

# Ankylosing Spondylitis Treatment after First Anti-TNF Drug Failure

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**ABSTRACT:** Although anti-tumor necrosis factor (TNF) therapy has revolutionised the management of spondyloarthritis (SpA), 20–30% of SpA patients discontinue biological treatment because they fail to respond or their response is inadequate, and 10–20% stop because of a lack or loss of efficacy or the onset of adverse events. Published data show that anti-TNF drugs in are highly effective in patients with ankylosing spondylitis, and associated with a higher drug persistence rate. Furthermore, studies suggest considering a switch to another anti-TNF drug if a first anti-TNF agent is discontinued because of loss of efficacy or adverse events.

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**KEY WORDS:** ankylosing spondylitis (AS), anti-tumor necrosis factor (anti-TNF) drugs, efficacy, adverse events

**A**nkylosing spondylitis (AS), a prototype of the spondyloarthritis (SpA) family, is a chronic, progressive, inflammatory disease of the axial skeleton that mainly involves the spine and sacroiliac joints [1] but may also affect other sites such as the anterior joints of the chest wall [2]. It can lead to severe chronic pain and discomfort [1–3], and treatment should be started as early as possible to prevent skeletal deformity and physical disability [4].

Although anti-tumor necrosis factor (anti-TNF) therapy has revolutionised the management of spondyloarthritis (SpA), 20–30% of SpA patients discontinue biological treatment because they fail to respond or their response is inadequate [5], and 10–20% stop because of a lack or loss of efficacy (LOE) or the onset of adverse events [6].

Delaunay and colleagues [7] first reported that switching to another anti-TNF drug may be useful in SpA patients who are unresponsive to, or cannot tolerate, a first anti-TNF drug. Subsequent prospective observational studies have confirmed the safety and efficacy of switching from one anti-TNF drug to another [8,9]. As anti-TNF drugs are

**Although anti-tumor necrosis factor therapy has revolutionised the management of spondyloarthritis, 20–30% of patients discontinue biological treatment because of failure or inadequate response**

structurally different and have different mechanisms of action, unsuccessful treatment with one does not preclude a response to another [10].

The efficacy of switching anti-TNF drugs has been evaluated in some large studies of patients with AS or axial SpA. The RAPID-axSpA trial [11] found that, if the initial discontinuation was for reasons other than primary failure, 40% of patients could be successfully treated with anti-TNF drugs for about 3 months before requiring certolizumab pegol treatment; however, the subgroup analysis has not yet been published [11]. One open-label trial showed that 26.1% of 1250 AS patients treated with adalimumab had previously received etanercept and/or infliximab, and that these patients had worse Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) 50 and Assessment of Spondyloarthritis International Society (ASAS) 40 responses. A response with partial remissions was obtained after the switch, compared to patients treated with adalimumab as a first-line treatment [12].

## LITERATURE SEARCH

A search was conducted using the PubMed databases from 1999 to 2016 using the keywords: “ankylosing Spondylitis,” “spondyloarthritis,” and “anti-TNF drugs” and coupled with “failure.” To be included in this review, the study had to be a randomized control trial (RCT), systematic review, or observational study (i.e., cross-sectional, non-interventional case-control, or cohort studies) evaluating AS treatment after the first anti-TNF failure.

## REGISTRY DATA

Compared to RCTs, drug prescription and use in the real world vary and involve many more people. The treatment compliance and health expectations of real-world patients are different from those participating in RCTs [13]; consequently, the biological drug sequences used in normal clinical practice (e.g., a switch to a third or fourth drug, and then a return to a previously used drug) are also different from those used in RCTs. Moreover, the effectiveness and safety anti-TNF drug switching and drug sur-

vival rates have never been studied in RCTs. There is an increasing need to use registry data in analyses of the cost effectiveness of switching from one drug to another [14].

The national Danish and Norwegian registries have provided data relating to AS patients who switched to another anti-TNF drug [15,16]. The DANBIO [15] registry analysed data relating to 432 patients who switched to a second, and 137 patients who switched to a third anti-TNF drug, and compared the finding with those relating to 1004 non-switchers. Response and drug survival rates were lower among the switchers. The NORDMARD registry [16] evaluated the effectiveness of a second anti-TNF drug in 77 switchers with AS and found that switching to a second anti-TNF drug is useful in everyday clinical practice even though overall effectiveness is lower [Table 1].

Fifteen percent of the AS patients in the Norwegian registry and 30% of those in the Danish registry switched to a second anti-TNF drug over a period of 8–9 years, and similar switching frequencies (13–15%) have been reported in observational studies of 100 AS patients [17,18]. The median

baseline BASDAI values of the patients in the national registries were similar, but the switchers included a higher percentage of women, patients with a shorter duration of disease and symptoms, and patients with higher disease activity and functional indices [13,14]. Furthermore, the national registries and observational studies included relatively large numbers of patients switching anti-TNF drugs, but no data are available concerning individual drug treatment outcomes.

Among the switchers, the effects of the first and second anti-TNF drug on disease activity (BASDAI) and response rates (BASDAI-50) were similar during the 1 year follow-up period, but there was a higher rate of patients achieving BASDAI-50 than that reported by other investigators [13,14]. One study found no difference between the anti-TNF drugs used during the switch, and a Spanish study of SpA patients found no difference in drug survival rates [19]. A review of the literature indicates that 30% of SpA patients starting anti-TNF therapy switch to a second anti-TNF drug, that there is no difference in drug survival between the first, second, and third anti-TNF drug, and that the main reason for switching is LOE. Furthermore, the switchers were more frequently women, had higher BASDAI values, a higher erythrocyte sedimentation rate, and higher pain and global status visual analogue scale values than non-switchers [20].

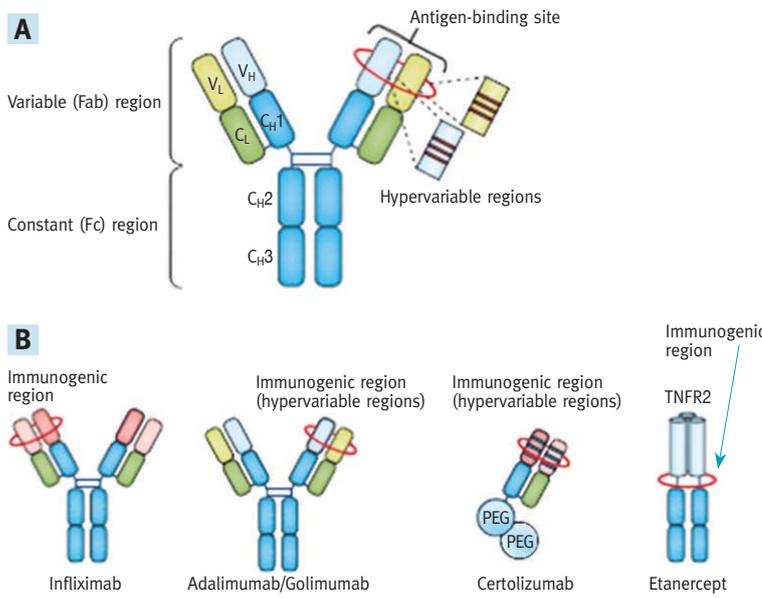
Data concerning AS patients treated with at least one anti-TNF drug between November 2005 and November 2013 showed that switchers were older than non-switchers at the time of starting the first anti-TNF drug. The improvement in BASDAI were similar in both groups, but switchers had lower response rates to the first and second anti-TNF drugs than the non-switchers [21].

**Of spondyloarthritis patients, 10–20% stop anti-tumor necrosis factor therapy because of a lack or loss of efficacy or the onset of adverse events**

**Table 1.** Frequency of switcher in registry data

Registry	Frequency	References
DANBIO	432 patients	<i>Ann Rheum Dis</i> 2013; 72: 114–55
NORDMARD	77 patients	<i>Ann Rheum Dis</i> 2011; 70: 157–63
NORWEGIAN	50%	<i>Rheumatology</i> 2011; 50: 714–20
DANISH	30%	<i>Rheumatology</i> 2011; 50: 714–20

**Figure 1.** Structure of tumor necrosis factor antagonist and immunogenic regions



**IMMUNOGENICITY**

Secondary LOE can be explained by the unique chemical structure of the anti-TNF drugs [22]. The chimeric monoclonal antibody (infliximab) induces the production of anti-drug antibodies more intensively than humanised antibodies (adalimumab and golimumab) and the receptor fusion protein, etanercept [Figure 1]. One study found anti-drug antibodies in 25.9% of SpA patients, 81.8% of whom were found in the patients treated with infliximab, 18.2% in these in treatment with adalimumab, and none in these treated with etanercept [23].

As concomitant treatment with methotrexate or other immunosuppressive drugs reduces the production of these antibodies in patients with rheumatoid arthritis (RA) and because these drugs are usually not indicated for patients with axial SpA, evaluating anti-drug antibody levels in AS patients experiencing LOE may help when making drug switching decisions. A meta-analysis of the presence and effects of anti-drug antibodies in patients with different inflammatory diseases (RA, SpA, and inflammatory bowel disease) found that drug response was worse in the presence of serum anti-drug antibodies, and that

the effect of anti-drug antibodies on anti-TNF drug responses was higher in the AS and SpA patients than in those with other diseases [24].

**RETENTION RATES AND PREDICTIVE FACTORS**

In a large cohort of 1250 patients with active AS, 1159 patients (92.7%) completed 12 weeks of treatment with adalimumab and, at the end of the treatment period, 57.2% had achieved BASDAI 50, 53.7% ASAS40, and 27.7% ASAS partial remission. These outcomes were strongly associated with a younger age, higher C-reactive protein (CRP) levels, human leukocyte antigen B27 positivity, and anti-TNF drug naïvety [25].

Another study found that the overall 10 year retention rate of a first-line anti-TNF drug was about 23%, and significantly higher in SpA than in RA patients. The drug survival rate of etanercept was significantly higher than that of infliximab and adalimumab [26].

A recent study investigating the potential predictors of switching anti-TNF drugs in Korean patients with AS found that that 3 and 5 year drug survival rates were 52% and 48%, respectively, for infliximab, 62% and 42% for etanercept, and 71% and 51% for adalimumab. A history of joint surgery and complete ankylosis of the sacroiliac joint was more frequent in switchers. A multivariate Cox's proportional hazard analysis showed that the use of adalimumab as the first anti-TNF drug was less likely to lead to switching, and complete ankylosis of the sacroiliac joints was more likely to do so. The main reasons for switching were drug inefficacy and adverse events, but the differences in the clinical data of the patients in these two groups were not significant [27].

The national Swedish Biologics Registry (which is connected with national population-based registers) has shown that the co-administration of conventional disease-modifying rheumatic drugs (cDMARDs) was associated with a better 5 year retention of the first anti-TNF drug [28] in patients with a clinical diagnosis of AS or undifferentiated SpA who started treatment with adalimumab, etanercept, or infliximab as their first anti-TNF drug between 2003 and 2010.

A retrospective analysis of the data from RADIUS 1 (a 5 year observational registry of patients with RA) designed to determine the time to the first and second course discontinuation of etanercept, infliximab, and adalimumab (first course therapy was defined as the first exposure to an anti-TNF drug, and second course therapy as exposure to an anti-TNF drug after the first discontinuation) found that the first and second course retention of anti-TNF drugs was similar, but there was less first course discontinuation due to adverse events with etanercept than with infliximab [29].

Finally, another retrospective study of AS patients treated with adalimumab, etanercept, or infliximab between 2000 and

2012 confirmed the effectiveness of these drugs as first or second line, but the baseline presence of enthesitis, psoriasis or low CRP levels led to a lower probability of obtaining partial remission [30].

The data from observational studies and clinical practice are conflicting but suggest that, although there are no published guidelines suggesting which is the best strategy to adopt after a first anti-TNF failure, switching from one TNF inhibitor to another

**In the Norwegian registry, 30% percent of the ankylosing spondylitis patients switched to a second anti-tumor necrosis factor drug**

has become common practice in patients who fail their initial treatment. As all these drugs have a similar mechanism of

action, it is difficult to explain why patients may respond to one and not another. Suggested reasons include differential bioavailability, differences in the stability of the drug/TNF complex, the development of anti-drug antibodies, and possible differences in patient adherence to therapy. The most frequent reason for discontinuing is lack of efficacy but, regardless of the reason and the sequence of drugs administered, disease activity is reduced after switching. Survival on the second biological therapy is longer than on the first, but shorter than the survival on treatment of non-switchers. AS patients can be successfully treated with a second TNF antagonist.

**LIMITATIONS**

The main limitation of this review was that we evaluated only the switching among anti-TNF drugs without considering the new therapy with anti-interleukin (IL)-12/23 and anti-IL-17 drugs.

**CONCLUSIONS**

Published data primarily suggest that anti-TNF drugs are highly effective in AS cohorts and can be associated with a high drug retention rate. They also suggest considering the positive effects of switching to another anti-TNF drug after the discontinuation of a first because of LOE over time or the occurrence of adverse events.

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## Capsule

### Lifetime risk of primary total hip replacement surgery for osteoarthritis from 2003 to 2013: a multinational analysis using national registry data

**Akerman** and co-authors tried to compare the lifetime risk of total hip replacement (THR) surgery for osteoarthritis between countries and over time. In 2003, lifetime risk of THR ranged from 8.7% (Denmark) to 15.9% (Norway) for females and from 6.3% (Denmark) to 8.6% (Finland) for males. With the exception of females in Norway (where lifetime risk started and remained high), lifetime risk of THR increased significantly for both genders in all countries from 2003 to 2013. In 2013, lifetime risk of THR was as high as 1 in 7 women in Norway, and 1 in 10 men in Finland. Females consistently demonstrated the highest lifetime risk of THR at both time points. Notably,

lifetime risk for females in Norway was approximately double the risk for males in 2003 (females 15.9%, 95% confidence interval [95%CI] 15.6–16.1; males 6.9%, 95%CI 6.7–7.1), and 2013 (females 16.0%, 95%CI 15.8–16.3; males 8.3%, 95%CI 8.1–8.5). Using representative, population-based data, this study found statistically significant increases in the lifetime risk of THR in five countries over a 10 year period, and substantial between-gender differences. These multinational risk estimates can inform resource planning for osteoarthritis service delivery.

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Eitan Israeli

### “Nobody can be exactly like me. Sometimes even I have trouble doing it”

Tallulah Brockman Bankhead, (1902–1968), American screen and stage actress known for her husky voice, outrageous personality, and devastating wit