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Second-line biologic therapy optimization in rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis

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ABSTRACT

Objective: The Italian board for the TAilored BIOlogic therapy (ITABIO) reviewed the most consistent literature to indicate the best strategy for the second-line biologic choice in patients with rheumatoid arthritis (RA), spondyloarthritis (SpA), and psoriatic arthritis (PsA).
Methods: Systematic review of the literature to identify English-language articles on efficacy of second-line biologic choice in RA, PsA, and ankylosing spondylitis (AS). Data were extracted from available randomized, controlled trials, national biologic registries, national healthcare databases, post-marketing surveys, and open-label observational studies.
Results: Some previously stated variables, including the patients' preference, the indication for anti-tumor necrosis factor (TNF) monotherapy in potential childbearing women, and the intravenous route with dose titration in obese subjects resulted valid for all the three rheumatic conditions. In RA, golimumab as second-line biologic has the highest level of evidence in anti-TNF failure. The switching strategy is preferable for responder patients who experience an adverse event, whereas serious or class-specific side effects should be managed by the choice of a differently targeted drug. Secondary inadequate response to etanercept (ETN) should be treated with a biologic agent other than anti-TNF. After two or more anti-TNF failures, the swapping to a different mode of action is recommended. Among non-anti-TNF targeted biologics, to date rituximab (RTX) and tocilizumab (TCZ) have the strongest evidence of efficacy in the treatment of anti-TNF failures. In PsA and AS patients failing the first anti-TNF, the switch strategy to a second is advisable, taking in account the evidence of adalimumab efficacy in patients with uveitis. The severity of psoriasis, of articular involvement, and the predominance of enthesitis and/or dactylitis may drive the choice toward ustekinumab or secukinumab in PsA, and the latter in AS.
Conclusion: Taking in account the paucity of controlled trials, second-line biologic therapy may be reasonably optimized in patients with RA, SpA, and PsA.

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Introduction

Recently, the ITABIO (Italian board for the TAilored BIOlogic therapy) task force focused on the first-line biologic choice driving variables in patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA), and ankylosing spondylitis (AS) to ensure the best results in terms of clinical outcome and safety [1]. However, data from clinical trials and national registries show that first-line biologics, either combined with methotrexate (MTX) or in monotherapy, should be discontinued in approximate 30–40% of the patients due to inadequate response or adverse events in the majority of the cases [2–4]. Overall, biologic survival is lower in RA compared with PsA and AS [5], though in all the three disorders the discontinuation rate seems time-dependent with a progressive increase related to the length of follow-up [6].

To date, nine biologics including interleukin-6 (IL-6) inhibitor tocilizumab (TCZ), anti-CD20 rituximab (RTX), anti-interleukin-1 (IL-1) anakinra (ANK), anti-CD28 abatacept (ABA), and anti-tumor necrosis factor alpha agents (anti-TNFs) adalimumab (ADA), etanercept (ETN), infliximab (IFX), golimumab (GOL), certolizumab pegol (CTP), and, limited to Europe, infliximab biosimilar (bio-IFX), are approved for RA treatment, anti-TNFs, anti-interleukin-12–23 (IL-12–23) ustekinumab (UTK), and anti-interleukin-17 (IL17) secukinumab (SCK) for PsA, while only anti-TNFs and SCK are licensed for AS.

Compared to the first-line biologic therapies, the second-line ones have been less investigated in terms of effectiveness, safety, and drug survival. Moreover, controlled trials (RCTs) and current recommendations do not provide sufficient indication concerning the best strategy between switching and swapping among biologics [1]. In absence of well-defined response predictors, several variables may drive the second biologic choice in clinical practice, including the data on the efficacy, safety, disease severity, infection risk, patient's age and gender, route of administration, and comorbidities.

Objective

The aim of present paper was to provide appropriate indications for the best choice of second-line biologic therapy in patients with RA, PsA, and AS through a systematic review of the literature.

Methods

As previously described [1], a multidisciplinary expert panel, the Italian board for the TAilored BIOlogic therapy (ITABIO), including specialists in rheumatology (M.B., F.C., E.F., R.F., S.G., and L.N.), infectious diseases (D.G. and F.B.), and, immunology (M.M.), was constituted to review the literature on the existing evidence on the efficacy, safety, and the different variables influencing the second-line biologic choice in patient with RA, AS, n-rx-AxSpA, and PsA. Each ITABIO member separately developed and shared by e-mail a single topic, and finally all members met to examine, discuss, assemble the single elaborates, and to draw up the final manuscript. No funding source was available. The following topics were analyzed: disease severity, second-line biologic efficacy and safety, second-line monotherapy biologic choice, comorbidities, infection, LTBI reactivation, cardiovascular and malignancy risk, interval, and route of administration, and patient's preference. Taking into account the emerging evidence on the different factors, appropriate statements and decisional trees useful to tailor the second-line biologic choice to the single patient were formulated.

Literature search

The literature review was made using PubMed database to identify English-language articles related to the previously mentioned topics. Data were extracted from available recommendations, systematic reviews, and meta-analyses, RCTs, national registries of biologics, national healthcare databases, and post-marketing surveys. When these source data were not available for specific topics, the evidence was derived from open-label studies on variable sample-size clinical series.

The following drugs were investigated: IFX, bio-IFX, ETN, ADA, GOL, CTP, RTX, TCZ, ANK, ABA, UTK, and SCK. The research was performed by crossing the single drug name with the following key terms: RA, SpA, PsA, efficacy, safety, monotherapy, switching, swapping, latent tuberculosis infection (LTBI), infections, tuberculosis (TB), comorbidities, cardiovascular risk, malignancy risk, and atherosclerosis.

The literature review was extended to December 31, 2016.

Results

General indications

As previously stated [1], some choice driving variables, including the patients' preference for self-administered subcutaneous route with the longest administration intervals, the indication for anti-TNF monotherapy in potential childbearing women, and its interruption at positivity of pregnancy test, are valid also for the second biologic choice after interruption of the first for inefficacy or adverse events occurrence.

Choice of the second or third biologic agent in RA

The first choice of biologic therapy for the treatment of synthetic DMARD (sDMARD) inadequate responders (IR) is usually an anti-TNF-α (anti-TNF) agent. However, clinical response is not universal and approximately 30–40% of patients discontinue anti-TNF because of primary failure, secondary loss of response, or intolerance [7–9]. Options for the management of anti-TNF failures include switching to an alternative anti-TNF (cycling) or to another class of targeted agent with a different mode of action (swapping) [10].

The cycling strategy is a well-established approach, and the efficacy of the second anti-TNF is clearly supported only by 4 trials. An open-label, pilot study (the OPPOSITE trial) demonstrated IFX is more effective than ETN in the treatment of 28 ETN failures [11]. The GO-AFTER represents the only one controlled study designed to evaluate the effectiveness and safety of GOL in patients with RA failing ADA, ETN, or IFX administered as first- or second-line therapy [12]. Treatment with GOL produced a significantly greater 24-week ACR20, 50, and 70 responses compared with placebo [12], with a good persistence of efficacy and no new safety signals through 5 years [13] . In the REALISTIC study, treatment with CZP was associated with a greater chance of achieving low disease activity at week 12 when compared to placebo regardless of prior anti-TNF exposure [14]. More recently, the EXXELERATE study, an head-to-head trial between CZP and ADA, showed a good efficacy of cycling to the other anti-TNF after primary insufficient response to the first [15]. Beside these four RCTs, several observational studies based on national registries or multicentric cohorts have demonstrated an improvement in disease activity and a favorable drug retention rate in patients receiving a second anti-TNF [16–22]. However, at least three limitations should be considered. First, in both RCTs [12] and retrospective studies [23–25], the proportion of responders is generally lower in switchers compared with biologic naïve patients and the likelihood of clinical response declines with the increasing number of previous treatments with anti-TNF. Thus, available data support the switching to a second anti-TNF, but the rationale for the use of the third or more seems to be poor