# Is There a Gender Difference in the Response to onabotulinumtoxinA in Chronic Migraine? Insights from a Real-Life European Multicenter Study on 2879 Patients

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## ABSTRACT

*Introduction*: Migraine is mostly a female disorder because of its lower prevalence in men.

Less than 20% of patients included in the available studies on migraine treatments are men; hence, the evidence on migraine treatments might not apply to men. The aims of the present study were to provide reliable information on the effectiveness of onabotulinumtoxinA (BT-A) for chronic migraine in men and to

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compare clinical benefits between men and women.

*Methods*: We performed a pooled patient-level gender-specific analysis of real-life data on BT-A for chronic migraine of patients followed-up to 9 months. We reported the 50% responder rates during each BT-A cycle, defined as percentage of reduction in monthly headache days (MHDs) compared to baseline, along with 75% and 30% responder rates. We also reported the mean decrease in MHDs and in days of acute medication use (DAMs) during each BT-A cycle as compared to baseline. We also evaluated the reasons for stopping the treatment within the third cycle.

*Results*: We included an overall cohort of 2879 patients, 522 of whom (18.1%) were men. In men, 50% responder rates were 27.7% during the first BT-A cycle, 29.2% during the second, and 35.6% during the third cycle; in women, the corresponding rates were 26.6%, 33.5%, and 41.0%. In the overall cohort, responder rates did not differ between men and women during the first two cycles; during the third cycle, the distribution was different ($P < 0.001$) mostly because of higher rates of treatment stopping and non-responders in men. In the propensity score matched cohort, the trend was maintained but lost its statistical significance. Both men and women had a significant decrease in MHDs and in DAMs with BT-A treatment ($P < 0.001$). There were no gender differences in those changes with the only exception of MHD decrease which, during the third cycle, was lower in men than in women (7.4 vs 8.2 days, $P = 0.016$ in the overall cohort and 9.1 vs 12.5 days, $P = 0.009$ in the propensity score matched cohort). At the end of follow-up, 152 men and 485 women stopped BT-A treatment (29.1% vs 20.6%; $P < 0.001$). The relative proportion of patients stopping treatment because of inadequate response (less than 30% decrease in MHDs from baseline) was higher in men than in women (42.8% vs 39.6%), while the proportion of patients stopping because of adverse events was higher in women than in men (5.6% vs 0%; $P = 0.031$).

*Conclusions*: Our pooled analysis suggests that the response to BT-A is significant in both men and women with a small gender difference in favor of women. Men tended to stop the treatment more frequently than women. We emphasize the need for more gender-specific data on migraine treatments from randomized

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controlled trials and observational studies.

## Key Summary Points

### Why carry out this study?

The available data on gender-specific response to migraine treatments are scarce because of the low proportion of male study participants.

We performed a large, retrospective, multicenter study to assess the response to onabotulinumtoxinA for chronic migraine in men compared with women.

### What was learned from this study?

We found that onabotulinumtoxinA was effective in both men and women; there was a slight gender difference in favor of women that was, however, not substantial, as it lost significance after propensity score matching.

Persistence to onabotulinumtoxinA treatment was lower in men than in women; this finding is in line with previous data on oral migraine treatments and should encourage headache physicians to monitor men's persistence to treatments.

## INTRODUCTION

Migraine is the most prevalent neurological disease, affecting about 20% of the European population [1]. Migraine has remarkable gender differences. Its prevalence, during adulthood, is three times higher in women than in men [2]. Additionally, women with migraine have generally more severe attacks and a higher disease-related disability [3]. On the other hand, men with migraine are less likely to receive the correct diagnosis than women [4].

Factors which may contribute to gender differences are multiple and not entirely understood. Genetic factors and the periodic fluctuations of estrogen levels during the ovarian cycle contribute to the increased susceptibility to migraine in women [3, 5, 6]. On the other hand, hormonal stability and a potential preventive effect of male sex hormones contribute to the lower prevalence of migraine in men [7, 8]. The trigeminal ganglion, the structure supposed to play a pivotal role in generating migraine pain, has a sexual dimorphism as it hosts estrogen receptors [9] that can respond to estrogen fluctuations. Additional psychosocial factors which are remarkably different between men and women, including coping abilities and pain catastrophizing, may impact on the course of migraine and affect its management [10].

Providing gender-specific information for treatments is a mainstay of modern medicine and is of utmost importance in a disorder such as migraine [11]. Unfortunately, gender-specific information for migraine treatments is scarce and mostly related to some data on triptans [12–14]. As men were in a minority (less than 20% of the total study population) in studies aiming to develop migraine preventive treatments [3, 15–20], generalizability to men of the overall findings of those studies is unclear.

OnabotulinumtoxinA (BT-A) is the first treatment that was approved specifically for CM. Randomized clinical trials [15, 16, 21–23] and real-life studies [24–26] confirmed the efficacy and safety of BT-A in mixed populations composed of many more women than men. In the PREEMPT studies, men comprised 12.4% of patients treated with BT-A and 14.8% of those treated with placebo [23]. Real-life studies equally included few men and did not report the gender-specific effect of BT-A [24, 25, 27–32]. The response to migraine treatments can be influenced by the same genetic, hormonal, medical, and psychological factors that determine gender differences in migraine susceptibility. Given the availability of a large amount of data from a European collaboration [33], we aimed to provide reliable information on the effects of treatment with BT-A in men with CM, which were so far underrepresented in available studies, and to

compare clinical benefits between men and women.

# METHODS

This is a pooled patient-level analysis of data from real-life studies on patients with CM treated with BT-A at 16 European headache centers. The methods of the study have been previously published [33]. Briefly, all the centers which joined this project had already performed a local real-life prospective data collection on patients with CM. All included patients had a CM diagnosis according to the International Classification of Headache Disorders (ICHD) criteria, were aged at least 18 years, and received treatment with BT-A 155–195 units quarterly according to the phase 3 REsearch Evaluating Migraine Prophylaxis Therapy (PREEMPT) protocol [15]. Inclusion periods varied across centers and ranged from 2010 to 2020.

Pooling of previously collected data for the present collaborative study was approved by the Internal Review Board of the University of L'Aquila with protocol number 23/2020; local ethical approval to pool data was obtained if needed. All centers had their former data collections approved by the local ethics committees if necessary, according to the local regulations; informed consent was obtained from patients. The study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments.

## Variables and Outcomes

All included patients were followed up for 9 months, irrespective of treatment discontinuation. The 9-month follow-up was chosen to include the first three BT-A injection sets, after which more than 70% of patients showed a 50% response according to the PREEMPT trials [34].

Monthly headache days (MHDs) and monthly days of acute medication use (DAMs) were collected in all centers by using headache diaries. Baseline was defined as the monthly mean of the 3 months preceding BT-A treatment. Patients reporting at least a 50% reduction in MHDs during a BT-A cycle compared with baseline were defined as "50% responders" during that cycle. We also defined patients as "30–49% responders" if reporting a 30–49% reduction in MHDs and as "75% responders" if reporting at least a 75% reduction in MHDs. Patients reporting a smaller than 30% reduction in MHDs compared with baseline were defined as "non-responders".

For each patient who stopped the treatment before the third cycle, we recorded whether stopping occurred because of inadequate response, good response, adverse events, or loss to follow-up. Inadequate response was defined as application of a "negative stopping rule" as per the UK guidelines (i.e., smaller than 30% decrease in MHDs from baseline after two BT-A cycles [35]) or patient decision due to perceived ineffectiveness of BT-A. Good response was defined as application of a "positive stopping rule" as per the UK guidelines (i.e., less than 15 MHDs for more than 3 months [35]) or patient decision due to perceived high effectiveness of BT-A.

## Statistical Analysis

Descriptive statistics were reported as numbers and proportions and means and standard deviations (SDs), as appropriate. We performed chi-square test with adjustment by linear trend data to compare categorical variables and Student's $t$ test to compare continuous variables according to gender. Continuous outcome variables, including MHDs and DAMs, were imputed by carrying forward the last observation in patients withdrawing the treatment. All analyses used the intent-to-treat population including all patients who started BT-A treatment. The co-primary efficacy outcomes of our analyses included the proportion of 50% responders, mean decrease in MHDs from baseline, and mean decrease in DAMs from baseline during each BT-A cycle. Secondary efficacy outcomes included the proportions of 30% and 75% responders during each BT-A cycle. We also reported the proportion of patients stopping the treatment within the third cycle with reasons. Given the absence of gender-specific data on BT-A, all outcomes were considered as

exploratory; hence, no adjustment for multiple comparisons was performed.

Variables were considered for the analyses if available for at least two thirds of patients; no imputation was done for missing baseline data. To impute missing diary data of patients stopping the treatment, we repeated the last available observation according to a "last observation carried forward" approach.

To adjust for possible differences between men and women, we performed a propensity score matching with the exact method between a subset of men and one of women, considering age, CM duration, and baseline MHDs as matching variables. Age was chosen as a matching variable to ensure a balance of demographic characteristics between men and women; CM duration and baseline MHDs were chosen because previous studies showed that high frequency of headache at baseline and a long history of CM negatively affect the response to BT-A [31, 36]. To assess the validity of the propensity score model, we performed a test of significance on the matched variables between men and women. To account for possible age differences, a comparison between men and women within three age groups (18–34, 35–49, and 50 years or older) was also performed in the overall cohort, referring to the third BT-A cycle.

No sample size calculation was planned, as we used a convenience sample based on the available data. Two-tailed $P$ for significance was set at less than 0.05. Statistical analyses were conducted using SPSS version 20 and R version 4.0.0.

# RESULTS

We included an overall cohort of 2879 patients, 522 of whom (18.1%) were men. Supplemental Table 1 reports the proportion of men in each center, which ranged from 10.3% to 27.1%. Men were older than women ($47.8 \pm 13.2$ vs $46.3 \pm 12.1$ years; $P = 0.024$), while the remaining baseline characteristics did not differ between men and women (Table 1). The propensity score matched cohort included 291 patients, 121 of whom were men (Table 1).

In the overall cohort of men, 145 (27.7%) were 50% responders during the first BT-A cycle, 152 (29.2%) during the second, and 186 (35.6%) during the third cycle (Fig. 1). In the overall cohort of women, the corresponding numbers were 628 (26.6%), 790 (33.5%), and 967 (41.0%) respectively (Fig. 1). At the statistical analysis, response rates did not differ between men and women in the overall cohort during the first cycle; during the second and the third cycle, the distribution was different ($P = 0.019$ and $P = 0.010$, respectively) mostly because of higher rates of treatment stopping and non-responders in men compared to women. In the propensity score matched cohort, the numerical difference was still present but lost its statistical significance (Fig. 1).

In the overall cohort, 87 (%) men were aged 18–34 years, 212 (%) 35–49 years, and 223 (%) 50 years or older; the corresponding numbers for women were 429 (%), 1036 (%), and 892 (%). During the third BT-A cycle, response rates were different between men and women in patients aged 35–49 years ($P = 0.014$) and in those aged 50 years or older ($P = 0.002$), mostly because of a higher rate of treatment stopping in men than in women (Fig. 2). In patients aged 18–24 years, there was no gender difference ($P = 0.229$; Fig. 2).

In the overall cohort of men, mean MHDs decreased from baseline by 6.7 days (95% confidence interval [CI] 6.0–7.3; $P < 0.001$) during the first cycle, 7.8 days (95% CI 7.1–8.5; $P < 0.001$) during the second cycle, and 8.5 days (95% CI 7.8–9.3; $P < 0.001$) during the third cycle; the corresponding numbers in women were 7.0 days (95% CI 6.7–7.3; $P < 0.001$), 8.6 days (95% CI 8.3–8.9; $P < 0.001$), and 9.7 days (95% CI 9.4–10.0; $P < 0.001$) (Fig. 3). The decrease in MHDs was comparable in men and women during the first two cycles, while it was lower in men than in women during the third cycle ($P = 0.016$; Fig. 3). In the propensity score matched cohort, mean MHDs decreased from baseline in men by 6.9 days (95% CI 5.4–8.4; $P < 0.001$) during the first cycle, 8.1 days (95% CI 6.5–9.8; $P < 0.001$) during the second cycle, and 9.1 days (95% CI 7.4–10.9; $P < 0.001$) during the third cycle; the corresponding numbers in women were

8.6 days (95% CI 7.2–9.9; $P < 0.001$), 10.8 days (95% CI 9.4–12.2; $P < 0.001$), and 12.5 days (95% CI 9.4–10.0; $P < 0.001$) (Fig. 3). The decrease in MHDs from baseline was significant ($P < 0.001$) in both men and women during all the three BT-A cycles; however, men reported a lower decrease in MHDs than women during the second ($P = 0.032$) and the third cycle ($P = 0.009$) (Fig. 3).

In the overall cohort of men, mean DAMs decreased from baseline by 6.2 days (95% CI 5.4–7.0; $P < 0.001$) during the first cycle, 7.0 days (95% CI 6.2–7.8) during the second cycle, and 7.4 days (95% CI 6.5–8.2; $P < 0.001$) during the third cycle; the corresponding numbers in women were 6.0 days (95% CI 5.6–6.3; $P < 0.001$), 7.2 days (95% CI 6.9–7.6; $P < 0.001$) during the second cycle, and 8.2 days (95% CI 7.8–8.6; $P < 0.001$) during the third cycle. The decrease in DAMs from baseline did not differ between men and women during the second and third cycle, while it was slightly higher in men than in women during the first cycle ($P = 0.046$). In the propensity score matched cohort, mean DAMs decreased in men from baseline by 5.4 days (95% CI 3.9–6.9; $P < 0.001$) during the first cycle, 6.3 days (95% CI 4.7–8.0) during the second cycle, and 7.2 days (95% CI 5.4–9.0; $P < 0.001$) during the third cycle; the corresponding numbers in women were 6.8 days (95% CI 5.3–8.2; $P < 0.001$), 8.9 days (95% CI 7.3–10.6; $P < 0.001$) during the second cycle, and 9.7 days (95% CI 8.2–11.3; $P < 0.001$) during the third cycle. There were no gender differences during any of the three BT-A cycles (Fig. 3).

Table 2 reports the proportions of patients stopping BT-A treatment with reasons in the overall cohort. At the end of follow-up, 152 men and 485 women stopped BT-A treatment (29.1% vs 20.6%; $P < 0.001$). Among men stopping the treatment, the reason was inadequate response for 65 patients (42.8%), and good response for 52 (34.2%), while 35 (23.0%) were lost to follow-up; among women stopping the treatment, the reason was inadequate response for 192 patients (39.6%), good response for 162 (33.4%), and adverse events for 27 (5.6%), while 104 (21.4%) were lost to

**Table 1** Baseline characteristics of the included subjects in the overall cohort and in the propensity score matched cohort

| | Men | Women | P value |
|---|---|---|---|
| *Overall cohort, n* | 522 | 2357 | |
| Age (years), mean ± SD | 47.8 ± 13.2 | 46.3 ± 12.1 | 0.024 |
| Medication overuse, n (%) | 366 (70.1) | 1686 (71.5) | 0.385 |
| Baseline headache days, mean ± SD | 23.8 ± 6.3 | 23.8 ± 5.9 | 0.900 |
| CM duration (years), mean ± SD | 8.5 ± 9.0 | 7.9 ± 7.8 | 0.209 |
| Acute medication days (number), mean ± SD | 18.8 ± 9.7 | 19.5 ± 8.9 | 0.157 |
| *Propensity score matched cohort, n* | 121 | 170 | |
| Age (years), mean ± SD | 45.2 ± 10.9 | 44.9 ± 11.1 | 0.822 |
| Medication overuse, n (%) | 85 (70.2) | 121 (71.2) | 0.912 |
| Baseline headache days, mean ± SD | 27.1 ± 5.0 | 27.2 ± 4.9 | 0.794 |
| CM duration (years), mean ± SD | 6.1 ± 5.7 | 6.2 ± 5.5 | 0.916 |
| Acute medication days (number), mean ± SD | 20.5 ± 10.8 | 20.7 ± 10.4 | 0.884 |

*CM* indicates chronic migraine, *SD* standard deviation

follow-up. The causes for treatment stopping were different between men and women ($P = 0.031$).
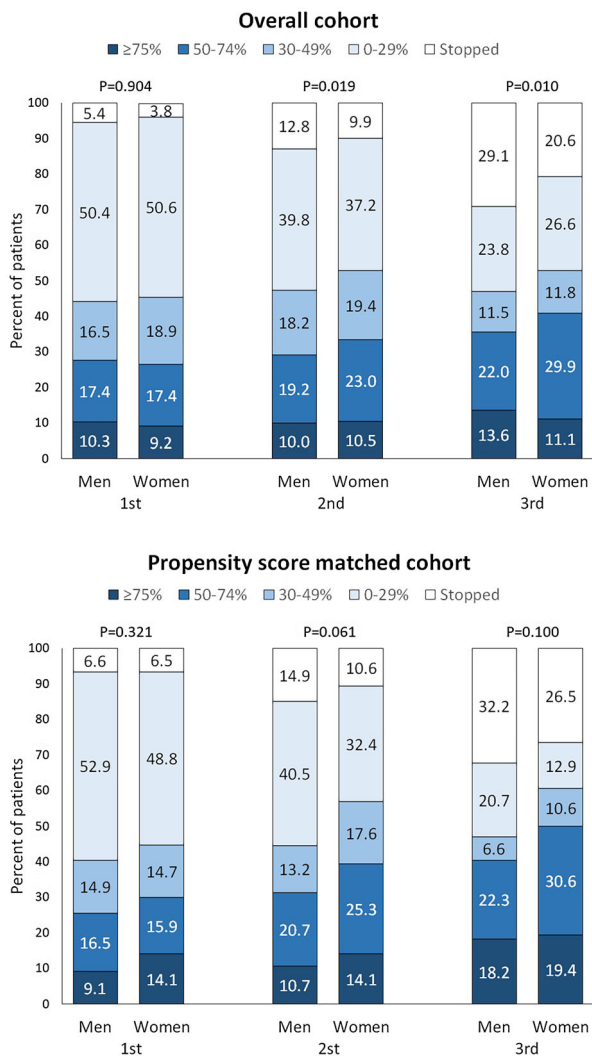
Fig. 1 Response and discontinuation rates of onabotulinumtoxinA during the first three cycles in the overall cohort (men = 522; women = 2357) and in the propensity score matched cohort (men = 121; women = 170). *P* values refer to the comparison between men and women according to the chi-squared test adjusted for linear trend data
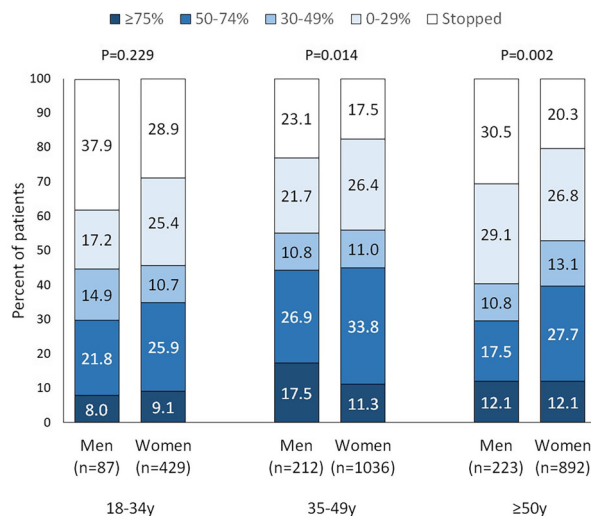


Fig. 2 Response and discontinuation rates of onabotulinumtoxinA during the third cycle according to gender and age groups. *P* values refer to the comparison between men and women according to the chi-squared test

# DISCUSSION

Reporting gender-specific data is relevant to discuss with patients the expected outcome of BT-A treatment and to improve our understanding of migraine and its gender differences. To our knowledge, our data are the first gender-specific analysis on the efficacy of BT-A. We found that BT-A was effective in both men and women; the proportion of responders increased over the first three BT-A cycles and more than one third of patients were 50% responders during the third cycle in both genders. A significant and stable decrease in headache frequency and acute medication use was also found in both men and women. We found a slightly lower response in men than in women that was, however, apparent only during the third BT-A treatment cycle and likely not substantial from a clinical point of view. The difference was significant only in patients aged 35 years or more, even if the non-significant difference in younger patients could be attributed to low numbers. As the difference was not present after propensity score matching, it can be attributed to differences in some characteristics of men and women which may affect treatment response. A further finding was that, at the end of the study follow-up, men reported a lower decrease in headache frequency compared with women. Again, the between-group difference was small, both in the overall and in the propensity score matched cohort. Besides, acute medication use did not show gender differences.

## Overall cohort



## Propensity score matched cohort
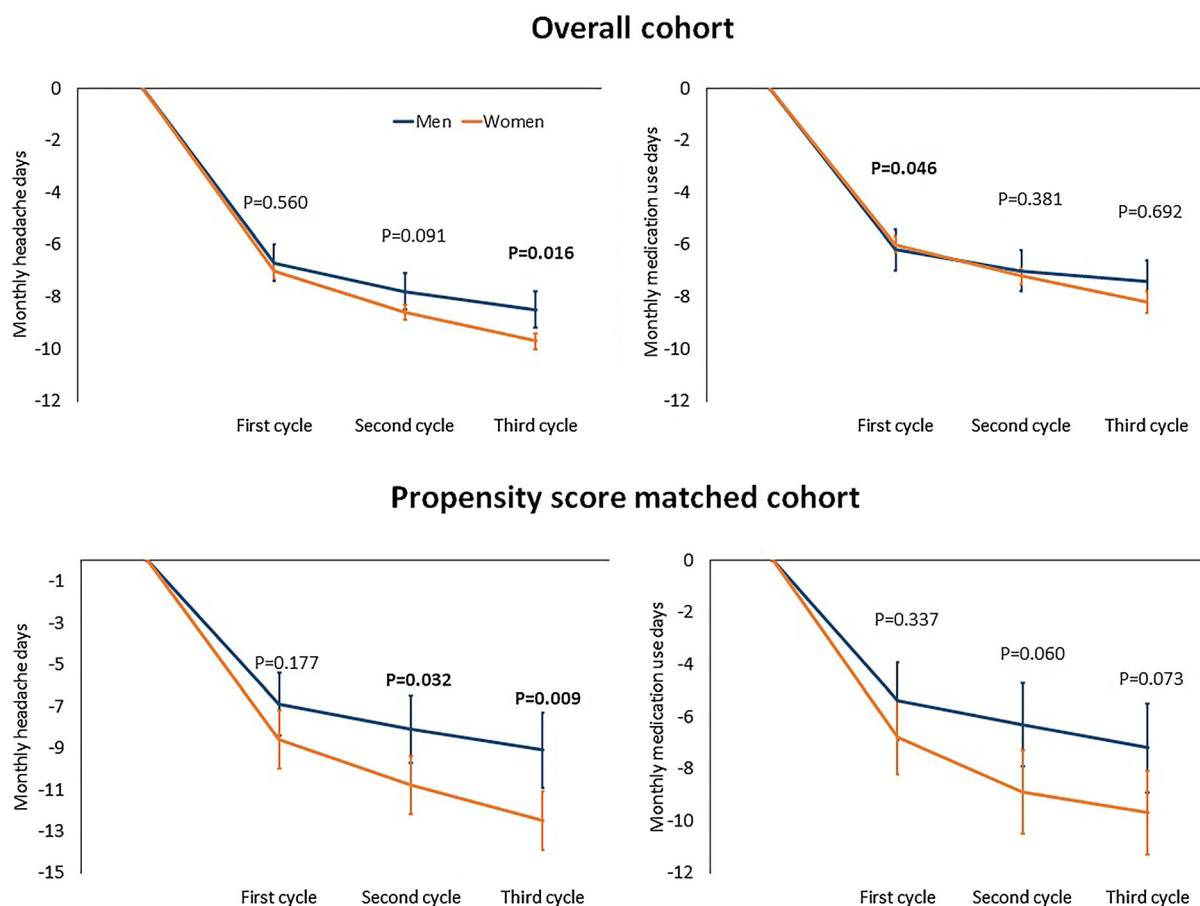


**Fig. 3** Mean decrease in monthly headache days and monthly acute medication use days over the study period in the overall cohort and in the propensity score matched cohort. *P* values for men and women are less than 0.001 at all timepoints with respect to baseline. The *P* values shown in the figure refer to the comparison between men and women (*t* tests). Error bars show 95% confidence intervals

In our study, men tended to stop BT-A treatment more often than women. As BT-A treatment stopping was due to both inadequate and good response (Table 2), the lower persistence with BT-A treatment of men might reflect a different attitude towards care rather than a lower response to the treatment. The issue of a lower persistence to migraine treatments in men than in women was already noted by previous literature [37, 38]; however, definite reasons for that gender difference are still not clear. Factors potentially impairing men's persistence to CM treatments should be adequately monitored and managed in clinical practice.

Gender differences in migraine primarily depend on sex hormones. The high fluctuations in estrogen levels that accompany the menstrual cycle and perimenopause are associated with a possible exacerbation of migraine, leading to the particularly higher prevalence of migraine in women than in men during the female fertile period [39–41]. On the other hand, male sex hormones are likely protective against migraine, as suggested by the cessation of migraine in women treated with testosterone for reasons other than their migraines [7]. Animal models indicate that estrogen receptors are present in the trigeminal ganglion, which releases calcitonin gene-related peptide (CGRP), a peptide implied in migraine pain [42, 43]. Besides, a correlation was found between the different phases of estrous cycle and the

**Table 2** Detail of onabotulinumtoxinA stopping rates and reasons

| | Overall cohort ($n = 2879$) | Men ($n = 522$) | Women ($n = 2357$) |
|---|---|---|---|
| Inadequate response, $n$ (%) | 257 (8.9) | 65 (12.5) | 192 (8.1) |
| Good response, $n$ (%) | 214 (7.4) | 52 (10.0) | 162 (6.9) |
| Adverse events, $n$ (%) | 27 (0.9) | 0 | 27 (1.1) |
| Lost to follow-up, $n$ (%) | 139 (4.8) | 35 (6.7) | 104 (4.4) |
| Total, $n$ (%) | 637 (22.1) | 152 (29.1) | 485 (20.6) |

$P = 0.031$ for distribution (men vs women)

amount of CGRP released from the trigemino-vascular system [9]. In humans, there is also evidence that female sex hormone fluctuations can alter the "set point" for the generation of migraine attacks [44]. However, the ways in which estrogens modulate migraine-generating structures are still not clear. Besides, it is not known how estrogens can interact with migraine preventatives acting on CGRP release, which include BT-A [45]. Other factors which may contribute to gender differences in the presentation of migraine and its response to medication include comorbidities and mostly psychiatric conditions. Two cross-sectional studies suggest that the association between symptoms of anxiety or depression and migraine is stronger in men than in women [46, 47]. Depressive symptoms have been already associated with lower response to BT-A [48]. Hence, the effect of comorbidities such as anxiety or depression could explain a lower response to BT-A in men compared with women. However, the presence of anxiety and depression could not be retrieved from our dataset.

The main strength of our study was the inclusion of a high number of men. We also reported the first available data on adherence to BT-A treatment in men compared with women.

Being multicenter, international, and reflecting the real-life headache care setting, our findings have a good generalizability. Additionally, all study centers prospectively recruited all BT-A treated patients, thus reducing the possibility of selection bias. A further strength of the present paper is the use of an exact propensity score matching between men and women which enhanced the between-group comparability. Propensity score matching has been already used in previous studies to assess the risk for migraine comorbidities [49–51] and the effect of migraine treatment on several outcomes [52]. However, in the present study, the matching variables only included age, length of CM history, and baseline headache frequency; matching for medical comorbidities could not be performed as those data were not included in our dataset. Data collection across centers was heterogeneous, resulting in a limited number of variables to consider for the present analysis. The present analysis was primarily designed to assess BT-A effectiveness; therefore, the assessment of gender differences could not be complete. Moreover, we could not collect data on BT-A safety except from BT-A discontinuation due to adverse events. However, BT-A has shown an excellent tolerability profile in the trials [15, 16] and in real-life studies [26–28, 30, 31, 53–56]. Lastly, our study is limited by its observational nature and lack of randomization, which may introduce biases we cannot adjust for.

## CONCLUSIONS

BT-A is an effective treatment for CM prevention both in men and in women. We only found slight and probably unmeaningful differences in BT-A efficacy favoring women over men. On the other hand, adherence to treatment was a more important concern in men than in women. There is an unmet need for gender-specific data on migraine treatments which should be reported first in randomized controlled trials and then in observational studies.

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***Prior Presentation.*** The study was accepted as oral presentation for the 2021 International Headache Society/European Headache Federation Joint Congress (virtual, 8–10 September 2021).

***Compliance with Ethics Guidelines.*** The present analysis was approved by the Internal Review Board of the University of L'Aquila with protocol number 23/2020. The approval was shared with all the participating centers. Patients did not have to sign an additional informed consent as no additional data were required for the present analyses. The study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments.

***Data Availability.*** The datasets analyzed during the current study are available from the participant centers upon reasonable request.

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