1st Post-European Headache Federation Meeting: a review of the latest developments presented at the 2020 European Headache Federation Congress

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Introduction. After the European Headache Federation (EHF) Congress, renowned Spanish neurologists specialised in migraine presented the most significant latest developments in research in this field at the Post-EHF Meeting.

Development. The main data presented concerning the treatment of chronic and episodic migraine were addressed, with attention paid more specifically to those related to preventive treatments and real-life experience in the management of the disease. An important review was carried out of the new therapeutic targets and the possibilities they offer in terms of understanding the pathophysiology of migraine and its treatment. An update was also presented of the latest developments in the treatment of migraine with fremanezumab, a monoclonal antibody recently authorised by the European Medicines Agency. Participants were also given an update on the latest developments in basic research on the pathology, as well as an overview of the symptoms of migraine and COVID-19. Finally, the repercussions of migraine in terms of its burden on the care and economic resources of the health system were addressed, along with its impact on society.

Conclusions. The meeting summarised the content presented at the 14th EHF Congress, which took place in late June/early July 2020.

Key words. Chronic migraine. EHF. Episodic migraine. Fremanezumab. Headache. Migraine. Post-EHF.

Introduction

The 1st Annual Post-EHF Meeting was held on 25-26 September 2020, where national and international headache specialists presented the latest developments in migraine management from the 14th Congress of the European Headache Federation (EHF), held between 29 June and 2 July 2020. Due to mobility and safety restrictions imposed as a result of the COVID-19 pandemic, both the congress and the subsequent meeting were held online. The different speakers who participated reviewed various interesting topical papers on migraine management presented at the EHF Congress. The aim of the meeting was to facilitate the dissemination of new data on the management of the disease and to set up a space for debate in which to discuss them.

This article offers an overview of the papers presented at the post-EHF Meeting. It summarises the main data presented on the management of chronic and episodic migraine, preventive treatment, novel therapeutic targets, real-life data on the management of the disease, and the care and economic burden resulting from migraine. We include a comprehensive review of the most important new advances in the use of fremanezumab in the treatment of migraine, as the most significant therapeutic development recently authorised by the European Medicines Agency. We also review the latest developments in the different topics of interest related to basic and clinical research in migraine, the data available so far on the relationship between COVID-19 and migraine and, finally, some aspects regarding the migraine-society dyad.

Migraine treatment

Care and economic burden of migraine and the need for new treatments

Migraine is the fifth most prevalent disease worldwide, with the highest incidence occurring in the most productive stages of patients' lives, between the ages of 25 and 40 [1]. In addition, it is a disease

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Conflicts of interest:
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that is extremely disabling for the patient [1]. Yet, despite its impact on prevalence and disability, the management of migraine (both episodic and chronic) is generally inadequate, as the diagnosis of migraine is sometimes delayed, patients do not always visit their primary care physician and they do not always receive appropriate treatment. Moreover, a considerable amount of time elapses before those with disabling migraine are referred to neurology [2,3]. For all these reasons, diagnostic and therapeutic management is often inadequate.

The new preventive treatments offer good results in terms of reducing the number of days with migraine per month and also the high percentage of patients who experience a reduction in their attacks by ≥ 50% [4-6]. In Europe, the European Medicines Agency considers that these treatments can be prescribed for patients suffering from migraine ≥ 4 days per month and there is a consensus among specialists in the management of the disease that candidate patients would be those who have failed to respond to at least two preventive treatments [7,8].

The funding of new preventive treatments for migraine by national health systems varies widely from one European country to another. In Spain, it differs depending on whether it is episodic or chronic migraine. In the first case, reimbursement of preventive treatment is considered for patients with ≥8 migraine days/month and for whom three previous preventive treatments have been unsuccessful. In the case of chronic migraine, its use is also considered after three previous preventive treatment failures, one of which must necessarily be botulinum toxin type A [9].

The diagnosis of migraine and its therapeutic management, guided by clinical practice guidelines, have been based on the results of clinical trials and the experience of each physician. The availability of treatments that have been designed specifically according to the pathophysiology of migraine offers us an opportunity not only to improve its management, but also to further our knowledge of the pathology. The role of calcitonin gene-related peptide (CGRP) is relevant in the production of pain. A number of groups are working to discover the factors that predict a response to these new drugs, which will almost certainly help us to classify a CGRP-dependent migraine. Proposals for a CGRP provocation test would be along these lines [10]. Pending the results of these research projects, it seems clear that candidate patients for the prescription of the new treatments would be those who experience important effects on their quality of life, both at work and at home and in leisure activities, and who have not responded to or tolerated previous preventive treatments [11].

Clinical development and studies conducted with the new treatments based on monoclonal antibodies have shown fairly homogeneous responses, but as yet there is no clear definition of which may be the best response marker. In addition to the usual parameters used in clinical trials, such as reduction in the number of headache days and the percentage of patients who reduce their attacks by ≥ 50%, it is also necessary to take into account the different levels of pain that patients have to deal with, the need for symptomatic treatment, the number of visits to the emergency department and the outcomes based on the activities the patient is able to cope with, as well as their quality of life.

Challenges in routine clinical practice in migraine management

One of the main challenges in the management of migraine is focused on patients who are particularly difficult to treat, due either to the lack of efficacy of the different preventive treatments or to their lack of tolerability to them [12,13]. The novel biological treatments are specifically designed for this patient profile and, in fact, the phase III studies carried out to analyse their efficacy and safety include a high percentage of participants with previous treatment failure. Specifically, the FOCUS (fremanezumab) study included patients who had unsuccessfully followed two to four types of previous preventive treatments [14]. Although this was a difficult patient profile to treat, the study showed a positive response compared to placebo as early as one week after the first administration. In the analyses by subgroups, this positive response was found to be independent of previous treatment failures, in patients who had ≥ 3 and ≥ 4 previous treatment failures, with and without symptomatic medication overuse criteria. In the open-label extension phase of the study, a sustained and persistent response was observed over time [15].

Another important challenge in the real-life management of the pathology is the presence of comorbidities and, specifically, the joint diagnosis of depression. Patients with depression as a comorbidity of migraine have proved to be affected by a greater number of days of migraine and a higher degree of symptomatic medication overuse [12,16]. The new treatments have yielded good re-

sponse data in patients with migraine and comorbid depression, who also show an improvement in their migraine and its impact on their productivity and quality of life, with a positive evolution of data on work disability and productive activity for participants in the open-label extension phases of studies in phase III [17,18].

Migraine has been associated with increased cardiovascular morbidity. New monoclonal antibody treatments appear to behave safely in this respect. In particular, fremanezumab has shown a low incidence of cardiovascular problems in the HALO and FOCUS studies, even in patients with a previous history of cardiovascular pathology [4,14,19].

Preventive treatment of migraine: new targets and treatments

Research into the genetics and pathophysiology of migraine has provided a wealth of information about the disease and its origin. On the one hand, it appears to be a polygenic disease in which genes with a neurovascular function are significantly involved [20]. On the other hand, modern neuroimaging techniques have provided information about the different phases that are recognised in a migraine attack with or without aura [21]. Furthermore, in a high percentage of patients, migraine is comorbid with psychological and other neurological disorders.

This has led to a pathophysiology of the disease centred on the trigeminal complex, the sympathetic and parasympathetic pathways and a number of neuropeptides that have become the new targets for the treatment of migraine [22].

CGRP has been shown to be the new key molecule in the pathophysiology of the disease. It is a peptide widely present in the trigeminal system, which causes vasodilation of the cerebral arteries [23]. In relation to the pathology, its infusion can be considered a good provocation test, as it triggers symptoms of migraine [24]. Furthermore, its levels have been shown to increase during a migraine attack and to decrease afterwards [25]. Finally, treatment with triptans lowers levels of CGRP [26]. All this evidence has made this peptide a very important target for the development of new treatments for both episodic and chronic migraine. Several monoclonal antibodies and small molecules are currently under development or have already been approved for use against CGRP or its receptor. Monoclonal antibodies have shown good short- and long-term efficacy and have a longer half-life in the body [27] (Table I). They are administered subcutaneously or intravenously in monthly or three-monthly (quarterly) doses [28].

Table I. General characteristics of the small molecules and calcitonin gene-related antipeptide monoclonal antibodies.

	Small molecules	Monoclonal antibodies
Affinity	Low	High
Elimination	Renal and hepatic	Reticuloendothelial system
Size	<1 kD	≈150 kD
Administration	Oral	Subcutaneous/intravenous
Blood-brain barrier	Yes	No
Half-life	Minutes/hours	Weeks
Immunogenicity	No	Yes

Table adapted from [28].

Other molecules being researched include the parasympathetic peptides, pituitary adenylate cyclase-activating polypeptide (PACAP) and vasoactive intestinal peptide (VIP). These molecules play different roles in the central nervous system and in pain, as well as in the cardiovascular system, the endocrine system and in inflammation [22]. Both molecules have joint effects on the same receptors (VPAC1 and VPAC2), although PACAP seems to play a more prominent role and would be a better target for treatment [29,30]. The two peptides have been able to trigger migraine attacks in patients undergoing a provocation test, but in a higher proportion in the case of patients tested with PACAP (73% of patients for PACAP vs. 18% of patients for VIP) [31]. Some data suggest that PACAP levels increase during attacks and decrease during the periods between attacks; in the periods when they are not affected, peptide levels in migraine patients would be decreased compared to controls [32], although divergent results have been reported in this respect. With regard to the clinical development of potential treatments that use PACAP as a target, monoclonal antibodies directed against the molecule itself and against the receptor have been developed. However, a phase II study (AMG301 molecule) has recently been discontinued due to an apparent lack of efficacy, although another of the molecules under development is

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still in phase I of the study (ALD1910 molecule). It therefore appears that the use of antagonists for these peptides is not yet yielding positive results while also raising concerns about the possibility of systemic adverse effects.

Sensory peptides, specifically adrenomedullin, have been presented as possible candidates for treatment, since 55% of patients who underwent a provocation test with this molecule had a migraine attack [33]. Adrenomedullin has a vasodilatory effect and a change in facial blood flow is observed in these patients.

Furthermore, K^+ channels are considered potential targets for treatment, as previous results with drugs that open these channels (e.g. levcromakalim) have shown that they produce headaches similar to those that occur in migraine attacks in virtually all patients [34]. These targets lie downstream of the CGRP receptors and, specifically, the K^+ channels that are sensitive to Ca^{+2} (BK_{Ca}) are present in the trigeminal pathways. Provocation tests with MaxiPost, which causes these channels to open, triggered migraine episodes in 90% of the patients tested, in whom there was localised vasodilation and an increase in the diameter of the superficial temporal arteries [35]. It is not known whether the effects on migraine treatment by modulating these channels would be specific or, on the contrary, it would be non-specific due to their vasoactive action.

Other molecules of interest are the ditans, which would have an efficacy similar to that of triptans but without the safety concerns related to cardiovascular events that triptans generate, and they have already been approved by the US Food and Drug Administration [36]. They do, however, have some side effects, such as episodes of dizziness and some drowsiness.

Finally, although botulinum toxin type A is not a novelty in the preventive treatment of migraine and its use is widely recognised, a recombinant form is currently under development that appears to display less paresis after treatment than the currently approved and marketed forms [37].

In determining the pathophysiology of the disease and possible targets for treatment, it is also very important to consider other signs and symptoms of migraine apart from the headaches. In this respect, the role of the hypothalamus in these migraine-associated symptoms is being studied to determine possible targets [38]. In the case of photophobia, both PACAP and CGRP appear to play a key role. With respect to nausea and/or vomiting (symptoms very commonly associated with migraine attacks) research has not yet identified any key targets, but it seems that they could be determined depending on whether they appear as symptoms in early or later stages of the attack. Finally, with regard to the postdrome or 'hangover' phase after a migraine attack, dopamine levels have been seen to decrease, which could be a possible target for future treatment resources [39].

Neuromodulation in the treatment of migraine

To date the European Medicines Agency has approved four non-invasive neuromodulation devices, based on magnetic/electrical stimulation of the trigeminal nerve, vagus nerve or cerebral cortex, by blocking or modulating the nociceptive stimulus [40]. We are thus referring to transcutaneous trigeminal stimulation; non-invasive vagus nerve stimulation; single-pulse transcranial magnetic stimulation; and remote stimulation. In all cases, treatment is self-administered by the patient on a preventive and/or symptomatic basis. The mode of action of neuromodulation is based on the administration of non-painful stimuli that block the painful stimuli associated with migraine [40].

One of the main questions regarding neuromodulation concerns the need for this treatment option, as a significant therapeutic armamentarium is currently available for the preventive and symptomatic treatment of migraine. However, despite this, there is a relatively high rate of treatment failure or dropouts due to side effects [41]. In this regard, it is important to take into account the patient's preferences as regards the treatment administered. In fact, after being informed of the potential adverse effects and therapeutic benefits of oral preventive medications, only 20-60% of patients would take them, even in cases in which there would be a full response [42]. In the case of neuromodulation, dropout rates due to adverse effects are between 2 and 3%, similar to those of other treatments such as riboflavin or monoclonal antibodies.

Another question of interest related to the efficacy of neuromodulation is its possible placebo effect. However, in double-blind placebo-controlled studies, a treatment effect has been observed with respect to the control group that is maintained after at least three months [43]. The therapeutic benefit of neuromodulation as preventive and acute treatment has, in some studies, shown similar efficacy to other preventive or seizure treatments with a very good tolerability profile. A recent meta-analysis, which reviewed all the studies

published to date, concluded that positive results have been obtained with different devices, but the quality of the evidence is low [44].

The profile of patients who are candidates for treatment with neuromodulation would be those with refractory or chronic migraine, but also those who prefer this therapeutic alternative to pharmacological treatment. It is important to inform the patient of the expected efficacy and it would be desirable for the patient to be able to try the device prior to actually purchasing it.

Management of chronic migraine with botulinum toxin type A

The treatment of chronic migraine presents three fundamental issues: speed of efficacy, especially in patients who have already had previous treatment failures; prolongation of efficacy in the long term; and taking into account other response criteria beyond the number of days with migraine attacks per month.

More than 10 years after botulinum toxin type A was first marketed for the treatment of chronic migraine, a wealth of real-life scientific evidence has been collected on the above-mentioned aspects, with some 40 phase IV studies conducted in 11 different countries. In Spain alone, real-life studies have gathered data from nearly 1,900 patients.

The PREEMPT study demonstrated that treatment efficacy can be observed one week after the first administration [45]. Furthermore, at week 56, about 70% of patients have a reduction ≥ 50% in the number of attacks per month, and at week 108 more than 50% of patients have a clinically significant improvement in their quality of life (measured with the Headache Impact Test-6 questionnaire), with rates of adverse events similar to those reported in the short term and in phase III clinical studies [45,46].

The cumulative analysis of data from about 1,000 patients (Hull, UK) has shown that the efficacy data for different aspects of migraine attacks are positive [47]. Results showed that 38.8% and 20.2% of patients had more than a two- and threefold increase in the number of pain-free days, respectively, after the first course of treatment. Regarding the tolerability of the treatment, the most frequent adverse effects are stiffness and discomfort at the injection site, along the same lines and at the same rates as described in phase III clinical studies.

The proposed mechanism of action in chronic migraine would be related to the inhibition of neuropeptide release and neuroinflammatory processes by botulinum toxin type A, thereby reducing peripheral sensitisation. Indirectly, central sensitisation would be reduced and, consequently, both the frequency and the severity of migraine-associated headaches would also be lower [48].

Treatment of episodic and chronic migraine with the monoclonal antibody fremanezumab

As highlighted above, new treatments for migraine are aimed at new key targets in the pathophysiology of the disease and based on monoclonal antibodies that specifically target them [28]. One such target of particular interest because of the results offered by treatments directed against it is CGRP and the antibodies designed to specifically bind to the peptide or its receptor [27]. Of particular note due to its recent approval and commercialisation was the review of the latest data on the antibody fremanezumab carried out at the 2020 EHF Congress.

Fremanezumab is a humanised monoclonal antibody of the IgG2Δa/κ isotype, designed to target CGRP [27]. A notable molecular feature is that some of its potential immunogenicity features are attenuated, as the constant region of the antibody heavy chain has two point mutations that reduce binding to the FcγR [49]. Administration is subcutaneous and dosing is flexible, as it can be administered monthly or quarterly [50].

Efficacy and safety of preventive treatment with fremanezumab in chronic and episodic migraine

Another review presented considered the results of the randomised, double-blind, placebo-controlled HALO study, which provides efficacy and safety data on nearly 2,000 patients with chronic (≥ 15 days/month) or episodic (<15 days/month) migraine, comparing the monthly and quarterly regimens [4,19].

In chronic migraine, fremanezumab reduced the number of migraine days per month by 4.9 and 5 days in quarterly and monthly administration, respectively (vs. 3.2 days/month in the placebo group; $p < 0.001$) [19]. The percentage of patients with ≥ 50% and ≥ 75% reduction in the number of days with pain per month was 37.6% and 15.2% (quarterly administration) and 40.8% and 14.7% (monthly administration), respectively (vs. 18.1% in patients and 7% in the placebo group; $p < 0.001$).

The results were similar regardless of whether patients were being treated with concomitant preventive medication or whether they met the criteria for symptomatic medication overuse. Altogether 61% (quarterly administration) and 63% (monthly administration) of patients had a clinically relevant improvement in their Headache Impact Test-6 score, which assesses aspects of the patient's quality of life (social and professional relationships, vitality, cognitive function and psychological impairment) ($p < 0.001$ vs. placebo) [19]. These results are complemented by notable safety and tolerability data, with less than 1% of patients experiencing serious adverse events. The majority of adverse events consisted of pain and reaction at the injection site [19]. These data demonstrated that therapeutic goals are met with fremanezumab in chronic migraine in both the monthly and the quarterly regimens, with a very low dropout rate due to tolerability issues.

For episodic migraine, treatment with fremanezumab, administered quarterly or monthly, has proved to be superior to placebo at weeks 4, 8 and 12 in terms of the percentage of patients with ≥ 50% reduction in the number of days with migraine attacks per month [4]. The response was observed quickly, with 44.4% and 47.7% of patients on quarterly and monthly administration, respectively, this reduction being presented after four weeks (vs. 27.9% in the placebo group; $p < 0.0001$). Again, ≤ 1% of adverse events reported were serious, the most frequent of them were related to pain at the injection site. Two adverse events related to hypertensive crises, but not related to fremanezumab, were reported [4].

Long-term results from the extension phases of the phase III studies (HALO-LTS) showed that nearly 80% of patients completed the treatment [51]. Efficacy results improve and persist after 12 months in both chronic and episodic migraine patients, and safety data from short-term studies are confirmed [51].

Efficacy of preventive migraine treatment with fremanezumab in patients with previous failure in other treatments

The profile of a patient who would be a candidate for preventive treatment of episodic or chronic migraine with monoclonal antibodies is one who has previously failed with more than two preventive treatments. The randomised, double-blind, placebo-controlled FOCUS IIIb study analysed the efficacy of preventive management with fremanezumab in patients with episodic or chronic migraine who had previously failed preventive therapy (continued for at least three months) with two to four previous monthly or quarterly treatments [14].

The study showed a decrease at 12 weeks of -3.7 and -4.1 migraine days/month in the quarterly and monthly dosing, respectively, in the total population tested (vs. -0.6 days/month in the placebo group; $p < 0.0001$) [14]. This decrease can reach -3.9 and -4.5 days/month in patients with chronic migraine (vs. -0.7 days/month in the placebo group; $p < 0.0001$). Altogether 47% (episodic migraine) and 27% (chronic migraine) of patients had ≥ 50% reductions in migraine days/month with quarterly dosing and 43% (chronic migraine) and 29% (episodic migraine) with monthly dosing, compared to 10% (episodic) and 8% (chronic) of patients in the placebo group; $p < 0.0001$. The use of symptomatic medication for acute pain also showed reductions in the number of days per month: −3.7 and −3.9 days/month in the total population evaluated, in the quarterly and monthly regimens, respectively (compared to −0.6 days/month in the placebo group; $p < 0.0001$) [14].

In the results from the FOCUS study, very low responses were observed in the placebo group, which highlights the value of the responses obtained in the fremanezumab treatment groups. This was especially so in patients who have previously failed other preventive treatments and whose migraine is therefore, *a priori*, more complicated to manage.

On the other hand, a substantial speed of response was confirmed, as two days after administration of the treatment there was a statistically significant difference in the percentage of patients with at least one day of migraine in the quarterly administration group ($p < 0.002$ compared to placebo), which was maintained seven days after administration and was also accomplished by patients with monthly administration [14].

In the open-label extension phase of the FOCUS study, patients were analysed by subgroups depending on the previous treatment they had failed (valproic acid, topiramate or botulinum toxin type A), and it was observed that in all cases, regardless of the previous treatment, therapy with fremanezumab resulted in a reduction in the number of migraine days per month and an increase in the percentage of patients with a reduction ≥ 50% in the number of migraine days per month [14]. Furthermore, a statistically significant difference was observed in the percentage of patients achieving this reduction regardless of the number of pre-

vious treatments (two, three or four). In the open-label extension phase, patients in the placebo group were also switched to fremanezumab and these results were also replicated, the same efficacy values being achieved as in patients who had been treated with fremanezumab since the first weeks of the study [15].

The impact of fremanezumab treatment efficacy on other aspects of the disease was also analysed in both the placebo-controlled phase and the open-label extension phase. A decrease in the Patient Health Questionnaire-9 scale, which analyses aspects related to the patient's depressive state, and better data regarding improvement were observed in patients with the quarterly regimen in the double-blind phase of the study [14]. The deterioration of work productivity and work activities due to the impact of migraine was analysed using the different domains of the work disability and productive activity scale. Improvement in these aspects was observed in the two dosing regimens and even in patients in the placebo arm in the double-blind phase, who went on to be treated with fremanezumab in the open-label extension phase [14].

Regarding safety data, there were no differences in serious adverse events and adverse events in patients in the placebo group; the most common was pain at the injection site, and the percentage of discontinuation was < 1% [14].

Clinical experience with fremanezumab in quarterly dosing: real-life data

During the meeting, Dr Dagny Holle-Lee shared her real-life experience in routine clinical practice at the West German Headache Centre in Essen, Germany, which is specialised in migraine management. At this institution they use the three monoclonal antibodies for the preventive treatment of migraine that have been approved by the European Medicines Agency (erenumab, fremanezumab and galcanezumab). When one of these treatments is indicated, it is maintained for at least three months. If there is a good response, it is continued for one year and then they attempt to withdraw it. If the patient does not respond, treatment is stopped for three months and then switched to another antibody directed against the CGRP receptor or the peptide, depending on the previous treatment.

Of the 30 patients who have been given fremanezumab to date at the centre, the majority have been treated with quarterly dosing. There has been no difference between monthly and quarterly dosing regimens in terms of the real-life efficacy and safety data for these patients. Moreover, no differences in efficacy and safety have been observed between patients treated with fremanezumab on a quarterly basis and all other patients treated with other monoclonal antibodies.

It is therefore important to define a profile of patients who would benefit from treatment with fremanezumab administered quarterly in real clinical practice. To this end, three clinical cases of patients with different profiles were presented, where different patient conditions made it preferable to implement quarterly administration.

The first was a chronic migraine patient with four preventive treatment failures (including botulinum toxin type A) and an associated anxiety disorder. The patient felt unsure about self-administering an injected treatment and preferred a quarterly injection. The second was a patient with high frequency (10 days per month) and very disabling episodic migraine, with previous failure of four preventive treatments and a history of poor compliance due to mental disability. The third was another woman with chronic migraine and a history of multiple preventive treatment failures (including botulinum toxin type A) and who was constantly travelling, thus making it difficult for her to administer the monthly dose.

These cases clearly illustrate the different circumstances in which the administration of fremanezumab on a quarterly basis would be recommended in routine clinical practice as a first option in certain patient profiles: those who may have difficulties in self-administering the drug, due to lack of ability or some kind of disorder; those with a history of poor compliance; or those who, due to their lifestyle or profession, need a longer spacing of administrations without this affecting efficacy.

Pharmaceutical impact of fremanezumab from a safety point of view

As discussed above, migraine is a disabling disease. Patients requiring preventive treatment report ≥ 4 migraine days per month, and it has been estimated that 42-73% of these patients have moderate-severe disability [52]. More healthcare resources are consumed in high-frequency chronic and episodic migraine (≥ 4 days/month), both in medical consultations and in visits to the emergency department, and even in hospitalisations [53]. In Spain, migraine affects 12% of the popula-

tion [54]. According to recent data, healthcare expenditure is higher in patients with chronic migraine (16,578 euros/patient-year compared to 6,227 euros/patient-year in the case of episodic migraine) [55]. In patients with preventive treatment who accomplish a reduction of ≥ 50% in the number of migraine days per month, savings of 2,232 euros/patient-year are achieved in episodic migraine and 6,631 euros/patient-year in chronic migraine [55].

Treatment with the monoclonal antibodies that have currently been approved by the European Medicines Agency (erenumab, fremanezumab and galcanezumab) is indicated in patients with ≥ 8 days/month in episodic migraine and ≥ 15 days/month in chronic migraine [7,27]. All three currently marketed antibody treatments have excellent efficacy and safety data, although some differences in dosing can be highlighted, as fremanezumab can be administered on a quarterly basis, whereas the other two monoclonal antibodies available today are administered on a monthly basis (Table II). On the other hand, in terms of safety data, the percentage of patients reporting adverse events and severe adverse events is low in all cases [27]. All three antibodies present several common side effects (pain and reaction at the injection site and allergic reactions), while some are more specific for erenumab (constipation and muscle spasms) and galcanezumab (dizziness and constipation) [50,56,57].

Given these differences in adverse events associated with preventive migraine treatments, data were presented from a study estimating the costs of managing adverse events observed in phase III clinical trials of fremanezumab versus other preventive treatments available in Spain, namely, erenumab, galcanezumab and botulinum toxin type A [58]. In this analysis, the evaluation of a probability model was performed by analysing 1,000 Monte Carlo simulations (second-order simulations) in patients with ≥4 migraine days/month, with a time horizon of 12 weeks and using public cost values taken from the Spanish Health System and several related Spanish publications. Data included were taken from clinical studies of fremanezumab (HALO and FOCUS), erenumab (STRIVE and ARISE) and galcanezumab (EVOLVE-1, EVOLVE-2 and REGAIN); and phase III clinical studies (PREEMPT 1 and 2) and a study of botulinum toxin type A in routine clinical practice (COMPEL). Bearing in mind that this is a theoretical model and that the cost of the different treatments is not taken into account, all simulations show that the cost of managing adverse events is lower for treatment with fremanezumab than for the others. Specifically, treatment with fremanezumab would result in savings of 469 euros in the cost of adverse event management compared to erenumab, 268 euros compared to galcanezumab, and 1,100 (real-life study)/1,295 euros (phase III clinical trials) compared to botulinum toxin type A [58]. These results therefore suggest that the different safety profile of fremanezumab treatment with respect to erenumab, galcanezumab and botulinum toxin type A results in comparative savings in the healthcare resources needed to diagnose or treat adverse drug events.

Oral Presentations at the 2020 European Headache Federation

Basic research

Oral communications on advances in basic research in migraine were again focused on CGRP and its receptor, but other communications dealing with other pathophysiological mechanisms and possible therapeutic targets are also reviewed here.

Biology of the calcitonin gene-related peptide receptor

With regard to the biology of the CGRP receptor, a review was carried out of the molecular and physiological implications of the receptor family and the peptides that bind to it. The peptides, on the one hand, and the receptors to which they bind, on the other, have many structural similarities in common. The peptides (37-53 amino acids) adrenomedullin 1, adrenomedullin 2 or intermedin, calcitonin, CGRP α and β, and amylin, which bind to the CGRP receptor family, share the C-terminal end [59]. The receptors have a subunit that is a G protein coupled to the receptor –calcitonin-type receptor (CTR) or calcitonin-like receptor (CLR)– along with a receptor activity modifying protein (RAMP) and a receptor component protein (RCP) [60]. This is important because the same peptide can bind to different receptors of the same family, and different peptides can bind to the same receptor, albeit with lower affinity [61]. This widens the range of possible targets for treatments and also the adverse events associated with them. Indeed, the monoclonal antibody erenumab binds to the CGRP receptor in its extracellular region, both to CTR and to RAMP1 [62]. In this regard, unpub-

Table II. Characteristics of the monoclonal antibodies approved for the treatment of episodic and chronic migraine.

	Eptinezumab (ALD403)	Erenumab (AMG334)	Fremanezumab (TEV-48125)	Galcanezumab (LY2951742)
Target	CGRP	CGRP receptor	CGRP	CGRP
Molecule	Humanised antibody IgG1	Human antibody IgG2	Humanised antibody IgG2	Humanised antibody IgG4
Half-life	32 days	28 days	30 days	27 days
Dosage	Quarterly	Monthly	Monthly/quarterly	Monthly
Route of administration	Endovenous	Subcutaneous	Subcutaneous	Subcutaneous
Antidrug antibodies	14%	6.3% (70 mg) 2.6% (140 mg)[a]	2%[b,d]	12.5%[c,d]
Frequent adverse effects	Dizziness; respiratory infection; urinary infection; fatigue; nausea; sinusitis	Pain at the injection site; constipation; pruritus; spasms	Pain at the injection site; erythema; pruritus	Pain at the injection site; pruritus; dizziness; constipation
Interaction with hepatic enzymes	No	No	No	No
Blood-brain barrier	No	No	No	No
Placenta	Yes	Yes	Yes	Yes
Specificity	High	High	High	High

CGRP: calcitonin gene-related peptide; IgG: immunoglobulin type G (Table adapted from [27]). [a] Erenumab 70/140 mg injectable solution for prefilled syringe (summary of product characteristics). [b] Fremanezumab 225 mg injectable solution for prefilled syringe (summary of product characteristics). [c] Galcanezumab 120 mg injectable solution for prefilled syringe (summary of product characteristics). [d] At one year.

lished results regarding immunoreactivity in adult rat brain in which CTR was observed at multiple locations were presented at the 2020 EHF Congress, suggesting that there may be cross-reactivity phenomena. The specific location of the receptors and their topographical distribution is important to describe their function and their role as a target for treatment.

Vasoactive intestinal peptide

One of the targets discussed earlier is VIP, which has VPAC1 and VPAC2 receptors in common with the peptide PACAP, and has multiple effectors in the body, including vasodilation in the endothelium [63]. Data were presented from a double-blind, randomised, placebo-controlled, crossover design study of healthy volunteers who were administered VIP (intravenously for two hours) to assess locally whether any changes occurred in the diameter of the superficial temporal arteries, and generally whether headaches and accompanying migraine-associated symptoms appeared within 12 hours. Participants had delayed mild headaches, even as of the period in which the infusion took place. In addition, there was a long-lasting increase in vasodilation of the cranial region and an increase in parasympathetic-related cranial autonomic symptoms and changes in lacrimation as assessed by Schirmer's test. These results are in line with those previously published regarding migraine symptoms associated with the cranial autonomic trigeminal pathway and the use of VIP as a predictor of response to botulinum toxin type A [64-66].

Adrenomedullin

Another target addressed in the oral communications on basic research was adrenomedullin and its role in migraine without aura. Adrenomedullin is a peptide that is smaller than CGRP, but has a structure that is somewhat homologous to it, as well as an affinity for the same receptors [67]. An-

other presentation offered the results of a randomised, placebo-controlled, crossover design study with 20 participants that sought to assess whether intravenous administration of adrenomedullin could result in headache symptoms and changes in facial flushing measured by laser. Eighty per cent of the patients developed headache and 55% had migraine-type pain. In addition, symptoms such as palpitations and a feeling of warmth or flushing were recorded 10 minutes after infusion. The interest of this molecule in the pathophysiology of migraine is due to the role of adrenomedullin at the vascular level recently reviewed in the literature; it has been suggested that it is involved in the regulation of the endothelial barrier and vascular tone, as well as in the process of angiogenesis. It has also been related to the pathophysiology of cardiac insufficiency and Alzheimer's disease [68,69].

Clinical research

Hypersensitivity to CGRP in post-traumatic headaches

At the 2020 EHF Congress, data were presented on hypersensitivity to CGRP in post-traumatic headache, a very prevalent type of headache, but with a poorly understood pathophysiology. Specifically, the results of a randomised, placebo-controlled, crossover design study of 15 patients who were administered intravenous CGRP were presented [70]. Migraine-type headaches were exacerbated in 70% of patients (compared to 20% in the placebo group; $p < 0.001$). This result could open the door to the use of anti-CGRP therapy in this patient profile.

Medication-overuse headaches

The most significant latest developments in clinical research dealing with medication-overuse headache were also reviewed. The International Headache Society classification, third edition (ICHD-III) [71], defines medication-overuse headache on the basis of the causal relationship between overuse and headache, and criteria for overuse over a certain period of time (headaches ≥ 15 days/month and symptomatic medication overuse for > 3 months). However, in routine clinical practice it is difficult to distinguish whether headache is a cause, a consequence or both [72]. The epidemiology of medication-overuse headache varies between countries, mainly due to differences in drug use. While in the United States there is an abusive use of barbiturates in 73% of patients who are treated with them and 44% of those treated with opioids develop medication-overuse headache, other studies, such as the CaMEO study on chronic migraine, indicate that 17.7% of patients have medication overuse and one third of them would have developed medication-overuse headache [73,74]. The profile of the patient with this headache tends to be older, mostly female, overweight, with a low level of education and often unemployed [74]. In many cases, medication-overuse headache is associated with depression and anxiety, a higher degree of disability and a greater number of visits to the emergency department [74]. In terms of treatment, a study conducted with the monoclonal antibody erenumab in patients with and without medication overuse evidenced a higher response rate in patients without medication overuse, but a greater gain in the number of headache-free days in the group of patients with medication-overuse headache [75]. Different *post hoc* evaluations of studies with gepants (rimegepant, atogepant and ubrogepant) suggest that they would not produce medication-overuse headache [76,77]. If these data were confirmed, it would raise the possibility of using them prior to the onset of pain, not only because they would not produce medication-overuse headache, but also because of their long half-life in the body and good tolerability data. Moreover, they could also help to understand the natural history of migraine and medication-overuse headache, as they do not alter the frequency of migraine.

Effect of exenatide in patients with idiopathic intracranial hypertension

Exenatide is used in the treatment of diabetes and, also, for weight reduction, and has been shown to reduce the synthesis of cerebrospinal fluid in the choroid plexus and intracranial pressure in animal models [78]. A randomised, double-blind, placebo-controlled study of 15 patients who were administered exenatide subcutaneously (IIH Pressure Clinical Study; ISRCTN12678718) was presented at the congress. The results of this exploratory study showed a reduction in intracranial pressure in both the short term (2.5 hours) and the long term (24 hours and 12 weeks), as well as fewer headache days per month, reduced symptomatic medication consumption and improved visual acuity. The main adverse effect reported in the study was the occurrence of nausea, although possible alterations in the pancreas, previously reported with this drug, need to be followed up.

Relationship between cortical spreading depression and headache due to migraine with aura

Cortical spreading depression is a wave of neuronal depolarisation that appears to be related to the basis of the auras in migraine with aura [79]. The sequence of events occurring between the onset of aura and nociceptor activation has been defined, from cortical spreading depression leading to rapid dilatation and prolonged vasoconstriction of the pial arteries to delayed activation of the nociceptors in Aδ-type meningeal fibres and the high-threshold trigeminovascular neurons with which they are associated [79,80]. The data suggest that there would be an early release of CGRP in the first steps and a late release just before the activation of Aδ-type fibres [81].

New developments in migraine management

Several oral communications related to the latest developments in the pathophysiology of migraine and the management of the disease were reviewed at the meeting.

Migraine with brainstem aura

The diagnosis and existence of migraine with brainstem aura, as an entity, has been a matter of debate and it is speculated that the symptoms may originate in the cortex [82,83]. One of the reviews presented at the congress involved an analysis conducted at the Danish Headache Centre in Denmark aimed at identifying how many convincing cases of migraine with brainstem aura exist, their prevalence and possible recommendations for diagnosis [84]. To this end a literature review was performed, the cases contained in the centre's medical records were analysed and an extensive telephone survey of patients suspected of the condition was conducted. Of the 79 cases described in detail in the literature, 44 fulfilled the diagnostic criteria for ICHD-III and a high percentage could be explained solely by involvement of the cortex. Based on telephone interviews of the cases at the same centre, it is concluded that the diagnostic criteria are not very effective, and the recommendations in clinical practice would be: always conduct a personal interview with the patient; check for at least three brainstem-related symptoms; and rule out other possible entities so that a confusing diagnosis is not made [84].

Optimisation of acute treatment

The results of a survey analysing the influence of optimising the treatment for acute migraine symptoms on the patient's quality of life (OVERCOME study) were presented [85]. The study assumes that an optimised acute symptomatic treatment is one that resolves pain and restores the patient's activity, and is therefore associated with less disability and better quality of life. The aim of the OVERCOME study was to relate better optimisation to better quality of life by analysing categories of frequency of headache days per month. Data were collected from about 20,000 patients in the United States and parameters concerning treatment optimisation, migraine-related disability, impact on daily activity and quality of life in relation to migraine were analysed using specific questionnaires: Migraine Treatment Optimisation Questionnaire, Migraine Disability Assessment Questionnaire (MIDAS) and Migraine-Specific Quality-of-Life Questionnaire–Role Function-Preventive. The results confirmed that, if treatment optimisation improves, migraine-related disability, impact on daily activity and quality of life also improve. Treatment optimisation should therefore be part of the daily clinical practice of migraine specialists [85].

Offset analgesia in migraine

A frequently used method to quantify the inhibitory pain modulation system is offset analgesia, defined as a disproportionately large decrease in the perception of pain in response to a small decrease in pain stimulation. It has been shown to be altered in chronic pain, but had not been evaluated in patients with headache. In migraine, pain modulation and pain perception might be altered depending on the phase [86]. At the congress, data were presented from a study of patients with episodic migraine, compared with a control group, in which this method was used to assess the inhibitory pain modulation system [87]. Stimuli in trigeminal and extra-trigeminal areas were used, and a reduced response in the trigeminal areas was found in migraine patients. This leads to the conclusion that episodic migraine patients in the headache-free interval exhibit somatotopic differences in endogenous pain modulation.

Use of opioids in the acute symptomatic treatment of migraine

Opioid abuse has become a major public health concern. In the treatment of headache, opioids are an important cause of medication-overuse headache. The results of a systematic review and meta-analysis of the use of opioids in the acute symptomatic treatment of migraine are presented in order to assess whether there is sufficient scientific evidence to support their use in this condition.

Thirty studies (2,445 patients) published between 1973 and 2017 were analysed, of which 17 looked at opioids in combination with other analgesics, 11 had a placebo group and 19 were compared with other treatments. Pain relief occurred in 55.1% of patients treated with opioids (compared to 63.7% of patients with the comparator treatment), resulting in an odds ratio of 1.42 (95% confidence interval 1.18-1.71). Adverse effects were reported by 74.2% of patients treated with opioids. It was concluded that the evidence supporting the use of opioids in migraine is scarce and of poor quality, as most of the studies published are old and contain methodological shortcomings and a high risk of conflicts of interest.

Burden of episodic and chronic migraine in France, Spain and the UK

The impact of migraine on health-related quality of life is worse in patients with multiple previous preventive treatment failures [88]. The results of a cross-sectional observational survey-format study of disability and quality of life in patients with episodic and chronic migraine who had previously failed ≥ 2 preventive treatments in the UK, France and Spain were presented [89]. Around 100 patients from each country participated and the *EuroQoL 5-Dimension 5-Level* (health-related quality of life) and MIDAS (limited activity due to migraine) questionnaires were analysed. The main conclusion was that disability and quality of life are more affected in chronic migraine than in episodic migraine. Differences between countries were observed, with greater impairment in the UK than in France or Spain.

Is migraine a neuropathic pain?

Despite many advances in the study of the pathophysiology of the pain experienced in migraine, there is little evidence about which fibres are activated or what activates them [90]. Olesen et al. suggested that the origin of a migraine attack may be central, based on the appearance of premonitory symptoms, while the origin of the pain itself (the main, but not the only, symptom of the attack) is still under debate. The same authors nevertheless claimed that it could be peripheral, based on the activation of perivascular receptors at the extra- and intracranial levels. All nociceptive information from intra- and extracranial tissues converges in the trigeminal spinal nucleus via the polymodal A and C fibres of the first trigeminal branch [91,92]. CGRP release at the level of the Cfibres activates voltage-dependent channels and RAMP1/CLR receptors of the Aδ fibres at the level of the Ranvier node [93].

The pathophysiology of migraine has aspects in common with that of neuropathic pain. Thus, the latter is caused by a lesion of the nociceptive afferents and, through the intervention of multiple inflammatory mediators, the phenomenon of peripheral and central sensitisation is generated, with the participation of mast cells, macrophages and microglia; and the release of CGRP at a central and peripheral level [48,94-96].

We also found commonalities between the two entities from a clinical perspective. The aim of the study by Ziegeler et al. was to analyse the prevalence of facial pain (V2, V3), which is neuropathic in nature, in a series of almost 3,000 patients with primary headache [97]. Approximately 10% of the patients in this series had primary headache and V2, V3 facial pain. In addition, an important common clinical feature of migraine and neuropathic pain is allodynia. Under pathological conditions, activation of microglia and overexpression of certain mediators lead to the release of brain-derived neurotrophic factor (BDNF) and the development of allodynia [98]. BDNF is closely related to CGRP and is present along the entire nociceptive pathway [99,100]. In animal models of neuropathic pain, there is increased synthesis of BDNF and its levels are elevated during the migraine attack, and this increase correlates with the time course of the headache [99,100]. Administration of an anti-BDNF antibody has been shown to reverse mechanical allodynia.

Finally, Piezo1 and 2 are mechanosensitive ion channels present in the membrane of neurons innervating the surface of the skin [101]. Their inactivation of the Piezo2 channel in knock-out animal models decreases the response of Aδ, Aβ and C nociceptors to mechanical stimuli. Thus, Piezo2 may behave as a novel therapeutic target for allodynia [102,103]. The link between migraine and neuropathic pain would be based on the fact that, during the attack, vasodilation and pulsatility of the meningeal arteries can activate Piezo1 and 2, and secondarily release CGRP [102].

Other headaches

Recommendations of the European Headache Federation for the management of giant cell arteritis

Giant cell arteritis is a pathology that predominant-

ly affects women aged ≥ 50 years and presents with secondary headache that is considered critical, as it is a medical emergency that can cause sudden and irreversible loss of vision (in 8-30% of patients), stroke (in 3-10%) and other complications. In recent years, new evidence has been generated for its diagnosis and treatment and this led the EHF to reach a consensus and to draw up a series of recommendations on the management of this entity based on a critical and systematic review of the data published up until January 2020 [104].

Headaches attributable to giant cell arteritis would be, according to the ICHD-III definition, those newly diagnosed in patients with giant cell arteritis in whom headache is closely related in time to the diagnosis of giant cell arteritis, has worsened concurrently with it, is relieved or resolves within three days of treatment with high doses of corticosteroids and/or is associated with scalp hypersensitivity and/or jaw claudication [71].

Headache is not only the most common symptom in giant cell arteritis, but may be the only initial symptom, and the intensity of the headache is usually severe, although sometimes moderate or mild [105,106]. Other signs and symptoms usually include visual symptoms, of which anterior ischaemic optic neuropathy is the most common (up to 88% of cases); systemic symptoms (fever, myalgia, fatigue, sweating, etc.); and large vessel manifestations.

The EHF recommendation is that, because it is a medical emergency, any recent-onset headache in a patient over the age of 50 years should be suggestive of giant cell arteritis. It should be promptly and accurately diagnosed and corticosteroid treatment initiated immediately, with follow-up to prevent any adverse effects due to the medication. A thorough history and examination in all patients with suspected giant cell arteritis helps to guide the examinations, which are based on laboratory markers prior to the initiation of treatment and confirmatory testing once treatment has been started, using colour duplex ultrasound and temporal artery biopsy. If an extracranial disease is suspected, positron emission tomography, computed tomographic angiography, magnetic resonance angiography or high-resolution magnetic resonance imaging may be used [104].

Treatment is based on high doses of prednisolone or methylprednisolone if there is a threat of loss of vision or stroke, although loss of vision may occur in one-third of patients in the first six days despite their use. There is insufficient evidence to recommend any other immunosuppressant except methotrexate, which exhibits modest activity [107]. Long-term treatment should be maintained for 6-24 months with dose reduction unless relapse occurs. Routine use of antiplatelet or anticoagulant medication cannot be recommended, but acetylsalicylic acid can be considered in patients in whom atherosclerosis may be a contributing cause, although no randomised clinical trials have been conducted to determine its efficacy and safety [108].

As this is a long-term treatment with high doses of corticosteroids, gastrointestinal protection and prevention of osteoporosis with proton pump inhibitors and bisphosphonates, respectively, must be considered. Monitoring is performed for both disease activity and adverse effects associated with corticosteroids.

The main new development in the treatment of giant cell arteritis is the use of the monoclonal antibody tocilizumab, which targets the interleukin-6 receptor. Previous data has suggested that interleukin-6 levels are elevated in patients with giant cell arteritis, and even remain elevated despite treatment with corticosteroids [109]. The GiACTA study analysed the efficacy and safety of treatment with tocilizumab in combination with prednisolone versus the standard treatment in 250 patients with giant cell arteritis [110]. At 52 weeks, 56% of the patients were in complete remission, compared to 17.6% of those treated with prednisolone. Treatment with tocilizumab would be indicated in patients with refractory giant cell arteritis or those with comorbidities that may be affected by corticosteroid therapy.

Headache and COVID-19

One of the key symptoms and among the earliest to be reported as associated with SARS-CoV-2 infection and the development of COVID-19 is the presence of headache [111]. Until now, headaches attributed to systemic viral infections (in the absence of meningitis or encephalitis), as listed in the ICHD, had not been defined in detail. The first series published on the clinical symptoms associated with COVID-19 reflected percentages of patients reporting headaches between 10% and 14%, although in clinical practice these percentages appeared to be higher [112-114]. When the inflammatory parameters in these series were analysed, levels were elevated in general, and more particularly so in the case of markers associated with localised inflammation in the central nervous system, but the elevation was not excessively high.

The results of a review of cases of COVID-19 collected at the Vall d'Hebron Hospital in Barcelona were presented at the meeting. Between March and May 2020, this hospital had more than 2,000 admissions related to the disease. In this prospective study of 130 cases, data were collected on dyspnoea and cough in 63.2% and 80.5% of patients, respectively; fever in 88%; diarrhoea in 27.1%; anosmia in 45.9%; and headache in 74.4% [115]. These data seemed to reflect more the perception gathered in hospitals regarding headache as a symptom of COVID-19 and suggest that in the first series the presence of all the different symptoms was probably not captured in detail. In fact, other series reviewed since then have yielded higher percentages than those early publications, with figures of around 60% [116].

When patients who had experienced headaches were compared by subgroups with those who did not report this symptom, it became possible to define two different patient profiles. The COVID-19 patient with headache also had anosmia in 55.6% of cases, was predominantly female (58.6%) and had a previous history of migraine in 32.3% of cases. In contrast, patients with COVID-19 without headache were mostly male (70.6%) and older (63 years versus 50 years in the case of headaches). A different headache phase pattern was collected depending on whether they started at the same time as other COVID-19 symptoms or began before the other symptoms [115]. In the latter case, the phase pattern was similar to that of migraine-associated headaches. Among the inflammatory markers, interleukin-6 levels were elevated, although higher levels were observed in patients who had not reported headaches ($p = 0.04$), and in the case of patients with headaches, levels remained stable over time [115].

The question therefore arises as to why headache is a symptom that is part of the picture associated with COVID-19. SARS-CoV-2 binds to the angiotensin-converting enzyme 2 receptor on the surface of host cells. Expression of the enzyme and receptor is found at multiple sites in the body, including in the central nervous system [117]. The virus would have two routes of entry into the central nervous system from the respiratory organ: first, via the nasal cavity and second, via the lungs [118]. Through the nasal cavity it would have access to the olfactory nerve and the olfactory bulb, and from there to the trigeminovascular system, which would be associated with the symptoms of headache and anosmia [119-122]. Local neuroinflammation would occur through the release of different cytokines, leading to systemic inflammation [123].

With regard to the evolution of headaches over the course of COVID-19 disease progression, some patients were observed to continue with headaches even after the disease had resolved [124]. Persistent headaches of this kind were reported in 21.4% of patients in whom headaches were a prodromal symptom of COVID-19 [115]. On comparing the two groups of patients, those with headache as a symptom were found to undergo shorter hospitalisations. A possible hypothesis to explain these data could be that presenting with local neuroinflammation lowers the levels of systemic inflammation, and this may be explained by higher levels of basal expression in these patients due to genetic and epigenetic mechanisms.

The presence of headache among the most common symptoms associated with COVID-19 indicates once again that it is an important clinical symptom in a large number of diseases and may be a predictor of their development. Furthermore, attention was drawn to the need for a better and broader understanding of the role of inflammation in the pathophysiology of migraine and, specifically, the role of CGRP at the local and systemic level.

Migraine and society

At the end of the meeting, other aspects of migraine were discussed that were framed within the migraine and society dyad. The survey 'Beyond Migraine: The Real You', conducted between November and December 2019 in 10 countries (Belgium, Czech Republic, France, Germany, Italy, the Netherlands, Poland, Spain, Sweden and the UK), was taken as a reference. In the survey a total of 7,520 patients with ≥ 4 days/month with migraine were consulted; 93% of the patients stated that migraine had a negative effect on their quality of life and 50% said they had concealed their migraine. The results of the survey indicated that migraine has a major impact on the family, with two-thirds of respondents saying that their partner is the person most affected by the disease and 40% stating that the disease has affected their children's happiness. The survey also revealed a delay in diagnosis, with at least three years elapsing before being diagnosed in almost 50% of participants, and one in three having to wait a further three years for specific treatment. Other studies have reported new aspects of the impact of migraine on the family,

such as a delay in the desire to have children and the impact on both the patient and their partner in terms of their financial situation and their job [125].

Migraine is a disease in search of diagnostic, therapeutic and prognostic biomarkers. Diagnosing migraine solely on the basis of clinical criteria makes it an 'invisible disease', the diagnosis of which remains an act of faith. This can stigmatise some patients, especially in personal and occupational settings where the suffering of others is only recognised with the existence of objective evidence. One of the main research goals is the development of biomarkers that not only improve diagnostic accuracy in migraine, but also help to personalise treatment, predict therapy response and monitor disease progression/regression.

The delay in the diagnosis of migraine suggests that greater involvement and a deeper understanding of the disease is needed on the part of all the actors involved: from the patient and their setting to the primary care physician, the general neurologist, the neurologist specialised in headaches and the authorities, among others. The role of the pharmaceutical industry in this scenario is also of great importance as it is responsible not only for developing new treatments, but also for providing quality scientific information and training, for helping to make the disease visible to the population and, in short, for improving the quality of life of those who suffer from it.

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I Reunión Post-European Headache Federation: revisión de las novedades presentadas en el Congreso de la European Headache Federation de 2020

Introducción. Tras la celebración del congreso de la European Headache Federation (EHF), reconocidos neurólogos españoles expertos en el tratamiento de la migraña expusieron en la Reunión Post-EHF las principales novedades presentadas en el congreso y relacionadas con ese ámbito.

Desarrollo. Se abordan los principales datos presentados relacionados con el tratamiento de la migraña crónica y episódica; concretamente, los relacionados con los tratamientos preventivos y la experiencia en vida real en el manejo de la enfermedad. Se hizo una importante revisión de las nuevas dianas terapéuticas y las posibilidades que ofrecen en cuanto al conocimiento de la fisiopatología de la migraña y su tratamiento. Asimismo, se hizo una actualización de las novedades presentadas en el tratamiento de la migraña con fremanezumab, anticuerpo monoclonal recientemente autorizado por la Agencia Europea de Medicamentos. Se hizo una actualización de las novedades en investigación básica en la patología, así como una relación de los síntomas de migraña y COVID-19. Finalmente, se abordaron las implicaciones de la migraña en la carga sanitaria asistencial y económica, y su impacto en la sociedad.

Conclusiones. En la reunión se hizo un resumen del contenido presentado en el 14 Congreso de la EHF, que tuvo lugar a finales de junio y principios de julio de 2020.

Palabras clave. Cefalea. EHF. Fremanezumab. Migraña. Migraña crónica. Migraña episódica. Post-EHF.