15 years. Mean DAS28 5.9 | ADA: 40 mg/ 2 weeks sc | a) Efficacy (Comparison previous vs no previous IFX):<br>• SJC: p> 0.05<br>• Patient global assessment: p> 0.05<br>• Physician global assessment: p> 0.05<br>• ACR20: 75% vs. 76% (p> 0.05)<br>• ACR50: 50% vs. 56% (p> 0.05)<br>• ACR70: 33% vs. 36% (p> 0.05)<br>• DAS28: 3.2 vs. 3.2 (p> 0.05)<br>b) Safety. There were 11 AEs in each group |
| Van der Bijl, 2005[14] Germany. Observational prospective study Study duration: 16 weeks | 42 RA pts who switched from IFX to ADA (36 due to LOE, 6 to AEs)<br>88% women. Mean age 55. Mean RA duration 12 years. Mean DAS28 6.1. Mean HAQ 1.85 | ADA: 40 mg/ 2 weeks sc | a) Efficacy at 16 weeks (change from baseline):<br>• ACR20: 49%<br>• ACR50: 26%<br>• Moderate EULAR response: 65%<br>• DAS28: -1.6<br>• SJC: -5.2<br>b) Safety. 4 pts abandoned treatment, 3 to AEs, 1 due to LOE. |
| Gomez-Reino, 2006[8] Spain. Prospective cohort from a biologic registry (BIOBADASER) | 33 pts with chronic arthritis on IFX who switched to ADA. Full description not provided. | Doses not provided. | a) Effectiveness (drug survival): First-year survival of switch to ADA was 0.69 (95% CI: 0.43-0.85).<br>b) Safety. Not provided. |
| Wick MC, 2005[28] Sweden. Observational prospective study for 6 months | 27 RA pts who switched from IFX to ADA due to LOE. Mean age 50. Mean DAS 28 5.2 | IFX: 3 mg/kg at weeks 0, 2, 6 and then every 8 weeks. ADA: 40 mg/2 weeks sc | a) Efficacy (before and after):<br>• At 3 months: mean DAS28 4.5 (p<0.003)<br>• At 6 months: mean DAS28 4.2 (p<0.001)<br>• 70% of the pts reached ACR20 at 6 months<br>b) Safety. Not provided |

Abbreviations: pt, patient; ETN, etanercept; IFX, infliximab; MTX, methotrexate; ADA, adalimumab; LEF leflunomide; RA, rheumatoid arthritis; JIA, juvenile idiopathic arthritis; SpA, spondyloarthritis; AS, ankylosing spondylitis; PsA, psoriatic arthritis; DMARD, disease modifying anti-arthritis drug; SJC, swollen joints count; LOE, lack of efficacy; AE, adverse event.

**Table IV. Characteristics of Studies Included in the Systematic Review in which the Analysis Focused on a Different Switch, the Switch was Unspecified, or the Focus was on Risk Factors for Failure in the Switch.**

| Study | Patients | Intervention | Results |
|---|---|---|---|
| Bombardieri S, 2006[39] Italy. Study ReAct, multicentre, observational prospective. Duration 12 weeks | 819 RA pts who switched to ADA from ETN and/or IFX. Causes for switching (categories not mutually exclusive): ETN: no response (n=47), loss of response (n=29), intolerance (n=31) IFX: no response (n=84), loss of response (n=186), intolerance (n=86) Mean DAS28 6.3; HAQ 1.85. | ADA: 40 mg/ 2 weeks sc | a) Efficacy at week 12, withdrawals due to LOE were 1.2% among patients without anti-TNF history and 2.2% among patients with. <br> Previous biologic: IFX <br> Cause / No response (n=110) / Loss of response (n=258) / AEs (n=139) <br> ACR20: 59% / 67% / 67% <br> ACR50: 25% / 37% / 37% <br> ACR70: 7% / 13% / 16% <br> DAS28: -1.9 / -2.0 / -2.3 <br> Previous biologic: ETN <br> Cause / No response (n=63) / Loss of response (n=48) / AEs (n=40) <br> ACR20: 41% / 67% / 67% <br> ACR50: 26% / 34% / 42% <br> ACR70: 11% / 14% / 19% <br> DAS28: -2.1 / -2.0 / -2.3 <br> b) Safety. Withdrawals due to AEs were 4% among patients without and 4.8% with anti-TNF history. |
| Burmester GR, 2005[27] United States. Study ReAct, multicentre, observational prospective for 12 weeks | 78 RA pts who switched from ETN and IFX to ADA. Mean age 54; disease duration 11 years; DAS28 6.0; HAQ 1.62. | ADA: 40 mg/ 2 weeks sc | a) Efficacy at 12 weeks (change from baseline): • ACR20: 42% • ACR50: 27% • ACR70: 13% • SJC: -5 • HAQ: -0.35 • DAS28: -1.4 b) Safety. Not enough information. |
| Atzeni, 2006[40] Italy. Observational prospective study. Duration not provided. | 15 RA pts who switched from IFX and ETN to ADA due to LOE. 80% women. Mean age 52. Mean RA duration 9 years. | ADA: 40 mg/ 2 weeks sc, 8 injections. | a) Efficacy (change from baseline after 8 injections): • Mean SJC: from 10 to 3 (p=0.02) • Mean ESR: from 35 to 24 (p=0.001) • Mean DAS28: from 5.4 to 2.7 (p=0.024) b) Safety not provided. |
| Brocq O, 2002[29] France. Observational prospective study Study duration: 2 years 6 months | 10 RA pts who switched from IFX and ETN to ADA (due to AEs or to no response). 89% women. Mean age 57. Mean disease duration 18 years. | No doses or regimens provided. | a) Efficacy (ad hoc outcome variable): 5 responded, 5 did not. b) Safety. Not provided. |

*(continued)*

**Table IV.**

| Study | Patients | Intervention | Results |
|---|---|---|---|
| Hyrich, 2007[10]<br>UK. Prospective cohort from a biologic registry (BSRBR).<br>Mean 15 months of follow-up | 503 RA pts who stopped taking a first anti-TNF due to inefficacy and 353 who stopped due to toxicity, and were switched to a second anti-TNF agent. 79% women. Mean age 54. Mean RA duration 13 years. Mean DAS28 6.8 | Doses or regimes not specified. | a) Effectiveness (drug survival):<br>• 73% of pts who switched to a 2nd anti-TNF agent remained on the new therapy by the end of follow-up.<br>• 1st drug discontinuation due to inefficacy was associated with an increased rate of 2nd drug discontinuation due to inefficacy (HR 2.7; 95% CI: 2.1-3.4) but not toxicity (HR 1.1; 95% CI 0.9-1.5)<br>• 1st drug discontinuation due to toxicity was associated with an increased rate of 2nd drug discontinuation due to toxicity (HR 2.3, 95% CI 1.9-2.9) but not inefficacy (HR 1.2, 95% CI 0.8-1.6).<br>b) Safety. If the reason for switching to a 2nd agent was inefficacy, the risk of developing an AE with a 2nd biologic agent was roughly the same as the risk of developing an AE with the 1st agent. If the reason for the switch was an AE, then the likelihood of a recurrent AE with the 2nd agent was increased more than 2-fold. Of the 71 pts who had recurrent AEs, only 19 experienced the same AE during switch therapy. |
| Gomez-Reino, 2006[8]<br>Spain. Prospective cohort from a biologic registry (BIOBADASER) | 488 pts (68% RA, 11% AS, 10% PsA, and 11% other forms of chronic arthritis) on biologics who switched to a successive one. | Switches or doses not specified. | a) Effectiveness (drug survival):<br>• First switch: 1 year survival decreased from 0.83 to 0.68.<br>• Survival was better in patients replacing the first TNF antagonist because of AEs (HR for discontinuation 0.55; 95% CI: 0.34-0.84), and worse in pts older than 60 (HR 1.10; 95% CI 0.97-2.49) or who were treated with IFX (HR 3.22; 95% CI 2.13-4.87).<br>• Effectiveness of the switch was greater in AS and PsA than in RA or JIA.<br>b) Safety. Not provided.<br>*(continued)* |

**Table IV.**

| Study | Patients | Intervention | Results |
|---|---|---|---|
| Hjardem, 2007[41] Denmark. Prospective cohort from a biologic registry (DANBIO) | 235 RA pts who switched biologic before 2005. Reasons for switching were 109 LOE, 72 AEs, 54 other reasons | Most patients switched from IFX to ETN or ADA. Doses or regimes not specified. | a) Effectiveness:<br>• Median survivals for switchers' 1st/2nd treatment were 37/92 weeks (All patients' 1st treatment: 119 weeks).<br>• If pts had AE with 1st drug, 15% had AE with the 2nd.<br>• Median DAS28 improvements in 1st/2nd treatment at 3 months were: LOE switchers: 1.1/1.6; AE switchers: 1.5/0.8.<br>• In LOE switchers, a good/ /moderate EULAR response was more prevalent during the 2nd treatment course than during the 1st (63% vs. 54%, p=0.02).<br>• AE switchers achieved similar EULAR responses to both treatments (59% vs. 50%, p=0.38).<br>b) Safety. Not provided. |
| Solau-Gervais, 2006[42] France. Case series | 70 and 20 RA pts who had received 2 and 3 anti-TNF-α agents, respectively. Switches:<br>a) 32 pts from an antibody (Ab) to a soluble receptor (Sr)<br>b) 30 pts from Sr to Ab<br>c) 8 pts from Ab to Ab. | Doses and regimes as by indication. | a) Effectiveness (% clinical response):<br>• switch Ab to Sr 45%<br>• switch Sr to Ab 45%<br>• switch Ab to Ab 33%<br>• 7/20 pts who had received 3 anti-TNF-α agents stopped receiving the 3rd anti-TNF-α agent due to LOE, all of whom had previously failed to the 2nd one, without AEs. |
| Finchk, 2007[43] Switzerland. Prospective cohort study nested within the Swiss Clinical Quality Management RA cohort. | 116 RA pts who had an inadequate response to at least 1 anti-TNF agent. No significant differences between the 2 groups in age, sex, disease duration, and disease activity at baseline. 87% women. Mean age 55. | a) 1 cycle of RTX (n=50)<br>b) or an alternative anti-TNF agent (n=66) | Effectiveness at 6 months: Mean decrease in DAS28 was -1.61 (95% CI: -1.97, -1.25) among patients receiving RTX and -0.98 (95% CI -1.33, -0.62) among those receiving subsequent anti-TNF therapy. |

Abbreviations: pt, patient; ETN, etanercept; IFX, infliximab; MTX, methotrexate; ADA, adalimumab; LEF, leflunomide; RA, rheumatoid arthritis; JIA, juvenile idiopathic arthritis; SpA, spondyloarthritis; AS, ankylosing spondylitis; PsA, psoriatic arthritis; DMARD, disease modifying anti-arthritis drug; SJC, swollen joints count; LOE, lack of efficacy; AE, adverse event; RTX, rituximab.

in 17 (74%) out of 23 patients, ASAS50 in 14 (61%) out of 23, and ASAS70 in 9 (39%) out of 23, with no serious adverse events. The authors refer that 16 of the 23 patients included in this study had initially responded to infliximab but acquired drug resistance due to an escape phenomenon despite dose adjustments. Delaunay et al, followed up 13 patients with spondyloarthropathies (7 ankylosing spondylitis, 6 undifferentiated spondylitis, and 2 psoriatic arthritis) who had had an inadequate response or adverse events with infliximab, and in whom therapy was changed to etanercept.[12] Patients were evaluated for response to the change in anti-TNF-α therapy at baseline, after 3 months, and then every 6 months. During the mean 10--month follow-up after the change in therapy, 9 out of 13 patients with spondyloarthropathies and both patients with psoriatic arthritis responded to etanercept and none experienced intolerance to this agent, suggesting that switching between anti--TNF-α drugs may be useful for patients with spondyloarthropathies who are unresponsive or intolerant to a first anti-TNF-α agent. In another small study of 15 patients with rheumatoid arthritis (n=8) or juvenile idiopathic arthritis (n=7), no clear differences in the response to the second treatment were found between diseases, both being fairly good (13/15) at six months.[13] In BIOBADASER, where rheumatoid arthritis and other forms of arthritis are included, switching between biologics decreases on year drug survival rate of the second drug to a higher degree in rheumatoid arthritis (83% to 79%) and specially in juvenile idiopathic arthritis (90% to 49%), than in spondyloarthropathies (89% to 85%).[8]

## Predictors of Response to Switch Between Biologics

Identification of factors that predict the response to a given anti-TNF-α agent would be valuable for selecting the best initial agent and for determining whether a switch to another agent is warranted when the first agent tried is ineffective or responsible for side effects or whether, on the contrary, the entire therapeutic class should be abandoned permanently. Few studies have addressed this important question. Gómez-Reino et al, found that second drug survival was better in patients replacing the first TNF antagonist because of adverse events, and worse in patients older than 60 years, or that were treated with infliximab as a second drug, or that had rheumatoid arthritis.[8] Cantini et al, in their open trial, noticed that all ankylosing spondylitis patients who had initially responded to infliximab, but whom eventually lost response to this drug as a consequence of an escape phenomenon, had a good response to etanercept.[11] What is becoming clearer is the fact that a third biologic will surely fail unless used as a result of adverse events with the previous ones.[10]

With few exceptions, patients experiencing loss of effect of a TNF-α inhibitor after an initial response are more likely to respond to another agent, than patients failing a TNF-α inhibitor initially. For example, Van der Bijl and colleagues showed that patients who switched to adalimumab after no initial response to infliximab had little response compared to those who lost their initial response to infliximab.[14]

Although TNF-α inhibitors seem effective regardless of which agent precedes them, there is little data as to the relative merits of using any one agent preferentially, in terms of the order in which they are used. Preliminary data from a large, open--label study suggest that etanercept was more effective after infliximab than infliximab was after etanercept.[15] This result, however, could have been due to other treatment failures in the infliximab--second group as a consequence of human-antichimeric antibody responses; no information was available in this regard.

## From TNF Antagonists to other Biologics

Unfortunately, there is not much information about switching to new biologics from the TNF-antagonists, and whether this is a safe strategy. The only study captured with our strategy, however, is really promising.[16] In this study, switching to another TNF antagonist was compared to using a completely different molecule, rituximab. Other recent reports on the efficacy of new biologic agents carry out subgroup analyses in patients with previous failure to TNF-α inhibitors. Placebo-controlled studies of abatacept and rituximab demonstrated that ACR responses substantially decreased in patients who had failed treatment with a TNF-α inhibitor, compared with those who were TNF-inhibitor naive. The marked reduction in placebo responses in patients who had prior TNF-α inhibitor exposure, however, was significant. Some differences in the

effect size were seen between abatacept[17] and rituximab[16] before and after previous TNF treatment. The results of uncontrolled studies of responses to TNF-α inhibitors could be quite misleading because of this. Anyway, switching between TNF-antagonists has not demonstrated a higher effect size or effectiveness than switching to a different molecule. Perhaps the best alternative when a first TNF--antagonist fails is to start a different type of biologic, and leave the switch to another TNF-antagonist in the case of adverse event to the previous one. The dilemma we now face in front of patients who have not adequately responded to one or more TNF-α antagonists is whether starting a new biologic will increase the risk of infections or malignancies, as a secondary effect of prolonged immunosuppression.

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