

# Non-medical switching from originators to biosimilars in patients with rheumatic disease in routine clinical care: what is the best strategy?

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## Abstract

Rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis are common rheumatic diseases leading to irreversible joint damage and increase in mortality. The introduction of highly effective biologic drugs has resulted in substantial benefit in the treatment of these diseases, but these therapies take a high toll on healthcare systems. The recent availability of biosimilars, biologic drugs which are highly similar to their respective originator products, is changing the treatment landscape allowing substantial reduction in costs and potentially larger access to this therapeutic option. In this scenario switching stable patients from originators to biosimilars may represent a reasonable and cost-saving treatment strategy. The safety and efficacy of non-medical switching have been evaluated in randomized controlled and real-world evidence studies, with conflicting results and the nocebo effect is a well-recognized phenomenon. The aim of this review is to evaluate the evidence in this area trying to delineate which might be the best strategy in routine clinical care.

**Keywords:** Biosimilar, Biologic drug, TNF inhibitor, Non-medical switch, Nocebo effect

## Introduction

Rheumatoid arthritis (RA), ankylosing spondylitis (AS) and psoriatic arthritis (PsA) globally affect about 2% of adult population in westernized countries [1,2]. A large proportion of patients do not adequately respond to traditional synthetic disease modifying drugs (DMARDs), whereas most of them show good response to biologic drugs [3,4]. Biologic medicines are derived from living organisms, often by using recombinant DNA technology and differ from traditional, small molecule medicines, which are generally structurally simple, chemically synthesized and easily characterized analytically. We have been using anti-TNF biologic drugs for almost 20 years in patients with RA, AS and PsA and several studies have shown their safety and long-term efficacy [5-7]. Biosimilars have established similarity to the biologic reference product. There are stringent regulatory requirements for demonstration of biosimilarity— including demonstration of comparable physicochemical characteristics, biological activity, efficacy and immunogenicity – and the approval process of biosimilars is rigorous and includes evidence from randomized clinical trials (RCTs) [8]. Today, the therapeutic armamentarium of the rheumatologist includes biosimilars of first-generation anti-TNF drugs (adalimumab, etanercept, infliximab). Several head-to-head RCTs have been conducted in rheumatic diseases and have demonstrated that treatment of biologic-naïve patients with either an originator biologic or its biosimilar resulted in similar efficacy and safety profiles [9-12]. Approximately 70% of patients achieved the pre-defined clinical response (for example an American College of Rheumatology 20% improvement response in RA) with both the originator and the biosimilar. Due to this large evidence from RCTs, in routine clinical care biosimilars have become the first-line drug of choice in most patients with RA, AS and PsA, with a significant reduction of costs. In this new scenario the act of non-medical switching, defined as switching stable patients who are doing well with their current therapy from an originator biologic to its biosimilar, has been endorsed

as a reasonable treatment strategy. It has been evaluated in RCTs as well as in real-life studies, which have showed that although many patients maintain treatment response after switching, some of them may experience therapy failure, resulting in therapy discontinuation [13,14]. Analyses of these data and understanding the reasons of this failure may be crucial to define the optimal therapeutic strategy and the correct approach to the act of non-medical switching.

### **Non-Medical Switching from Originators to Biosimilars**

Two different strategies for the use of biosimilars can be used in patients already treated with an originator: mandatory switch or physician-patient shared decision. In some countries the act of non-medical switching from an originator anti-TNF biologic product to its biosimilar has been mandated as a treatment strategy in patients who are stable and doing well with the originator biologic [15,16]. Obviously, this practice is driven by economic reasons and has been based on data from several studies. One of the key studies supporting non-medical switching is NOR-SWITCH a Norwegian nationwide RCT that investigated switching from the originator infliximab to its biosimilar CT-P13 versus continued use of the originator in patients with stable control of immune-mediated inflammatory diseases (IMID) for a minimum of six months. The primary endpoint of the study was the non-inferiority of switching compared with not switching as assessed by disease worsening in the pooled cohort of six IMIDs (including AS, RA and PsA). The overall discontinuation rates were similar in the two groups and disease worsening rates fell within the pre-specified non-inferiority margin of 15% in the pooled analysis [17]. However, the design of the study has been criticized and difficulties in the interpretation of results have been aroused [18]. The safety and efficacy of non-medical switching have been investigated in several other RCTs and also in real-life studies. Many of these studies reported favorable outcomes with similar discontinuation rates between non-switch and switch groups [19-22]. However, higher risk of failure or treatment withdrawal among patients who switched have been observed in some studies [23,24]. Interestingly, some studies allowed switchback to the originator therapy after non-medical switch failure and demonstrated that patients often regain efficacy or experience resolution of adverse events after resuming the originator therapy [25,26]. The most commonly reported reason for biosimilar discontinuation in these studies was loss of response/inefficacy that was often based on subjective evaluation without objective evidence of deterioration of disease activity. Moreover, some studies included not only stable patients who have received the originator for at least one year but also patients who have only recently begun treatment [27]. It is well known that retention rates increase incrementally with each subsequent year of treatment in patients with rheumatic diseases, and patients who have received at least one year of biologic therapy are less likely to discontinue treatment than patients initiating therapy [28,29].

### **Nocebo Effect and Patient Education**

It has been suggested that failure following a non-medical switch may often result from the so-called “nocebo effect”. This effect was first described in the 1960s and is defined as a negative outcome (including failure of therapy) resulting from a patient’s negative expectation toward a new therapy as well as a change of therapy [30]. It is the opposite face of the “placebo effect”. Most research on this effect has been in the area of pain, but it has been reported in clinical drug trials and clinical practice in patients with many other diseases, including rheumatic diseases [31,32]. The act of mandatory non-

medical switching may have a negative impact on patients and it is noteworthy that response criteria to therapy in RA, AS and PsA rely on composite scores which include subjective evaluation. Treatment discontinuations in patients who undergo non-medical switch from an originator anti-TNF to its biosimilar has been reported more frequently following a mandatory switch [13,14]. Physician-patient shared decision has been favored by many rheumatology scientific societies and patient association [33-35]. Moreover, communication play a major role in patient’s treatment expectations having either a positive or negative impact on the outcome of therapy [36,37]. In any case forcing the switch on a patient is likely to increase the nocebo effect and has a negative effect on physician-patient relationship [38]. Another crucial concern is the manner in which information is presented to the patient. There are studies reporting acceptance rates of switch higher than 92% in case of shared decision together with an optimized communication strategy [39,40] and we have recently reported data from a prospective monocentric cohort of patients with RA, AS and PsA and stable disease who were asked to switch from anti-TNF originator to biosimilar with an acceptance rate of 98% and extremely high long-term retention rate on biosimilar therapy (84.8%) [41].

### **Conclusions**

In westernized countries, biologic therapies take high costs to healthcare systems. Availability of biosimilars and their wider use by rheumatologists is necessary to provide sustainable healthcare to patients with chronic rheumatic disease and cannot be further delayed. A large body of evidence supports non-medical switching from originators to biosimilars as a safe and effective practice in routine clinical care. In some countries the act of non-medical switching has been mandated in order to facilitate the use of biosimilar and obtain a fast reduction of costs. However, this strategy may have a negative impact on patients. On the other side a physician-patient shared decision strategy may minimize the nocebo-effect and reduce failure of switching. Moreover, a correct selection of patients to switch, namely patients with stable disease and treated with originators at least for one year, is crucial to optimize the efficacy of non-medical switching. Finally, reimbursement strategy by payers could probably encourage non-medical switching re-investing spared resources to improve rheumatic patients’ care.

### **Authors contribution statements**

Giuseppe Provenzano made substantial contribution in reviewing literature and writing the manuscript. Chiara Arcuri contributed in reviewing literature and revising the manuscript.

### **Competing interest**

Giuseppe Provenzano served as advisory board member and/or received lecture grants from AbbVie, Biogen, BMS, Grunenthal, Lilly, MSD, Roche, Sandoz, Sanofi, UCB. Chiara Arcuri served as advisory board member and/or received lecture grants from Celgene, Roche, UCB, Novartis, MSD, BMS.

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