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Positioning filgotinib in the therapeutic landscape of rheumatoid arthritis - alternative or complementary?

Filgotinibin romatoid artrit tedavisindeki konumu - alternatif mi, tamamlayıcı mı?

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Abstract

Rheumatoid arthritis is a chronic inflammatory disease characterized by persistent immune activation and progressive joint damage. Although conventional and biological disease-modifying antirheumatic drugs have substantially improved disease control, treatment resistance and failure to achieve sustained remission remain important clinical challenges. This narrative review evaluates filgotinib, a preferential Janus kinase 1 inhibitor, focusing on its clinical efficacy, safety profile, and therapeutic potential for rheumatoid arthritis. Clinical studies have demonstrated that filgotinib provides rapid and sustained clinical benefits in patients with moderate-to-severe rheumatoid arthritis, particularly in those with an inadequate response to, or intolerance of, methotrexate or biologic therapies. The most commonly reported adverse events include mild infections and nasopharyngitis, while overall tolerability remains favorable. Overall, filgotinib represents a well-tolerated targeted therapeutic option for patients with difficult-to-treat rheumatoid arthritis. Nevertheless, further long-term studies and real-world evidence are required to better define its safety profile and clarify its optimal positioning within contemporary treatment strategies.

Keywords: Adverse effects, DMARDs resistance, filgotinib, JAK1 inhibitor

Özet

Romatoid artrit, bağışıklık sisteminin süreğen aktivasyonu ve ilerleyici eklem hasarı ile karakterize kronik bir enflamatuvar hastalıktır. Geleneksel ve biyolojik hastalık modifiye edici antiromatizmal ilaçlar hastalık kontrolünü önemli ölçüde iyileştirmiş olsa da, tedaviye direnç ve sürekli remisyon elde edilememesi önemli klinik zorluklar olmaya devam etmektedir. Bu derleme makalesi, romatoid artritte klinik etkinliği, güvenlik profili ve terapötik potansiyeline odaklanarak, seçici bir Janus kinaz 1 inhibitörü olan filgotinibi değerlendirmektedir. Klinik çalışmalar, filgotinibin orta ila şiddetli romatoid artritli hastalarda, özellikle metotreksat veya biyolojik tedavilere yetersiz yanıt veren veya intoleransı olanlarda hızlı ve sürekli klinik faydalar sağladığını göstermiştir. En sık bildirilen yan etkiler arasında hafif enfeksiyonlar ve nazofarenjit yer alırken, genel tolere edilebilirlik olumlu kalmaktadır. Genel olarak, filgotinib, tedavisi zor romatoid artritli hastalar için iyi tolere edilen hedefe yönelik bir tedavi seçeneğidir. Bununla birlikte, güvenlik profilini daha iyi tanımlamak ve güncel tedavi stratejileri içindeki en uygun konumunu netleştirmek için daha uzun vadeli çalışmalara ve gerçek dünya verilerine ihtiyaç duyulmaktadır.

Anahtar Kelimeler: Advers etkiler, DMARD direnç, filgotinib, JAK1 inhibitörü

Introduction

Rheumatoid arthritis (RA) is a chronic, immune-mediated inflammatory disease characterized by persistent synovitis, progressive joint damage, and systemic manifestations that significantly impair quality of life.[1] The primary goal of RA treatment is to achieve sustained remission; when this is not attainable, therapeutic strategies aim to control symptoms, minimize pain, preserve functional capacity, improve quality of life, and slow structural joint damage. RA is managed through symptomatic treatment, including non-steroidal anti-inflammatory drugs and glucocorticoids, in conjunction with disease-modifying antirheumatic drugs (DMARDs), which are the cornerstone of first-line therapy. Failure of or intolerance to first-line therapy necessitates escalation to alternative DMARDs.[2,3] In cases of inadequate response, biological therapies such as anti-tumor necrosis factor alpha (TNF-α) agents or interleukin-6 (IL-6) receptor blockers are used.[4]

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Over the past two decades, the introduction of DMARDs, particularly biologic DMARDs (bDMARDs) and targeted synthetic DMARDs (tsDMARDs), has markedly improved disease outcomes. Nevertheless, a substantial proportion of patients do not achieve sustained remission or low disease activity despite sequential treatment with conventional synthetic DMARDs (csDMARDs) and biologic agents, prompting recognition of difficult-to-treat RA.[5]

Difficult-to-treat or refractory RA is defined by persistent disease activity that remains inadequately controlled despite the use of conventional therapeutic strategies. A considerable percentage of RA patients develop resistance to two or more (≥2) bDMARDs during the course of their treatment, according to certain studies. In particular, anti-TNF biologics are frequently associated with primary or secondary non-responsiveness.[5]

Janus kinase (JAK) inhibitors have emerged as an important class of therapeutics within this evolving treatment paradigm, allowing oral administration and broad inhibition of cytokine signaling. Filgotinib, a preferential JAK1 inhibitor, is one of the newer agents in this class. While its clinical efficacy and safety have been demonstrated in multiple randomized controlled trials, its precise positioning within the RA therapeutic landscape remains a subject of clinical debate.

Specifically, whether filgotinib should be regarded primarily as an alternative to existing advanced therapies or as a complementary option within sequential treatment algorithms requires a careful narrative synthesis rather than a purely descriptive enumeration of clinical trial data.[6]

Accordingly, this narrative review focuses exclusively on RA and aims to contextualize filgotinib within contemporary RA management. Rather than adopting a systematic review framework, this article integrates evidence from key clinical trials, comparative analyses, and safety evaluations to provide an interpretative assessment of filgotinib's therapeutic role. Through this approach, we aim to address unmet clinical needs and clarify whether filgotinib should be viewed as an alternative or complementary agent in the management of RA.

The Therapeutic Landscape of Rheumatoid Arthritis and Unmet Needs

Current RA management follows a stepwise, treat-to-target strategy, with methotrexate (MTX) remaining the cornerstone of initial therapy. In patients with an inadequate response to or intolerance of csDMARDs, bDMARDs targeting TNF, IL-6, or immune cell co-stimulation are recommended. Despite this structured approach, real-world data indicate that a substantial subset of patients experience primary non-response, secondary loss of efficacy, or unacceptable toxicity across multiple therapeutic classes.[2]

Within this therapeutic landscape, tsDMARDs—particularly JAK inhibitors—have expanded therapeutic options by offering oral administration and modulating intracellular cytokine signaling. Tofacitinib, baricitinib, upadacitinib, and filgotinib are the principal JAK inhibitors evaluated for RA. Current international guidelines do not preferentially recommend one JAK inhibitor over another, reflecting comparable efficacy across the class and the absence of definitive head-to-head superiority data.[7]

The emergence of difficult-to-treat RA has underscored the need for greater therapeutic flexibility. These patients often require multiple treatment switches, and the availability of mechanistically distinct yet clinically effective agents remains essential. Filgotinib's development and approval in several regions occurred within this context, positioning it as a potential solution for patients with refractory disease.[3]

Filgotinib: Mechanism of Action and Pharmacological Profile

JAK inhibitors are considered an effective therapeutic strategy for managing autoimmune diseases, as they enable targeted modulation of inflammatory signaling pathways. Key advantages of JAK inhibitors include oral administration and demonstrated efficacy with acceptable safety profiles.[3,8] Among these agents, filgotinib was one of the most recently introduced JAK inhibitors to the global market for the treatment of RA as of 2020.[9] Filgotinib is a preferential JAK1 inhibitor that selectively suppresses signaling pathways mediated by pro-inflammatory cytokines implicated in RA pathogenesis, thereby inhibiting signaling by IL-6, interferon-γ, interferon-α/β, and γc-chain cytokines through suppression of signal transducer and activator of transcription (STAT) phosphorylation and activation within the JAK-STAT pathway, ultimately leading to reduced innate immune responses, inflammation, and lymphocyte proliferation (Figure 1).[10,11] Compared with earlier JAK inhibitors, which exhibit broader inhibition profiles (e.g., tofacitinib targeting JAK1/3 and baricitinib targeting JAK1/2), filgotinib's selectivity was designed to maintain therapeutic efficacy while potentially limiting adverse effects associated with JAK2 inhibition, such as hematopoietic suppression.[10]

In patients with an inadequate response to conventional therapies, filgotinib represents a clinically viable therapeutic option.[12] Filgotinib has demonstrated a favorable tolerability profile and clinical efficacy comparable to those of biologic agents.[13,14]

Pharmacokinetically, filgotinib is administered orally once daily and primarily metabolized by carboxylesterase 2 (CES2) and, to a lesser extent, by CES1, leading to formation of its major active metabolite, GS-829845, which contributes substantially to sustained JAK1 inhibition. After oral administration, only

a limited percentage of the parent compound is recovered unchanged, with 9.4% excreted in urine and 4.5% in feces. The majority of the administered dose (~87%) is eliminated as metabolites, with approximately 54% and 8.9% excreted in urine and feces, respectively, as GS-829845.[15]

Dose adjustment of filgotinib is not required in individuals with mild renal impairment, defined as those with a calculated glomerular filtration rate (eGFR) of 60-90 mL/min/1.73 m².[16] For patients aged ≥75 years and those with moderate to severe renal impairment, the starting dose is recommended at 100 mg/day. Following recent label revisions, initiation of filgotinib at 100 mg once daily, with up-titration to 200 mg once daily if tolerated, is recommended for this patient population.[8] Filgotinib is not recommended for use in patients with end-stage renal failure (eGFR <15 mL/min/1.73 m²), as it has not been tested in this population.[16]

Filgotinib administration does not require dose adjustment in cases of mild-to-moderate hepatic dysfunction. Filgotinib is not recommended for use in patients with severe hepatic impairment, as this population has not been evaluated in clinical studies.[16,17]

Overall, dose adjustment is generally unnecessary in patients with mild to moderate hepatic or renal impairment; howeveruse is not recommended in individuals with severe organ dysfunction. Filgotinib is contraindicated during pregnancy and breastfeeding; effective contraception is recommended throughout the treatment period.[18]

While these pharmacological characteristics differentiate filgotinib mechanistically, their clinical relevance ultimately depends on whether selective JAK1 inhibition translates into meaningful differences in efficacy or safety compared with other JAK inhibitors.

Clinical Efficacy of Filgotinib in Rheumatoid Arthritis

Clinical development programs have consistently demonstrated the efficacy of filgotinib across diverse RA populations. Phase II DARWIN trials established proof of concept, showing significant improvements in disease activity with both monotherapy and combination therapy with MTX in patients with inadequate response to csDMARDs.[19]

Phase III interim analyses from the filgotinib clinical trials in RA (FINCH) long-term extension program further clarified filgotinib's therapeutic role. In FINCH-1, filgotinib combined with

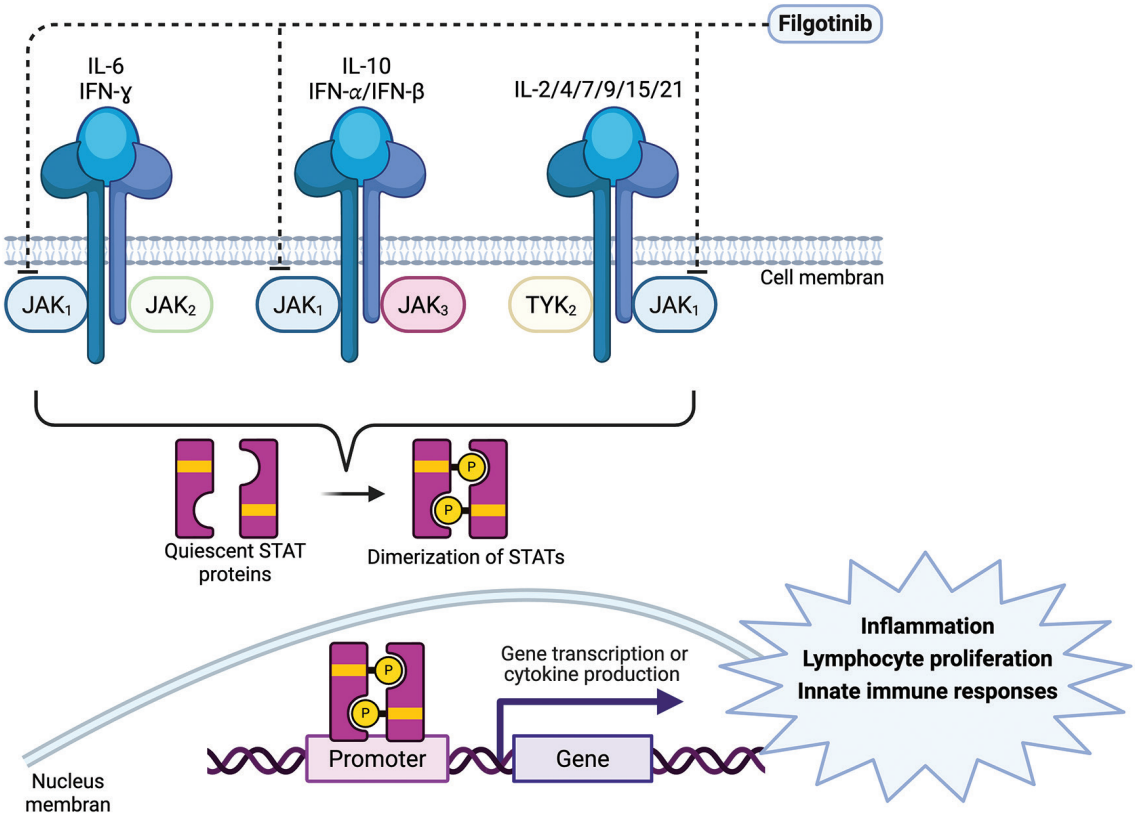

Figure 1. Filgotinib selectively inhibits signal transduction by JAK-1
Filgotinib exhibits strong selectivity for JAK1, thereby inhibiting signaling mediated by IL-6, IFN-γ, IFN-α/β, and γc-chain cytokines. As a result, innate immune responses, inflammation, and lymphocyte proliferation are reduced[10,11]
IFN: Interferon, IL: Interleukin, JAK: Janus kinase, STAT: Signal transducer and activator of transcription, TYK2: Tyrosine kinase 2 (License: https:/BioRender.com/oa72sov)

MTX demonstrated non-inferiority to adalimumab in patients with MTX-refractory RA, supporting its use as an alternative to established biologic therapies.[20] FINCH-2 specifically addressed biologic-refractory disease, revealing robust efficacy in patients who had failed one or more bDMARDs, a population representative of difficult-to-treat RA.[21] FINCH-3 extended these findings to patients without prior MTX exposure, suggesting potential utility earlier in the disease course, particularly in combination with MTX.[22]

Across trials, filgotinib demonstrated a rapid onset of action, meaningful improvements in patient-reported outcomes, and sustained disease control. Importantly, efficacy was consistently maintained across patient subgroups, reinforcing the view that filgotinib is broadly effective rather than confined to a narrow clinical niche.

Safety Profile of Filgotinib and Class-related Considerations

Safety evaluation remains central to the positioning of any JAK inhibitor. In pooled analyses from phase III trials and long-term extension studies, filgotinib exhibited a safety profile largely comparable to that of other agents within the class. Rates of serious infections, malignancies, venous thromboembolism, and major adverse cardiovascular events were low and comparable to those observed in control groups, given the limitations of trial duration and population size.[23] Evidence from randomized trials, long-term follow-up, and pharmacovigilance sources supports a generally consistent safety profile for filgotinib, with no new or unexpected safety signals reported to date.[23-26]

Class-wide safety concerns emerged following post-marketing data with tofacitinib, leading to regulatory warnings applicable across the JAK inhibitor class. Although filgotinib trials did not demonstrate an increased risk of these events, caution remains warranted, particularly in older patients and in those with cardiovascular or malignancy risk factors.[27]

Infections

According to systematic reviews and meta-analyses, tofacitinib, baricitinib, upadacitinib, and filgotinib are effective in the treatment of RA, although differences in efficacy and tolerability have been observed across these agents.[13,15,28,29] The overall risk of infection appears broadly comparable among these agents; however, herpes zoster infections have been reported less frequently with filgotinib.[13,15]

Across clinical trials, the most commonly reported infections associated with filgotinib were nasopharyngitis and upper respiratory tract infections, which were predominantly mild to moderate in severity. Serious infections were infrequent, with pneumonia reported in less than 1% of treated patients.[30] In patients with inadequate response to MTX, filgotinib monotherapy (100 mg and 200 mg) demonstrated rapid clinical improvement and was generally well tolerated, with no reported cases of tuberculosis or opportunistic infections.[19]

In the referenced study, the combinations of tofacitinib 10 mg plus MTX and filgotinib 200 mg plus MTX were associated with improved efficacy in RA patients refractory to bDMARDs.[28] FINCH 4 further demonstrated that the incidence of serious infections remained low and did not differ significantly between the filgotinib treatment groups and placebo.[31] Serious infections were reported more frequently among older patients and those receiving concomitant immunosuppressive therapy. The observation of lymphopenia in a subset of patients underscores the importance of appropriate infection risk mitigation strategies, including screening for tuberculosis, hepatitis B, and hepatitis C prior to treatment initiation, as well as updating recommended vaccinations.[32]

Adverse event reports in the U.S. Food and Drug Administration Adverse Event Reporting System (FAERS) database for filgotinib are consistent with findings from clinical trials. The FAERS analysis included reports submitted between 2017 and 2025, with data retrieved up to the date indicated in reference.[33] In the system organ class distribution based on FAERS data, infections and infestations constituted the most frequently reported adverse event group, accounting for 108 (42.5%) of 254 reports (Figure 2). These findings indicate that infections constitute commonly reported adverse events associated with filgotinib and are generally mild and clinically manageable.

Overall, available clinical trial and real-world evidence suggests that filgotinib is associated with an infection risk comparable to that of other JAK inhibitors, without a disproportionate increase in serious or opportunistic infections. Its relatively low incidence of herpes zoster and a predominantly mild infection profile support its use in appropriately selected patients, provided that standard infection screening and preventive measures are applied.

Laboratory Findings and Metabolic Effects

Across phase II and III clinical studies involving patients with RA, filgotinib treatment was associated with limited, clinically manageable laboratory abnormalities. Platelet counts showed a mild early decline followed by stabilization; neutrophil levels remained largely unaffected, and no cases of clinically relevant neutropenia were reported.[15,34] Notably, filgotinib demonstrated minimal impact on hemoglobin levels and other hematologic parameters, a finding attributed to its preferential JAK1 inhibition. This observation suggests a potentially favorable laboratory profile, although its clinical significance relative to other JAK inhibitors remains uncertain.[34,35]

Transient, asymptomatic elevations in creatine kinase were observed, consistent with class-related effects reported for other

JAK inhibitors, but these changes did not necessitate clinical intervention.[21]

With respect to metabolic parameters, available data suggest that filgotinib treatment is associated with early, dose-dependent increases in total cholesterol, triglycerides, and high-density lipoprotein levels; low-density lipoprotein-to-high-density lipoprotein ratios generally remain stable, and lipid levels tend to stabilize over time.[15]

Cardiovascular Effects

Available data suggest that the incidence of major adverse cardiovascular events with filgotinib is low and comparable to rates reported for other JAK inhibitors. No clear dose-dependent increase has been observed. Although a modest numerical increase has been noted in older patients (≥65 years), a definitive association with filgotinib dose has not been established.[24,36]

Safety studies indicate an increased risk of venous thromboembolism and pulmonary embolism with tofacitinib in the ORAL surveillance study, whereas no comparable safety signal has been identified for filgotinib. Consistent with this, real-world data from the Scottish cohort reported by Gros et al.[24] did not identify such events, even among patients with established cardiovascular risk factors.[27]

Available evidence from thorough QT studies suggests that short-term, once-daily administration of filgotinib at therapeutic and supratherapeutic doses is not associated with QT interval prolongation.[37]

Malignancies

Compared with the general population, patients with RA have an increased risk of developing malignancies, particularly lymphoma, melanoma, and lung cancer. Although filgotinib is associated with a low overall incidence of malignancies, including non-melanoma skin cancer, a numerically higher incidence of malignancies has been observed in patients aged >65 years receiving the 200-mg dose.[15,36] This observation has been hypothesized to reflect potential suppression of immune surveillance at higher doses. Deaths from pneumonia and lymphoma were infrequently recorded during treatment in the DARWIN 3 study, and the low frequency of these events supports the overall safety profile of filgotinib.[23]

Common Adverse Events

Evidence from clinical studies suggests that treatment discontinuation with filgotinib is most commonly driven by lack of efficacy, whereas adverse events and non-adherence occur less frequently. Patients who discontinued treatment due to inefficacy predominantly had prior exposure to advanced-line DMARDs and JAK inhibitors. Adverse events resulting in discontinuation were generally uncommon and most frequently included gastrointestinal symptoms, dizziness or vertigo, and infections.[8]

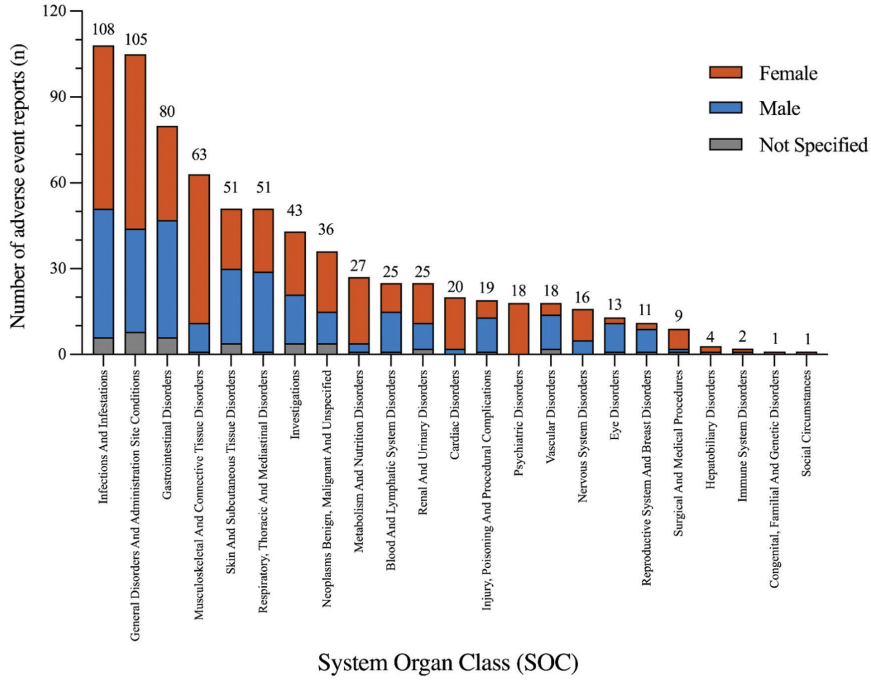

Figure 2. Systematic distribution of adverse event reports associated with filgotinib
Distribution of adverse events associated with filgotinib by system organ class according to the FAERS database (2017-2025)[33]
FAERS: U.S. Food and Drug Administration Adverse Event Reporting Systems

Comparative Perspective: Filgotinib and Other JAK Inhibitors

In patients with RA who had a poor response to bDMARDs, a randomized clinical trial comparing JAK inhibitors, including tofacitinib, baricitinib, filgotinib, and upadacitinib, found that baricitinib and filgotinib were therapeutically comparable to upadacitinib. Nevertheless, further evidence is required because some discrepancies have been reported between the findings for tofacitinib and upadacitinib.[38]

Clinical pharmacology studies indicate that filgotinib can be safely co-administered with therapies commonly used in RA. Phase II and III trials demonstrated that filgotinib does not significantly alter MTX pharmacokinetics and can be be coadministered with MTX without dose adjustment, resulting in improvements in physical function and disease activity.[22,39] In patients without prior MTX exposure, combination therapy demonstrated superior outcomes compared with MTX monotherapy; however, filgotinib monotherapy was inferior to MTX monotherapy in this population.[22] Consistent with these findings, filgotinib 200 mg plus MTX demonstrated disease activity outcomes comparable to those observed with adalimumab plus MTX in MTX-inadequate responders.[20]

Drug-drug interaction studies further support filgotinib's favorable pharmacokinetic profile. No clinically relevant interactions were observed with statins, hormonal contraceptives, P-glycoprotein modulators, or cytochrome P450 3A4 (CYP3A4) substrates, and no dose modification was required when filgotinib was co-administered with these agents.[32,39-42] These findings suggest that filgotinib is compatible with the polypharmacy commonly encountered in RA management.

Indirect comparisons and network meta-analyses indicate broadly comparable efficacy among approved JAK inhibitors in RA. While subtle differences in ranking have been reported, these variations are unlikely to translate into major clinical distinctions at the individual patient level.[38]

From a safety standpoint, all JAK inhibitors share class-wide warnings, and no agent has conclusively demonstrated superior long-term safety. Filgotinib's selectivity may offer theoretical advantages; however, current evidence supports its classification as therapeutically equivalent to, rather than categorically distinct from, other agents within the class.

Positioning Filgotinib: Alternative or Complementary?

Integration of efficacy, safety, and clinical context suggests that filgotinib primarily serves as an alternative advanced therapy in RA management. Its demonstrated efficacy in MTX-refractory and biologic-refractory populations supports its use as a substitute for biologic agents or other JAK inhibitors when prior therapies have failed or are contraindicated.

Filgotinib also complements existing treatment strategies by expanding the therapeutic armamentarium. Its oral administration, consistent efficacy, and acceptable safety profile provide clinicians with greater flexibility in tailoring treatment sequences, particularly in patients with difficult-to-treat RA.

Conclusion and Future Perspectives

Filgotinib represents a meaningful addition to the RA therapeutic landscape. While it does not fundamentally redefine treatment paradigms, it offers an effective alternative among advanced therapeutic options and complements existing strategies by addressing unmet clinical needs. Ongoing real-world data and long-term safety surveillance are expected to further clarify its optimal positioning and inform individualized treatment decisions.

As a result, filgotinib emerges as a well-tolerated targeted therapeutic option, particularly for patients who are intolerant of or do not respond adequately to conventional treatment regimens. Nevertheless, its broad clinical application remains limited in certain regions because regulatory approval has not yet been granted in several countries. Consequently, further evidence is needed to better characterize its long-term safety profile, rare adverse events, and potential drug-drug interactions. Comparative studies supported by pharmacovigilance databases and real-world evidence will be essential to further elucidate its role within therapeutic algorithms.

Footnotes

Author Contributions

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