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Professional Paper

ERENUMAB IN THE PREVENTION OF MIGRAINE HEADACHES – A PILOT STUDY

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SUMMARY – This research aimed to assess the efficiency of erenumab (Aimovig) in the preventive treatment of patients with episodic and chronic migraines. In Croatia, migraine prevention is applied to patients with ≥ 4 days of migraine headaches per month. Prevention efficiency was assessed with the Migraine Disability Assessment Test (MIDAS) scale. The research included 26 subjects, comprising 25 women and 1 man. The mean duration of migraine headache in our patients was 13 ± 1.8 years. All the patients had already been taking ≥ 2 preventive medication therapies and most of them had also been subjected to acupuncture and/or neurofeedback therapies, but with no significant effect. The MIDAS mean value at the first examination, i.e. one week before starting preventive erenumab therapy, was 17.69. The MIDAS scale mean value six months after migraine preventive therapy with 70 mg erenumab subcutaneously (SC) was 4.81. Thus, disability was decreased by almost 75%, which is deemed to be significant. Only one subject had no improvement in six months, wherefore we increased his dosage of erenumab to 140 mg SC. With the increased drug dosage and elimination of exogenous triggering factors, the effect was significant, with a significant decrease of disability (MIDAS 4) in the following three months.

Keywords*: Erenumab; CGRP; Migraine; Prevention*

Introduction

According to the internationally accepted headache classification set by the International Headache Society (IHS), migraine is classified as a primary headache, together with tension and cluster headaches, other trigeminal autonomic cephalgias and other primary headaches. The latest revised headache classification guidelines were published in February 2018[1].

Together with sciatica, migraine headaches are the most common cause of pain. The World Health Organization (WHO) assesses migraine prevalence to be around 15% in the general population, with a 3:1 frequency ratio of women to men[1-4]. Migraine is most often episodic, but in 1–2% of the cases it is chronic, meaning that migraine headaches are present ≥ 15 days per month[1,2]. According to the IHS classification, migraine can present with or without aura. Aura may manifest with a typical visual aura, or more rarely another type of neurological deficit, followed by

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headache[1,2]. IHS recommends practicing prevention with all patients suffering episodic migraine headaches ≥ 4 days per month and chronic migraine headaches (≥ 15 days per month)[1,5,6]. Therapy decreasing the frequency of headaches by ≥ 50% is considered efficient. Until recently, nonspecific drugs not registered for migraine prevention were used, such as β-blockers, calcium antagonists, antiepileptics (e.g. topiramate and valproate), as well as gabapentin and pregabaline, flunarizine and antidepressants, and a number of other drugs lacking clear efficiency meta-analyses[5-13].

The subject matter of our interest was the effect of the human monoclonal antibodies of erenumab in migraine prevention. We assessed the degree of disability according to the Migraine Disability Assessment Test (MIDAS) scale[14]. Disability is classified as little, mild, moderate or severe. All the mentioned disability qualities are scored with five numeric categories, except for severe disability, which is classified as 21+[24,15].

Patients and Methods

The study included subjects with episodic or chronic migraines. All the subjects, in accordance with the migraine prevention guidelines, had migraines lasting ≥ 4 days per month. All the subjects had already been subjected to migraine prevention therapies with two or more drugs, and some to acupuncture and/or neurofeedback as well. However, previous therapies produced no satisfactory results. Their migraine headaches were assessed with the MIDAS scale one week before therapy was started and again after six months of erenumab therapy. The MIDAS scale defines headache by the degree of disability from little/none to mild, moderate and severe (Table 1)[14,15].

Table 1. MIDAS scoring scale*

MIDAS grade	Definition	MIDAS score
I	Little or no disability	0–5
II	Mild disability	6–10
III	Moderate disability	11–20
IV	Severe disability	≥ 21

* Migraine Disability Assessment Test

Erenumab (Aimovig) was applied in migraine prevention regularly every four weeks for six months in a dose of 70 mg subcutaneously (SC).

Results

This research included 26 subjects; 25 women and 1 man. The mean age of the female participants was 40 ± 2 years, whereas the only male participant was 29 years old. The mean duration of migraine in our subjects was 13 ± 1.8 years. All the subjects had already been taking ≥ 2 migraine prevention drug therapies not registered for this purpose, but applied for practicality reasons. Most subjects' therapy also included acupuncture, and all of them were included in neurofeedback treatment, with only partial effects.

In all the patients, headache severity was assessed with the MIDAS assessment scale one week before erenumab therapy was started, and again after six months of its regular application (Table 2).

The mean value of the MIDAS assessment scale at the first examination, that is before erenumab therapy was started, was 17.69. The mean value of the MIDAS assessment scale after six months of migraine preventive therapy with 70 mg of erenumab SC was 4.81. Thus, a difference in the MIDAS assessment scale (describing the disability degrees on a scale of 0-21) values that occurred during six months of migraine prevention with erenumab was 12.92. This is a disability improvement of almost 75%, which is deemed significant. Only one subject had no improvement over the six months of preventive therapy. After a repeated elaboration of this test subject, their erenumab dosage was increased to 140 mg SC. It should to be noted that this subject was male, had numerous exogenous psychological frustrating factors and suffered professional exposure to very low temperatures of -30 °C while working in cold storage. At a check-up three months later, following prevention with 140 mg of erenumab SC and elimination of working in cold storage, his condition significantly improved. He had headaches twice a month and they were markedly less intense. So much so that he assessed his disability as mild (MIDAS 4), with significant satisfaction after the application of the drug.

Table 2. Disability assessment with the MIDAS scale*

Subject	MIDAS1**	MIDAS2***	DIFFERENCE 1-2****
A. T.	21	3	18
T. L.	15	5	10
M. S	18	7	11
J. G.	17	4	13
R. L.	19	5	14
A. J.	20	3	17
M. B.	21	6	15
A. Z.	18	7	11
A. M.	17	4	13
M. U.	19	3	16
A. S.	20	6	14
A. T.	16	3	13
Ž. R.	13	4	9
G. N.	20	5	15
N. Š.	14	3	12
K. M.	15	4	11
S. B.	19	6	13
K. Č.	20	3	17
H. P.	21	2	19
M. K.	18	4	14
L. B.	17	5	12
T. T.	12	3	9
Z. M	14	2	12
M. U.	16	3	13
N. M.	19	4	15
I. V.	21	21	0
Mean value	17.69	4.81	12.92

* Migraine Disability Assessment Test
** MIDAS assessment scale one week before therapy was started
*** MIDAS assessment scale after six months of therapy
**** MIDAS value difference before starting therapy and after six months of preventive therapy

Discussion

Treating migraine includes treating migraine attacks and including migraine prevention when necessary.

According to the IHS guidelines, migraine prevention is applied in cases where headaches occur ≥ 4 days per month, either as episodic or chronic migraine. The European Headache Federation (EHF) recommends the application of monoclonal antibodies acting on the calcitonin gene–related peptide in migraine prevention[16]. The Food and Drug Administration (FDA) and the European Medicines Agency (EMA) approved the erenumab (Aimovig) humane monoclonal antibody in migraine prevention in 2018, and it has been used in Croatia since February 2019. Erenumab is a human monoclonal antibody linked to the calcitonin gene–related peptide (CGRP). The CGRP receptor is located at places relevant for migraine pathophysiology, such

as the trigeminal ganglia. Erenumab potently and specifically competes with the binding receptor of CGRP and inhibits its function at the CGRP receptor, having no significant activity relative to other members of the calcitonin family of receptors[17,18].

CGRP is a neuropeptide that modulates nociceptive signalization and a vasodilator related to migraine pathophysiology. It has been noticed that, unlike other neuropeptides, CGRP peptide levels significantly rise during a migraine attack, only to return to their normal values as the headache decreases. Intravenous infusion of CGRP causes migraine-like headache in patients[18-22]. Research performed by numerous authors has shown that administering erenumab in migraine prevention is efficient and safe[21,22]. Ashina et al. state that administering erenumab in migraine prevention to patients with chronic migraine decreases the number of days with headache by 50–75%[20]. Other research groups established a decrease of the headache days per month in patients with episodic and chronic migraines as well[21-24].

Our pilot study included a small number of subjects (26) with episodic and chronic migraines. All the subjects had previously been treated with presently available therapies — at least two forms of drug therapies and acupuncture and/or neurofeedback — but with no significant effect. All the subjects received 70 mg erenumab SC for six months. Subsequently, over an additional period of time, one patient's dosage was increased to 140 mg SC once a month. We assessed the efficiency of treatment with the MIDAS scale. We established an improvement of disability by 75%, which is deemed significant. It should be noted that increasing the dosage of erenumab to 140 mg for the patient that did not respond to the 70 mg dosage made a significant improvement.

Our pilot study, using the MIDAS assessment scale, showed a significant effect of erenumab in patients with migraine. Our research results correlate with research by other authors who assessed quality of life in patients with migraine who used erenumab in migraine prevention. Other authors reported significant positive effects of erenumab in the prevention of episodic and chronic migraine[25-27]. Additional tests of the effects of erenumab on disability and quality of life in patients with migraine should be performed on larger numbers of subjects. Further research is required into the effects of erenumab on disability and quality of life in patients with particular subtypes of migraine.

Conclusion

This pilot study of migraine prevention with erenumab showed the drug to be highly effective. Disability status assessments with the MIDAS scale showed a 75% improvement in the patients' conditions. Further research on larger numbers of subjects and relative to migraine subtypes is required.

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Sažetak

ERENUMAB U PREVENCIJI MIGRENSKE GLAVOBOLJE – PILOT STUDIJA

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Cilj ovog istraživanja bio je procijeniti učinkovitost erenumaba (Aimovig) u profilaktičnom liječenju bolesnika s migrenom; epizodičnom i kroničnom glavoboljom. Profilaksa migrene provodi se u bolesnika koji imaju migrensku glavobolju ≥ 4 dana/mjesečno. Djelotvornost prevencije procijenjena je temeljem MIDAS (eng. Migraine Disability Assessment Test) ljestvice. Istraživanje je obuhvatilo 26 ispitanika: 25 žena i jednog muškarca. Srednje vrijeme trajanja migrenske glavobolje u naših ispitanika bila je 13 ± 1,8 godina. Svi su ispitanici već ranije uzimali ≥ 2 preventivne medikamentozne terapije, a kod većine je primijenjena i akupunktura i/ili *neurofeedback* terapija bez značajnijeg učinka. Srednja vrijednost MIDAS ljestvice pri prvom pregledu, odnosno tjedan dana pred početak primjene profilaktičke terapije erenumabom, iznosila je 17,69. Srednja vrijednost MIDAS ljestvice nakon šest mjeseci primjene profilaktičke terapije migrene uporabom erenumaba od 70 mg s.c. iznosila je 4,81. Dakle, smanjenje onesposobljenosti iznosilo je gotovo 75%, što se smatra značajnim. Samo jedan ispitanik nije imao poboljšanja tijekom šest mjeseci te smo povećali njegovu dozu erenumaba na 140 mg s.c. Uz povećanje doze lijeka i isključivanje egzogenih provocirajućih čimbenika učinak je bio značajan sa značajnim smanjenjem onesposobljenosti (MIDAS 4) tijekom sljedeća tri mjeseca.

Ključne riječi: *Erenumab; CGRP; Migrena; Prevencija*