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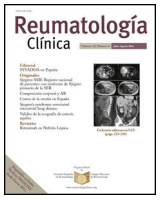

Letter to the Editor

Comment on: "Safety of biologic and synthetic targeted therapies in patients with immune-mediated diseases: Data from the BIOBADAGUAY registry"

Comentario sobre: «Seguridad de las terapias biológicas y sintéticas dirigidas en pacientes con enfermedades inmunomediadas: datos del registro BIOBADAGUAY»

Dear Editor,

We have thoroughly engaged with the article "Safety of Biologic and Synthetic Targeted Therapies in Patients with immune-mediated Diseases: data from the BIOBADAGUAY registry" authored by Paloma de Abreu.[1] We sincerely appreciate the author's diligent work on this crucial topic, which merits reader recognition. We concur with the article's primary conclusion of providing necessary information regarding the safety of bDMARD and tsDMARD therapies in inflammatory rheumatic disease patients by using the data from the BIOBADAGUAY registry, summarizing the predominance of only mild adverse events with infection as the most common adverse event, highlighting the need of monitoring and control throughout the treatment to ensure safety. However, there are a few methodological limitations that could affect the reliability of the study's conclusion.

A major concern is that the study lacks a non-DMARD control group, which makes it unable to compare the incidence of adverse events in untreated patients and those receiving conventional treatments. The lack of a defined comparator group makes it difficult to assess whether the adverse effects were due to BDMARDS/tsDMARDS or simply a result of disease progression or baseline risk factors.

Moreover, the study's risk estimates are not sufficiently adjusted for the confounding effects of these medications. For instance, Methotrexate was received by 68.1% of the patients as first line. 59% of the patients as concomitant treatment. Additionally, 51.3% of the patients also received glucocorticoids. This additional treatment creates ambiguity as many of the adverse events including infections are solely the result of BDMARDS/tsDMARDS treatment or are worsening conditions of these additional treatments.[2]

A further constraint is that the study uses Poisson regression for statistical analysis which assumes that everything happens independently and at a steady rate. However, infections may cluster (e.g. occurring more frequently in the initial months of immunosuppressive therapy) or alter over time, violating the assumptions. Therefore, it would be beneficial to use negative binomial regression, a modification of Poisson regression that permits overdispersion, which should be applied to real data where there is a possibility that conditional variance will become greater than the mean, a phenomenon known as overdispersion.[3]

Beyond these methodological limitations, the usage of MedDRA classifications for adverse effects (AEs) in the study is a notable limitation. MedDRA classifications are broad and may not distinguish between drug-class-specific risks. For instance, Tumor necrosis factor (TNF) inhibitors and Janu kinase (JAK) inhibitors have different infection risks as TNF inhibitors are mainly associated with bacterial infections[4] while JAK inhibitors are linked to viral infection.[5] However, MedDRA classifies all bacterial, viral, and fungal infections under the general category "infections". This reduces its clinical relevance and applicability in treatment-based decision-making.

While registries like BIOBADAGUAY are extremely useful for long-term drug safety monitoring, addressing these limitations—such as adding a control group, accounting for confounding medications, and enhancing AE stratification by drug class—is important to enhance the reliability of its conclusions. Registries like RABBIT, BIOBADASER, and ARTIS have already addressed these limitations. For example: studies using BIOBADASER and ARTIS have defined comparator groups to evaluate treatment outcomes,[6,7] while a study by Richter A et al. accounted for confounding factors including methotrexate and corticosteroids using data from the RABBIT registry.[8] Implementation of these practices would allow BIOBADAGUAY to generate outcomes that are reliable, offering actionable insights and clinically relevant data to strengthen rheumatology practice worldwide.

Disclaimer

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Conflict of interest

The authors have no relevant financial or non-financial interests to disclose.

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