Evolocumab and headache

Introduction

Evolocumab Repatha® is indicated for *homozygous familial hypercholesterolemia in combination with other lipid-lowering treatments, heterozygous familial of non-familial primary hypercholesterolemia or combined (mixed) dyslipidemia and atherosclerotic cardiovascular diseases, in patients who cannot tolerate cholesterol synthesis inhibitors or with insufficient effect of other lipid-lowering treatments*. Evolocumab is a human monoclonal IgG2-antibody. Evolocumab binds selectively to proprotein convertase subtilisin/kexin type 9 (PCSK9) and prevents that circulating PCSK9 binds to the 'low-density'-lipoprotein receptor (LDLR) on the liver cell surface, and so preventing PCSK9-mediated LDLR degradation. Increasing liver-LDLR-expression results in decrease of LDL-cholesterol. Evolocumab was granted marketing authorization in the Netherlands in 2015 [1].

Headache is a very common symptom with many variable etiologies. In population-based studies episodic tension-type headache (TTH) is the most frequent headache type. Other common primary headaches include migraine and cluster headache [2].

Reports

From 8 September 2016 to 1 March 2019 the Netherlands Pharmacovigilance Centre Lareb received 50 reports of headache and 4 reports of migraine in association with the use of evolocumab, in the MedDRA High Level Group Term (HLGT) Headaches [3].

Reports of headache

Of the 50 reports of headache, 12 reports were directly sent to Lareb, and 38 reports were received through the Marketing Authorisation Holder (MAH).

The reports concerned 32 women and 18 men. Ages varied from 38 up to and including 82 years, (mean 62.6 years, median 63 years). The ages were not known in 2 reports.

Latencies were less than a day in 4 reports, between a day and up and including 1 week in 4 reports, 14 days in 1 report, 1 month in 1 report, more than a month in 7 reports, and unknown in 33 reports.

There were 4 reports (3 reports directly sent to Lareb, and 1 received through the MAH), that described a continuous headache.

In 14 reports flu-like symptoms (defined as flu-like symptoms reported as reaction and/or symptoms that may be compatible with a flu-like reaction like cough, rhinorrhoea, sinusitis or a sore throat) were also reported as reactions. Besides these 14 reports, there were 21 other reports where reported reactions besides headache included dizziness, pain, nausea, fatigue and/or muscle discomfort. In 7 other reports, reported reactions included inappropriate schedule of drug administration (2 reports), abdominal pain (1 report), hyperhidrosis (1 report), itching on the back (1 report), neck pain (1 report) and swollen tongue (1 report).

The actions for evolocumab after occurrence of the headaches and the outcomes of the headaches at the moment of reporting were: drug withdrawn/outcome unknown (13 reports), action for drug unknown/outcome unknown (11 reports), drug withdrawn/recovered or recovering (7 reports), action for drug unknown/recovered (7 reports), dose not changed/recovered or recovering (4 reports), drug withdrawn/not recovered at the moment of reporting (3 reports), dose not changed/not recovered at the moment of reporting (3 reports), action for drug unknown/not recovered at the moment of reporting (2 reports).

Reported treatments of the reactions included pain relieving medication.

In one report it was mentioned that the patient was familiar with headaches. In one report the reaction only occurred in combination with a glass of wine. Furthermore, there were several reports in which concomitant medication was reported of which the SmPCs report headache as adverse drug reaction.

Reports of migraine

Of the 4 reports of migraine, 1 report was directly sent to Lareb, and 3 reports were received through the MAH.

The reports concerned 3 women and 1 man. Ages varied from 35 up to and including 61 years, (mean 50.5 years, median 53 years).

Latencies were less than a day in 1 report, 30 days in 1 report, and unknown in 2 reports.

In 1 report cold and throat pain were also reported as reactions, and in 1 report fatigue and skin rash were also reported as reactions.
The actions for evolocumab after occurrence of the migraines and the outcomes of the migraines at the moment of reporting were: drug withdrawn/recovered (2 reports), drug withdrawn/outcome unknown (1 report), action for drug unknown/outcome unknown (1 report).

In consultation with the CBG, reports describing a pattern of recurrent headache after several administrations and/or short latencies of less than a day for the reactions headache or migraine, were described in more detail in table 1.

Table 1. Reports of headache or migraine in association with the use of evolocumab describing a pattern of recurrent headache after several administrations and/or with short latencies

Patient, Sex, Age (years), Source	**Drug Indication for use**	**Concomitant medication**	**Suspected adverse drug reaction**	**Time to onset, Action with drug Outcome for the reaction headache or migraine**
a: NL-LRB-00286045, M, 61-70, Other health professional	evolocumab injection fluid 140 mg/ml Indication not reported	acetylsalicylic acid clopidogrel lisinopril metoprolol ezetimib etanercept	Headache Dizziness Flu-like symptoms	4-5 hours Dose not changed Recovered
b: NL-LRB-00302098 F, 41-50, Consumer	Repatha® injection fluid 140mg/ml pen 1ml 1x /2 weeks Familial hypercholesterolaemia	ezetimib rosuvastatin	Headache Fatigue extreme Nausea Influenza Rhinorrhoea Myalgia	12 hours Drug withdrawn Recovering
c: NL-LRB-00313693 F, 61-70, Other health professional	Repatha® injection fluid 140mg/ml pen 1ml 1x/2 weeks Hypercholesterolaemia	atorvastatin metoprolol zolpidem losartan amlodipine clopidogrel chlortalidone	Headache	Hours Dose not changed Unknown
d: NL-LRB-225480 F, 51-60, Physician	evolocumab 140 mg/ml Familial hypercholesterolaemia	calcium carbonate/ colecalciferol ezetimib	Headache Nausea	7 days Drug withdrawn Unknown
e: NL-AMGEN-NLDSL2016167623 M, 51-60, Physician	Repatha® 140 mg/ml 1x/2 weeks Hypercholesterolaemia	ketoconazole verapamil	Flu like symptoms Allergic reaction Feeling bad Headache Adverse event Nausea	14 days Drug withdrawn Not recovered
f: NL-AMGEN-NLDSL2017080345 F, 51-60, Physician	Repatha® 140 mg/ml 1x/ 2 weeks Hypercholesterolaemia	clopidogrel ezetimib	Headache Hypertension Fatigue	1 month Drug withdrawn Recovered
g: NL-LRB-241734 F, 61-70, Physician	Repatha® injection fluid 140mg/ml pen 1ml 1x/2 weeks Hypercholesterolaemia and TIA	pantoprazole acetylsalicylic acid dipyridamole furosemide ezetimib clonidine sertraline	Headache Pyrexia Influenza like illness	The reaction started immediately Drug withdrawn Recovering

Patient, Sex, Age (years), Source	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug Outcome for the reaction headache or migraine
h: NL-LRB-233444	evolocumab injection fluid 140mg/ml 1x/2 weeks Familial hypercholesterolaemia	rosuvastatin	Migraine	On the same day after start of the drug evolocumab Drug withdrawn Recovered

Additional details on the reports described in table 1.

Report a: The patient experienced headache and dizziness, starting 4-5 hours after the injection and lasting for 3 days; after the 3rd injection there were also flu symptoms; after the 4th injection there were no symptoms any more.

Report b: Concerning the headache, the patient reported that the headache lasted for the first few days after administration and necessitated pain-relieving medication.

Report c: The patient experienced severe headache after all 3 injections on the first 2 days.

Report d: The patient experienced headache and nausea following administration of evolocumab with a latency of 7 days after start and 7 days after each injection. The patient was hospitalized with severe headache, nausea and vomiting. The headache severity increased after each injection and lasted for 2 days each time. The patient received treatment with metoclopramide and paracetamol. A MRI cerebrum and CT brain showed no abnormalities. The medical history included non-Hodgkin's lymphoma.

Report e: This report concerned a study report received through the MAH. Concerning the headache, the patient experienced severe headaches after injection for 3 days. After administration of evolocumab, the following days the patient had flu-like symptoms, nausea and headache. It was reported that at first no relation was reported but after the fourth administration of evolocumab with the same symptoms, the medication was stopped.

Report f: This report concerned a study report received through the MAH. It was reported that the patient received eight injections so far. After every injection, during one weeks she had the same symptoms. The medication was shifted to alirocumab. The patient's medical history included a cerebrovascular accident.

Report g: The patient experienced flu symptoms, pyrexia and headache that was reported as unbearable. It was reported that the reaction started immediately. After 4 weeks the patient was not yet fit.

Report h: The patient experienced migraine on the same day after start of the drug evolocumab. The patient recovered 5 days after the drug evolocumab was withdrawn. The medical history indicated migraine, where the patient rarely experienced migraine attacks.

Other sources of information

SmPC

In the Dutch SmPC of evolocumab, headache is not reported as an adverse drug reaction. Influenza and nasopharyngitis are reported as commonly (1-10%) occurring adverse reactions.
In the Dutch patient leaflet of evolocumab headache is also not mentioned as adverse drug reaction. The patient leaflet of evolocumab does report as commonly occurring adverse reactions, flu (high temperature, sore throat, runny nose, cough and chills), and common cold, such as runny nose, sore throat or sinus infections (nasopharyngitis or upper respiratory tract infections) [1].

In the FDA label of evolocumab Repatha®, headache is reported in the paragraph "Adverse reactions" in the table of adverse reactions occurring in greater than or equal to 3% of Repatha®-treated patients and more frequently than with placebo in a 52-week, double-blind, randomized, placebo-controlled trial, where 3.6% of placebo-treated patients (n=302), and 4.0% of Repatha®-treated patients (n=599), experienced headache [4].

Literature

In an interim subset analysis of the open-label TAUSSIG study, concerning long-term treatment with evolocumab added to conventional drug therapy, with or without apheresis, in patients with homozygous familial hypercholesterolaemia, headache was among the most commonly reported treatment-emergent adverse events. Of 106 patients 11 patients reported headache as treatment-emergent adverse event [5].

In the LAPLACE-2 randomized clinical trial, concerning evolocumab or ezetimibe added to moderate- or high-intensity statin therapy on LDL-C lowering in patients with hypercholesterolemia, headache was among the most common adverse events in evolocumab-treated patients (all <2%). Headache occurred in 19 (1.7%) patients in the group “any statin + evolocumab” (n=1117), in 15 (2.7%) patients in the group “any statin + placebo” (n=558) and in 5 (2.3%) patients in the group “atorvastatin + ezetimibe” (n=221) [6].

Database

Table 2. Reports of the PT “headache” associated with the use of evolocumab in the Lareb and WHO database [3,7,8].

Database	MedDRA PT	Number of reports	ROR (95% CI)
Lareb	Headache	18*	1.53 (0.94–2.47)
Eudravigilance	Headache	175	1.62 (1.39–1.89)
WHO	Headache	1400	0.89 (0.85–0.94)

*For administrative reason not all reports were included in the ROR calculation.

Prescription data

Table 3. Number of patients using evolocumab in the Netherlands [9].

Drug	2016	2017
Evolocumab	2,087	4,924

Mechanism

No possible mechanism of headache in association with evolocumab is described in the literature.

Discussion and conclusion

The Netherlands Pharmacovigilance Centre Lareb received 50 reports of headache and 4 reports of migraine, in association with the use of evolocumab. Headache is a very common symptom [2]. It was remarkable though that several reports described in table 1, mentioned a pattern of recurrent headache after several administrations and/or short latencies of less than a day for the reactions headache or migraine.
In 14 reports flu-like symptoms were also reported as reactions, and also in many other reports other reactions besides headache were reported.
The FDA label of evolocumab describes headache as adverse drug reaction, where this label mentions that in a study headache occurred more frequently in association with the use of evolocumab than with the use of placebo [4].
Based on the reports received by Lareb, further attention to headache in association with the use of evolocumab is warranted.

References

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This signal has been raised on July 17, 2019. It is possible that in the meantime other information became available. For the latest information, including the official SmPC's, please refer to website of the MEB www.cbg-meb.nl