Janus kinase inhibitors: between prescription authorization and reimbursability

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Following the restrictions on the reimbursability of Janus kinase inhibitors (JAKi) introduced by the Italian Medicines Agency (AIFA), the Italian Society of Rheumatology has drafted this document to shed light on the clinical conditions and reimbursability criteria set out in the prescription forms.

JAKi have become part of the pharmaceutical armamentarium for rheumatoid arthritis (RA) since 2012, with the Food and Drug Administration's (FDA) approval of tofacitinib, the first compound of the class. The European Medical Agency (EMA) approved the first two JAKi (baricitinib and tofacitinib) in early 2017. Four different molecules are currently available in Europe: baricitinib, tofacitinib, upadacitinib, and filgotinib, for the treatment of RA; in addition, tofacitinib and upadacitinib have also been approved and are reimbursable for the treatment of psoriatic arthritis (PsA) and ankylosing spondylitis (AS). Notwithstanding the efficacy and safety data from registration studies, the distinguishing features of this class of drugs include oral administration, efficacy in monotherapy, fast onset of the clinical response, and a short half-life, the latter allowing good manageability if the drug needs to be discontinued for any reason (*e.g.*, adverse reactions, planned surgical procedures, or unplanned pregnancy).

In November 2022, EMA concluded its review of the safety data of JAKi by formulating measures to minimize the risk of adverse events potentially associated with the class as a whole. On January 23, 2023, guidance was published by the Pharmacovigilance Risk Assessment Committee to reduce the risk of serious side effects, including major cardiovascular events (MACE), thromboembolic events, neoplasms, and varicella zoster virus infection, associated with the use of JAKi for the treatment of chronic inflammatory diseases.

The EMA suggests that JAKi should only be used if no suitable therapeutic alternatives are available in subjects:

1) aged 65 years or older;
2) at increased risk of MACE (myocardial infarction and stroke);
3) who smoke or have done so for a long time in the past;
4) at increased risk of neoplastic disease. Furthermore, the EMA suggests caution in patients with thromboembolic risk factors (1).

The EMA warning is mainly based on data from the ORAL Surveillance study, an open-label, phase 3b/4 clinical trial that aimed to compare tofacitinib (5 mg and 10 mg twice daily) and tumor necrosis factor inhibitors (TNFi) (adalimumab or etanercept) in patients aged >50 years with active RA and at least one of the following additional risk factors: cigarette smoking, hypertension, high-density lipoprotein (HDL)

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<40 mg/dL, diabetes mellitus, family history of cardiovascular disease, extra-articular manifestations, and history of coronary artery disease (2). The ORAL Surveillance study was required by the FDA and enrolled 4632 patients, followed for a median of 4 years and failed to demonstrate the non-inferiority of tofacitinib compared to TNFi in terms of MACE and malignancies, excluding non-melanoma skin cancer, occurrence (2). Post-hoc analyses of the above-mentioned study showed that the differences in the incidence of MACE and malignancies affected specific risk groups, mainly current and former smokers, subjects aged >65 years, and subjects with previous cardiovascular events. In addition to the data from randomized controlled clinical trials of the four JAKi and the ORAL Surveillance study, the EMA also took into account the BI023 study, a multicenter observational study comparing baricitinib and TNFi. This study showed an incidence rate ratio of 1.54 [95% confidence interval (CI) 0.93-2.54] and 1.51 (95% CI 1.10-2.08) for MACE and thromboembolic events, respectively (3). The ORAL Surveillance and BI023 studies were conducted in patients with RA, a disease that, untreated or inadequately treated, is associated with an intrinsically increased risk of cardiovascular (4) and thromboembolic (5, 6) complications, as well as an increased risk of lymphoma and other malignancies (7). To date, there have been no similar studies conducted on patients with other inflammatory diseases.

AIFA implemented the EMA warning by issuing a reimbursability form for JAKi. At the beginning of March 2023, AIFA released the first prescription reimbursability form for JAKi in the treatment of RA and updated the prescription forms for PsA and AS. On April 20, 2023, the last updated prescription forms were released (8-10).

PRESCRIPTIVE APPROPRIATENESS

AIFA separately lists the authorized indications of the different JAKi and those reimbursed by the National Health System. In the form for RA, for example, AIFA reiterates that baricitinib, filgotinib, tofacitinib, and upadacitinib are indicated for the treatment of moderately to severely active RA adult patients who have had an inadequate response or are intolerant to one or more disease-modifying antirheumatic drugs (DMARDs). The active compound may be used as monotherapy or in combination with methotrexate (MTX) (except for tofacitinib, which is indicated as monotherapy only in the case of intolerance or inappropriateness of MTX). Similarly, the forms for PsA and SA confirm the indications given in the summary of product characteristics for the four compounds. Hence, prescriptive reimbursement forms do not substitute prescription indications.

In patients with RA, PsA, and AS, AIFA limits the reimbursability of JAKi to the following conditions:

1) in the absence of EMA-indicated risk factors (age >65 years, increased risk of severe cardiovascular problems, long-term smoker or ex-smoker, and increased risk of cancer): following inadequate response or intolerance to previous therapy with one or more DMARDs and failure of treatment with one or more TNFi reimbursed for the indication;
2) in the presence of EMA-indicated risk factors: only upon failure of all treatment options reimbursed for the indication.

The last updated form published in April specifies that the failure of reimbursed treatment options for each indication refers to “all those considered clinically appropriate/possible by the prescribing physician” (8-10). However, the prescriptive autonomy of the physician should not disregard the discussion between the treating rheumatologist and the patient, given the importance of sharing the therapeutic decision (11-13). In addition, AIFA specifies that failure means ineffectiveness or loss of efficacy, the occurrence of adverse events, but also the presence of factors that contraindicate treatment with TNF inhibitors, anti-interleukins, and other biotechnological (rituximab and abatacept) and synthetic targeted drugs (apremilast).

Every patient who is a candidate for treat-

ment with a JAKi according to the labeled indications of the different drugs (to be distinguished from the AIFA reimbursability form of these drugs) should undergo an appropriate assessment of the individual risk of potential side effects of special interest, and the treatment decision should be the result of sharing between the rheumatologist and the patient.

Even for patients already treated with JAKi, the clinician should weigh the risks and benefits of the therapy. In fact, AIFA suggests that in subjects with risk factors, "where the prescribing physician considers it clinically appropriate/possible to prescribe alternative treatments, JAKi should be replaced with another molecule" (8-10). Similarly, in patients without risk factors, the continuation of therapy should be evaluated on a risk/benefit basis and discussed with the patient. Therefore, in patients in whom the therapeutic target has been achieved, the AIFA form should not be interpreted as a prohibition to continue therapy, even in the presence of risk factors; the balance between the possibility of adverse events and the possible deleterious effect on disease activity of therapy discontinuation must be assessed and shared with each patient. Treatment must favor the best possible control of disease activity (remission or low disease activity), avoiding the chronic use of glucocorticoids and non-steroidal anti-inflammatory drugs, which are associated with increased cardiovascular risk (14).

HOW TO ASSESS CARDIOVASCULAR, THROMBOEMBOLIC, AND NEOPLASTIC RISK

A relevant aspect concerns the risk assessment of adverse events potentially associated with the treatment of inflammatory arthritis with JAKi or any other drug. If age >65 years is unquestionable and non-modifiable, the interpretation of the other risk factors might be ambiguous and, in any case, modifiable factors should be controlled by appropriate lifestyle intervention or drugs. AIFA, acknowledging the EMA's warning, limits the reimbursability to subjects "at increased risk of serious cardiovascular problems, long-term smokers or ex-smokers and at increased risk of cancer" (8-10).

Cardiovascular risk

According to the European Alliance of Associations for Rheumatology (EULAR) recommendations for cardiovascular risk management, the determination of each individual patient's risk profile should be based on algorithms using values such as gender, age, smoking status, blood pressure, lipid profile, and the presence of diabetes mellitus (12). EULAR recommends using national guidelines or, if unavailable, the SCORE algorithm (15). In Italy, the Department of Cardiovascular, Endocrine-Metabolic Diseases and Aging of the *Istituto Superiore di Sanità* has been coordinating the activities of the *Progetto Cuore* since 1998, including the derivation and validation of risk charts and individual score assessment software for the prediction of cardiovascular risk in subjects aged between 35 (individual risk) or 40 (risk cards) and 69 years (16). The risk calculation includes the following parameters: gender, age, smoking habit, systolic blood pressure value, total and HDL cholesterol value, diabetes mellitus, and arterial hypertension (17). It should be pointed out that the identification of people at risk is not based on the contribution of each risk factor considered individually but takes into account their global assessment. Moreover, the key point is that in patients with RA and other inflammatory arthritis, in addition to the traditional cardiovascular risk factors, the intrinsic risk of low-grade chronic inflammatory status contributes to the increased risk of major cardiovascular events; EULAR, indeed, advises applying a multiplication factor of 1.5 to the score obtained by algorithms that do not already include arthritis as a cardiovascular risk factor (15). According to the recommendations for cardiovascular risk management in patients with RA released from the CORDIS study group of the Italian Society of Rheumatology, the individual risk score should be cal-

culated, regardless of the treatment choice, in patients with high disease activity and negative prognostic factors, in those on glucocorticoids or non-steroidal anti-inflammatory drugs that have failed multiple DMARDs, and in the presence of traditional cardiovascular risk factors (18). In patients with PsA and AS, the cardiovascular risk assessment should be based on cardiovascular risk algorithms similarly to those for RA. According to *Progetto Cuore*, subjects with an estimated cardiovascular risk >20% are considered to have a high probability of developing a MACE. The updated version of the European Society of Cardiology algorithm (SCORE2) can be used as an alternative in patients older than 70 years of age but also younger; subjects with a score >15% if >70 years old, or >10% if between 50 and 69 years old, or >7.5% if <50 years old, are to be considered at high cardiovascular risk (19, 20).

Also worth mentioning is the opportunity to target the individual modifiable cardiovascular risk factors with therapeutic strategies aimed at improving the cardiovascular risk profile of each patient, sharing with the patient, the general practitioner, and/or other specialists the most appropriate approach. In particular, given the possible effect of JAKi on lipid metabolism, as reported in the summaries of product characteristics, careful monitoring of the lipid profile is recommended, and statins or other lipid-lowering agents are suggested for those patients showing a worsening atherogenic index during the treatment with JAKi.

Neoplastic risk

The most frequent malignancies reported in the ORAL surveillance study were lymphoma and lung cancer. For these malignancies, there have been no specific recommendations for screening to date. In the absence of indications for the assessment of neoplastic risk in patients with inflammatory arthritis, patients with previous malignancy, patients with pre-cancerous lesions, or with a positive family history of hereditary-familial neoplasms (breast, ovary, colon, familial melanoma, familial neuroendocrine tumors) should be at increased risk. Nevertheless, it should be kept in mind that the neoplastic risk is higher in smokers. Thus, in the absence of specific recommendations, patients with RA, PsA, and SA should perform cancer screening as recommended for the general population.

Thromboembolic risk

The venous thromboembolic risk results from the interaction among genetic, environmental, and metabolic factors, which weigh differently in the development of thrombotic events (21). When estimating the thromboembolic risk according to the Padua Score, a score used to identify patients at thromboembolic risk to start prophylaxis with anticoagulants at the time of hospitalization, the following triggering factors are to be taken into account in addition to demographic factors:

1) current malignancy (patients with local or distant metastases and/or in whom chemotherapy or radiotherapy has been given in the previous 6 months);
2) previous deep vein thrombosis;
3) bed rest (for at least 3 days);
4) genetically determined or acquired thrombophilia (antithrombin III deficiency, protein C or S factor V Leiden and prothrombin G20210A mutation in homozygosis, anti-phospholipid antibody syndrome);
5) recent trauma and/or surgery (≤1 month);
6) age >70 years;
7) heart and/or respiratory failure;
8) myocardial infarction or ischemic stroke;
9) acute infections or rheumatological diseases;
10) obesity (body mass index >30);
11) hormone therapy.

This predictive algorithm gives different weights to the various factors, with 3 points for neoplasms, previous thromboembolic events, bed rest, and thrombophilia, 2 points attributed to trauma, and 1 point for all other risk factors. When 6 points are reached, the subject is considered at high risk for thromboembolic events and should undergo prophylaxis (22).

MANAGEMENT OF PATIENTS ALREADY TREATED WITH JANUS KINASE INHIBITORS

AIFA outlines the indication for starting JAKi in patients who are refractory to other treatments, pointing out that the therapeutic decision must be based on the evaluation of all clinically appropriate/possible treatment options. Assessment of cardiovascular, thromboembolic, and neoplastic risk is mandatory in all patients with chronic arthritis. On the other hand, the management of those patients who are already treated with JAKi and who have turned 65 years old during treatment could be uncertain. These are often patients who have started JAKi after failing previous treatment lines with multiple drugs with different mechanisms of action and who should be carefully evaluated. If the treatment led to achieving the therapeutic target (remission or low disease activity), considering the overall reduction in cardiovascular, thromboembolic, and neoplastic risk due to the decline in the contribution of the active disease and the sparing of glucocorticoids and non-steroidal anti-inflammatory drugs, JAKi should not necessarily be stopped; in these patients, after careful risk assessment, therapy with JAKi may be continued. So, for those patients who achieved the therapeutic target, the rheumatologist should decide, in agreement with the patient, whether to continue therapy after having informed him or her of the possible risks and benefits arising from the opportunity to continue effective therapy. If the patient still has active disease, following the treat-to-target strategy, the discontinuation of the JAKi should be considered in favor of another drug with a different mechanism of action, if available and appropriate, or even another JAKi.

CONCLUSIONS

In conclusion, the last update of the AIFA reimbursability form restores to the rheumatologist a central role in the management of patients with RA, PsA, and spondyloarthritis, a role that requires weighing and sharing the risks and benefits of each therapeutic decision. The role of the clinician is to treat the inflammatory disease as best as possible, considering possible adverse events of the drugs and comorbidities, but even before that, aiming to reach the therapeutic target.

Contributions
All the authors made a substantive intellectual contribution, read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Conflict of interest
The authors declare no potential conflict of interest.

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