CZARNECKI, Bartłomiej, WERENKOWICZ, Wiktor, BORAL, Aleksandra, KRYŚ, Dominika, BRZOZA, Joanna, KOCZUR, Julia, GÓRSKI, Michał, PNIOK, Wiktoria and KURKIEWICZ, Wojciech. Modern Strategies in the Pharmacotherapy of Inflammatory Bowel Diseases – A Literature Review. Journal of Education, Health and Sport. 2025;83:60642. eISSN 2391-8306.
https://doi.org/10.12775/JEHS.2025.83.60642
https://apcz.umk.pl/JEHS/article/view/60642

The journal has had 40 points in Minister of Science and Higher Education of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of 05.01.2024 No. 32318. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).
Punkty Ministerialne 40 punktów. Załącznik do komunikatu Ministra Nauki i Szkolnictwa Wyższego z dnia 05.01.2024 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).
The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 29.04.2025. Revised: 25.05.2025. Accepted: 25.06.2025. Published: 01.07.2025.

Modern Strategies in the Pharmacotherapy of Inflammatory Bowel Diseases – A Literature Review

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Abstract

Introduction and Aim:

Inflammatory bowel diseases (IBD), including Crohn's disease and ulcerative colitis, are chronic, immune-mediated disorders of the gastrointestinal tract. Conventional therapies, such as corticosteroids, immunosuppressants, and biologics, do not consistently induce long-term remission and carry a risk of adverse events. This review aims to evaluate and compare three novel small-molecule oral agents—ozanimod, filgotinib, and upadacitinib—in terms of their mechanisms of action, clinical efficacy, and safety profiles in the treatment of IBD.

Materials and Methods:

This study is a literature review based on data from Phase I–III clinical trials and pharmacological analyses retrieved from PubMed and ClinicalTrials.gov. Major registration studies (e.g., TRUE NORTH, SELECTION, U-ACHIEVE) and comparative publications on long-term efficacy and safety were included.

Results:

Ozanimod has demonstrated efficacy in ulcerative colitis by modulating S1P1 and S1P5 receptors, with a favorable safety profile. Filgotinib, a selective JAK1 inhibitor, offers a good balance between efficacy and low thrombotic risk, particularly in biologic-naive patients. Upadacitinib shows rapid and robust clinical responses, including in treatment-refractory populations, though it requires closer safety monitoring due to potential adverse effects.

Conclusions:

Ozanimod, filgotinib, and upadacitinib enrich current IBD treatment strategies. Their distinct pharmacological and safety profiles enable more personalized therapeutic approaches. Further comparative studies and the development of predictive biomarkers are essential for optimizing treatment selection and improving patient outcomes.

Keywords:
Inflammatory Bowel Disease (IBD), Ulcerative Colitis, Crohn's Disease, Ozanimod, Filgotinib, Upadacitinib, JAK Inhibitors, S1P Receptor Modulators.

Introduction and Background:

Inflammatory bowel diseases (IBD), which include Crohn's disease (CD) and ulcerative colitis (UC), are chronic, immune-mediated conditions characterized by relapsing inflammation of the gastrointestinal tract. Over recent decades, their incidence and prevalence have increased distinctly, particularly in industrialized countries, resulting in a growing global disease burden [1]. The etiology of IBD is multifactorial, involving genetic predisposition, environmental factors, gut microbiota alterations, and an inappropriate immune response to intestinal antigens [2].

Traditional therapeutic approaches, including corticosteroids, aminosalicylates, thiopurines, and anti-TNF biologics, have significantly improved disease control for many patients. However, a substantial proportion of individuals experience primary non-response, secondary loss of response, or adverse events necessitating treatment discontinuation [3]. These challenges have catalyzed the development of novel therapeutic agents aimed at more precisely targeting disease mechanisms while offering improved convenience and tolerability.

Among these newer agents, small-molecule oral therapies have emerged as a promising class. These include Janus kinase (JAK) inhibitors, which modulate intracellular signaling pathways associated with pro-inflammatory cytokines, and sphingosine-1-phosphate (S1P) receptor modulators, which interfere with lymphocyte trafficking [4,5]. Unlike biologics, these drugs are administered orally, do not induce anti-drug antibodies, and may provide faster onset of action [6].

Three agents—ozanimod, filgotinib, and upadacitinib—represent innovative therapeutic strategies in this category. Ozanimod selectively targets S1P1 and S1P5 receptors to limit lymphocyte egress from lymph nodes, reducing intestinal immune infiltration [7]. Filgotinib and upadacitinib are selective JAK1 inhibitors that suppress signaling from key cytokines such as IL-6, IL-12, and IFN-γ, thereby diminishing mucosal inflammation [8,9]. These agents have demonstrated efficacy in pivotal phase 3 clinical trials, particularly in moderate-to-severe UC and CD, and are now integrated into international treatment guidelines [10].

The aim of this literature review is to synthesize current evidence regarding the pharmacology, clinical efficacy, and safety of ozanimod, filgotinib, and upadacitinib in IBD. It further seeks to contextualize their roles within the evolving treatment landscape and identify future directions in therapy optimization.

Pathophysiology of IBD and Therapeutic Targets

Inflammatory Bowel Diseases (IBD), encompassing Crohn's Disease (CD) and Ulcerative Colitis (UC), are chronic, relapsing inflammatory disorders of the gastrointestinal tract. Their pathogenesis involves a complex interplay of genetic predisposition, environmental factors, gut microbiota, and immune system dysregulation. A hallmark of IBD is the aberrant immune response leading to sustained intestinal inflammation.

Inflammatory Mechanisms in IBD

The immune dysregulation in IBD is characterized by an imbalance between pro-inflammatory and anti-inflammatory cytokines. Key pro-inflammatory cytokines implicated include tumor necrosis factor-alpha (TNF-α), interleukins such as IL-6, IL-12, IL-17, IL-23, and interferon-gamma (IFN-γ). These cytokines perpetuate inflammation by promoting the recruitment and activation of immune cells, disrupting the intestinal barrier, and inducing tissue damage [11].

Lymphocyte migration to the intestinal mucosa is mediated by adhesion molecules and chemokine receptors, such as integrin α4β7 and CCR9, facilitating the homing of T cells to the gut. This targeted migration contributes to the localized inflammation observed in IBD [12].

Therapeutic Targets: JAK Inhibitors and S1P Modulators

Advancements in understanding the molecular pathways of IBD have led to the development of targeted therapies.

Janus Kinase (JAK) Inhibitors: JAKs are intracellular tyrosine kinases that transduce signals from various cytokine receptors via the JAK-STAT pathway. Inhibiting JAKs can modulate the signaling of multiple pro-inflammatory cytokines simultaneously. Selective JAK1 inhibitors, such as filgotinib and upadacitinib, have shown efficacy in reducing inflammation and inducing remission in IBD patients [13].

Sphingosine-1-Phosphate (S1P) Receptor Modulators: S1P is a lipid mediator that regulates lymphocyte egress from lymphoid tissues. Modulators like ozanimod bind to S1P receptors, particularly S1P1, sequestering lymphocytes in lymph nodes and preventing their migration to inflamed intestinal tissues. This mechanism reduces lymphocyte-mediated inflammation in the gut [14].

Potential of Targeted Therapies in Disease Pathogenesis

Targeted therapies offer a strategic approach to modulate specific components of the immune response implicated in IBD. By inhibiting key cytokine signaling pathways or lymphocyte trafficking, these therapies aim to restore immune homeostasis, reduce inflammation, and promote mucosal healing. The specificity of these agents allows for effective disease control with potentially fewer systemic side effects compared to traditional immunosuppressive treatments [15].

Continued research into the molecular mechanisms of IBD will further refine these therapeutic strategies, enhancing their efficacy and safety profiles, and paving the way for personalized medicine approaches in the management of IBD [15].

Pharmacological Characteristics of the Medicaments:

Ozanimod is an oral selective sphingosine-1-phosphate (S1P) receptor modulator that primarily targets S1P1 and S1P5 receptors. Its mechanism of action involves preventing the egress of lymphocytes from lymphoid tissues by downregulating S1P1 receptor signaling, thereby reducing the number of circulating T and B cells available to infiltrate inflamed intestinal tissue [16].

This lymphocyte sequestration mechanism is key to its anti-inflammatory effect, as it directly impacts immune cell trafficking, a critical component of the inflammatory cascade in IBD [16]. In the TRUE NORTH clinical trial, ozanimod was shown to effectively reduce inflammatory activity in patients with moderate-to-severe ulcerative colitis [17].

Ozanimod has a favorable pharmacokinetic profile with a gradual onset of action and a half-life that supports once-daily dosing. It is administered orally, which contributes to patient compliance. Its pharmacodynamics allow for receptor modulation with relatively minimal off-target activity, reducing the risk of bradycardia and other cardiovascular adverse effects seen in non-selective S1P modulators [18].

Filgotinib is a selective inhibitor of Janus kinase 1 (JAK1), an intracellular enzyme that mediates signal transduction from several pro-inflammatory cytokine receptors, including IL-6, IL-12, IL-23, and IFN-γ [19]. By selectively inhibiting JAK1 over JAK2, JAK3, and TYK2, filgotinib minimizes unwanted hematologic and immune-related side effects while still exerting a potent anti-inflammatory response [19].

This selective inhibition results in suppression of cytokine-induced inflammation, thereby reducing mucosal injury and disease symptoms. In clinical trials, including the SELECTION

and DIVERSITY studies, filgotinib demonstrated significant efficacy in both induction and maintenance of remission in IBD patients [20].

Pharmacologically, filgotinib is administered orally once a day and has a favorable safety profile, including a lower risk of thromboembolic complications compared to less selective JAK inhibitors. It is rapidly absorbed, with a relatively short half-life that limits systemic accumulation and supports a fast onset of action [21].

Upadacitinib is another selective JAK1 inhibitor developed to reduce the pro-inflammatory cytokine signaling associated with IBD pathogenesis. Similar to filgotinib, it inhibits the JAK-STAT signaling pathway involved in the action of multiple interleukins and interferons [22].

Compared to other JAK inhibitors like tofacitinib (which inhibits JAK1 and JAK3), upadacitinib demonstrates a higher selectivity for JAK1, which may translate to improved efficacy and reduced off-target effects [22]. In the U-ACHIEVE and U-EXCEED trials, upadacitinib showed robust results in inducing and maintaining clinical and endoscopic remission in both UC and CD patients [23].

From a pharmacodynamic perspective, upadacitinib is characterized by potent and sustained JAK1 inhibition with a half-life that supports once-daily oral administration. Its safety profile includes manageable adverse events such as acne, nasopharyngitis, and transient liver enzyme elevations [24]. However, careful monitoring remains necessary, particularly for infection risk and thromboembolic events in higher-risk populations [24].

Review of Clinical Trials

Ozanimod

One of the most pivotal clinical trials investigating ozanimod in ulcerative colitis (UC) is the **TRUE NORTH** phase 3 trial. This double-blind, placebo-controlled study evaluated both induction and maintenance therapy in patients with moderately to severely active UC. Results demonstrated that ozanimod significantly improved clinical remission rates at week 10 (induction) and maintained remission through week 52 (maintenance) compared to placebo [25].

In terms of clinical efficacy, ozanimod led to notable improvements in endoscopic healing, symptomatic relief, and biomarker reductions (e.g., C-reactive protein and fecal calprotectin) [25]. Importantly, the drug showed consistent benefits across biologic-naive and biologic-experienced patient subgroups.

Ozanimod exhibited a favorable safety profile in the TRUE NORTH trial. Common adverse events included nasopharyngitis, headache, and elevated liver enzymes. Notably, the risk of bradycardia or serious infection was low, likely due to ozanimod's gradual receptor engagement and selectivity for S1P1 and S1P5 [26].

Filgotinib

Filgotinib has been evaluated in two key clinical programs for IBD: the **SELECTION** trial for ulcerative colitis and the ongoing **DIVERSITY** trial for Crohn's disease.

In the SELECTION study, filgotinib (particularly the 200 mg dose) was associated with significantly higher rates of clinical remission at week 10 in biologic-naive patients compared to placebo. The drug also demonstrated sustained remission through week 58 in the maintenance phase [27].

Filgotinib's efficacy was linked to rapid symptom improvement and mucosal healing. It was generally well tolerated, although there were some reports of headache, nausea, and nasopharyngitis. Importantly, filgotinib exhibited a low incidence of venous thromboembolism and serious infections, which is notable for a JAK inhibitor [28].

The DIVERSITY study (phase 3) is ongoing, with interim results supporting the utility of filgotinib in Crohn's disease. Early-phase trials have suggested efficacy in symptom reduction and endoscopic response, particularly in biologic-refractory populations [29].

Upadacitinib

Upadacitinib has shown strong clinical results in both ulcerative colitis and Crohn's disease through the **U-ACHIEVE** and **U-EXCEED** trial programs.

In U-ACHIEVE (a phase 3 program for UC), upadacitinib demonstrated significant efficacy in achieving clinical remission by week 8, with improvements in stool frequency, rectal bleeding, and endoscopic appearance [30]. At the maintenance phase (week 52), the drug maintained remission in a substantial proportion of patients, including those previously treated with biologics.

The **U-EXCEED** study, a global phase 3 trial in Crohn's disease, revealed similarly encouraging results. Upadacitinib outperformed placebo in terms of clinical response and endoscopic improvement, even in patients with prior biologic failure [31].

When compared to existing biologic therapies, upadacitinib showed competitive or superior efficacy, especially in inducing rapid symptom control. Adverse events included acne, increased creatine kinase, and liver enzyme elevations. Though rare, serious infections and herpes zoster reactivation have been reported, necessitating periodic monitoring [32].

Comparative Analysis

The development of oral small-molecule therapies such as ozanimod, filgotinib, and upadacitinib marks a paradigm shift in the management of inflammatory bowel diseases (IBD). These drugs offer advantages over traditional biologics, including easier administration,

potentially faster onset of action, and lack of immunogenicity. Nevertheless, each agent presents unique features in terms of mechanism of action, clinical efficacy, safety profile, and their suitability for specific patient populations.

Ozanimod is a selective sphingosine-1-phosphate (S1P) receptor modulator that primarily targets S1P1 and S1P5. By preventing lymphocyte egress from secondary lymphoid organs, ozanimod reduces lymphocytic infiltration into inflamed intestinal mucosa. The phase 3 TRUE NORTH trial demonstrated its effectiveness in inducing and maintaining clinical remission in moderate-to-severe ulcerative colitis (UC). Notably, ozanimod provided significant improvements in endoscopic and histologic healing, with a favorable safety profile and minimal systemic immunosuppression [33]. Most adverse events were mild to moderate, including nasopharyngitis, headache, and transient liver enzyme elevation [34]. Ozanimod's gradual receptor engagement mitigates risks of bradycardia and serious infections, making it a viable long-term treatment option, especially for biologic-naïve patients [35].

Filgotinib is a highly selective Janus kinase 1 (JAK1) inhibitor. It blocks intracellular signaling mediated by pro-inflammatory cytokines such as IL-6, IL-12, IL-23, and interferon-gamma. This targeted inhibition disrupts the inflammatory cascade central to IBD pathophysiology. The SELECTION trial, a large phase 2b/3 study, confirmed filgotinib's efficacy in both induction and maintenance phases of UC treatment. The 200 mg dose demonstrated statistically significant improvements in clinical remission and mucosal healing versus placebo [36]. Additionally, filgotinib has shown promise in Crohn's disease through ongoing trials, including the DIVERSITY study [37]. In terms of safety, filgotinib was well tolerated with a low incidence of serious infections or thromboembolic events, a concern seen with broader-spectrum JAK inhibitors [38]. It is particularly attractive for patients at elevated cardiovascular risk or with concerns about immunosuppression-related adverse effects.

Upadacitinib, another selective JAK1 inhibitor, has demonstrated superior efficacy in patients with both UC and Crohn's disease, including those with prior biologic failure. In the U-ACHIEVE and U-EXCEED phase 3 trials, upadacitinib led to rapid induction of clinical remission and sustained efficacy in long-term maintenance [39, 40]. It has been associated with deep mucosal healing and symptom relief within the first weeks of treatment, making it an excellent option for patients requiring rapid disease control. However, its powerful immunomodulatory action comes with a higher risk of adverse effects. Clinical trials and real-world evidence report increased rates of acne, elevated creatine kinase levels, transient liver enzyme elevations, and reactivation of herpes zoster [41]. As with other JAK inhibitors, regulatory agencies recommend routine monitoring for infections, lipids, and liver function

during treatment. Despite these concerns, upadacitinib remains one of the most effective options for refractory or treatment-resistant IBD cases.

In comparative terms, ozanimod offers a safer and more gradual mechanism suited for patients with milder disease or heightened infection risk. Filgotinib provides strong efficacy with minimal systemic toxicity, especially relevant for those concerned with thrombotic events. Upadacitinib, while necessitating more careful safety monitoring, is unmatched in terms of speed and depth of response, particularly valuable in severe or biologic-refractory IBD.

Overall, the choice between these agents should be individualized, taking into account the patient's disease phenotype, treatment history, risk factors, and therapeutic goals. Future head-to-head trials and real-world comparative studies will be crucial in better defining the optimal use of each therapy.

Future Directions

The therapeutic landscape for inflammatory bowel diseases (IBD) is rapidly evolving, shaped by growing insights into disease pathogenesis, immunological mechanisms, and patient-specific treatment responses. While small-molecule therapies like ozanimod, filgotinib, and upadacitinib have significantly expanded the armamentarium available to clinicians, several areas remain the focus of ongoing and future research.

Personalized Medicine and Biomarker-Driven Therapy

One of the most promising directions in IBD management is the integration of personalized medicine. Current treatment strategies are largely based on population-level evidence rather than individual disease biology. However, variability in therapeutic response and adverse event profiles highlights the need for more precise approaches.

Biomarkers—such as serum cytokines, fecal calprotectin, genetic polymorphisms, and pharmacogenomics—are being investigated to predict treatment response and disease prognosis [42]. For example, elevated IL-6 or IFN-γ levels may help identify patients more likely to benefit from JAK inhibitors [43]. Similarly, research into S1P receptor expression could guide patient selection for ozanimod therapy. The ultimate goal is to match patients with the most effective and safest therapy from the outset, improving outcomes and reducing trial-and-error prescribing.

Combination and Sequential Therapy Strategies

As with oncology and rheumatology, there is increasing interest in combining or sequencing targeted therapies to enhance efficacy while minimizing resistance and toxicity. Although current guidelines emphasize monotherapy, preclinical studies and early clinical trials suggest that combining small molecules or pairing them with biologics could offer synergistic benefits

[44]. For example, short-term induction with a JAK inhibitor followed by maintenance with a safer biologic or S1P modulator may balance efficacy and safety. Nonetheless, such strategies require rigorous testing in controlled trials to assess immunologic risks such as infection or malignancy.

Expanding Use in Special Populations

While most clinical trials have focused on adult patients with moderate-to-severe disease, future research is increasingly addressing the use of these therapies in special populations, including pediatric, elderly, pregnant, and immunocompromised patients.

Pediatric IBD remains challenging due to differences in immune development and disease behavior. Trials such as the PEACH study (evaluating upadacitinib in children with UC and CD) are underway to establish age-specific dosing and safety profiles [45]. Similarly, long-term registries are needed to assess the reproductive safety of these agents in pregnant individuals, as data remain limited and extrapolated primarily from rheumatoid arthritis studies [46].

Real-World Evidence and Long-Term Safety

Although randomized controlled trials (RCTs) provide critical efficacy and safety data, real-world studies offer complementary insights into how therapies perform outside of idealized settings. Observational cohorts, national registries, and electronic health record studies will help clarify long-term effectiveness, adherence patterns, and the incidence of rare or delayed adverse events.

This is particularly relevant for JAK inhibitors, where post-marketing surveillance has revealed rare but serious risks including thromboembolic events, reactivation of herpes zoster, and laboratory abnormalities [47]. For ozanimod, extended follow-up is needed to monitor cardiovascular and hepatic safety, especially in patients with comorbidities [48].

New Targets and Emerging Molecules

The pipeline for IBD therapy continues to expand beyond JAK and S1P pathways. Novel agents targeting IL-23, integrins (e.g., αEβ7), TYK2, and gut-homing chemokines are in various stages of development. These include agents such as mirikizumab, etrasimod, and brepocitinib, which may offer additional therapeutic options with unique benefit-risk profiles [49]. Future therapeutic success may lie in identifying mechanistically distinct drugs that can address unmet needs in non-responders or those with extraintestinal manifestations.

Summary, the future of IBD therapy lies in precision, safety, and versatility. While ozanimod, filgotinib, and upadacitinib have each demonstrated significant therapeutic value, ongoing advances will focus on optimizing the right drug for the right patient, at the right time. Combining personalized approaches with emerging molecular targets, clinicians may soon be

able to tailor treatment strategies in a way that maximizes remission and improves long-term quality of life for individuals living with IBD.

Discussion

The emergence of small-molecule therapies such as ozanimod, filgotinib, and upadacitinib has marked a significant advancement in the management of inflammatory bowel diseases (IBD). These agents offer several potential benefits over conventional biologics, including oral administration, lack of immunogenicity, and in some cases, more rapid onset of action [50]. However, despite their promising profiles, questions remain regarding optimal patient selection, long-term safety, and positioning within treatment algorithms.

Current data demonstrate that upadacitinib exhibits the most rapid and profound clinical response among the three agents, with high rates of remission and mucosal healing in both ulcerative colitis (UC) and Crohn's disease (CD) [51]. This makes it an attractive choice in patients with severe or refractory disease. However, this efficacy comes with increased vigilance for safety concerns, including serious infections, thromboembolic events, and herpes zoster reactivation, especially in older adults or those with comorbidities [52].

Filgotinib represents a more selective JAK1 inhibitor with a comparatively favorable safety profile. Clinical trials such as SELECTION have shown that it is effective in achieving remission, particularly in biologic-naïve UC patients [53]. Preliminary data from the DIVERSITY trial in CD are encouraging, although more mature data are needed. Importantly, filgotinib has shown a relatively low risk of venous thromboembolism and minimal impact on lipid profiles, which may make it preferable for patients at cardiovascular risk [54].

Ozanimod, acting through modulation of S1P1 and S1P5 receptors, provides a unique mechanism focused on lymphocyte trafficking. Its safety profile is notably favorable, with a lower risk of systemic immunosuppression compared to JAK inhibitors. The TRUE NORTH trial confirmed its efficacy in inducing and maintaining remission in UC [55]. However, some limitations include the gradual onset of action and lack of approval (so far) in CD, although studies are ongoing.

There is also a notable gap in head-to-head comparative trials. Most available evidence is derived from placebo-controlled studies, making it difficult to directly compare the efficacy and safety of these agents. Future trials should focus on such direct comparisons, as well as real-world effectiveness in diverse patient populations. Additionally, while these therapies show strong performance in induction and maintenance phases, long-term outcomes such as prevention of complications, hospitalization rates, and surgery remain under-explored [56].

Another area of discussion involves positioning these agents within treatment pathways. Should small molecules be used before biologics in certain patients? Are they suitable as first-line options or better reserved for post-biologic failure? These questions remain open, but data suggest that they may be especially valuable in biologic-experienced populations or patients with a preference for oral therapy [57].

Conclusion

Ozanimod, filgotinib, and upadacitinib have expanded the therapeutic landscape of IBD, offering effective and convenient treatment options for patients with moderate to severe disease. Each drug presents unique pharmacological characteristics, advantages, and potential limitations. Upadacitinib stands out for its rapid and potent anti-inflammatory effects, though careful monitoring is essential. Filgotinib offers a balance of efficacy and safety, particularly suited for patients with cardiovascular comorbidities. Ozanimod, with its novel mechanism, provides a safer immunological profile and is a promising option for UC.

These therapies are not merely additions to the therapeutic arsenal but represent a paradigm shift toward precision medicine in IBD. Their success will depend on the ability to individualize treatment based on disease phenotype, molecular markers, and patient-specific factors. Ongoing research into combination strategies, predictive biomarkers, and their use in special populations will further refine their role in clinical practice.

Ultimately, these small-molecule agents are poised to play a central role in future IBD management, helping to bridge the gap between efficacy, safety, and patient quality of life.

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All authors have read and agreed with the published version of the manuscript.

Conflict of interest

The authors report no conflict of interest.

Financial disclosure

The study did not receive any funding.

Institutional Review Board Statement

Not applicable.

Informed Consent Statement

Not applicable.

Data Availability Statement

Not applicable.

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