Tomoya Okazaki, MD, PhD

Author Affiliation: Department of Emergency and Critical Care Medicine, Tokyo Bay Urayasu Ichikawa Medical Center, Urayasu, Japan.

Corresponding Author: Tomoya Okazaki, MD, PhD, Department of Emergency and Critical Care Medicine, Tokyo Bay Urayasu Ichikawa Medical Center, 3-4-32 Todaijima, Urayasu 279-0001, Japan (tomoyaokazaki4028@gmail.com).

Published Online: January 22, 2025. doi:10.1001/jama.2024.25527

Conflict of Interest Disclosures: None reported.

1. Greer DM, Helbok R, Badjatia N, Ko SB, Guanci MM, Sheth KN; INTREPID Study Group. Fever prevention in patients with acute vascular brain injury: the INTREPID randomized clinical trial. *JAMA*. 2024;332(18):1525-1534. doi:10.1001/jama.2024.14745

2. Commichau C, Scarmeas N, Mayer SA. Risk factors for fever in the neurologic intensive care unit. *Neurology*. 2003;60(5):837-841. doi:10.1212/01.WNL.0000047344.28843.EB

3. Dahyot-Fizelier C, Lasocki S, Kerforne T, et al; PROPHY-VAP Study Group and the ATLANREA Study Group. Ceftriaxone to prevent early ventilator-associated pneumonia in patients with acute brain injury: a multicentre, randomised, double-blind, placebo-controlled, assessor-masked superiority trial. *Lancet Respir Med*. 2024;12(5):375-385. doi:10.1016/S2213-2600(23)00471-X

4. Taccone FS, Rynkowski Bittencourt C, Møller K, et al; TRAIN Study Group. Restrictive vs liberal transfusion strategy in patients with acute brain injury: the TRAIN randomized clinical trial. *JAMA*. 2024;332(19)1623-1633. doi:10.1001/jama.2024.20424

5. Hocker SE, Tian L, Li G, Steckelberg JM, Mandrekar JN, Rabinstein AA. Indicators of central fever in the neurologic intensive care unit. *JAMA Neurol*. 2013;70(12):1499-1504. doi:10.1001/jamaneurol.2013.4354

In Reply We appreciate Dr Okazaki's comments regarding the INTREPID study[1] and the interplay with ICU length of stay. Concerning the severity of primary brain injury and its correlation with ICU length of stay, several principles are important to consider. We enrolled a heterogeneous population, including ischemic stroke, ICH, and SAH, each with relatively predictable ICU courses.[2] For patients with ischemic stroke, the risk of swelling after stroke typically peaks around 3 to 5 days. For patients with ICH, while the swelling risk period (not the hematoma expansion period) is more unpredictable and varies among individual patients, it is generally longer than for ischemic stroke. Regarding patients with SAH, although they require extended monitoring for delayed cerebral ischemia, they may have periods of relative stability. Contrary to Okazaki's suggestion that enrolled patients were of "lower severity," the mean National Institutes of Health Stroke Scale score was 17.7 in the fever prevention group and 17.0 in the standard care group. The mean Glasgow Coma Scale score was 10.8 in both groups, and most enrolled patients with ICH and SAH were of higher grade based on the ICH and World Federation of Neurological Surgeons scores, respectively. Furthermore, we have not yet analyzed which patients were more or less likely to experience fever, so the effect of severity of injury is unknown at this time.

Okazaki's proposal that the relationship between fever and longer ICU stay could be "bidirectional" is reasonable. Patients with acute vascular brain injury are at risk for both central and infectious fever, with the latter likely being more common with longer ICU stays due to prolonged intubation, urinary catheterization, immobility, and other causes. However, because the 2 groups in this study were evenly matched, there is no reason to expect different underlying causes of fever between the groups. Thus, we can presume that there was an equal distribution of fever etiologies that would not significantly affect our findings.

We fully agree that accurately predicting which patients will develop a fever after acute vascular brain injury will be important for clinical trial selection in upcoming studies, and we look forward to presenting these data in the future.

David M. Greer, MD, MA
Kevin N. Sheth, MD

Author Affiliations: Boston University Chobanian and Avedisian School of Medicine, Boston Medical Center, Boston, Massachusetts (Greer); Yale University School of Medicine, Yale New Haven Hospital, New Haven, Connecticut (Sheth).

Corresponding Author: David M. Greer, MD, MA, Department of Neurology, Boston Medical Center, 85 E Concord St, First Floor, Boston, MA 02118 (dgreer@bu.edu).

Published Online: January 22, 2025. doi:10.1001/jama.2024.25530

Conflict of Interest Disclosures: Dr Sheth reported receiving grants from Bard to Yale during the conduct of the study, grants from Hyperfine and Biogen to Yale, and grants from the National Institutes of Health and American Heart Association; serving on the advisory board from Astrocyte; consulting for CSL Behring, Bexorg, Rhaeos, and BrainQ; serving on the data and safety monitoring boards for Sense DSMB and Phillips; and being cofounder of Alva.

1. Greer DM, Helbok R, Badjatia N, Ko SB, Guanci MM, Sheth KN; INTREPID Study Group. Fever prevention in patients with acute vascular brain injury: the INTREPID randomized clinical trial. *JAMA*. 2024;332(18):1525-1534. doi:10.1001/jama.2024.14745

2. Greer DM, Ritter J, Helbok R, et al. Impact of Fever Prevention in Brain-Injured Patients (INTREPID): study protocol for a randomized controlled trial. *Neurocrit Care*. 2021;35(2):577-589. doi:10.1007/s12028-021-01208-1

Risankizumab for Ulcerative Colitis

To the Editor The INSPIRE and COMMAND studies[1] provided important insights into the efficacy and safety of risankizumab for treatment of moderately to severely active ulcerative colitis.

However, it is important to address the racial and ethnic underrepresentation in these studies. According to a national survey of 4 administrative datasets in the US, the prevalence of ulcerative colitis in White individuals is significantly higher than in Black individuals. Similarly, based on a study[2] published in 2017, the prevalence of inflammatory bowel disease in the US was 812 per 100 000 White individuals compared with 504 per 100 000 Black individuals. In the INSPIRE and COMMAND studies,[1] 0.2% of patients (19/975) in the induction trial were Black individuals vs 69.4% (677/975) who were White individuals; the percentages were similar in the maintenance trial, 0.5% (7/548) vs 74.3% (407/548), respectively. This racial imbalance is a substantial limitation because it may affect the generalizability of the findings across diverse populations.

Another trial[3] (also published in 2024) exemplified this issue. In this study,[3] which compared risankizumab and ustekinumab for patients with moderate to severe Crohn disease, 3.3% of the patients (17/520) were Black individuals vs 73.7% (383/520) who were White individuals.

This disparity in representation is concerning because Black patients with inflammatory bowel disease often experience diagnostic delays and may receive different treatment regimens that potentially lead to poorer outcomes.[4]

It is important to include a more representative patient population in future trials to ensure the findings from these pivotal studies[1] are more broadly applicable, and to enhance the robustness and relevance of clinical research outcomes for all racial and ethnic groups affected by inflammatory bowel disease. In addition, more research is necessary to understand and mitigate the disparities in diagnosis, treatment, and outcomes between Black patients and White patients with inflammatory bowel disease.

Peng Li, MD

Author Affiliation: Beijing Hospital, National Center of Gerontology, Beijing, China.

Corresponding Author: Peng Li, MD, Beijing Hospital, 1 Dahua Rd, Beijing 100730, China (lipbenzi@126.com).

Published Online: January 22, 2025. doi:10.1001/jama.2024.25640

Conflict of Interest Disclosures: None reported.

1. Louis E, Schreiber S, Panaccione R, et al; INSPIRE and COMMAND Study Group. Risankizumab for ulcerative colitis: two randomized clinical trials. *JAMA*. 2024;332(11):881-897. doi:10.1001/jama.2024.12414

2. Ng SC, Shi HY, Hamidi N, et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. *Lancet*. 2017;390(10114):2769-2778. doi:10.1016/S0140-6736(17)32448-0

3. Peyrin-Biroulet L, Chapman JC, Colombel JF, et al; SEQUENCE Study Group. Risankizumab versus ustekinumab for moderate-to-severe Crohn's disease. *N Engl J Med*. 2024;391(3):213-223. doi:10.1056/NEJMoa2314585

4. Lewis JD, Parlett LE, Jonsson Funk ML, et al. Incidence, prevalence, and racial and ethnic distribution of inflammatory bowel disease in the United States. *Gastroenterology*. 2023;165(5):1197-1205, e2. doi:10.1053/j.gastro.2023.07.003

In Reply We appreciate the comments by Dr Li about our recent phase 3 risankizumab ulcerative colitis induction (INSPIRE) and maintenance (COMMAND) studies.[1]

Ulcerative colitis has become a global health challenge, and countries with a historically low incidence have experienced a slow increase in cases. In 2023, the prevalence of ulcerative colitis was estimated to be 5 million cases worldwide.[2] Europe and North America have the highest incidence rates in the world, with urban sites having a higher prevalence than less populated regions.[3] In 2020, the prevalence of inflammatory bowel disease in the US varied by race and ethnicity[4]; the prevalence was 403 (95% CI, 373-433) per 100 000 Asian individuals, 504 (95% CI, 482-526) per 100 000 Black individuals, 458 (95% CI, 440-476) per 100 000 Hispanic individuals, and 812 (95% CI, 802-823) per 100 000 White individuals.

A systematic review[5] of 32 phase 2 and phase 3 trials of inflammatory bowel disease therapies approved by the US Food and Drug Administration (from 1960-2020) reported a mean proportion of 0.1% (SD, 7.0%) Asian trial participants; 2.9% (SD, 3.3%) Black trial participants; 5.2% (SD, 4.5%) Hispanic trial participants; 85.8% (SD, 9.1%) White trial participants; and 3.2% (SD, 2.7%) Other trial participants. Although it is estimated that Black and Hispanic individuals represent approximately 30% of the US population and White individuals comprise 60.1%, more than 90% of clinical trial participants in the US are White individuals.[5]

The risankizumab ulcerative colitis induction and maintenance studies[1] were conducted across Africa, the Asia-Pacific region, Europe, North America, and South America at 261 clinical centers in 41 countries for the INSPIRE study and at 238 clinical centers in 37 countries for the COMMAND study. Participants self-reported race and ethnicity.[1] Of the trial participants,[1] 0.1% reported American Indian or Alaska Native; 27.4% reported Asian; 2.0% reported Black or African American; 6.6% reported Hispanic or Latino; 0.9% reported Multiple race categories; 0% reported Native Hawaiian or Other Pacific Islander; and 69.6% reported White. The racial and ethnic composition of the INSPIRE and COMMAND trials[1] was similar to other inflammatory bowel disease trials.[5]

Neither race nor ethnicity was part of the eligibility criteria for the risankizumab ulcerative colitis trials.[1] Furthermore, in both the INSPIRE and COMMAND trials,[1] risankizumab was superior to placebo for the primary outcome of clinical remission regardless of sex, geographic region, or race (self-reported White individuals vs individuals in the categories of American Indian or Alaska Native, Asian, Black or African American, Multiple, or Native Hawaiian or Other Pacific Islander). The safety analysis for participants in any of the risankizumab treatment groups indicated that the event rates for any adverse events, severe adverse events, serious adverse events, and adverse events leading to the discontinuation of the study drug were comparable between White individuals and all individuals in the categories in parentheses (American Indian or Alaska Native, Asian, Black or African American, Multiple, or Native Hawaiian or Other Pacific Islander). In the population analyses of pharmacokinetics, race was evaluated as a covariate and was not found to be clinically relevant.[6]

We acknowledge that there are several reasons why racial and ethnic disparities may exist in clinical trials. Racial and ethnic minority groups may have reduced clinical trial accessibility due to underresourced hospitals, limited transportation, and a lack of health insurance. However, there are growing efforts to increase diversity in clinical trials, particularly with the establishment of the National Institute on Minority Health and Health Disparities in the US. Future industry-sponsored ulcerative colitis clinical studies may include more racial diversity because of the more recent implementation of diversity action plans in accordance with guidance from regulatory agencies (such as the US Food and Drug Administration and the European Medicines Agency).

Edouard Louis, MD
Jasmina Kalabic, MD
Edward V. Loftus Jr, MD

Author Affiliations: Department of Hepato-Gastroenterology and Digestive Oncology, University Hospital CHU of Liège, Liège, Belgium (Louis); AbbVie Deutschland GmbH and Co KG, Ludwigshafen, Germany (Kalabic); Division of Gastroenterology and Hepatology, Mayo Clinic College of Medicine and Science, Rochester, Minnesota (Loftus).

Corresponding Author: Edouard Louis, MD, University Hospital CHU of Liège, Avenue de l'Hôpital 1, 4000 Liège, Belgium (edouard.louis@uliege.be).

Published Online: January 22, 2025. doi:10.1001/jama.2024.25643

Conflict of Interest Disclosures: Dr Louis reported receiving research grants from Janssen, Pfizer, and Takeda; receiving educational grants from AbbVie, Janssen, MSD (Merck Sharp & Dohme), and Takeda; receiving speaker fees from AbbVie, Falk, Ferring, Hospira, Janssen, MSD, Pfizer, and Takeda; serving on advisory boards for AbbVie, Arena, Celgene, Ferring, Galapagos, Gilead, Hospira, Janssen, MSD, Pfizer, and Takeda; and serving as a consultant for AbbVie. Dr Kalabic reported having a patent pending for risankizumab to treat Crohn disease and ulcerative colitis and is an employee of AbbVie. Dr Loftus reported receiving consulting fees from AbbVie, Alvotech, Amgen, Arena, Astellas, Avalo, Boehringer Ingelheim, Bristol Myers Squibb, Celltrion Healthcare, Eli Lilly, Fresenius Kabi, Genentech, Gilead Sciences, GSK, Gossamer Bio, Iota Biosciences, Iterative Health, Janssen, Morphic Therapeutic, Ono Pharma, Protagonist, Sun Pharma, Surrozen, Takeda, TR1X, and UCB Pharma; receiving research support from AbbVie, AstraZeneca, Bristol Myers Squibb, Celgene/Receptos, Genentech, Gilead Sciences, Gossamer Bio, Janssen, Pfizer, Receptos, Takeda, Theravance, and UCB Pharma; and being a shareholder of Exact Sciences. No other disclosures were reported.

Additional Contributions: Paulette A. Krishack, PhD (AbbVie), provided medical writing support and was compensated for her contributions as part of her normal salary.

1. Louis E, Schreiber S, Panaccione R, et al; INSPIRE and COMMAND Study Group. Risankizumab for ulcerative colitis: two randomized clinical trials. *JAMA*. 2024;332(11):881-897. doi:10.1001/jama.2024.12414

2. Le Berre C, Honap S, Peyrin-Biroulet L. Ulcerative colitis. *Lancet*. 2023;402 (10401):571-584. doi:10.1016/S0140-6736(23)00966-2

3. Ng SC, Shi HY, Hamidi N, et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. *Lancet*. 2017;390(10114):2769-2778. doi:10.1016/S0140-6736(17)32448-0

4. Lewis JD, Parlett LE, Jonsson Funk ML, et al. Incidence, prevalence, and racial and ethnic distribution of inflammatory bowel disease in the United States. *Gastroenterology*. 2023;165(5):1197-1205.e2. doi:10.1053/j.gastro.2023.07.003

5. Cohen NA, Silfen A, Rubin DT. Inclusion of under-represented racial and ethnic minorities in randomized clinical trials for inflammatory bowel disease. *Gastroenterology*. 2022;162(1):17-21. doi:10.1053/j.gastro.2021.09.035

6. Thakre N, Goebel A, Winzenborg I, et al. Population pharmacokinetic and exposure–response modeling to inform risankizumab dose selection in patients with ulcerative colitis. *Clin Pharmacol Ther*. 2024;116(3):847-857. doi:10.1002/cpt.3330

Guidelines for Letters

Letters discussing a recent *JAMA* article should be submitted within 4 weeks of the article's publication. Letters received after 4 weeks will rarely be considered. Letters should not exceed 400 words of text and 5 references and may have no more than 3 authors. Letters reporting original research should not exceed 600 words of text and 6 references and may have no more than 7 authors. They may include up to 2 tables or figures but online supplementary material is not allowed. All letters should include a word count. Letters must not duplicate other material published or submitted for publication. Letters not meeting these specifications are generally not considered. Letters being considered for publication ordinarily will be sent to the authors of the *JAMA* article, who will be given the opportunity to reply. Letters will be published at the discretion of the editors and are subject to abridgement and editing. Further instructions can be found at http://jamanetwork.com/journals/jama/pages/instructions-for-authors. A signed statement for authorship criteria and responsibility, financial disclosure, copyright transfer, and acknowledgment is required before publication. Letters should be submitted via the *JAMA* online submission and review system at https://manuscripts.jama.com. For technical assistance, please contact jama-letters@jamanetwork.org.

Section Editors: Kristin Walter, MD, and Jody W. Zylke, MD, Deputy Editors; Karen Lasser, MD, MPH, Senior Editor.