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REVIEW

JAK-Inhibitors – A Story of Success and Adverse Events

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Abstract: Rheumatoid arthritis (RA) is a systemic, chronic, immune-mediated inflammatory condition. Treatments options encompass conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), biologic disease-modifying antirheumatic drugs (bDMARDs) like tumor necrosis factor (TNF) inhibitors (TNFis) and targeted synthetic disease-modifying antirheumatic drugs (tsDMARDs) including Janus Kinase inhibitors (JAKinibs). Orally administered JAKinibs have demonstrated comparable or, in specific cases, superior efficacy compared to bDMARDs in inflammatory conditions. However, the escalating clinical utilization has been accompanied by the emergence of serious adverse effects, including major adverse cardiac events (MACE), malignancies and venous thrombotic episodes (VTE), leading to regulatory restrictions imposed by health authorities in both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA).

Keywords: rheumatoid arthritis, treatment, safety restrictions, major adverse cardiac events, malignancies, venous thrombotic episodes

Introduction

Rheumatoid arthritis (RA) stands as a persistent, systemic autoimmune ailment.[1]

Treatment options encompass conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), biologic disease-modifying antirheumatic drugs (bDMARDs), including tumor necrosis factor (TNF) inhibitors (TNFis) and targeted synthetic disease-modifying antirheumatic drugs (tsDMARDs), within which Janus Kinase inhibitors (JAKinibs) are categorized.[2,3]

Various JAKinibs (such as Tofacitinib, Baricitinib, Upadacitinib, Filgotinib, among others) have showcased notable effectiveness across different indications, with outcomes at least comparable to the established "classical" TNFis.[4,5] The clinical utility of these agents extends beyond traditional inflammatory rheumatic conditions, like rheumatoid arthritis (RA), psoriatic arthritis or ankylosing spondylitis. Some individual agents are also used for different conditions, including ulcerative colitis, atopic dermatitis, alopecia areata, juvenile idiopathic arthritis and others.[5]

Despite the rising popularity of JAKinibs, significant discussions have emerged regarding their safety profile. Early safety signals were evident in preclinical studies and initial clinical trials. Subsequently, as clinical usage increased, serious side effects were noted.

Currently, the prescription of these agents is governed by well-defined restrictions imposed by regulatory bodies, such as the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA).

This review will delve into the circumstances leading to these regulatory measures.

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Janus Kinase Inhibitors – Molecular Activities

In 1992 the first tyrosine kinase from the JAK family, Tyrosine Kinase 2 (TYK-2) was characterized. As a result of intensive further research, basic properties of tyrosine kinases in general and Janus kinases Janus Kinase 1, Janus Kinase 2, Janus Kinase 3 (JAK1, JAK2, JAK3, TYK2) in particular have been defined.[6–8]

Tyrosine kinases are evolutionarily highly conserved. If you affect a tyrosine kinase at its enzymatically active domain, you always affect the kinome in some way.[9]

To exert biological activity, JAKs often occur receptor-associated in heteromeric pairs. For example, if one removes JAK1 at the interferon-gamma receptor, then the presence of JAK2 does not help; the receptor is inactive.[10]

Regardless of whether a cytokine is bound to the receptor or not, there is a permanent back and forth between an active and inactive state of the JAK pair. Together with the basal level of cytokines found in all organs, this leads to having virtually permanent homeostatic JAK-STAT signaling, which is needed to maintain barrier function, a basal immune system. This is extremely important for homeostasis, if that is reduced, problems may arise.[11]

The type I JAK inhibitors, which include not only Tofacitinib but all JAK inhibitors currently on the market, are, at least with prolonged use, PAN-JAK inhibitors. They are ATP-competitors that target the JH1 domain of the enzyme, tyrosine kinase. According to the conservation and size of the kinome, so-called "side-hits" on other tyrosine kinases or another kinase are to be expected with some frequency in the process. Allosteric inhibitors, which target the pseudokinase, have a higher selectivity than competitive inhibitors. A first representative of this class has recently been approved for the treatment of moderate to severe plaque psoriasis.[5,12] Regarding specificity in general, it should be remembered that there is an enormous family of class I and class II cytokine receptors in tissues. In addition, if one JAK is inhibited for too long, another JAK may take over its activity.[13,14] In permanent inflammation, for example, somatic mutations occur just as they do in the "cancer genome". There, too, is an accumulation of mutations that allow JAK activity to be even higher than in the normal cell. Whenever JAKs are overexpressed, they have intrinsic activity without cytokine. And what also needs to be noted when you inhibit JAKs is that you are not only inhibiting the JAK-STAT pathway, but you are also affecting many other.

Janus Kinase Inhibitors – Safety Signals and Restrictions

Janus Kinase Inhibitors and FDA

In November 2011, Ruxolitinib was approved by the FDA in the indication "therapy of myeloproliferative neoplasms". This war the first approval ever for a JAKinib.[15]

One year later, in November 2012, Tofacitinib became the first JAKinib to be approved in the US for the treatment of rheumatoid arthritis. By now, four more JAKinibs have become available for the treatment of various rheumatic diseases: Baricitinib, Upadacitinib, Filgotinib and Peficitinib.[15]

There is no debate about the efficacy of the JAKinibs. They are, at least non-inferior, to the bDMARDs in any indication.

However, there have been and still are concerns about safety and the occurrence of serious adverse events.

The analysis of the first Phase 2 and Phase 3 trials had already revealed safety signals pointing to the possible occurrence of MACE, malignancy and VTE, but also an increased incidence of herpes zoster (HZ) and elevated blood lipids.[16,17]

In addition, studies of Tofacitinib for the prevention of renal transplant rejection showed an increased incidence of post-transplant lymphoproliferative disorders.[16,18]

Because of these safety signals, when the FDA approved Tofacitinib for the treatment of RA in 2012, it required the manufacturer (Pfizer) to conduct a Phase 4 safety trial with respect to the incidence of cancer, cardiovascular events and serious infections compared to treatment with TNFis, Tofacitinib was initially administered at doses of 5 mg bd and 10 mg bd in this study, called the ORAL Surveillance Study.

Early in 2019, the Data and Safety Monitoring Board (DSMB) of this trial found that more pulmonary embolisms had occurred in the Tofacitinib 10 mg group than in the TNFi groups, and the number of deaths in this group was higher than in both the Tofacitinib 5 mg group and the TNFi groups.

As a consequence, the protocol was changed and the dose in the 10 mg arm was reduced to 5 mg bd.[19]

Immediately afterwards, the FDA then announced that it was conducting an investigation into the risk of pulmonary embolism and death with Tofacitinib.

This investigation resulted in a boxed warning regarding the risk of pulmonary embolism or death with Tofacitinib at a dose of 10 mg bd for use in rheumatoid arthritis or ulcerative colitis. After Pfizer 2021 announced the final results of the ORAL Surveillance Study, which showed that Tofacitinib failed to meet the primary endpoint of non-inferiority with respect to the risk of cardiovascular disease and malignancy, the FDA amended the warning label to the risk of cardiovascular disease and malignancy with Tofacitinib in inflammatory arthritis or ulcerative colitis. This warning was also applied to the JAKinibs Baricitinib and Upadacitinib in September 2021 – with the additional comment that these substances had not been studied and analyzed to the same extent as Tofacitinib.[20]

The FDA recommended that the use of all JAKinibs should preferably be limited to patients where TNFis failed or cannot tolerate TNFis.[20]

This black box warning has not been changed or withdrawn since then; it is still valid!

Janus Kinase Inhibitors and EMA

In late October 2011, Pfizer approached the EMA with a Marketing Authorization Application (MAA) for Tofacitinib, aiming for its approval as a second-line agent in treating moderate to severe RA in adults.

By April 25th, 2013, the Committee for Medicinal Products for Human Use (CHMP) had formulated a negative stance on the application.

After Pfizer requested another look, the CHMP upheld its initial stance in July 2013.

The CHMPs refusal rested primarily on three pillars:

1st: Significant concerns arose due to the high number of severe and opportunistic infections related to Tofacitinib in clinical trials, pointing towards compromised cell-mediated immunity.

2nd: There were lingering apprehensions surrounding its overall safety profile, especially given the observed infections, malignancies, lymphomas, gastrointestinal complications, liver enzyme irregularities, and elevated blood lipid levels.

3rd: The unresolved safety issues were not balanced out by the treatment's potential benefits.

Fast forward to March 3rd, 2016, Pfizer presented a renewed application for Tofacitinib's marketing authorization. On January 26th, 2017, the CHMP adopted a positive opinion for Tofacitinib for the treatment of rheumatoid arthritis. Pfizer Limited was recognized as the official medicinal applicant. The positive outcomes associated with Tofacitinib encompassed symptomatic relief, improved physical functionalities, and potential deceleration in joint damage progression in rheumatoid arthritis patients. Common adverse effects included headaches, respiratory infections, diarrhea, and hypertension.

Nevertheless, the safety issues previously pinpointed were validated, but further extensive data offered a more holistic view, suggesting potential management of these side effects.[21]

By January 23rd, 2023 upon reviewing the ORAL Surveillance study, the CHMP acknowledged the Pharmacovigilance Risk Assessment Committee's (PRAC) recommendations to curtail severe adverse events linked to JAKinibs in managing chronic inflammatory conditions. These events encompassed MACE, VTE, cancers, and intense infections. This stance was grounded in the cumulative data, which incorporated Tofacitinib's definitive clinical trial results and Baricitinib's preliminary observational study insights.

The EMA advised a selective prescription of Janus Kinase inhibitors. Their use in patients above 65 years, those prone to cardiovascular complications, long-term smokers or past smokers, and those with elevated cancer risks was deemed appropriate solely for patients where other treatments were not viable options.[22]

It's crucial to note that these safety determinations are relevant to all authorized JAKinibs and their respective applications in chronic inflammatory disorders, such as rheumatoid arthritis, psoriatic arthritis, juvenile idiopathic arthritis, and more.[22]

Janus Kinase Inhibitors and EULAR

The European League Against Rheumatism (EULAR) adjusted their recommendations concerning dealing with rheumatoid arthritis in their 2022 revision. This update integrated insights from the ORAL Surveillance Study. While the 2019 guidelines placed JAKinibs on par with bDMARDs regarding efficacy and safety, the 2022 version incorporated an additional directive.

It articulated that while considering JAKinibs, relevant risk factors should be meticulously assessed.[3]

It's paramount to factor in certain risk parameters for cardiovascular incidents and malignancies when deliberating on prescribing a JAKinib. These encompass:

- Ageing past 65 years
- A current or historical smoking habit
- Other cardiovascular-related risks such as diabetes, obesity, and hypertension
- Additional malignancy risk indicators, excluding instances of successfully managed non-melanoma skin cancer (NMSC). This involves both current and previous cancer histories
- Risks leading to thromboembolic episodes. This includes histories of heart ailments like myocardial infarction or heart failure, genetic blood clotting disorders, past occurrences of blood clots, and instances where patients are on combined hormonal contraceptives or hormone replacement treatments.

Additionally, patients undergoing significant surgical procedures or those who are immobile also fall under this category.[3]

Furthermore, the guidelines advise adopting a cautious approach when prescribing JAKinibs to patients with potential risks for thrombosis in pulmonary and deep vein regions, beyond the previously detailed risks.

Oral Surveillance

The clinical trial „Cardiovascular and Cancer Risk with Tofacitinib in Rheumatoid Arthritis"– ORAL Surveillance was a randomized, open-label, non-inferiority end-point study.

Patients with active RA despite Methotrexate treatment, aged 50 years or older with at least one additional cardiovascular risk factor were included in the study.

Patients were randomized in a 1:1:1 ratio to receive Tofacitinib at a dose of 5 mg or 10 mg twice daily or a TNFi (Adalimumab or Etanercept depending on region of residence). The switch of patients from 10 mg to 5 mg during the course of the study for safety reasons has already been mentioned. The co-primary Endpoints were adjudicated MACE and cancer, excluding NMSC. The non-inferiority of Tofacitinib would have been demonstrated if the upper limit of the two-sided confidence interval for the hazard ratio were less than 1.8 for the combined Tofacitinib doses compared with a TNFi.[19]

This primary end point was not met because the upper limit of the two-sided 95% confidence interval versus TNFi was greater than 1.8 (ie, 80%) for MACE 1.94 and for malignancies 2.09.

The incidence rates (IR) per 100 patient years for MACE and malignancies were numerically higher for both doses of Tofacitinib compared to the TNFi, but the confidence intervals overlapped.

Proponents of JAKinibs often argue that incidence rates were not significantly different. However, it is important to remember that the comparison of incidence rates was not the primary endpoint of this study. The comparison of incidence rates was performed descriptively as a post-hoc analysis for additional information only. Similarly, it is not meaningful to compare incidence rates in ORAL surveillance with incidence rates in other studies, as it is sometimes done. Such differences are exactly the reason why randomized head-to-head studies must be conducted

The number needed to harm (NNH) for Tofacitinib 5 mg bd vs TNFi was 567 for MACE; for malignancies, the NNH was 276 for Tofacitinib 5 mg bd and 275 for 10 mg bd. This refers to patient year. The most common malignancies among Tofacitinib were lung cancer and breast cancer.[19]

Arguments About Available Data

ORAL Surveillance – First Reactions

The publication of the ORAL Surveillance data was accompanied by an editorial in the New England Journal of Medicine.[23] As expected for an editorial, it questions certain aspects and interpretations. The question of whether the difference in risk is due to an increased risk from the JAKinibs or to a stronger protective effect of the TNFi is posed here for the first time and still remains unanswered.

However, for the evaluation of the consequences of the study in patients with rheumatoid arthritis, the question of causality is of secondary importance.

It is sufficient to know that a scientifically proven difference exists.

The editorial also emphasizes the selection of the study population, a population selectively enriched with risk factors. The question is as to how far the data from this study could be applied to all patients with rheumatoid arthritis. For the author of the editorial, the matter is simple. He asks to whom do these results not apply? And he gives the answer himself: The ORAL Surveillance results do not lead to any consequence for the following groups of patients with RA: patients younger than 50 years of age, patients 50 years of age or older but with no additional cardiovascular risk factor. He is addressing a point that is still the subject of heated discussion. As well as two other points are: the question of extrapolation to other JAKinibs ("class effect") and extrapolation to indications other than RA.

Alternative Data for Discussion

Results of prospective randomized direct comparison studies are considered the gold standard of evidence generation. However, they are of course not available for every clinical question. Thus, in the course of the ORAL surveillance reception, various additions, rebuttals, relativizations, as well as confirmations have been discussed with the help of alternative methods. All these methods of data collection have their strengths, but also their weaknesses and limitations.

Data from clinical trials programs (pivotal trials): The main problem with data from pivotal or complementary clinical trials is that these studies are designed and calculated precisely for a primary efficacy endpoint. Safety data are recorded descriptively, which does not allow an objective and reproducible comparison.

In addition, there may be large differences between study participants and RA patients in general. Strict inclusion and exclusion criteria mean that only a relatively narrow segment of the real patient spectrum is under observation. For example, patients with serious comorbidities, a history of cancer, or cardiovascular problems are not included in phase 2 and 3 studies. The medical-clinical care of study patients can differ significantly from the respective general standards, and therapy adherence and compliance are certainly higher among study participants than under standard treatment. Thus, study patients often develop lower disease activity and a lower chronic inflammatory burden. All this may mean that the safety profile of a therapy as depicted from clinical trials does not correspond to the safety profile under real-world-conditions.[18]

Integrated safety profiles: Integrated safety profiles are analyses of pooled data from a clinical trial program. Therefore, they are subject to the same caveats as the clinical trial programs themselves. In addition, there may also be more or less significant differences between the different trial populations in terms of the risk of developing adverse events.[18]

Registry data: In contrast to randomized clinical trials, registries also include patients who are usually not included in clinical trials because of concomitant diseases or incompatible drugs. Overall, a collective composed in this way therefore corresponds more to clinical reality than the population of a pivotal study. However, the safety data are recorded descriptively, just as they are recorded in the clinical registration studies, and there is no definitive statistical plan a priori for the evaluation of the data. There is also no certainty that all patients in the observed collective who are treated with certain drugs for an identical indication will be included in the registry and regularly followed up. In addition, different collectives usually can only be compared with some reservations Overall, registry data are a valuable supplement to the results of clinical studies, but cannot replace them.

Insurance claims databases: Like registries, these databases include more and more diverse patients than a registration study and its long-term extensions (LTE). One can find the diagnosis, the drugs used and the occurrence of adverse events from these databases. The weakness is that you do not have access to original data, so you cannot be sure about the accuracy of the diagnosis, adherence and compliance, and the causality of an event.[18]

With all the advantages and disadvantages of the various methods, the gold standard for any comparison of two therapies is the randomized, prospective head-to-head trial, assuming that the population studied is appropriate to answer the scientific question. This applies not only to questions of efficacy, but also to those of safety. The EULAR recommendations also take this into account by emphasizing that the results of a single randomized controlled trial are to be considered higher level of evidence than other data not derived from such studies.[3,18]

Enriched Population – General Population

An attempt had already been made in the accompanying editorial to narrow the scope of ORAL Surveillance results to a specific patient subset. The data should be relevant only for patients matching the criteria of the selective ORAL population.[23]

In context with this, two further analyses were published to support this interpretation of the ORAL Surveillance results. Two subgroups were formed from the data of the STAR-RA study cohort, derived from data sourced from various insurance claims databases. A comparison was made between a so-called "real-world RA population" and a group intended to align with ORAL Surveillance criteria. While no significant disparity in the incidence of myocardial infarction and stroke was noted in the general group, the high cardiovascular risk group exhibited a difference with a hazard ratio of 1.24, which did not achieve statistical significance, yet closely mirrored the outcome for Tofacitinib 5 mg in the ORAL Surveillance.[24,25]

A post-hoc analysis of ORAL Surveillance revealed two subpopulations with distinct relative risk profiles compared to the original study data. The elevated risk relative to TNFi was limited to a subgroup of patients defined by specific, easily identifiable risk factors: age 65 or older and a history of long-term smoking (current or past). In "low-risk" patients —those under 65 and non-smokers—no discernible increase in risk compared to TNFi was observed with up to 6 years of follow-up in ORAL Surveillance.[26]

In risk compared to TNFi was observed with up to 6 years of follow-up in ORAL Surveillance.[26]

Can we confidently assert that the conclusions drawn from ORAL Surveillance results cannot be extended beyond the high-risk population? The objective of ORAL Surveillance was to identify potential discrepancies in cardiovascular risk and malignancy incidence between JAKinibs and TNFi. The inclusion of only patients with an elevated risk, determined at the group level through epidemiological studies, was a statistical and mathematical necessity. It is now widely recognized that events occur more frequently in individuals with a high underlying risk compared to healthy individuals with only a low suspected risk.[27,28] A broad inclusion in the study would have necessitated an enormous number of patients and/or an extended duration for ORAL Surveillance. However, this does not imply that patients without additional risk factors are not exposed to a risk that is higher than that of the general population regarding the disease. Certainly, the incidences would likely be lower—but by how much? Additionally, it's important to remember that malignant diseases in particular, as well as chronic cardiovascular diseases, often have a long latency period before manifesting. Can anyone truly assert with certainty that a therapy-associated malignancy will not occur within a timeframe that we have not yet observed?

Are Janus Kinase Inhibitors Worse or TNF-Alpha Inhibitors Better?

Given that Tofacitinib did not demonstrate non-inferiority concerning Major Adverse Cardiovascular Events (MACE) and malignancies, the question naturally arises: what accounts for this difference? Are TNFis potentially protective while JAKinibs pose a greater risk, or do both carry inherent risks with TNFis being less pronounced? Could it be that both offer some level of protection, but JAKinibs are comparatively less potent? Understanding the underlying processes governing these clinical distinctions, and whether they apply uniformly across all adverse effects, is a complex endeavor. Both classes of substances have profound impacts on the immune system, which is characterized by an immense redundancy of pathways and an almost infinite array of possible reactions. The brief and somewhat incomplete descriptions provided above might serve as a foundation for further exploration.

Certainly, all of this cannot be gleaned from a single trial. Nonetheless, it does not alter the risk-benefit assessment when it comes to choosing between the two drugs in terms of MACE risk and incident malignancies. Finally, when compared to no therapy, non-biologic Disease Modifying Anti-Rheumatic Drugs (DMARDs), or even other biologic DMARDs, both treatments could be protective.

Extrapolation to Other Janus Kinase Inhibitors – Class Effect?

The question remains unanswered due to a dearth of clinical data. The confidence in the safety profile of other JAKinibs largely stems from the relatively controlled data derived from registration trials and their long-term extensions. While it could potentially be coincidental, discernible distinctions are already apparent in cases where comprehensive data is available, as seen with baricitinib in the B023 study. If we had a deeper understanding of the underlying pathomechanisms, we might be better equipped to address the question of a potential "class effect" or its absence. Could these distinctions be attributed to variations in binding sites, binding types, specific pharmacological characteristics, or the frequently discussed selectivity and specificity? Frequently, the apparent cause is not the actual root.

Following the presentation of the ORAL Surveillance data, many promptly attributed the increased occurrence of MACE to the effectiveness of tofacitinib in the IL-6 signaling pathway. However, the situation is likely more intricate than it appears. Let us recall a safety study structured in a manner similar to ORAL Surveillance, which compared the IL-6 receptor blocker tocilizumab with the TNFi etanercept in terms of MACE occurrences. Unlike the ORAL Surveillance findings, the IL-6 receptor blocker tocilizumab successfully met its primary endpoint. This suggests that the IL-6 blockade might not be the sole determining factor.[29]

Extrapolation to Other Indications?

Answering this question, akin to the one about extending to different compounds or patient groups with varying risk profiles, remains challenging due to the absence of corresponding comparative data. While some integrated trial analyses and meta-analyses have pooled safety data for a specific JAKinib across different indications, their value is limited due to a scarcity of events. Epidemiological data hints at distinctions between different diseases in terms of systemic inflammation levels. However, these remain group-level estimates, often conflicting, and offer limited guidance for personalized therapy decisions.

The EMA has addressed this challenge by tailoring the risk assessment to individual profiles. Individuals with one or more risk factors are advised against receiving the therapy, with exceptions, regardless of the specific disease they may have 22. Of course, this approach allows for a degree of flexibility, enabling doctors and patients to collaborate in making informed decisions, a stance that some welcome and others contest.

Cardiovascular Risk, Thromboembolic Events, Malignancies – Risk in RA Populations

Patients with RA are at increased risk for a variety of comorbidities,[30] including cardiovascular events and cancer.[31–35]

Cardiovascular Risk

Cardiovascular-related deaths are significantly implicated in excess mortality in RA. In an analysis of 50 published studies involving 33,250 deaths in 91,618 patients, cardiovascular disease accounted for by far the largest proportion, 39.6%.[36,37]

In two meta-analyses involving a total of 150,000 patients, the risk of cardiovascular events was increased by 48% in patients with RA compared with the control group. The incidence of cardiovascular-related death was 50% higher.[32,38]

Thromboembolic Events

The relative risk of VTE, deep vein thrombosis (DVT) and PE, is about twice as high in RA patients as in the general population.[39,40] The risk correlates with the disease activity of RA.[41]

In an analysis of the risk of VTE, PE, DVT and arterial thrombotic events with tofacitinib in different indications, it was shown that the IRs for these events in trials in RA, psoriasis and psoriatic arthritis were very similar to each other and broadly consistent with data from observational studies and the published IRs of other therapies.[42] As is to be anticipated with registry cohorts, there is also a similarly designed cohort study in which the risk of VTEs does not appear to be increased with tofacitinib compared to TNFi.[43]

The topic of VTE takes us back to the EMA decision and the January 2023 mailing.

In addition to the final results of the ORAL surveillance, preliminary results of an observational study with baricitinib were also cited as a source of data in this mailing.

This study has since been completed and published.[44]

The aim of this study was to assess the safety of baricitinib primarily with regard to VTE, but also, MACE and serious infections compared to TNFis in patients with RA. This study is methodologically noteworthy as it sought to overcome the limitations of "real-world data" studies by including different populations and evaluating higher than usual event rates.

A meta-analysis was conducted comprising 14 post-marketing data sources, including bDMARD registries and disease registries, administrative databases and national health systems in Europe, the United States and Japan. A new active comparator user study design was used to reduce the risk of confounding and selection bias.[45]

Among the 9013 eligible patients who received treatment with Baricitinib, 7606 (84%) were matched in a 1:1 ratio with patients receiving TNFi based on propensity scores, and were subsequently included in the comparative analysis of VTE. This study currently stands as the most extensive real-world observational investigation into VTE, MACE, and serious infections in patients treated with Baricitinib as compared to similar patients treated with TNFi. Across all available data sources, 97 patients encountered a VTE over an average follow-up period of 9 months. The overall incidence rate ratio (IRR) for Baricitinib versus TNFi was found to be statistically significantly elevated. Although not reaching statistical significance, a numerically greater IRR was observed for Baricitinib in comparison to TNFi concerning the risk of MACE and serious infection. Given the available information, no discernible distinctions were noted between the 4mg and 2mg doses, leading to exposure to Baricitinib being defined based on combined doses (2 mg and 4 mg).[44,46]

In the forthcoming period, outcomes from two ongoing post-marketing randomized trials, namely RA-BRANCH (NCT04086745) and RA-BRIDGE (NCT03915964), will become accessible. These trials are anticipated to offer a more comprehensive understanding of the VTE, MACE, and serious infection risks associated with Baricitinib in comparison to TNFi, particularly in high-risk patients possessing one or more VTE risk factors, and who have shown an inadequate response or intolerance to one or more prior cDMARD or bDMARD.[44]

Malignancies

Individuals diagnosed with RA exhibit a heightened risk for cancers in comparison to the general population.[47,48] When examining the JAKinibs, they all present roughly the same malignancy IRs. Lymphoma and lung cancer are the malignancies most commonly noted. Relative to the general population, those with RA experience roughly double the risk for both lymphoma and lung cancer. Conversely, they display a reduced risk for cancers of the colon and breast.[49] Research indicates that the likelihood of lymphoma in RA patients correlates with the intensity of the disease's activity.[50]

Risk and Interventions

Cardiovascular Events - MACE

In the comprehensive safety data from all JAKinibs, instances of MACE were observed in trial participants, particularly those with predisposing risk factors.[18] A thorough analysis of the incident rates (IR) indicates minimal variance among JAKinibs within the clinical trial demographics. In comparison to historical controls, both csDMARDs and bDMARDs have shown a decreased risk of MACE in the wider population, with the risk being notably lower with TNFi in relation to csDMARDs.[31,38,51,52] Moreover, it has been established that effectively reducing disease activity plays a crucial role in diminishing MACE risk.[27] It is therefore reasonable to hypothesize that JAKinibs, given their potent anti-inflammatory properties, might also reduce the MACE risk. However, it is essential to recognize the potential for opposing mechanisms to counteract one another, neutralizing their individual impacts.

Malignancies

For some experts, the difference in cancer risk between tofacitinib and a TNFi as shown in ORAL surveillance was rather unexpected, as cancer is included as a severe warning on the TNFis' labeling.[19,23] TNFi usage in RA treatment might correlate with a marginally elevated risk of NMSC or melanoma but does not indicate an overall surge in cancer risks.[53] An observational study utilizing Swedish registry data aimed to gauge the relative cancer risks among RA patients undergoing treatment with biologic and targeted synthetic DMARDs (b/tsDMARDs). With over 8000 observed cancer incidents among RA patients, long-term use of TNFi in clinical practice for RA did not indicate elevated cancer risks.[54]

The STAR-RA study, which was previously discussed in the context of cardiovascular outcomes and incorporated Tofacitinib, also examined malignancy risks by comparing two distinct patient cohorts. Their main focus was on all cancer types, excluding non-melanoma skin cancer. The study found no increased risk of cancer with Tofacitinib in RA patients compared to those on TNFi. Yet, the possibility of elevated risks associated with extended Tofacitinib treatment could not be dismissed.[24]

For Upadacitinib, two safety assessments from clinical trials are accessible. One showcases a 3-year data span from an ongoing study, revealing its safety profile akin to Adalimumab for certain adverse events, which includes cancers.[18]

The other study, even more extensive, amalgamates data from trials of Upadacitinib for various conditions; the consolidated safety review, with over 15,000 patient-years of exposure, demonstrates a generally favorable safety profile, with cancer incidences mirroring those of the active comparators.[55]

A meta-analysis, encompassing data from 78 trials and long-term studies with various JAK inhibitors, evaluated cancer incident rates across different treatments. Although JAKinibs showed no heightened cancer risks when set against placebo or Methotrexate, there was a noticeable increase when compared with TNFis. The authors suggest this information might weigh in when selecting between a JAKinib or a TNFi for treatment.[56]

How to Proceed

It is clear that the requirements of the authorities, from the EMA (or FDA) downwards, must be strictly adhered to. There is no way around it. The concepts of shared decision and informed consent are crucial for a correct and justifiable procedure. The doctor is obliged to fully inform all patients, even if they do not belong to the risk group. On the basis of the legally existing treatment contract, he must fully inform the patient about the therapy options that correspond to the state of medical science.

Since science is conducted internationally, the stringent regulations of the FDA must also be communicated. Only if side effects and contraindications to alternative therapies are present, if other patient-related factors are in the foreground, oral JAKinib therapy should be started in patients with the defined risk factors.

In any case, a fully documented medical history and status should be obtained. Regular dermatological examinations during JAKinib therapy are strongly recommended.

Finally, the statements and opinions expressed here refer exclusively to the current perspectives. Like all life science, medicine is in constant flux. The data situation and thus the state of knowledge can change at any time, and new perspectives can always arise. Based on the current data and guidelines, these highly effective therapies should be used in any case if necessary, but otherwise with great care and conscientiousness.

Abbreviations

RA, rheumatoid arthritis; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; bDMARDs - biologic disease-modifying antirheumatic drugs; tsDMARDs, targeted synthetic disease-modifying antirheumatic drugs; TNF, Tumor Necrosis Factor; TNFi, Tumor Necrosis Factor inhibitor; JAK, Janus Kinase; JAKinibs, Janus Kinase inhibitors; MACE, major adverse cardiac events; VTE, venous thromboembolism; FDA, Food and Drug Administration; EMA, European Medicines Agency; TYK2, Tyrosine Kinase 2; JAK1, Janus Kinase 1; JAK2, Janus Kinase 2; JAK3, Janus Kinase 3; ATP, Adenosine Triphosphate; HZ, Herpes Zoster; bd, twice daily; DSMB, data safety monitoring board; PE, pulmonary embolism; MAA - Marketing Authorization Application; CHMP - Committee for Medicinal Products for Human Use; PRAC - Pharmacovigilance Risk Assessment Committee; EULAR - European League against Rheumatism; IR, incidence rates; NNH, number needed to harm; RCT, randomized controlled trial; CI, confidence interval; DVT, deep venous thrombosis; LTE, long-term extension study.

Authors´contribution

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work

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