Advances in Rheumatology

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Reply to the letter on "Brazilian guidelines for the management of tuberculosis infection in immune-mediated inflammatory diseases: is retesting in latent tuberculosis screening appropriate and safe?"

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Abstract

In response to a letter addressing the Brazilian guidelines for tuberculosis infection (TBI) screening in immune-mediated inflammatory diseases (IMID), we clarify that the recommendations reflect a structured, evidence-based consensus developed by a multidisciplinary panel, in accordance with internationally accepted standards. We reaffirm the rationale for annual TBI retesting during the first three years of immunosuppressive therapy, particularly with TNF inhibitors, and the outweighed risk of tuberculosis preventive treatment (TPT), given the benefits. These recommendations are aligned with national and international public health policies and underscore the need for flexibility in clinical judgment. Nonetheless, they are conditional, reflecting the limited robustness of the available

Communicated by Caio Machado

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evidence. Continued dialogue is essential to ensure the safety and protection of IMID patients in high-burden settings like Brazil.

Dear editor,

We thank the authors for their careful reading and thoughtful comments. Constructive dialogue is essential to refine and improve clinical recommendations, especially on topics of high relevance such as tuberculosis prevention in immune-mediated inflammatory diseases (IMID) patients.

We would like to offer some clarifications regarding the letter published in Advances in Rheumatology [1], regarding our recommendations, which do not represent individual viewpoints but rather a structured, evidence-based consensus by a multidisciplinary panel.

These guidelines development process was notably thorough and methodical [2], and represent a formal consensus developed by a panel of national experts in rheumatology, infectious diseases, pneumonology, dermatology, gastroenterology, and public health. They were developed following internationally recognized standards for guideline construction, with structured clinical questions, systematic literature review, quality of evidence grading (GRADE), and consensus through Delphi methodology. The participation of a representative from the Brazilian Ministry of Health further underscores their public health relevance and applicability. It should also be emphasized that, given the limited quality of the available evidence, these recommendations remain conditional, as outlined in the main manuscript.

All systematic reviews informing the recommendations were performed twice, as the COVID-19 pandemic interrupted the process, necessitating updated searches once the work was resumed. Although the available evidence was not always robust or free from limitations, the final recommendations [2] reflect the best current knowledge. They are aligned with the Brazilian Ministry of Health [3], as well as with international guidelines from organizations such as EULAR [4] and the World Health Organization [5].

Several critical points related to the published letter deserve emphasis:

1. TPT with isoniazid or rifamycin-based regimens has not been consistently linked to the emergence of drug resistance. In high-burden settings such as Brazil, TPT is a safe and cost-effective strategy that reduces tuberculosis disease (TBD) morbidity and mortality. Accordingly, any marginal risk of isoniazid resistance associated with wider TPT use must be carefully weighed against its substantial public health benefit in reducing TBD incidence [6, 7].
2. TPT significantly reduces the risk of progression from tuberculosis infection (TBI) to TBD and its related morbimortality, supported by a high-grade level of evidence [8, 9].
3. Individuals with positive TBI tests carry a markedly higher risk of developing TBD compared to those with negative tests [8, 9].
4. Cost-effectiveness studies have demonstrated the benefit of testing and treating TBI in multiple scenarios [6–9].
5. We wish to clarify that the Brazilian technical note cited in the letter, supporting annual repetition of TBI testing in immunosuppressed patients, was developed by experts in response to the country's high burden of TBD and the heightened risk in this population. In the absence of robust data specifically addressing immunosuppressed individuals, the recommendation extrapolates the rationale applied to other high-risk groups, including people living with HIV [10].

EULAR recommends TBI screening in patients with IMID before initiation of all immunosuppressive therapies, in special situations, not solely TNF inhibitors [4]. We reaffirm that the recommendation, until more robust and powered evidence is available, and justified by the cumulative increased risk of TBD in these patients, is to repeat the screening annually for the first 3 years of treatment, especially among TNFi users [2]. The reasons for that repetition in the first years of immunosuppression is based on the conversion rate after exposure to TNFi, that may be due to a new exposure, since chronic patients begin to attend regularly at health facilities, and also the risk of anergy, that has been demonstrated in patients with rheumatoid arthritis, psoriatic arthritis and inflammatory bowel diseases [11–14], which may account for the observed false negative baseline TST. We also clarify that the cited paper by Magalhães et al. [15] did not analyze patients who repeated TST annually, but considered only random repetition (median 3.3 years from the beginning of TNFi therapy), while the median time to TBD was 1.3 years after that, with 50% of the cases occurring between 1 and 2 years of follow-up. Similarly, Shimabuco et al. [13], also showed a median of 1.3 years to TBD after TNFi treatment in patients who did not repeat TST, all occurring up to 3.5 years of follow-up, suggesting that regular repetition after 1 to 3 years of treatment would be valuable, but not thereafter.

Although the overall incidence of TBD following test conversion may appear low, the recommendation to repeat testing is grounded in the precautionary principle and supported by its simplicity, low cost, and the potential to prevent a life-threatening disease in a highly vulnerable population.

Finally, we emphasize that these guidelines are intended as recommendations to support the clinical decision-making process and should be applied with appropriate flexibility and clinical judgment. While methodological perspectives may differ, we share the same ultimate goal: to minimize harm and protect individuals with IMID from TBD, particularly in high-burden settings like Brazil. We welcome continued dialogue in pursuit of evidence-based, patient-centered care.

Author contributions
All authors equally contributed to drafting this response.

Funding
There is no funding declaration for this manuscript.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that the research was carried out in the absence of any commercial or financial relationship that could be interpreted as a potential conflict of interest. Several authors of these guidelines, including voting members, have interacted with the pharmaceutical industry including the manufacturers of some of the drugs mentioned in these recommendations. However, none of the authors received any support or fee directly or indirectly related to or influencing the development of these guidelines. AKGM received speaker fees and consulting from Abbvie, Johnson & Johnson. AMK received consuting fees from Abbvie, Lilly, UCB, Organon, and Janssen. CF received speaker fees from Takeda, Janssen, Abbvie, Amgen, Organon. ESP received speaker fees and consulting from Abbvie, Novartis, Lilly, Johnson & Johnson. JSC received speaker fees from GSK and Janssen. KLLLM received speaker fees and consulting from Novartis and Johnson & Johnson. LAC received speaker fees and consulting from Johnson & Johnson, Takeda, Abbvie. LDAV received speaker fees and consulting from Novartis, Johnson & Johnson. LMHM received speaker fees and consulting from Johnson & Johnson, Abbvie, Pfizer, Novartis, Amgen, Organon, Celltrion, UCB. MFBRG received speaker fees and consulting from Johnson & Johnson, Abbvie, Amgen, Lilly, UCB. MIBFL received speaker fees and consulting from Abbvie, Novartis, Takeda, Johnson & Johnson. MMP received consuting fees from Abbvie, Lilly and Janssen. RMX received Speaker fees, consulting, research funding from Abbvie, Pfizer, Amgen, Biogen, Novartis, Janssen, UCB. RR is/has served as a scientific consultant, speaker, or clinical study investigator for AbbVie, Boehringer Ingelheim, Bristol Myers Squibb, Galderma, Janssen-Cilag, Eli-Lilly, Leo-Pharma, Novartis, Pfizer, Sanofi, and UCB. RSH received speaker fees and consulting from Abbvie, Novartis, Takeda, Johnson & Johnson. OAM received consulting fees from AstraZeneca and GSK; received payment or honoraria for lectures or presentations from AbbVie, Janssen, GSK, UCB and AstraZeneca; and participated in a data safety monitoring board or advisory board for GSK, CellTrion, Bristol, Novartis, Janssen, and AstraZeneca. VAS received speaker fees and consulting from Abbvie, Novartis, Lilly, Johnson & Johnson, GSK, Astrazeneca. VFA received speaker fees, consulting, clinical researches from Celltiron, Amgen, Janssen, Organon, Sandoz, Abbvie, Fresenius Kabi, Takeda, LG, Boehringer-Ingelheim, Bristol Myers-Squibb, GSK, AstraZeneca. Eduardo dos Santos Paiva is Co-EiC of Advances in Rheumatology. Ana Karla Guedes de Melo, Ana Cristina de Medeiros Ribeiro and Marcelo de Medeiros Pinheiro are Associate Editors of the journal Advances in Rheumatology; Ricardo Machado Xavier is a Consulting editor of the journal; Adriana Maria Kakehasi and Licia Maria Henrique da Mota are members of the editorial board of this journal. The peer-review of this paper was therefore overseen by an independent member of the editorial board while the submission was subject to the exact same review process as applied to any other manuscript.The authors not mentioned above declare no competing interests.

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Received: 17 July 2025 / Accepted: 14 November 2025
Published online: 19 November 2025

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