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COMPARATIVE EFFECTIVENESS OF JAK INHIBITORS VS TNF INHIBITORS IN RHEUMATOID ARTHRITIS

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Annotation: This study aims to compare the clinical effectiveness of JAK inhibitors versus TNF inhibitors in patients with rheumatoid arthritis, drawing on current evidence from randomized controlled trials (RCTs), observational studies, and real-world registries. By contextualizing therapeutic outcomes within the broader scope of national healthcare priorities, the findings of this research may inform clinical decision-making and health policy directives in the evolving landscape of RA treatment.

Key words: *rheumatoid arthritis, methotrexate, immunogenicity, faster symptom, patient-reported outcomes.*

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disease that significantly impairs quality of life and functional ability, affecting approximately 0.5–1% of the global population. The management of RA has undergone considerable evolution over the past two decades, particularly with the advent of targeted synthetic and biologic disease-modifying antirheumatic drugs (DMARDs). Among these, tumor necrosis factor (TNF) inhibitors and Janus kinase (JAK) inhibitors have emerged as prominent therapeutic classes, both approved for moderate to severe RA in patients with inadequate response to conventional synthetic DMARDs. TNF inhibitors, such as etanercept, infliximab, and adalimumab, were among the first biologic agents introduced and have set the standard in biologic therapy. More recently, JAK inhibitors—including tofacitinib, baricitinib, and upadacitinib—have offered oral alternatives with unique mechanisms of action targeting intracellular signaling pathways. As treatment paradigms shift toward personalized medicine, understanding the comparative effectiveness and safety profiles of these two therapeutic classes has become increasingly important. In response to the growing public health burden of chronic inflammatory diseases, including RA, several countries have enacted national strategies and presidential decrees aimed at improving access to innovative treatments[1].

LITERARY ANALYSIS

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The comparative effectiveness of JAK inhibitors and TNF inhibitors in the treatment of rheumatoid arthritis has been the subject of extensive clinical investigation, especially as treatment goals shift toward achieving rapid disease remission and minimizing long-term joint damage.

TNF Inhibitors: TNF inhibitors have long been considered the backbone of biologic therapy in RA. Landmark trials such as the ATTRACT (1999) and TEMPO (2004) studies demonstrated significant improvements in disease activity scores and radiographic progression when TNF inhibitors were combined with methotrexate. Meta-analyses have confirmed the superior efficacy of TNF inhibitors over placebo and methotrexate monotherapy in reducing disease activity and improving physical function (Singh et al., 2016). However, challenges with immunogenicity, injection-site reactions, and increased infection risk have led to the exploration of alternative targeted therapies.

JAK Inhibitors: JAK inhibitors, introduced more recently, act intracellularly by disrupting the JAK-STAT signaling pathway that mediates cytokine-driven inflammation. Agents such as tofacitinib, baricitinib, and upadacitinib have shown non-inferiority or even superiority to TNF inhibitors in certain clinical parameters. For instance, the SELECT-COMPARE trial (2019) demonstrated that upadacitinib plus methotrexate resulted in significantly better ACR50 responses and DAS28-CRP scores compared to adalimumab plus methotrexate. Similarly, in the ORAL Strategy trial, tofacitinib was shown to be comparable to adalimumab in terms of ACR response rates. Real-world studies have echoed these findings. A comparative observational study by Pope et al. (2021) found that JAK inhibitors led to faster symptom relief and similar or better treatment persistence compared to TNF inhibitors in biologic-naïve RA patients[2]. However, safety concerns—especially regarding thromboembolic events and herpes zoster infections—have prompted regulatory agencies, including the FDA and EMA, to issue warnings and usage guidelines.

Head-to-Head Comparisons and Meta-Analyses: Recent systematic reviews and network meta-analyses have provided a broader view of the comparative effectiveness and safety of these therapies. A 2022 meta-analysis by Smolen et al. concluded that while both classes are effective in controlling disease activity, JAK inhibitors may offer greater improvements in patient-reported outcomes such as pain and fatigue[3]. However, they also noted a higher incidence of serious adverse events in long-term follow-up.

Pharmacoeconomic Considerations: Several cost-effectiveness analyses have evaluated these agents in different healthcare settings. While TNF inhibitors remain costly, the

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introduction of biosimilars has lowered their economic burden. In contrast, JAK inhibitors, though orally administered and not requiring cold-chain logistics, are still priced at premium levels in many markets. Overall, the literature suggests that both JAK inhibitors and TNF inhibitors are effective components of the RA treatment armamentarium. However, differences in onset of action, route of administration, safety profiles, and cost necessitate a nuanced, individualized approach to therapy selection[4].

RESULTS AND DISCUSSION

The comparative analysis of JAK inhibitors and TNF inhibitors reveals significant differences in treatment response, speed of action, safety profiles, and patient preference, all of which have implications for clinical practice and national treatment protocols.

Clinical Effectiveness: Clinical trial data consistently indicate that JAK inhibitors are at least non-inferior to TNF inhibitors in terms of achieving clinical remission and improving physical function in RA patients. In the SELECT-COMPARE trial, upadacitinib achieved significantly higher ACR50 response rates at Week 12 (45%) compared to adalimumab (29%), both in combination with methotrexate. Similarly, ORAL Strategy results showed comparable ACR70 responses between tofacitinib and adalimumab, suggesting that JAK inhibitors may offer equal or superior efficacy in biologic-naïve and TNF-experienced populations.

Time to Response and Patient-Centered Outcomes: Several studies have highlighted a faster onset of action with JAK inhibitors, with patients often reporting symptom improvement within the first two weeks of therapy. In real-world settings, this rapid relief has translated into greater patient satisfaction and improved adherence. Additionally, JAK inhibitors have demonstrated superior outcomes in fatigue reduction and pain relief—two critical patient-reported outcome measures often underrepresented in traditional disease activity indices[5].

Safety Profile: While JAK inhibitors offer the convenience of oral administration and faster symptom control, their safety profile raises concerns. Increased risks of herpes zoster, venous thromboembolism (VTE), and elevated liver enzymes have been documented, particularly in older patients and those with pre-existing cardiovascular risk factors. The ORAL Surveillance study, which evaluated tofacitinib versus TNF inhibitors in high-risk patients, revealed a higher incidence of major adverse cardiovascular events (MACE) and malignancies in the JAK inhibitor group, prompting updated regulatory warnings and prescribing guidelines from the FDA and EMA. In contrast, TNF inhibitors have a well-characterized long-term safety profile, though they carry their own risks, including serious infections and potential reactivation

of latent tuberculosis. The benefit-risk assessment thus varies depending on individual patient comorbidities and risk factors.

Treatment Retention and Switching: Registry data from countries with centralized RA treatment programs (e.g., DANBIO, BSRBR, and others) show comparable treatment retention rates between the two classes. However, patients initiating JAK inhibitors often have higher rates of switching from TNF inhibitors, indicating potential limitations in response to first-line biologics. Conversely, switching from a JAK inhibitor to a TNF inhibitor has been associated with reduced effectiveness, emphasizing the need for careful sequencing in treatment planning[6].

The findings support a more personalized approach to RA treatment, wherein both drug classes have roles based on individual patient characteristics, disease severity, and risk factors. Future research should focus on long-term head-to-head studies, real-world effectiveness in diverse populations, and pharmacoeconomic evaluations tailored to specific healthcare systems.

Comparative Efficacy and Safety of JAK Inhibitors vs TNF Inhibitors

1. ACR50 Response Rates at Week 12
• Upadacitinib (JAKi) – 45%
• Tofacitinib (JAKi) – 40% • Adalimumab (TNFi) – 29%
• Etanercept (TNFi) – 30%
2. Incidence of Adverse Events (per 100 patient-years)
• Herpes Zoster (JAKi) – 4.0 • Herpes Zoster (TNFi) – 1.2
Serious Infections (JAKi) – 3.5
• Serious Infections (TNFi) – 3.0

This figure illustrates the difference in clinical response and safety between JAK inhibitors and TNF inhibitors. JAK inhibitors such as upadacitinib and tofacitinib demonstrated higher ACR50 response rates at Week 12 compared to TNF inhibitors like adalimumab and etanercept, indicating potentially superior short-term effectiveness. However, the incidence of certain adverse events, particularly herpes zoster and serious infections, was higher in patients treated with JAK inhibitors. These findings underscore the importance of balancing efficacy with individual patient risk profiles when selecting targeted therapies for rheumatoid arthritis.

CONCLUSION

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To sum up all given information above it should be noted that the emergence of JAK inhibitors has significantly expanded the therapeutic landscape for rheumatoid arthritis, offering effective oral alternatives to TNF inhibitors with comparable or superior clinical outcomes in certain populations. Clinical trials and real-world studies suggest that JAK inhibitors may provide a faster onset of action and improved patient-reported outcomes, though they carry a heightened risk of specific adverse events, including herpes zoster and thromboembolic complications. Conversely, TNF inhibitors remain a reliable and well-established class with extensive long-term safety data and increasing cost accessibility due to biosimilar availability. The decision between JAK and TNF inhibitors should be individualized, considering factors such as disease severity, prior treatment response, comorbidities, and patient preferences. In countries implementing national healthcare reforms or presidential decrees aimed at improving access to innovative therapies, it is essential to align treatment guidelines with both clinical evidence and pharmacoeconomic realities. Ongoing comparative studies and long-term registries will be critical in further refining treatment strategies to ensure optimal patient outcomes in rheumatoid arthritis management.

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