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EDITORIAL

Acute treatment of migraine: *quo vadis?*

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1. Introduction

Migraine represents the third cause of disability in the worldwide population aged under 50 years. Facing this enormous social impact, only onabotulinumtoxinA has been evaluated, on serendipity basis, as effective chronic migraine preventative treatment [1]. Pharmacological research is now moving important steps forward towards bridging the 30-year gap of new preventative class drugs for migraine, with a new molecule in its final phase of development: monoclonal antibodies for calcitonin gene-related peptide (CGRP) or its receptors (CGRPr) [2,3].

In the development pipeline of new drugs for the acute treatment, there is only one innovative compound, lasmiditan [4], while there are numerous devices and nutraceuticals in both categories [5]. This is surely not the scenario that one billion of migraine patients is hoping for from scientific research, and a new call for action is required in order to promote the study on new innovative drugs for the acute treatment of migraine. This would reduce the personal, working, and pharmaco-economic impact and the public health expenditure caused by this pathology, that could be appropriately defined as a social disease from now on.

2. Travelling from NSAIDs to triptans to CGRP

A quarter of a century has passed since the last spring of migraine acute treatment, when the progenitor or triptans, sumatriptan, came to light. Afterwards, the triptan family saw the development of other six members decreeing the end of ergot derivate [6]. This triptan event was a turning point for all primary headaches, who gained then a cultural and scientific attention never seen before. Afterwards, researchers' attention was driven towards comparing the effectiveness of the seven triptan brothers, alone or in combination with NSAIDs. The debate revolved around safety, efficacy, consistency, drug–drug interactions with prophylactic drugs, pharmacokinetics/pharmacodynamics, new delivery pathways, extension of this pharmacological class to the population aged under 18 or over 65 years, evaluation of common adverse events, disability levels [6–12]. Notwithstanding, only 27% of migraine patients receive a correct diagnosis and only 17% of them takes triptans for a crisis [13,14]. Therefore, two different studies in Italy and Australia show how in a real population of migraine patients only the great minority of them receive a correct advice for the treatment of the crisis [13,14].

In this long period of time, the scientific focus has been progressively oriented towards the definition of migraine chronic forms, and this brought to light another plague, known but concealed or labeled as exclusively psychiatric, patients' drug overuse for frequent migraine attacks [15]. It has been much and elusively debated, overtime, if drug overuse deserves its own slot in the classification or it is only an inevitable complication of chronic migraine [16]. What matters today is that triptans contributed to this alarming and harmful phenomenon of overuse. Monoclonal antibodies mark the entrance into a new era of migraine treatment, and the ones dedicated to prophylaxis treatment are close to approval.

3. Preventative treatment is now moving forward

The scenario revolving around migraine is populated today by various actors: the new pharmacological class of monoclonal antibodies, subcutaneous or intravenous, for CGRP (CGRP MoAbs) or its receptor (CGRPr MoAbs), and the small-molecule oral CGRPr antagonists [2,3].

While migraine preventative treatment shows a developing florid asset, with 37% new drugs versus a reconsideration of 31% drugs already known (Figure 1), in acute treatment, the prevalence of new therapeutic opportunities decreases dramatically to 15% of new molecules being developed (Figure 2). At the same time, devices are strongly represented in 20% of preventative treatments and they even raise up to 28% in acute treatments.

This is what results from a search of randomized control trials (RCTs), registered on ClinicalTrials.gov, using the Mesh Terms 'acute migraine treatment,' 'preventative migraine treatment,' group eligibility criteria 'Adult (18–65)', First Received 'From 01/01/2012 to 03/10/2017', Last Updated 'From 01/01/2012 to 03/10/2017' [17].

Unfortunately, for primary headache research, new RCTs are lacking [18]; therefore, we are still in the phase when old molecules are rehabilitated on the basis of a real-world evidence.

The request for innovative molecules for acute migraine treatment relies today on lasmiditan, the most important advancement in this sector [4] even if still presenting issues

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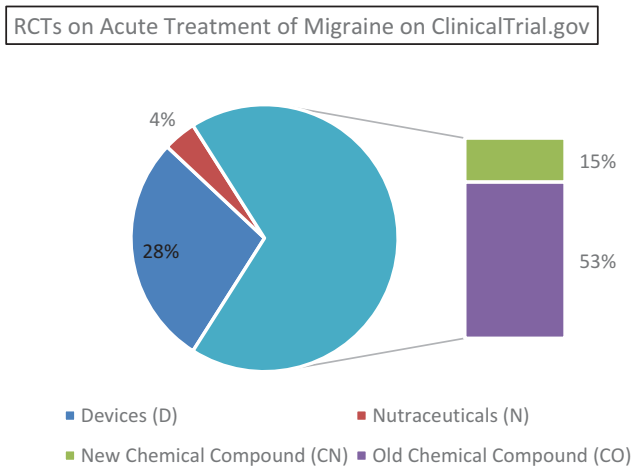

Figure 1. RCTs on acute treatment of migraine on ClinicalTrial.gov.
Studies received from 01/01/2012 to 08/03/2017 on ClinicalTrial.gov n = 72

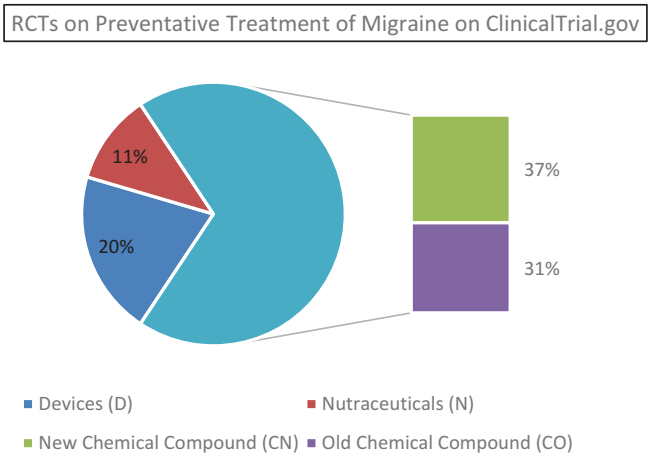

Figure 2. RCTS on preventative treatment of migraine on ClinicalTrial.gov.
Studies received from 01/01/2012 to 08/03/2017 on ClinicalTrial.gov n = 88

to be investigated. Lasmiditan is a new 5-HT receptor agonist with high affinity and selectivity for the 5-HT1_F receptor. Its chemical structure, as well as the pharmacological profile, is different from triptans.

The indole structure of triptans, identical to the neurotransmitter 5-HT, is replaced by a pyridinoyl–piperidine scaffold, which is not found in any other antimigraine classes. From the mechanism of action point of view, lasmiditan efficacy in migraine is mediated through a nonvascular, first neural pathway, with a loss of the typical vasoconstrictor activity expressed by triptans [4].

4. Meanwhile, acute migraine treatment loses ground

The ideal migraine treatment is still far, and it seems that there is not a resolved trend to cover the needs of 83% migraine patients never treated with triptans [13,14]. Precision medicine applied to migraine shows structural weaknesses, based on the variety of the genes involved and the well-known multifactorial nature of migraine itself [19,20].

Acute migraine treatment is an aging therapeutic area that faces enormous needs in terms of actively working population [21], and it might produce, at least for low- and medium-frequency brackets, an individual, social, economic, productive, and public health benefit of incommensurable value, given the well-known economic damage that both chronic and episodic migraine produce in the National Health Systems all over the Europe [22].

5. Expert opinion section

Migraine results to be one of the most spread pathologies in the world (14% of the entire population, one billion of patients), causes disability in people aged under 50 years, and ranks third among all illnesses, but it is correctly diagnosed only in 27% of the cases and adequately treated with triptans in barely 46% of them. Unfortunately, the majority of migraine patients treat their crisis with NSAIDs combined with or not with different compounds, such as caffeine, ergot derivatives, barbiturates, etc., carrying themselves towards a chronicity complicated by drug overuse. This evident therapeutic gap on the appropriateness of acute migraine treatment is scarcely filled by the development of new compounds, except lasmiditan. In fact, an accurate analysis of acute drugs actually being developed reveals that while two-third of preventative treatment consists in new compounds, barely one-sixth of acute treatment refers to new chemical compounds. Monoclonal antibodies towards CGRP or its receptor (CGRPr) will be one additional prophylactic treatment option, useful to an easier treatment of acute migraine attacks by reducing their frequency and mitigating the pain severity.

This unmet need requires new ideas that, starting from physiopathological mechanisms, can identify the target for a simple, rapid, and safe option in acute treatment.

Therefore, today, the unique possible reply to the question ‘Acute Treatment of Migraine: *Quo Vadis*?’ is, unfortunately, ‘I don’t know.’

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Declaration of interest

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