Start RA Treatment – Biologics or JAK-Inhibitors?

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Abstract (200 words)

Janus Kinase inhibitors (JAKis) have been approved for the treatment of Rheumatoid Arthritis (RA) for several years. They are the first oral advanced treatments with efficacy similar to, if not, greater than biologic agents. Recently, concern over their safety was raised by the results from Oral Surveillance trial suggesting that tofacitinib, one of the JAKis was associated with higher cardiovascular adverse events and malignancies than TNF inhibitors. Since then, regulatory authorities have added warnings the labels of JAKis. Should Rheumatologists use JAKis as first line advance treatment has become a controversial topic. Some rheumatologists have argued that biologics should be first line advance treatment since there are extensive effectiveness and safety data. In addition, with the advent of biosimilars, they are the most cost-effective treatment. On the other hand, JAKis are very efficacious and are generally safe apart from older and high-risk patients. When TNF inhibitors are contraindicated and in certain RA patients especially when an oral drug is

preferable, JAKis have significant advantage providing patients are involved in the decision-making process.

Highlights (3 to 5 bullet points)

- Biologics have extensive effectiveness and safety data in RA.
- Biologics especially biosimilars, are highly cost-effective.
- JAKis are very efficacious and have shown superiority to TNF inhibitors in randomized control trials
- JAKi are generally safe apart from older and high-risk patients.
- When TNF inhibitors are contraindicated and/or an oral drug is preferred JAKis can be used as first line treatment providing patients are informed of the risk and are involved in the decision-making process.

Introduction

Rheumatologists have many options when choosing advanced Disease Modifying Anti-Rheumatic Drugs (DMARDs) for patients with Rheumatoid Arthritis (RA). Since the start of the millennium, fourteen new biologic DMARDs (bDMARDs) and targeted synthetic DMARDs (tsDMARDs) have been approved in Europe for the treatment of RA, with five tumor necrosis factor alpha (TNFα) inhibitors, two, interleukin 6 (IL-6) inhibitors, one B cell depleting monoclonal antibody, a T-cell costimulatory, inhibitor and four Janus kinase (JAK) inhibitors. In the European Alliance of Rheumatology Associations (EULAR) 2020 recommendations for the management of RA, either bDMARDs or tsDMARDs are treatment options for RA patients with suboptimal treatment response to methotrexate or conventional synthetics DMARDs [1]. The recommendations did not specify preference except in the patients who do not tolerate csDMARDs then for monotherapy inhibitors of IL-6 or JAK are preferred. rheumatoid arthritis recommended. Since the launch of JAK inhibitors (JAKi), data from many European registries have shown that the use of JAKi in RA varies drastically. In some countries, JAKis were used as a first line advance therapy, whilst others used them in biologic experienced patients. Some countries used JAKis in monotherapy whilst others used them in combination with other csDMARDs. However, results of the Oral Surveillance trial suggested that tofacitinib, one of the JAKis was associated with higher cardiovascular adverse events and malignancies than TNF inhibitors in patients with RA [2]. Medicine licensing authorities in the USA and European have altered the labellings of JAKis. The Food and Drug Administration in the USA recommended "**Reserve these medicines for patients who have had an inadequate response or intolerance to one or more TNF blockers**". While the European Medicines Agency advised JAKi should **only be used in patients over 65 years of age**, in patients who are current or

past **smokers**, patients with other **cardiovascular risk factors**, and patients with other **malignancy risk factors if no suitable treatment alternatives** are available. In the 2022 update of the EULAR recommendations for the treatment of RA, it added “the following risk factors for cardiovascular events and malignancies must be considered when intending to prescribe a JAK-inhibitor: age over 65years, history of current or past smoking, other cardiovascular risk factors, other risk factors for malignancy, risk factors for thromboembolic disease” [3]. So what are the advantages and disadvantages of different approaches to use JAKi?

The Case for Biologics

The previous century has seen notable advancements in rheumatology, which currently have a positive impact on the quality of life for patients suffering from rheumatologic and musculoskeletal illnesses. Since the introduction of glucocorticoid therapy and the widespread use of methotrexate and other disease-modifying medications drugs (DMARDs), as well as the development of biologic DMARDs, therapeutic approaches have advanced significantly. Indeed, the emergence of Tumor necrosis alpha-inhibitors (TNFi) along with other bDMARDs targeting different molecule with pivotal role in inflammation (e.g. IL-1, IL-6, depleting B cells, or interfering with co-stimulatory molecules) demonstrated how targeting inflammatory processes and pathways can drastically modify the clinical course of rheumatologic diseases, and Rheumatoid arthritis (RA) in particular [4]. Another relevant breakthrough in the treatment of RA was brought by the evidence of JAK/STAT signaling as a central downstream mediator of several pro-inflammatory cytokines involved in the pathogenesis of RA [5]. This lead to the introduction of JAK inhibitors (JAKis) as a viable alternative to other bDMARDs in the treatment of RA in the last EULAR recommendations [1,3]. However, even if in 2019 JAKis were considered at a similar level as bDMARDs in terms of effectiveness and safety [1], this changed in the latest recommendations. Indeed findings from the ORAL-Surveillance study demonstrated how, in a court of people already prone to a higher cardiovascular risk, the incidence of MACE, along with the risk to develop a malignancy, was higher in those patients who assumed Tofacitinib regularly, compared to those taking TNFi [2]. This finding was further confirmed by a systematic review of literature that demonstrated how there was an actual tendency of more MACE and malignancies in patients receiving Tofacitinib in comparison with those assuming other bDMARDs [6]. Apart

from this side effect of treatment with Tofacitinib, however, there weren't other studies proving the same higher risk of MACE for other JAKis, except for one multi-database study using disease registries and claims database that showed only a non-statistically significant increase of MACE in patients treated with baricitinib [7]. Nonetheless this discovery prompted EULAR to revise the indication on whether to start any JAKis or not, suggesting a proper stratification of patients according to several clinical characteristics (e.g age > 65, smoke habit). Along with that, EMA as well confirmed these measures to minimize risk of cardiovascular complications from all JAKis, by limiting their assumption to those with aforementioned risk factors. These considerations drastically debunked JAKis role in the management of RA, prompting us to reevaluate other bDMARD as valuable cornerstone in the treatment of this illness. On this behalf it is useful to cite the NORD-STAR trial, a clinical trial which collected data form 812 patients and firstly compared the active conventional therapy (csDMARD + glucocorticoid) with a bDMARD plus MTX. The importance of this study derives from the fact that it first showed how, regarding rates of remission and also radiographic progression, treatment with bDMARDs, namely abatacept and certolizumab, had an higher efficacy compared with older treatments [8]. Along with this trial, several other studies collected 'real world' data proving the efficacy of each bDMARD. For instance, data from CORRONA registry proved how the efficacy of Adalimumab was consistent even after 10 years of treatment [9]. Data from the LORHEN registry ,as well, demonstrated the efficacy of Golimumab and particularly how the retention rate was similar whether it was used as a first or second line of therapy [10]. Another study, the ADEQUATE trial, was conducted to evaluate the efficacy of Etanercept showing how almost a quarter of patients taking Etanercept reached low disease activity (LDA) after only 12 weeks of treatment, but also that the it tended to increase even after 52 weeks of treatment [11]. Aside from studies

concerning TNFi, other mechanisms of action were taken into account. For example a study demonstrated how also Tocilizumab, a IL-6 blocker, had a good retention rate, regardless the use of other bDMARDs before, with no particular warnings about safety issues [12]. That being said, another advantage of common bDMARDS, unlike tsDMARDs, is given by the advent of biosimiliras. Indeed it has been demonstrated how biosimilar as well have an efficacy and a safety profile overlapping the one detained by bio-originator [13], thus improving equity of access to this kind of treatment and enabling a broader availability of therapies for an earlier control of diseases [14]. Apart from the intrinsic efficacy of bDMARDs, it is also important to mention how, in some clinical settings, bDMARDs are better indicated and in general give a better clinical outcome. For instance, in case of a pregnancy, due to the lack of safety trials, as for now, tsDMARDs should be avoided, whilst TNFi can be continued up to the third trimester, with the exeption of Certolizumab, that can be maintained until the end of pregnancy and beyond [15,16]. Another constitutional characteristic of patient which can lead to the use of bDMARDs instead of tsDMARDs is seniority. On this purpose several studies showed how Abatacept, as well as TNFi, proved a good efficacy and tolerance among elderly patients [17,18]. One more clinical issue that needs to be discussed when dealing with proper treatment of RA is the presence of particular comorbidities. One of the main comorbidity addressed in RA is represented by pulmonary involvement, and interstitial lung disease (ILD) in particular. On this behalf, a multicenter study has demonstrated how abatacept is an effective and safe option in treatment of RA-ILD, with also a good long term retention rate, at around 75% [19]. This data was also confirmed by a recent systematic review, proving how abatacept my hold a decisive role in the management of RA-ILD [20]. Another important comorbidity in RA patients is the rising incidence of obesity, that have a great impact in clinical response. On

this regard, Novella-Navarro et al proved that, due to underlying pathophysiological mechanisms associated with the development of proinflammatory adipokines, obesity affects the degree of LDA/remission in patients treated with TNFi but not in patients treated with tocilizumab, suggesting how the latter should be better suited for individuals who are overweight or obese [21].

In conclusion, in the last 20 years, the number of available drugs used in RA has been increasing exponentially, with bDMARDs still the most used drugs after MTX failure, due to the vastity of data collected, showing how efficient and safe, but also thanks to the cost-effectiveness brought by the emergence of biosimilars. That being said it is still appropriate to acknowledge JAKis role as an active actor in the scenario of RA management, but with a particular regard on safety concerns.

The Case for JAKi

Janus kinase (JAK) inhibitors (JAKi) have pleiotropic effects as they mediate the signalling of multiple cytokines. In other words: JAKi act as combined cytokine inhibitors. This might be one of their advantages. JAKs have four isoforms, JAK1, JAK2, JAK3 and TYK2. JAK selectivity may influence the efficacy and safety profile of the various JAKi registered for the treatment of RA, tofacitinib, baricitinib, upadacitinib and filgotinib [22].

With respect to efficacy, all four JAKi are highly effective in the treatment of RA. In the phase 3 program, baricitinib [23], upadacitinib [24] and filgotinib [25] had superior efficacy compared to the TNF-α inhibitor adalimumab. In addition, tofacitinib showed similar efficacy to adalimumab [26]. So if JAKi is at least or more effective than TNF-α inhibitors, why not to start with JAKi?

The multiple effects of JAKi also suggest that JAKi might have beneficial effects on comorbidities and tissue injury primarily mediated by systemic inflammation including JAK-dependent cytokines [27]. Indeed, our 18FDG-PET/CT study showed, that tofacitinib was able to simultaneously diminish both synovial and vascular inflammation in RA [28].

Regarding safety, the recent integrated safety analyses confirmed acceptable safety profiles of these JAKi [29]. Except for herpes zoster, in the development programme tofacitinib [30], baricitinib [31], upadacitinib [32] and filgotinib [33] did not increase the risk of severe infections, arterial (ATE) and venous thromboembolism (VTE) or malignancies. Another meta-analysis also confirmed that JAKi did not increase the risk of ATE and MACE [34]. Certainly, the ORAL Surveillance study that included patients with high cardiovascular risk treated with tofacitinib or TNF-α inhibitors for about 5 years suggested that tofacitinib might not be non-inferior to anti-TNF agents with respect to ATE/MACE and malignancies. JAKi treatment also resulted in more severe infections and VTE compared to TNF-α inhibitors [2]. Yet, the post hoc analyses of this trial indicated that most events occurred in RA patients who were older than 65 years, had a history of atherosclerotic cardiovascular disease (ASCVD), who smoked and who lived in North America. In addition, these patients had been undertreated for 10 years and were also undertreated with statins [2,35]. Therefore, under normal conditions, in younger patients with a negative history for ASCVD tofacitinib and other JAKi might be as safe as anti-TNF biologics [2,35]. Based on this both the European Medicines Agency (EMA) [36] and the latest EULAR recommendations [3] somewhat restrict the use of JAKi.

There are other issues with respect to preferential use of JAKi. RA might have several different phenotypes. TNF-α and IL-17 do not signal through JAKs. Therefore, in some RA

phenotypes with higher IL-6 dependence JAKi might be preferable over anti-TNF agents [37]. JAKi could be used as first line when TNF-α inhibitors are contraindicated (e.g. RA-SLE overlaps, demyelinating disease) or rejected by the patient (e.g. needle phobia) [3]. A great body of evidence, as well as the EULAR recommendations prefer JAKi and tocilizumab over other targeted therapies when monotherapy is indicated [3]. Indeed, numerous patient prefer monotherapy over combination with methotrexate [3,38]. Moreover, JAKi are oral drugs and patients also tend to prefer tablets over subcutaneous injections or intravenous infusions [19, 20]. Patients prefer the ease and speed of administration, as well as portability when taking oral compounds [39].

In summary, JAKi are very efficacious, could be even more effective than TNF-α inhibitors. JAKi are generally safe, with some restrictions in older patients, smokers and those with high risk for ASCVD. Moreover, JAKi might be preferred when monotherapy is needed, when anti-TNFs are contraindicated, in certain RA phenotypes and when an oral drug is preferable. Certainly, shared decision making together with the patient is crucial. So: why not start with a JAKi?

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