Influence of Gender on the Persistence of Different Tumor Necrosis Factor Inhibitor Treatments in Patients With Psoriatic Arthritis

To the Editor:

Psoriatic arthritis (PsA) affects men and women equally, although it is known that important differences exist between the sexes. We have read the recently published paper, “Women with psoriatic arthritis experience higher disease burden than men: findings from a real-world survey in the United States and Europe,” by Gossec et al.1 The authors highlight that in patients with similar PsA disease activity and treatment, women experienced greater disease impact than men. However, this issue is currently not resolved and further research is needed in this area.2 To this end, our group evaluated the efficacy of tumor necrosis factor inhibitors (TNFi) in patients diagnosed with PsA, and the influence of the patient's gender.

A multicenter and observational study was conducted in patients with PsA receiving treatment with etanercept (ETN), adalimumab (ADA), golimumab (GOL), and certolizumab pegol (CZP) between February 1, 2021, and February 1, 2022. Patients were evaluated using the Disease Activity Index for Psoriatic Arthritis (DAPSA) and its cut-off points at baseline and at 52 weeks or when the patient stopped treatment. Minimal disease activity (MDA) and 12-item Psoriatic Arthritis Impact of Disease (PsAID-12) scores were collected, wherein PsAID-12 < 4 identified a patient acceptable symptom state (PASS). Serious adverse events that occurred during the follow-up period were collected. For the analysis, the SPSS 23.0 software (IBM Corp.) was used. The patients signed informed consent to allow the collection and analysis of the data in an anonymous manner and their inclusion in a study registry of patients with PsA (Ethics Committee of Santiago-Lugo, registry code: 2015/671).

There was a total of 84 patients with PsA included: 28 were treated with ETN (33.3%), 24 with ADA (28.6%), 10 with GOL (11.9%), and 22 with CZP (26.2%). The age of the patients was 54 (IQR 44-60) years, with those taking CZP being younger (P = 0.17). The distribution by gender showed no differences (P = 0.49), nor did the time of evolution of PsA since diagnosis (P = 0.17). Of the patients, 50% and 19.3% had entheses at baseline and at 52 weeks, respectively, with no differences between groups (P = 0.54 and P = 0.72, respectively). The DAPSA at baseline was 23 (IQR 14-46), with no difference between treatment groups (P = 0.86), and decreased over 52 weeks to 3.4 (IQR 0-9) in patients continuing treatment, with no difference between TNFi groups (P = 0.68). However, there were differences in gender (P = 0.03). There were no differences in the 4 groups for the different DAPSA cut-off points at week 52 (P = 0.91). At week 52, the Health Assessment Questionnaire scores improved, although less improvement was seen in female patients (P = 0.001). The percentage of patients who reached the goal of MDA (5/7 or low disease activity) was 68.3% at 52 weeks; among these, there was a lower proportion of female individuals. There were no differences among the 4 TNFi groups (P = 0.36). The percentage of patients who reached the goal of very low disease activity (MDA7/7 or remission) was 32.9% at 52 weeks, with no differences among the 4 groups (P = 0.76). At baseline, the PsAID-12 was 5.4 (IQR 4-8) and at 52 weeks it was 2.8 (IQR 1-5), with no differences among the 4 groups (P = 0.45). The proportion of patients with a PASS was 79.2%, without differences between groups (P = 0.62), although a lower percentage of these patients were of the female gender. There were 18 (21.4%) dropouts from treatment, with no differences among the 4 TNFi groups, and persistence in treatment at 52 weeks was higher in men than in women (86.5% vs 61.9%, P = 0.02; Figures 1A,B).

In the Cox regression analysis, it was observed that the female gender was a predictor of treatment discontinuation throughout the study, from baseline to 52 weeks (P = 0.01; Table).

Our study highlights the role of gender in the response to treatment in patients with PsA regardless of the TNFi used. The female gender was an independent factor for treatment discontinuation for each TNFi. In a systematic review, Coates et al3 concluded that women had poorer responses to treatment, indicated by outcome measures such as American College of Rheumatology responses and MDA. Also, Van Kuijk4 analyzed data from the PsABio study to establish whether there are sex-related differences in response to and retention of biologic treatment in patients with PsA treated with ustekinumab or TNFi in routine clinical practice. Before starting biologic disease-modifying antirheumatic drugs, female patients had more severe disease than male patients, and a lower percentage reached favorable disease states, with lower treatment persistence after 12 months.4

We encourage the authors to continue investigating patients with PsA in clinical practice, considering that the existing information in this field is scarce, and the mechanism of this gender effect is not clear.

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REFERENCES
Figure 1. Treatment persistence for patients receiving (A) all TNFi until discontinuation, by gender, and (B) TNFi until discontinuation among TNFi groups. Time to discontinuation was defined as the difference between the end-of-study date and the date of first TNFi dose. The end date was the date of the last TNFi dose. Patients were censored at the end date. ADA: adalimumab; CZP: certolizumab pegol; ETN: etanercept; GOL: golimumab; TNFi: tumor necrosis factor inhibitor.

Table. Cox regression analysis to compare factors that affect response to treatment in patients with PsA.

<table>
<thead>
<tr>
<th></th>
<th>b</th>
<th>SE</th>
<th>Wald</th>
<th>df</th>
<th>P</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>1.25</td>
<td>0.51</td>
<td>6.15</td>
<td>1</td>
<td>0.01</td>
<td>3.50 (1.30-9.40)</td>
</tr>
<tr>
<td>Diagnosis &lt; 2 yrs</td>
<td>-1.36</td>
<td>1.04</td>
<td>1.72</td>
<td>1</td>
<td>0.19</td>
<td>0.26 (0.03-1.96)</td>
</tr>
<tr>
<td>Clinical pattern</td>
<td>-0.31</td>
<td>0.34</td>
<td>0.80</td>
<td>1</td>
<td>0.37</td>
<td>0.74 (0.37-1.44)</td>
</tr>
<tr>
<td>BMI</td>
<td>0.07</td>
<td>0.04</td>
<td>3.09</td>
<td>1</td>
<td>0.08</td>
<td>1.07 (0.99-1.15)</td>
</tr>
<tr>
<td>Combined therapy</td>
<td>-0.22</td>
<td>0.49</td>
<td>0.20</td>
<td>1</td>
<td>0.66</td>
<td>0.80 (0.31-2.10)</td>
</tr>
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Univariate Cox regression analysis used the following covariates: age, gender, early PsA (diagnosis < 2 years), clinical pattern (peripheral, axial, or mixed), BMI, and combined therapy (TNFi + csDMARD). Multivariate Cox analysis was then performed to identify how the factors jointly affected treatment survival. In the multivariate analysis, only gender remained significant (P < 0.05). csDMARD: conventional synthetic disease-modifying anti-rheumatic drug; df: degrees of freedom; OR: odds ratio; PsA: psoriatic arthritis; SE: standard error; TNFi: tumor necrosis factor inhibitor.