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JAK Inhibitors Safety in Ulcerative Colitis: Practical Implications

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Abstract

Janus kinase inhibitors [JAKi] are a new class of small molecule drugs that modulate inflammatory pathways by blocking one or more JAK receptors, and are increasingly being used in the treatment of immune-mediated diseases. Tofacitinib, a non-selective JAKi, is now approved for moderate-to-severe ulcerative colitis [UC] that is refractory or intolerant to tumour necrosis factor inhibitors [TNFi]. Whereas tofacitinib is associated with the advantages of oral administration, rapid onset of action, and lack of immunogenicity over TNFi, there are many safety considerations to take into account such as the risk of thromboembolism, infections, and hyperlipidaemia: each with specific nuances pertaining to prevention and monitoring strategies. Considerations such as pregnancy, breastfeeding, and history of malignancy also are to be navigated with utmost caution, given that very few data are available for guidance. With the use of JAKi in the real world progressively over time, safety implications will become more lucid, including caveats pertaining to JAK selectivity and gut-selective JAKi, as well as mechanistic data pertaining to adverse effects. This Viewpoint serves as a practical guide for clinicians managing inflammatory bowel disease [IBD] patients to navigate safety concerns around JAKi, including preventive and monitoring strategies.

Key Words: Inflammatory bowel diseases; ulcerative colitis; JAK inhibitors; tofacitinib; drug safety; adverse effects; monitoring; preventive; clinical care

1. Introduction

Janus kinase inhibitors [JAKi] are being increasingly used for the treatment of inflammatory bowel diseases [IBD] and other immune-mediated diseases. These are small molecule drugs with the advantages of oral administration, rapid onset of action, short half-life, and lack of immunogenicity, over biologics. JAKs represent a group of four membrane-bound receptors, which via the signal transducer and activator of transcription proteins [STAT] pathway, mediate regulation of genes that code for diverse inflammatory proteins.[1] These receptors are JAK1, JAK2, JAK3, and TYK2, each with mainly discrete and some overlapping functions.[1,2] Therefore, JAK selectivity as well as dose impact on the efficacy and safety of various JAKi.[1] Tofacitinib, a pan-JAK inhibitor with higher inhibitory activity for JAK1 and JAK3, is approved for the treatment of moderate-to-severe ulcerative colitis [UC], non-responsive to conventional therapy, after its efficacy over placebo was demonstrated for induction and maintenance of remission in the OCTAVE 1 and 2 and SUSTAIN trials.[3] Upadacitinib and filgotinib are JAK1 selective and are in phase 3 clinical trials for the therapy of Crohn's disease [CD] and UC [NCT03345836, NCT02819635, NCT02914561],[4–6] and TD-1473 [non-selective inhibitor of JAK1, 2, and 3 and TYK2 with exclusive enteral distribution] is in phase 2–3 trials for CD and UC [NCT03635112, NCT03758443].[7,8] Other JAKi have been studied for rheumatoid arthritis [RA] treatment, and additional ones are in development.

In this brief viewpoint, we focus on the main adverse effects associated with tofacitinib for the treatment of UC, which are relevant to the practising clinician. We then propose practical recommendations

on how to manage JAKi therapy in UC patients, including preventive care and monitoring. For a comprehensive review of JAKi safety, we refer readers to the several excellent and detailed works on the topic referenced in this Viewpoint.

2. Infections

2.1. Herpes zoster

JAKi, across studies in RA, psoriasis, and UC, are associated with an increased incidence of herpes zoster [HZ] infection or shingles.[9–11] In a pooled analysis of phase 2, 3, maintenance, and open label extension [OLE] global tofacitinib data on 1157 UC patients (1612.8 patient-years [PY] of exposure), 65 [5.6%] patients developed 69 events of HZ infection with incidence rate of 4.1 per 100 PY (95% confidence interval [CI] 3.1–5.2).[11] In this analysis, the risk of HZ with tofacitinib 10 mg twice daily was higher [6.6 per 100 PY; 95% CI 3.2–12.2], compared with 5 mg twice daily [2.1 per 100 PY; 95% CI 0.4–6.0] and placebo [1.0 per 100 PY; 95% CI 0–5.4]: suggesting a dose-response relationship. The majority of HZ events [51/69, 74%] had limited dermatomal distribution[11] which is consistent with tofacitinib data from clinical trial in RA and psoriasis.[9,10] Twelve events were multidermatomal HZ, and six were disseminated HZ, of which one was complicated by encephalitis; 16 patients withheld tofacitinib temporarily and five ultimately discontinued the study drug.[11] Risk factors for HZ include older age (hazard ratio [HR] 1.58; 95% CI 1.34–1.87; p <0.0001 for every 10-year increase in age) and previous tumour necrosis factor inhibitor [TNFi] failure [HR 1.92; 95% CI 1.15–3.21; p = 0.0122]. Whereas there was a trend toward higher risk in Asian patients [HR 1.76; 95% CI 0.97–3.19; p = 0.0612], this was not significant.[11] In a meta-analysis of 21 RA clinical trials, the risk of HZ was higher for baricitinib than placebo (incidence rate ratio [IRR] 2.86; 95% CI 1.26–6.50), but not for tofacitinib or upadacitinib [IRR 1.38; 95% CI 0.66–2.88, and 0.78 95% CI 0.19–3.22, respectively].[12]

Other data suggest a higher risk of HZ with JAKi use in Asia, particularly in Japan and Korea, compared with Western countries. In a post-hoc analysis of pooled data on tofacitinib in RA patients in the Asia Pacific, the incidence rate per 100 PY of HZ was higher [0.7; 95% CI 0.5–1.0], compared with that in the global population [0.3; 95% CI 0.2–0.3].[13] Genome-wide meta-analysis data suggest that these differences may be mediated by single nucleotide polymorphisms [SNPs] near the CD83 or IL17RB genes; such SNPs are implicated in immune pathways that mediate response to HZ, and are more frequent in East Asians than Caucasians.[14]

In phase 2 clinical trials for the treatment of moderate-severe CD, one case of HZ in the filgotinib trial [1/152, up to 20 weeks of follow-up] and one case in the upadacitinib trial [1/183, up to 16 weeks of follow-up] were observed. Although no significant risk was found compared with placebo, these results should be interpreted with caution as the trials were of short duration and tested a range of doses, some of which were ineffective.[15,16]

Current recommendations are to treat HZ with anti-virals in all IBD patients regardless of immunosuppression, in consultation with an infectious diseases specialist, for at least 7 days if immunosuppressed, or for 2 additional days after all skin lesions have crusted over.[17] The choice of anti-viral can be oral in uncomplicated cases, and intravenous in complicated, ophthalmic, multidermatomal, or disseminated HZ. Urgent ophthalmological consultation is recommended in ophthalmic HZ.[17] Most patients in the UC, RA, and psoriasis trials were able to continue tofacitinib through the course of HZ infection, whereas others temporarily discontinued and restarted after resolution of infection; even fewer patients discontinued it permanently.[10,11,18]

HZ risk associated with tofacitinib is preventable with vaccination. The adjuvanted recombinant HZ subunit vaccine [Shingrix] became available in 2017, is administered intramuscularly as two doses 2 months apart, and is effective in preventing HZ in 97.2% [95% CI 93.7–99.0] of persons older than 50 years, including those older than 70 years of age.[19] Although the attenuated subunit zoster vaccine is not studied specifically in UC patients, we recommend that the first dose be administered before starting tofacitinib therapy, followed by the second dose in 2 months. Zostavax, a live attenuated vaccine, is contraindicated in those on immunosuppressive medications,[20] a recommendation that is applicable to JAKi.

2.2. Other infections

In 4.4 years of follow-up data from global UC clinical trials, non-HZ opportunistic infections [OI] were very few and included one case each of cytomegalovirus colitis, cytomegalovirus hepatitis, pulmonary cryptococcosis, and histoplasmosis. Serious non-HZ infections included appendicitis [n = 4], anal abscess [n = 2], and *Clostridium difficile* infection [n = 2]. In the overall cohort, the IR per 100 PY of both non-HZ OI and serious non-HZ infections was 0.2 [95% CI 0.1–0.6]. Higher body weight [90 kg] was a risk factor for serious infections [HR 2.3; 95% CI 1.1–4.8; p = 0.0318].[21] In a meta-analysis of 21 RA trials, serious infections with JAKi were rare and comparable to the baseline risk in the population, [IRR for tofacitinib 1.22; 95% CI 0.60–2.45, for upadacitinib 1.14; 95% CI 0.24–5.43, and for baricitinib 0.80; 95% CI 0.46–1.38].[12]

The risk of tuberculosis [TB] with tofacitinib in pooled RA trials data varied with background risk in the population; IR [per 100 PY] was 0.02 [95% CI 0.003–0.15] in low-, 0.08 [95% CI 0.03–0.21] in medium-, and 0.75 [95% CI 0.49–1.15] in high-incidence countries.[22] In phase 3 studies, no case of TB was reported in the 263 patients with latent TB infection who were given isoniazid prophylaxis concurrently with tofacitinib.[22] The risk of hepatitis B among those on tofacitinib is reported in a small real-world retrospective Taiwanese study, in which 75/116 persons with RA, who were positive for hepatitis B core antibody, did not develop hepatitis B reactivation regardless of surface antigen status. Of those with chronic hepatitis B [hepatitis B surface antigen positive, n = 6], four persons did not receive prophylactic nucleotide analogues, of whom two had reactivation of hepatitis B; both were recaptured with therapy, and the other two who received prophylactic therapy did well.[23]

Based on these data, we recommend testing for TB and hepatitis B and institution of prophylactic therapy as needed, before tofacitinib therapy, similarly to guidance pertaining to TNFi therapy.[24]

3. Venous thromboembolism

In February 2019, the FDA issued a black-box warning after venous thromboembolism [VTE] was reported with the 10 mg twice daily dose [but not lower doses] of tofacitinib for RA among patients >50 years of age and with at least one other cardiovascular risk factor, in an ongoing safety trial, with VTE risk five times that associated with TNFi.[25] This trial is expected to be completed imminently, and will be highly informative. Robust long-term safety data for tofacitinib, especially in the context of the higher dose, are lacking. Tofacitinib has been approved for use in RA and psoriatic arthritis since November 2012 and December 2017, respectively,

the approved doses being 5 mg daily or twice daily.[26] The higher dose of 10 mg twice daily has been approved only since May 2018 for the treatment of moderate to severe UC.[26] Therefore, long-term safety data pertaining to this dose of tofacitinib are even more sparse.

In a pooled analysis of phase 2, phase 3, and OLE studies of tofacitinib for moderate-to-severe UC, with 1613 patients-years' exposure, 4.4 years of follow-up, and with most patients on the 10 mg twice daily dose [83.9%], one death due pulmonary embolism was reported in a patient with pre-existing metastatic cholangiocarcinoma. Major adverse cardiovascular events [MACEs] occurred in four persons, of whom three had underlying cardiovascular risk factors [IR 0.2; 95% CI 0.1–0.6].[21] In a meta-analysis of 26 randomised controlled trials [RCTs], including 11 799 RA patients on various JAKi, there was no significant increase in the risk of overall cardiovascular events [CVEs] (odds ratio [OR] 1.04; 95% CI 0.6–1.76), MACEs [OR 0.80; 95% CI 0.36–1.75], or VTEs [OR 1.16; 95% CI 0.48–2.81]. There was no difference in the risk of CVEs, MACEs, or VTEs between 5 mg or 10 mg a day of tofacitinib, or between 15 mg or 30 mg a day of upadacitinib.[27] Similarly, in a pooled analysis of over 50 000 persons with RA, using claims data from the Truven Marketscan database [2012–2016] and Medicare [2012–2015], the risk of VTE, although numerically higher for tofacitinib (pooled IR per 100 PY for tofacitinib 0.77 [95% CI 0.43–1.27]; for TNFi 0.74 [95% CI 0.65–0.83]), was statistically comparable between the two groups, with a propensity-score adjusted hazard ratio of 1.33 [95% CI 0.78–2.24].[28] Last, using the FDA's Adverse Event Reporting System [FAERS] pertaining to JAKi use between approval and March 31, 2017, there was a trend towards increase in composite thromboembolic adverse events as a class effect, but no increase in deep vein thrombosis and pulmonary embolism.[29]

Although reassuring, the applicability of these data is limited in the context of VTE in UC patients, as they do not reflect risk associated with 10 mg twice daily, which is the dose implicated in VTE risk and used most frequently in UC. They also do not account for the hypercoagulable state associated with active UC. Long-term safety data on high-dose tofacitinib in UC are needed. While we await these, it is prudent to avoid tofacitinib among persons with risk factors for VTE which include age >50 years [based on data from the ongoing safety trial[25]], history of VTE, hypercoagulable state, smoking, immobilisation or reduced mobility, recent trauma or surgery, cardiovascular disease, cancer, obesity, lower limb paralysis, frequent long flights, and hormonal therapy.[30] We also recommend a trial of de-escalation to the maintenance dose of 5 mg twice daily from 10 mg twice daily, once the patient is in endoscopic remission.[3,31]

4. Hyperlipidaemia

In a pooled analysis of 1157 UC patients enrolled in tofacitinib clinical trials, of whom 83.9% of patients received the higher dose of 10 mg twice daily, there was a dose-dependent and reversible increase in total cholesterol, low- and high-density lipoprotein cholesterol [LDL-c, HDL-c] but no increase in MACEs. There were no clinically significant changes in lipid ratios.[32] The Reynolds Risk Score [RRS], which is a predictor of 10-year cardiovascular events taking into account C-reactive protein in addition to traditional risk factors, remained unchanged with tofacitinib therapy. As reported above, four cases of MACEs occurred in these cohorts, of which three had pre-existing risk factors.[32] Similar data indicating increase in lipids, but no increase in MACE risk, are reported in clinical trials of tofacitinib in RA and psoriatic arthritis.[33,34]

We recommend checking the lipid profile at baseline before initiation of tofacitinib, and at Week 8 of treatment. If significantly abnormal, or if additional CV risk factors are noted, cardiac work-up and consideration of lipid-lowering agents are indicated.

5. Pregnancy and breastfeeding considerations

5.1. Pregnancy

There are very few human data on the safety of tofacitinib or other JAKi during pregnancy. Most of our knowledge in this regard is extrapolated from experimental studies. Although there are no data on placental transfer of tofacitinib, it is reasonable to assume that tofacitinib, a small-sized molecule, crosses the placenta.[35] Animal data demonstrate that in rats, at a dose 73 times, but not at 29 times, the therapeutic dose of 10 mg twice daily, tofacitinib was teratogenic and foeticidal.[36] Similarly in rabbits, at a dose 6.3 times, but not 1.5 times, the therapeutic dose of 10 mg twice daily, teratogenic and foeticidal effects and post-implantation loss were noted.[36] Tofacitinib had no impact on male fertility or sperm quality or motility in animal studies.[36] JAK1 maintains primordial ovarian follicle reserve in mice, and JAK1 blockage with ruxolitinib is associated with increased apoptosis, accelerated follicular activation, and loss of follicular reserve.[37] However, clinical data pertaining to these pathways are lacking.

In a pooled analysis of five UC studies, outcomes of maternal [$n = 11$] and paternal [$n = 14$] exposure to tofacitinib in the periconception period or during pregnancy were reported.[35] There were 15 healthy newborns, two spontaneous abortions, two medical terminations, and no foetal or neonatal death or congenital malformation. Data from RA and psoriasis studies are similar reassuring, with healthy newborns being the most common outcome.[38] However, these are very few data over a short period of follow-up, and long-term exposure across multiple pregnancies in the real world will be needed to inform the safety of JAKi in pregnancy.

In the absence of conclusive safety data, JAKi should be avoided in women planning pregnancy; tofacitinib should be avoided for at least i week before conception, given its short half-life.[39] When unavoidable, we recommend discussing the limited safety data around pregnancy with the patient, and advising contraception [non-hormonal] for the duration of JAKi therapy.

5.2. Breastfeeding

Similar to the limited pregnancy data, no human studies have reported outcomes of breastfeeding with JAKi. Tofacitinib is present in rat milk at twice the concentration of that in the serum of lactating rats. The presence of drug in animal milk makes it likely that it would be present in human milk as well.

Until more data become available, the recommendation is to not breastfeed for 18 h after taking tofacitinib.[36,39]

6. Malignancy

In the five tofacitinib trials in UC patients, 11 persons were diagnosed with a malignancy excluding non-melanoma skin cancer [NMSC], all of whom had previous treatment with thiopurines and eight had previously been treated with TNFi.[21] All reported malignancies were discrete and included cervical cancer, hepatic

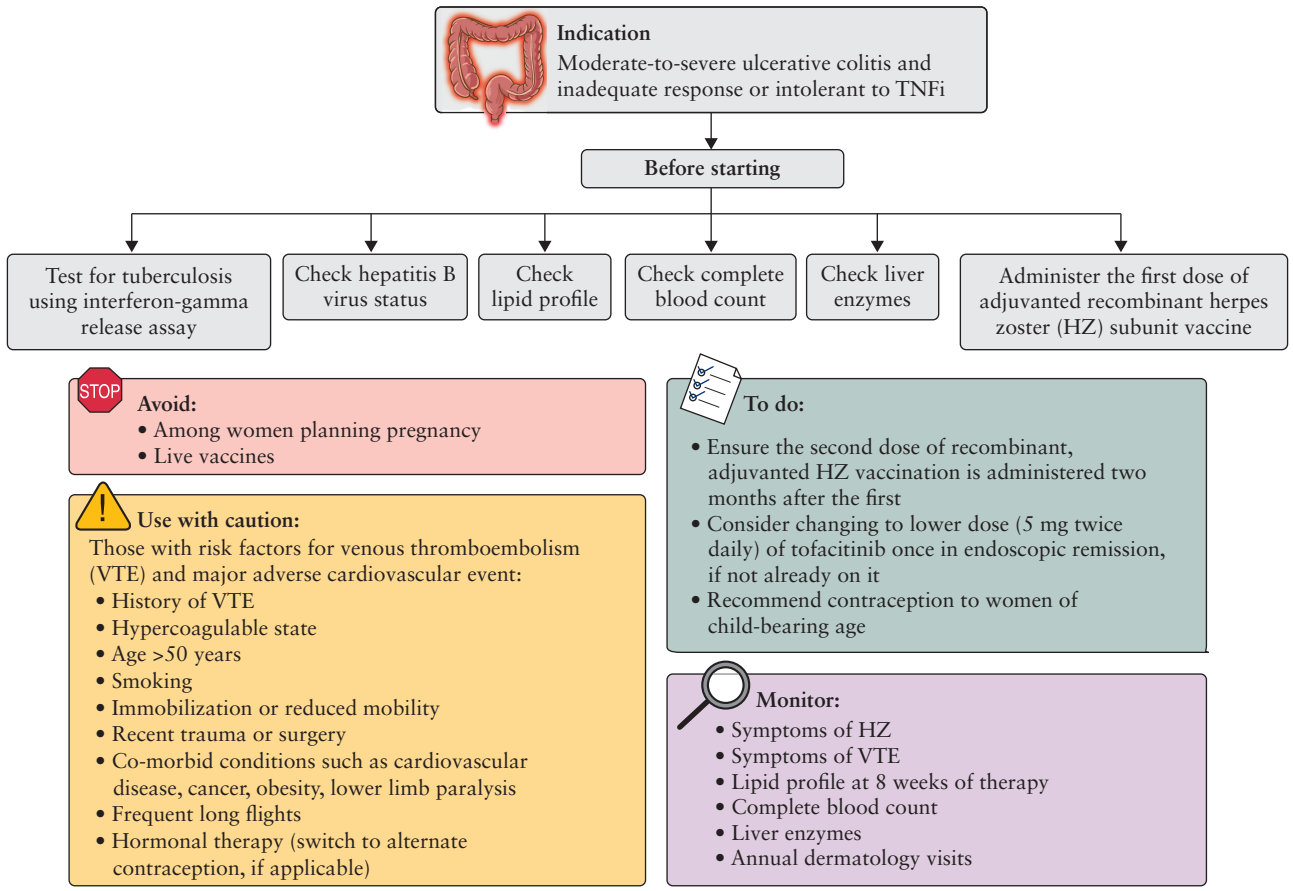

Figure 1. Strategies to navigate safety concerns pertaining to tofacitinib for the treatment of moderate-to-severe ulcerative colitis. TNFi, tumour necrosis factor inhibitors.

angiosarcoma, cholangiocarcinoma, cutaneous leiomyosarcoma, Epstein-Barr virus-associated lymphoma, renal cell carcinoma, essential thrombocythaemia, acute myeloid leukaemia, adenocarcinoma of colon, lung cancer, and breast cancer. Eleven patients with NMSC were reported, of whom 6, 10, and 10 had previous history of NMSC, previous therapy with thiopurines, and previous therapy with TNFi, respectively The incidence rates of malignancy [excluding NMSC] and NMSC were each 0.7 [95% CI, 0.3–1.2] per 100 PY of exposure.[21] In a network meta-analysis comparing various biologic therapies and JAKi for RA in clinical trials and long-term extension studies, malignancy risk was insignificant across all drugs [OR 1.68; 95% CI 0.48–5.92 for infliximab, 1.15; 95% CI 0.24–5.47 for tofacitinib].[40]

At this time, there are not enough data to determine cancer risk due to tofacitinib and other JAKi. In the absence of clear evidence, it is prudent to avoid JAKi, or use them with caution among those with history of cancer. Similarly, for patients who develop cancer while on JAKi therapy, we would advise switching to a medication with a more acceptable safety profile, if feasible.

7. Gastrointestinal perforation

In the overall cohort of UC patients on tofacitinib, the three cases of perforation were: one patient on tofacitinib 10 mg twice daily who had active colitis, concomitant steroid use, and recent endoscopy; another in OLE, on non-steroidal anti-inflammatory drugs, who was noted to have perforated appendicitis; and a third in OLE with sigmoid colon perforation at the site of Epstein-Barr virus lymphoma.[21] Two patients with CD, who received the higher dose of upadacitinib [each received 24 mg twice daily and 24 mg daily], experienced small bowel perforations.[16] Similarly, in pooled data from tofacitinib trials in RA, 22 perforations [IR 0.11; 95% CI 0.07–0.17] were reported. These rates were similar between the two doses of 5 mg and 10 mg twice daily. Interestingly, all patients were on concomitant therapy with corticosteroids [$n = 3$], non-steroidal anti-inflammatory drugs [$n = 9$], or both [$n = 10$].[41]

No signal pertaining to perforation risk has been reported with JAKi in the real world, but we advise vigilance, especially in the context of concerning symptoms.

8. Others

Given that JAK2 signalling is involved in the haematopoiesis,[42] JAK inhibition may lead to altered blood cell counts. Tofacitinib, a pan-JAK inhibitor, has been associated with an initial decrease in haemoglobin and neutrophil, lymphocyte, and platelet counts, although these changes were mild and reversible.[2,43] In contrast, no significant change in lymphocyte or neutrophil counts was reported with filgotinib, a JAK1 selective inhibitor. It is reasonable to monitor complete blood count [CBC] after initiating tofacitinib and to be specially cautious in initiating tofacitinib in persons with significant anaemia or leucopenia. JAK inhibitors were related to the minimally elevated level of serum liver transaminases and creatine kinase, but they did not result in clinically noticeable changes.[44]

9. Conclusion

Overall, tofacitinib can be used safely to treat refractory UC so long as all relevant risks are considered before treatment, informed decisions are made jointly with the patient, and preventive and monitoring strategies are in place [Figure 1]. Of course, while considering the risk/benefit profile of the drug, we must also take into account the risks associated with untreated disease, and those associated with other available therapeutic options. It is also relevant to reiterate here that rare, serious, and clinically meaningful adverse effects can take several years of real-word data before becoming apparent, and that post-marketing surveillance strategies, such as the Sentinal Network and spontaneous adverse event reporting, are critical to recognising a drug's safety profile over time.[45,46]

Future research pertaining to the impact of JAK selectivity on the adverse effect profile of JAKi will be highly informative. Phase 1b data on TD-1473, a pan-JAK inhibitor distributed exclusively in the intestinal tract, suggest minimal systemic distribution in UC patients,[15] and further safety and efficacy data are awaited. Last, mechanistic data on the risk of VTE, hyperlipidaemia, and other adverse effects associated with JAKi will help identify strategies to minimise and prevent these.

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Conflict of Interest

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Author Contributions

MA and ESK: concept, literature search, drafting of manuscript and critical revision of the manuscript for important intellectual content. JFC: concept and critical revision of the manuscript for important intellectual content. All authors approved the final version of the manuscript.

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