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Perceived ease-of-usability and local tolerability using CGRP monoclonal antibody autoinjectors *vs.* syringes: an online questionnaire-based study in patients with migraine

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ABSTRACT

Background: Monoclonal antibodies acting on the CGRP pathway (CGRP-mAbs) are characterized by subcutaneous administration via autoinjectors or prefilled syringes. Unfortunately, significant local tolerability concerns about injection site pain (ISP) may degrade patient comfort, increase the fear and stress of dose administration, and negatively impact patient adherence. The aim of the present cross-sectional study was to assess the experience of patients with migraine using either CGRP-mAbs prefilled syringes or autoinjectors regarding local tolerability and perceived ease-of-usability.

Methods: A self-administered electronic questionnaire was created using "Google questionnaires" to collect from migraine inpatients treated with CGR-mAbs: i) demographic and clinical parameters; ii) data related to ongoing preventive CGRP-mAb treatments and their local tolerability (in particular, evaluated by numerical rating scale); iii) data on perceived ease-of-usability; and iv) data on putative previous onabotulinumtoxinA treatment.

Results: The questionnaire was sent to 405 migraine patients. After 10 days, 283 (69.87%) patients had completed the electronic form. No significant differences were found among groups regarding data on ease-of-usability and local tolerability of CGRP-mAbs regarding simplicity and modality of administration (self-administered or not), ISP, or reactions at the site of administration. However, we did identify young females (OR=0.22; p<0.001) with chronic migraine (OR=4.87; p=0.007) to be the phenotype most prone to experience ISP during CGRP-mAbs treatment. Of 96 patients who had previously received at least 3 onabotulinumtoxinA administrations, injection site pain was significantly higher with onabotulinumtoxinA compared to CGRP-mAbs (6±4 *vs.* 4±5; p<0.001).

Conclusions: Devices used for CGRP-mAbs administration (auto-injector and prefilled syringes) are characterized by several strengths and disadvantages, one compensating for the other so that no differences in perceived ease-of-usability and local tolerability can be observed. These findings may also result in economic and ecological implications, considering the lower impact on costs and environmental pollution of prefilled syringes compared to more expensive and polluting plastic autoinjectors.

Key words: CGRP, onabotulinumtoxinA, migraine, autoinjectors, prefilled syringes.

Introduction

Preventive treatment for migraine represents the mainstay approach for patients whose attacks may be either frequent or infrequent, but are disabling, and who are poorly responsive to painkillers. (1) Until a few years ago, the pharmacological armamentarium for migraine prevention included only oral drugs with daily administration (sometimes more than once a day), often affecting patient adherence to treatment. (2,3)

In the last decade, new preventive medications, such as onabotulinumtoxinA and, more recently, monoclonal antibodies acting on the CGRP pathway (CGRP-mAbs), have been developed and are characterized by subcutaneous administration. (1)

Specifically, while the onabotulinumtoxinA injection paradigm entails quarterly pericranial injections (from 31 to 39), CGRP-mAbs are designed to be administered every 28 or 30 days via prefilled syringes for fremanezumab or autoinjectors for galcanezumab and erenumab. (4-6)

Subcutaneous injection may represent an important administration route for biopharmaceutical delivery able to improve treatment experience. (7) In particular, perceived ease-of-usability improvements in terms of treatment compliance and feeling of freedom and flexibility have been demonstrated in patients with chronic diseases (*e.g.*, diabetes, rheumatoid arthritis, etc.) using prefilled pens compared with drug administration via prefilled syringes. (8,9)

Unfortunately, significant local tolerability concerns about injection site pain (ISP) with both prefilled syringes and autoinjectors can decrease patient comfort and increase fear and stress of dose administration, negatively impacting patient adherence. (10) Moreover, prefilled autoinjectors could be associated with increased cost issues and ecological implications compared to prefilled syringes. (11)

However, although RCT studies and real-world experiences have reported ISP as the most frequent adverse event concerning both onabotulinumtoxinA and CGRP-mAb administration, only one study to date has evaluated migraine patient experience in terms of perceived ease-of-usability and local tolerability of prefilled syringes and autoinjectors. (12-14)

The aim of the present study was to assess the experience of patients with migraine using either CGRP-mAbs prefilled syringes or autoinjectors regarding patient local tolerability and perceived ease-of-usability. Furthermore, in migraine patients who have used CGRP-mAbs before or after onabotulinumtoxinA treatment, preference and local tolerability were compared.

We hypothesized that distinctive features of prefilled devices (*i.e.*, autoinjectors and prefilled syringes) may make a difference in perceived ease-of-usability and local tolerability between the CGRP-mAbs in patients with migraine.

Results

Population. The questionnaire was sent to 405 migraine patients treated with CGRP-mAbs, all under treatment at the Headache Centre of the University of Campania "Luigi Vanvitelli". After 10 days, 283 (69.87%) patients had filled in the electronic form. Among these, 219 patients were female, and the median age was 49 (±16). A diagnosis of chronic migraine was reported by 202 patients, while the remaining 81 patients had a diagnosis of high-frequency episodic migraine without aura. At baseline, the average migraine frequency (headache days/month) in the three months before starting CGRP-mAbs administration was 20 (±13) days, and ictal cutaneous allodynia was reported in 132 patients with a median score of 4 (±9) at ASC-12 (**Table 1**).

Groups according to CGRP-mAbs treatment type. Regarding CGRP-mAbs treatment, 106 were in treatment with erenumab, 98 with galcanezumab, and 79 with fremanezumab. No significant differences were found among groups in demographic and clinical parameters such as age, male/female ratio, headache diagnosis, frequency of monthly headache days, and ictal cutaneous allodynia.

Considering the three patient groups according to the CGRP-mAbs administration devices used (*i.e.*, two different autoinjectors and one syringe), no differences were found among groups regarding perceived ease-of-usability, modality of administration (self-administration and not self-administration), and local tolerability (*i.e.*, ISP and other reactions at the site of administration). No differences between groups were found with respect to other parameters (**Table 2**).

Table 1. Baseline demographic and clinical parameters of patients treated with CGRP-mAbs.

Characteristics	N=283
Gender, *n (%)*	
Male	64 (22.61)
Female	219 (77.39)
Age, *median±IQR*	49 ±16
Headache days baseline, *median±IQR*	20 ±13
Chronic migraine, *n (%)*	202 (71.38)
CGRP-mAbs, *n (%)*	
Fremanezumab	79 (27.92)
Galcanezumab	98 (34.63)
Erenumab	106 (37.46)
Preferred injection site, *n (%)*	
Thigh	55 (19.43)
Arm	188 (66.43)
Periumbilical region	17 (6.01)
Site rotation	23 (8.13)
Previous disinfection of injection site, *n (%)*	267 (95.35)
Use of topical analgesic after administration, *n (%)*	5 (1.77)
Other Injection-Based Therapy ongoing, *n (%)*	13 (4.59)
Other painful condition, *n (%)*	87 (30.74)
Previous BoNT-A treatment, *n (%)*	96 (33.92)
Belonephobia, *n (%)*	57 (20.14)
ASC12, *median±IQR*	4±9

Values are median±interquartile range (IQR) or number (%).
IQR, interquartile range; n, number; CGRP-mAbs, calcitonin gene-related peptide antibodies monoclonal antibodies; BoNT-A, onabotulinumtoxinA; ASC-12, Allodynia Symptom Checklist-12.

Table 2. Demographic and clinical parameters of patients with migraine treated with CGRP-mAbs divided according to the antibody received (fremanezumab, galcanezumab, erenumab).

	Fremanezumab	Galcanezumab	Erenumab	p-value
Gender, M:F	18:61	18:80	28:78	0.389
Age, *median±IQR*	47±23	48 ±10.75	49±15.75	0.132
Chronic migraine, *n (%)*	57 (72.15)	72 (73.47)	73 (68.87)	0.756
Headache days baseline, *median±IQR*	18±13	19±14.25	20±11.75	0.727
Headache days after 3 administrations, *median±IQR*	5±7	7.5±11.75	6±7	0.174
Responders, *n (%)*	62 (78.48)	63 (64.29)	82 (77.36)	0.049
Ease of usability, *median±IQR*	9±3	9±2	9±2	0.266
Previous disinfection of injection site, *n (%)*	75 (94.94)	93 (94.90)	99 (93.40)	0.866
Use of topical analgesic after administration, *n (%)*	2 (2.53)	1 (1.02)	2 (1.89)	0.734
Other Injection-Based Therapy ongoing, *n (%)*	4 (5.06)	0 (0)	9 (8.50)	0.367
Other painful condition, *n (%)*	29 (36.71)	29 (29.59)	29 (27.36)	0.377
Belonephobia, *n (%)*	9 (11.39)	18 (18.37)	30 (28.30)	0.015
ASC12, *median±IQR*	5±10.5	4±7	4±9	0.277
Self-administration, *n (%)*	30 (37.97)	35 (35.71)	43 (40.57)	0.775
Characteristics of injection site pain				
NRS, *median±IQR*	4±4	5±6	4±6	0.109
Duration (min), *median±IQR*	2±4	2±3	2±4	0.369
Injection site-dependent pain, *n (%)*	31 (39.24)	42 (42.86)	43 (40.57)	0.675
More painful injection site, *n (%)*	Periumbilical 16 (20.25)	Periumbilical 24 (24.49)	Periumbilical 16 (15.09)	
Less painful injection site, *n (%)*	Arm 21 (26.58)	Arm 33 (33.67)	Arm 33 (31.13)	
Preferred injection site, *n (%)*				
Thigh	6 (7.59)	21 (21.43)	28 (26.42)	0.004
Arm	55 (69.62)	68 (69.39)	65 (61.32)	
Periumbilical region	10 (12.66)	4 (4.08)	3 (2.83)	
Site rotation	8 (10.13)	5 (5.10)	10 (9.43)	
Erythematous skin reaction, *n (%)*	31 (39.24)	42 (42.86)	37 (34.91)	0.506

Values are median±interquartile range (IQR) or number (%).
IQR, interquartile range; n, number; CGRP-mAbs, calcitonin gene-related peptide antibodies monoclonal antibodies; ASC-12, Allodynia Symptom Checklist-12; NRS, numerical rating scale; min, minutes.

Secondary post-hoc analyses have been conducted considering i) two different patient groups according to modality of administration (self-administration and not self-administration) and ii) three different patient groups according to administration site (*i.e.*, arm, leg, or periumbilical region) failed to demonstrate differences in perceived ease-of-usability of autoinjectors and syringes and in related local pain and reactions at the site of administration.

Correlation analyses showed statistically significant correlations between the occurrence of ISP (Yes/No) and i) reactions (redness) at the sites of administration (r: 0.53; p=0.005), ii) chronic migraine (r:0.42; p=0.04), and iii) male gender (-0.48; p=0.008). Moreover, statistically significant correlations between the intensity of ISP (NRS) and i) age (r:-0.19; p=0.023), and ii) ISP duration following administration (r:0.21; p=0.007) were found.

No significant correlations were demonstrated between the occurrence and intensity of ISP and perceived ease-of-usability, modality of administration, comorbid painful conditions, belonephobia, and ictal cutaneous allodynia (ASC-12).

Logistic regression analysis based on age, gender, baseline headache attack frequency, migraine chronification, ictal cutaneous allodynia, perceived ease-of-usability, and belonephobia was able to predict the occurrence of ISP ($\chi^2(4)=43.89$, p<.001) with good accuracy, as witnessed by the ROC curve analysis exhibiting an AUC of 0.754 for the full model. Specifically, the analysis of odds ratio demonstrated that female gender (OR=0.22; p<0.001) and chronic migraine (OR=4.87; p=0.007) were associated with an increased likelihood of experiencing ISP (**Figure 1**, **Table 3**).

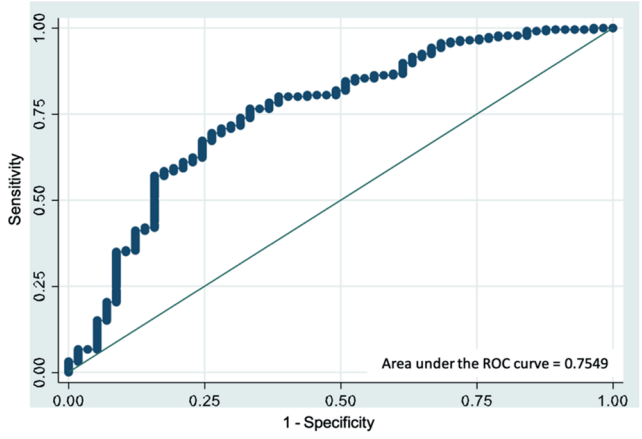

Figure 1. ROC curve analysis (AUC=0.754).

CGRP-mAbs *vs.* onabotulinumtoxinA. Among patients treated with CGRP-mAbs, 96 patients had previously received at least 3 onabotulinumtoxinA administrations in accordance with the PREEMPT protocol. ISP was significantly higher with onabotulinumtoxinA compared to CGRP-mAbs (6±4 *vs.* 4±5; p<0.001) (**Table 4**).

Discussion

In the present study, we demonstrated comparable perceived ease-of-usability and local tolerability (*i.e.*, ISP and reactions at the site of administration) between CGRP-mAb autoinjectors (*i.e.*, galcanezumab and erenumab) and prefilled syringes (*i.e.*, fremanezumab) in patients with migraine. As expected, patients currently treated with CGRP-mAbs experiencing previous onabotulinumtoxinA injections considered the latter significantly worse than CGRP-mAbs in terms of ISP. Interestingly, a clinical profile predicting the occurrence of ISP has been identified based on demographic and clinical characteristics (specifically female gender and chronic migraine).

Preventive treatments represent the mainstay approach for migraine patients suffering from attacks that are frequent (more than 5 days per month) or not frequent but disabling and poorly responsive to painkillers. (1) Until a few years ago, the therapeutic armamentarium for migraine prevention was constituted only by oral drugs designed for other disorders, such as arterial hypertension, depression, and epilepsy, so-called "repositioning drugs". Although sometimes effective, these treatments were burdened by frequent adverse events and the necessity of administration on a daily basis (sometimes more than once a day), both of which affect patient adherence to treatment. (2,3)

In the last decade, novel migraine preventive therapeutic strategies characterized by subcutaneous routes of administration, such as onabotulinumtoxinA and CGRP-mAbs, have been developed. (4,5) However, as observed in patients with other chronic diseases (*e.g.*, diabetes, rheumatoid arthritis, etc.), if, on the one hand, subcutaneous injection improves the patient's feeling of freedom and flexibility, reducing the risk of both accidental overdose and lack of dose administration, on the other hand, pain and other reactions at the sites of administration remain significant concerns that may degrade patient experience by increasing dosing fear or stress, thereby affecting therapeutic adherence. (7-9)

Specifically, onabotulinumtoxinA, administered quarterly by specialized healthcare personnel to 31-39 subcutaneous sites of the head, is burdened by ISP during administration, which results to be a reason for discontinuation in about 10% of therapy dropouts, despite proven efficacy and absence of systemic adverse events. (15) Similarly, CGRP-mAbs, administered monthly subcutaneously with autoinjectors (in the case of erenumab and gal-

Table 3. Logistic regression analyses assessing whether demographic and clinical parameters are able to predict patients with migraine who will develop injection site pain.

Variable	Odds ratio [CI 95%]	p-value	SE
Simple Regression			
Sex (male:1; female:0)	0.22 [0.11, 0.45]	**0.000**	0.08
Age (years)	0.97 [0.95, 1.00]	0.142	0.01
Headache diagnosis (chronic migraine:1; episodic migraine:0)	4.87 [1.55, 15.26]	**0.007**	2.84
Headache attacks frequency (headache days/month)	0.99 [0.92, 1.06]	0.745	0.04
Ease-of-usability	1.00 [0.86, 1.17]	0.967	0.08
Cutaneous allodynia (ASC-12 score)	0.98 [0.92, 1.05]	0.607	0.03
Belenofobia (yes:1; no:0)	1.89 [0.76, 4.68]	0.169	0.87

RS-Fc, resting state functional connectivity; SE, Standard Error; a, Model χ^2 (2)=43.89, **p-value<0.001**, pseudoR2=0.15; ASC-12, Allodynia Symptom Checklist-12.
In bold: statistically significant value.

canezumab) or prefilled syringes (in the case of fremanezumab), can induce reactions at the site of administration, as reported in randomized controlled studies as well as real-world observations where the ISP is considered the most frequent adverse event, although never leading to treatment discontinuation. (16-18)

Perceived ease-of-usability of CGRP-mAb devices. Subcutaneous autoinjectors are a convenient and efficient way to self-administer biopharmaceutics, although they raise cost issues and ecological implications. (19) Several crossover studies have shown a patient preference for autoinjectors compared to vials or prefilled syringes since they may offer substantial improvement in patient freedom and flexibility, resulting in a significantly higher therapeutic adherence. (20-22)

Specifically, erenumab and galcanezumab devices are autoinjectors provided with safety unlocking mechanisms to prevent unintended activation of drug delivery. (23)

More specifically, after needle shield removal, the safety guard has to be pressed against the skin to unlock the erenumab device; to unlock the galcanezumab device, the knob must be twisted. For both (*i.e.*, erenumab and galcanezumab), the needle is not directly visible before device activation to reduce patient stress, and a mechanical "click" sound alerts the patients to injection completion. However, while the "click" sound is a reliable confirmation of completed galcanezumab administration, for the erenumab device, the "click" sound precedes the complete dose administration, potentially inducing an erroneous premature device removal that could affect the accuracy of dose injection. (23) Less information is available to date regarding fremanezumab prefilled syringe perceived ease-of-usability in patients with migraine.

It is noteworthy that in the present study, we did not find differences in the perceived ease-of-usability between galcanezumab and erenumab autoinjectors nor between the autoinjectors and fremanezumab prefilled syringes. Indeed, as a proxy of perceived ease-of-usability, the self-administration of CGRP-mAbs did not differ in the three subgroups according to the different devices, although the non-automatic administration by prefilled syringes could appear less manageable for the patient or caregiver. These findings are in line with previous observations reporting that both perceived ease-of-usability and tolerability of galcanezumab via self-administered prefilled syringes or autoinjectors were comparable among patients with migraine. (14)

Local tolerability. *Injection site pain (ISP).* Several factors have been purported to affect the nociception component of subcutaneous administrations. (7,22) Among these, formulation characteristics (buffer type, pH, and osmolality), delivery factors (volume, injection speed, and viscosity), device parameters (needle gauge, contact area, and lateral needle movement), and the skill of the injector have been considered of paramount importance.

Several differences can be observed in buffer types. Galcanezumab formulation includes: diluted in sterile water for injection USP (United States Pharmacopeia) (and excipients such as 150 mm sodium chloride, 0.02% polysorbate 80), 10 mm sodium citrate as buffer with a pH of 6.0. (24) On the other hand, erenumab formulation includes: diluted in sterile water for injection USP (and excipients such as A52SuT, 9.0% (w/v) of sucrose, 0.0004% (w/v) of polysorbate 20), 10 mm of sodium acetate as buffer with a pH of 5.2. (25) Finally, fremanezumab formulation includes: diluted in sterile water for injection USP (and excipients such as sucrose, disodium ethylenediaminetetraacetic acid (EDTA) dihydrate, polysorbate 80, L-histidine hydrochloride monohydrate as buffer with a pH of 5.5. (26) Osmolality does not represent a factor of difference between the CGRP-mAbs. Peculiarities in type, concentration, and tonicity of buffer play a prominent role in ISP. (27) Indeed, while citrate and histidine are significantly more painful than acetate or, even more, saline (*i.e.*, without buffer), no differences have been observed between citrate and histidine. (7) Therefore, erenumab, based on acetate buffer,

Table 4. Demographic and clinical parameters among patients treated with CGRP-mAbs who have previously received onabotulinumtoxinA.

	CGRP-mAbs	*OnabotulinumtoxinA*	*p-value*
Gender, n (%)	96		
Male	29 (30.21)		
Female	67 (69.79)		
Age, median±IQR	50.5±13.5		
CGRP-mAbs, n (%)			
Fremanezumab	17 (17.71)		
Galcanezumab	43 (44.79)		
Erenumab	36 (37.5)		
Ease of administration, median±IQR	9±2		
Preferred injection site, n (%)			
Thigh	24 (25)		
Arm	59 (61.46)		
Periumbilical region	7 (7.29)		
Site rotation	6 (6.25)		
Other Injection-Based Therapy			
Ongoing, n (%)	3 (3.14)		
Other painful condition, n (%)	37 (38.54)		
Belonephobia, n (%)	27 (28.13)		
ASC12, median±IQR	4±8		
Injection site pain (NRS), median±IQR	4±5	6±4	**<0.001**
Injection site pain (duration), median±IQR	2±3.75 min	1±1 hour	**<0.001**

Values are median±interquartile range (IQR) or number (%).
n, number; IQR, interquartile range; CGRP-mAbs, calcitonin gene-related peptide antibodies monoclonal antibodies; ASC-12, Allodynia Symptom Checklist-12; NRS, numerical rating scale.

should be less painful compared to galcanezumab and fremanezumab.

On the other hand, the more the pH moves away from physiological (*i.e.*, pH 7.0) towards either acidic or basic, the greater the ISP. (7) Consequently, based on pH values, galcanezumab should be less painful compared to erenumab and fremanezumab.

Nevertheless, delivery factors have recently been investigated for galcanezumab (120 mg/mL) and erenumab (140 mg/mL) autoinjectors, since differences in the devices' mechanical design can affect their functionality and performance. (23) First, differences in injection speed have been found. Specifically, at room (25 C°) and storage temperatures (5 C°), the injection speed of galcanezumab was 0.40 mL/s and 0.28 mL/s, while for erenumab it was 0.24 mL/s and 0.16 mL/s. (23) However, if on the one hand, a fast injection speed is able to reduce the duration of drug administration, reducing the stress for patients, on the other hand, the positive correlation between injection speed and pain at the site of injection is well-known (*i.e.*, the higher the speed, the greater the pain perception). It has been argued that slow injection allows time for tissue under the skin to accommodate the injected volume, resulting in reduced pressure, capillary bleeding, and ISP, thereby minimizing the likelihood of bruising at the injection site. (28) Therefore, considering injection speed, galcanezumab should be more painful compared to erenumab.

However, at room temperature, galcanezumab is characterized by a lower viscosity compared with erenumab (4.5 cP *vs.* 7.4 cP), and viscosity is directly correlated with ISP (*i.e.*, the higher the viscosity, the greater the pain perception). (7) Therefore, according to the biopharmaceutic viscosity, erenumab should be more painful compared to galcanezumab (see **Table 5** for further information about volume parameters among the different CGRP mAbs).

Finally, regarding the parameters of the devices, although the needle diameters are equal (27G) among the different CGRP-mAbs, several differences have been observed in contact area and lateral needle movement. While the galcanezumab autoinjector is more stable as its skin contact area is ten times larger than erenumab (*i.e.*, 1000 mm^2 *vs.* 100 mm^2), the lateral needle movement using the galcanezumab device seems to be greater than during injection with the erenumab device, even though the difference in lateral needle movement during both the insertion and the injection has been found not statistically significant in a comparison study. (14) It is conceivable that lateral movement during injection may have an influence on ISP, as demonstrated by several studies about pain discomfort associated with subcutaneous drug administration. (7,10,19) Therefore, regarding the stability of the device, erenumab is expected to be more painful compared to galcanezumab. However, considering the lateral needle movement, galcanezumab should be more painful compared to erenumab.

Considering the foregoing, it can be argued that fremanezumab, administered through a prefilled syringe, could be more exposed to issues depending on non-skilled injectors (especially regarding the skin contact area limited to the needle diameter and the possibility of a wide range of lateral needle movement) and, consequently, burdened by a lower local tolerability in terms of ISP.

Herein, we observed that the average intensity of ISP reported by patients with migraine in the course of CGRP-mAbs administration is 4 (±5)/10 on the NRS. Surprisingly, there are no statistically significant differences in ISP between the different CGRP-mAbs, although two of them require the use of autoinjectors, while the other is provided by a prefilled syringe. It is interesting to note that no statistically significant differences were found in ISP based on whether the CGRP-mAbs were self-administered or not. The lack of differences in ISP between CGRP-mAbs with different devices (*i.e.*, autoinjectors and prefilled syringes) is in line with data emerging from a recent study comparing usability and injection-site-related adverse events (AEs) among patients with migraine-experiencing galcanezumab self-administration by means of autoinjectors or prefilled syringes. (14)

Contrarywise, we speculate on the possibility that self-regulating the injection speed during fremanezumab administration, which is different from the predefined injection speed characterizing the autoinjectors, could positively affect the ISP related to injection speed.

Correlation analysis showed that both the occurrence and intensity of ISP were directly associated with the occurrence of reactions at the sites of administration as well as with ISP duration following the administration of CGRP-mAbs. It is conceivable that some migraine patients may be characterized by particular susceptibility to reactions at the sites of administration, resulting in higher occurrence and intensity of ISP, redness, and long-lasting ISP, regardless of the devices and the substances injected. However, the occurrence of ISP showed positive significant correlations with female gender and chronic migraine, whereas the severity of ISP exhibited negative correlation with age. The correlation with chronic migraine may suggest the key role of central sensitization in these patients when compared to patients with episodic migraine (specifically the patients with high-frequency

Table 5. Advantages and disadvantages of each CGRP-mAbs device.

	Erenumab	Galcanezumab	Fremanezumab
Needle visibility	No	No	Yes
Administration completion click	Yes	Yes (accurate)	No
Buffer	Sodium Acetate	Sodium Citrate	L-histidine
pH	5.2	6.0	5.5
Volume	1 mL	1 mL	1.5 mL
Injection speed	0.24 mL/s	0.40 mL/s	Manual
Injection duration	4.1-6.5 s	2.5-3.6 s	Manual
Viscosity	7.4 cP	4.5 cP	-
Needle gauge	27-gauge	27-gauge	27-gauge
Contact area	100 mm^2	1000 mm^2	0.10 mm^2
Lateral needle movement	0.2-0.25 mm	0.35-0.4 mm	Manual
Anti-roll feature	Yes	Yes	None
Patient's skill	None	None	Yes

Green, advantages; red, disadvantages.

migraine in our sample population). More specifically, it is well known that migraine chronification is strongly associated with central sensitization, where repeated nociceptive input leads to heightened pain sensitivity and altered pain processing pathways in the brain. (29) This is probably due to the fact that chronic migraines involve structural and functional changes in brain areas that contribute to a reduced pain threshold and increased vulnerability to persistent pain. (30) Similarly, it is well known that pain threshold is lower in women with migraine and tends to increase with age. (31,32) Interestingly, a full model considering age, gender, headache attack frequency, migraine chronification, ictal cutaneous allodynia, perceived ease-of-usability, and belonephobia is able to predict the occurrence of ISP as supported by the values of ROC curve analysis (AUC=0.754). In other words, we can identify young women with chronic migraine as the phenotype more prone to experience ISP during CGRP-mAbs treatment.

Reactions at the site of administration other than injection site pain (ISP). In addition to ISP, 38% of patients reported redness as a reaction at the site of administration. No other reactions at the site of administration have been reported by the patients. No differences were found in the percentage of patients reporting redness between the three patient groups according to the different CGRP-mAbs.

CGRP-mAbs *vs.* onabotulinumtoxinA. Ninety-six patients were treated with onabotulinumtoxinA before CGRP-mAbs and clearly reported that the ISP related to administration of onabotulinumtoxinA (according to the PREEMPT protocol) is higher than ISP related to CGRP-mAbs administration. It can be argued that the cranial and cervical sites of administration, as well as the higher number of injections, could justify the differences in terms of ISP. We are aware that there is also a risk for response bias and for a memory recall bias; however, the exclusive use of onabotulinumtoxinA in patients with chronic migraine and the well-known low pain threshold in these patients may further explain the reported differences in ISP at the site of administration. (29,30) Concerns in local tolerability of the PREEMPT protocol are also widely recognized as potentially able to affect therapeutic adherence, representing a reason for onabotulinumtoxinA discontinuation in about 10% of therapy drop-outs. (15)
These data, beyond the obvious considerations of adding pain to patients already burdened by disabling pain conditions, suggest the need for further in-depth research aimed at prioritizing anti-migraine treatments characterized by greater tolerability in terms of ISP. We believe that these results should be considered by the stakeholders in regulating the provisions for access to "second level" therapies.

Limitations. We are aware that the absence of a crossover study design (due to the Italian Health Agency provisions not allowing patients with migraine to switch between different CGRP-mAbs) affects a reliable evaluation of patient preference regarding the different CGRP-mAb devices. Furthermore, although the difference in devices seems to be a momentous topic in different clinical practice scenarios, our results are not applicable to countries in which all CGRP-mAbs are administered via autoinjectors (*e.g.*, USA). Finally, as the questionnaire was self-administered, the information was not properly checked by a clinician, and recall bias cannot be ruled out.

Conclusions

The present study demonstrates that the devices used for CGRP-mAbs administration (autoinjectors and prefilled syringes) are characterized by strengths and disadvantages, balancing one another so that no differences in perceived ease-of-usability and local tolerability can be observed. However, from a clinical point of view, a clinic-demographic profile of patients may predict the occurrence of ISP, making both clinicians and patients aware of the manifestation.

Finally, despite the absence of differences in perceived ease-of-usability and local tolerability between the different CGRP-mAbs devices, we cannot disregard some economic and ecological concerns that could arise, considering the lower impact on costs and environmental pollution of prefilled syringes compared to more expensive and polluting plastic autoinjectors. Further studies are required to explore the economic and ecological impact of autoinjectors compared to other modalities of administration.

Materials and Methods

In the present cross-sectional study, a self-administered publicly available online questionnaire was developed to collect from inpatients with migraine treated with CGRP monoclonal antibody: i) demographic and clinical parameters, such as age, gender, headache diagnosis (migraine without aura, chronic migraine), frequency of attacks (headache days/month before and after the third CGRP-mAbs administration), ictal cutaneous allodynia (by ASC-12), belonephobia, other chronic painful condition, other ongoing injection therapies; ii) data related to ongoing preventive CGRP-mAbs treatment (galcanezumab, fremanezumab, erenumab), such as site of injection (shoulder, leg, periumbilical area or in rotation), reactions at the site of administration, ISP (with numerical rating scale); iii) data on administration procedure as perceived ease-of-usability, administration modality (self-administered or not), previous disinfection of injection site, and use of topical analgesic; iv) data on putative previous onabotulinumtoxinA treatment and related ISP (with numerical rating scale). An electronic questionnaire (**Supplementary Material 1**) was created using "Google questionnaires" and sent by mail or WhatsApp to all patients referring to the Headache Centre of the University of Campania "Luigi Vanvitelli". Subjects were informed that data were collected anonymously in compliance with the recommendations of the ethics committee of the University of Campania "Luigi Vanvitelli" and, due to the anonymization, it was not possible to revoke participation in the study after the questionnaire had been sent.

Statistical analysis. No statistical power calculation was conducted prior to the study, and the sample size was based on the available data. All demographic and clinical data were checked for normality using Shapiro-Wilk test. Continuous variables conforming to normal distribution are reported as mean ± standard deviation (SD), while continuous data not conforming to normal distribution and categorical variables are expressed as median ± interquartile range, and rate values are reported as subject-counts and percentages. We used the one-way ANOVA test to compare continuous variables conforming to normal distribution and Pearson's chi-square test to compare categorical variables, while the non-parametric Kruskal-Wallis test was used for data not conforming to normal distribution. Hypothesis testing was 2-tailed, and results were considered statistically significant if $p<0.05$. Bonferroni correction for multiple comparisons was applied. Spearman's rank correlation coefficient was used to conduct the correlation analysis between continuous parameters, while tetrachoric correlation was used to identify the association between dichotomous variables. Statistical significance was set at $p<0.05$, and Bonferroni correction was applied. Finally, a logistic regression analysis was performed to ascertain whether, based on demographic and clinical parameters, the occurrence of ISP could be predicted. All analyses were performed using STATA version 16 (StataCorp, College Station, TX, USA).

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Online supplementary material:

Supplementary Material 1. Simplified electronic questionnaire (Italian and English version).

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Conflict of interest: MarS has received speaker honoraria from Lilly, Novartis, and Teva; AT has received speaker honoraria from Novartis, Schwarz Pharma/UCB, Lundbeck, Abbvie, and Glaxo, and serves as an associate editor of the European Journal of Neurology; GT has received speaker honoraria from Sanofi-Aventis, Merck Serono, Bayer Schering Pharma, Novartis, Biogen-Dompé AG and has received funding for travel from Bayer Schering Pharma, Biogen-Dompé AG, Merck Serono, Novartis, and Sanofi Aventis; GT also serves as an associate editor of Neurological Sciences; AR has received speaker honoraria from Allergan, Novartis, Lilly, and Teva, and serves as an associate editor of Frontiers in Neurology (Headache Medicine and Facial Pain session). The other authors declare no potential conflict of interest.

Ethics approval and consent to participate: participants were informed that data were collected anonymously in accordance with the recommendations of the ethics committee of the University of Campania "Luigi Vanvitelli."

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