Chapter

Introductory Chapter: Migraine in Post-Triptan Era: New Therapeutic Horizons

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1. Introduction

Migraine is described as a chronic, most probably genetically determined disease, in vast majority of patients characterized by the occurrence of headache attacks. The bouts of headache are accompanied by specific symptoms and signs as nausea—in majority of patients and vomiting—in almost half of them, as well as photophobia and phonophobia [1]. Since they left untreated, the attacks last—in adult patient—from 4 hours up to 3 days. The onset of the disease falls between 18 and 35 years and migraine is regarded as a life-long condition, however it may present a different clinical face in different period of patient's life as far as frequency and severity of the attacks are concerned. In general, migraine is more than twice more common in adult women (approx. 15% of general population) than in adult men—roughly 6% of the population [2], especially in the period of highest occurrence. However, relations and proportions might be entirely different in childhood and senescence—approximately the same percentage of young boys suffer from migraine as girls [3] and the disease is almost three times more common among elderly men than postmenopausal women [4].

The vast majority of the patients usually experience the moderate and/or severe pain intensity during attacks. It results in the fact that almost three-quarters of migraine victims present highly diminished effectiveness during disease attack [5]. It means the effective treatment of each single attack plays a decisive role in the reduction of both biological (i.e. pain, accompanying symptoms), social and economic aspects of the disease.

2. Triptans

For a long time specific and selective 5-$HT_{1B/1D}$ receptor agonists—a class of drugs called triptans (including sumatriptan, zolmitriptan, naratriptan, rizatriptan, almotriptan, eletriptan, and frovatriptan)—have been used as an effective and relatively safe measures against migraine attacks, regarded as almost the drugs of choice in migraine episodes [6, 7]. The drugs were especially recommended in patients with attacks poorly responded to NSAIDs or in whom NSAIDs were contraindicated. What is more—the fewer side effects were associated with triptans than in other anti-migraine drugs, and triptans were more effective at aborting migraine bouts [8]. However, during the years of triptan administration, it was noticed, that these group of drugs, even used in proper dose and manner are ineffective in some 16–18% of migraine victims [9]. What is more the side effects of triptans

(coronary-like pain symptoms) appeared dangerous and strictly unacceptable for quite a percentage of patients [10]—in fact, triptans are contraindicated in most cardiovascular diseases. In these situation the strong need of new—effective and especially cardiac—safe migraine killers—became obvious.

3. After triptans

The next selective drugs tried in abortive treatment in migraine were ditans—a class of molecules that selectively bind to 5-HT_{1F} receptors. The ditans are not encountered in vessels, being widespread in CNS, especially in brain stem, hampering the increased trigeminal system activity during migraine attack [11]. After the years of clinical studies, one of these molecules—lasmiditan, after first—relatively positive trials [12]—finally—has been approved by the FDA for the acute treatment of migraine with or without aura in adults [13].

Also the next seemingly promising group—gepants, calcitonin-gene related peptide (CGRP) receptor antagonist—after first enthusiastic results concerning the efficacy of the first generation of antagonist—telcagepant [14] or ubrogepant [15], were the subject of more detailed debates and considerations. The main reason for the doubts was their accented hepatotoxicity [16]. Eventually, the FDA has approved an orally disintegrating tablet formulation of rimegepant [17], that was the second, after ubrogepant, oral drug of this group, available in anti-migraine armamentarium. We still waiting for the final results and the potential approval of the next two molecules from second gepants generation, i.e. atogepant, vazegepant.

4. Monoclonal antibodies against CGRP and the CGRP receptor as new-generation drugs for migraine treatment

Monoclonal antibodies (mAbs) developed against CGRP receptor (as erenumab) or CGRP molecule itself (namely—fremanezumab, galcanezumab, and eptinezumab) were the next big hope in therapeutic attitude to migraine. The drugs of these group exert strong inhibiting effect on CGRP release during migraine attack, thus hampering its vasodilative effect [18, 19]. The results of many registered pharmacoclinical studies/trials showed both effectiveness and safety of these drugs, that reduced both the number of migraine episodes, days with headache and administration of acute headache killers per month in migraineurs. The next advantages of these group were very convenient, patient-friendly dose regimen (once a four weeks) and—as it looks now—the absence of serious side effect [20, 21]. It seems that relatively fast onset of action (in the first month of implementation), high efficacy, and good tolerability make this class of drugs the real revolution in migraine treatment [22, 23] compared with that of ergotamine introduction (in 1927) or the first triptans in 1990. In fact, they are the second characteristic molecule—after methysergide—targeting the most specific mechanism of migraine attacks. This group of drugs showed effectiveness both in episodic and chronic migraine—and what is more, also, in migraine-like episodes in patients with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), that is quite a phenomenon [24].

We do hope that in time and gaining more experience with these group of antimigraine drugs, monoclonal antibodies against CGRP complex will become the first-line treatment of the disease.

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