1.1. Statins and diplopia

Introduction

Statins inhibit the enzyme HMG-CoA (3-hydroxy-methylglutaryl-coenzyme A-reductase, which plays an important role in the synthesis of cholesterol by catalysing the conversion from HMG-CoA to mevalonate. Statins are indicated for *hypercholesterolemia* and they are effective in both *the primary and the secondary prevention of ischemic heart diseases and stroke prevention*. Among the statins simvastatin (Zocor®) was granted marketing authorization in 1988, atorvastatin (Lipitor®) in 1997, fluvastatin (Lescol®) in 1995, pravastatin (Selektine®) in 1990, rosuvastatin (Crestor®) in 2002 and pitavastatin (Livazo®) in 2010. Pitavastatin is not available in the Netherlands. Blurred vision, vision disturbance or decreased vision are described in association with a few statins. Diplopia is only described with pravastatin [1].

Diplopia, or double vision, may be monocular of binocular. Monocular diplopia is mostly a problem of the anterior segment, as cataract, corneal shape problems and astigmatism. Binocular diplopia suggests disconjugate alignment of the eyes. Most common causes are cranial nerve palsy brain stem lesions, , thyroid diseases, myasthenia gravis and orbital infiltration [2].

Reports

Lareb received 17 reports of diplopia associated with the use of statins, in a period from July 18, 1996 till July 20, 2015. The reports are listed in Table 1. The latency usually was between one day and several months, with one exception (patient J). This patient experienced diplopia five years after start of atorvastatin. Ten patients recovered or were recovering after discontinuation of the statin. Two patients (N and Q) also had complaints of diplopia in association with a statin on an earlier occasion.

Table 1. Reports of diplopia associated with the use of statins

Patient, Number, Sex, Age, Source	Drug, daily dose Indication for use	Concomitant Medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
A 19467 M, 71 years and older General practitioner	simvastatin 10mg once daily pure hypercholesterolemia	acetylsalicylic acid nitrazepam	diplopia	1 day discontinued after 2 years unknown
B 40290 F, 71 years and older Pharmacist	pravastatin 40mg once daily pure hypercholesterolemia	omeprazole	vision blurred diplopia	months drug withdrawn recovered
C 40352 M, 51-60 years General Practitioner	rosuvastatin 10mg once daily hyperlipidemia NOS	metoprolol acetyl salicylic acid diltiazem nitroglycerine spray subling	headache diplopia	15 days drug withdrawn after 4 weeks/switch to simvastatin unknown
D 48262 F, 61-70 years Pharmacist	pravastatin 20mg once daily	hydrochlorothiazide metoprolol nitrazepam	visual acuity reduced diplopia	5-7 weeks* unknown unknown
E 50120 M, 51-60 years Pharmacist	pravastatin 40mg once daily	acetyl salicylic acid dipyridamole hydrochlorothiazide	diplopia	months dose not changed not recovered
F 58542 F, 41-50 years Pharmacist	pravastatin 10mg unknown	betahistine	visual impairment diplopia vision blurred	unknown dose not changed unknown

G 62997 F, 61-70 years, Pharmacist	pravastatin 40mg once daily hypercholesterolemia	metoprolol candesartan/hydrochlorothiazide diltiazem	vision blurred myalgia paraesthesia oral diplopia	3 weeks after dose increase to 40 mg dose reduced recovered
H 66427 M, 71 years and older Pharmacist	rosuvastatin 10mg once daily	hydrochlorothiazide omeprazole calciumcarbonate/colecalciferol alendronate metformin glimepiride mesalazine azathioprine fluticasone nose spray acetylcystein dipyridamole tiotropium	diplopia(increasing) vision blurred	3 months discontinued recovering
I 78874 M, 61-70 years Specialist eye doctor	simvastatin 40mg once daily hypercholesterolemia		diplopia eye movement disorder	4 months drug withdrawn recovered
J 79620 M, 61-70 years Specialist eye doctor	atorvastatin 10mg once daily hypercholesterolemia		diplopia myalgia gait disturbance pos. antiacetylcholine receptor antibody **	5 years drug withdrawn recovered, diplopia improving
K 83268 F, 71 years and older General Practitioner	simvastatin 40mg once daily hypercholesterolemia	metoprolol hydrochlorothiazide allopurinol	diplopia vision blurred	2-3 weeks drug withdrawn, recovered in days
L 102623 F, 41-50 years General Practitioner	simvastatin 10mg pravastatin 10 mg once daily diabetes mellitus	insulin	diplopia sensory disturbance	1 month drug withdrawn, recovered
M 110774 M, 61-70 years Consumer	pravastatin 20mg once daily CVA		diplopia headache	1 week drug withdrawn, recovering
N 126483 M, 71 years and older Consumer	pravastatin 40mg once daily hypercholesterolemia		diplopia libido decreased pollakiuria myalgia sleep disorder heart rate increased fatigue	1 week drug withdrawn, recovered with sequel
O 130294 F, 61-70 years General Practitioner	pravastatin 40mg once daily hypercholesterolemia		diplopia	14 days drug withdrawn, recovered
P 154361 Unknown,unknown Pharmacist	atorvastatin 20mg unknown		diplopia	unknown unknown unknown
Q 176643 M, 61-70 years Consumer	simvastatin 20mg once daily hypercholesterolemia	acetyl salicylic acid	diplopia condition aggravated	3 months dose not changed not recovered

Patient D: Directly prior to use of pravastatin, patient had used brand pravastatin (Selektine®) during 3.5 years. Patient had cataract surgery.

Additional information on cases
Patient I experienced also slight pain in the orbit; according to the reporting eye specialist, in older patients this can be caused by microvascular changes of the cranial nerves

Patient J was known with non-insulin dependent diabetes mellitus. Patient had prior surgery due to paresis of cranial nerve IV, which resulted in improvement, but still with slight complaints of diplopia. Between two and five years after start of simvastatin patient experienced no specific complaints of diplopia. Then again diplopia developed and for this reason anti-acetylcholine receptor antibodies were assessed, and found positive. Atorvastatin was discontinued, where after the anti-acetylcholine receptor antibodies test turned negative.

Patient L was recently diagnosed with diabetes mellitus. She had double vision and sensory disturbances one month after starting simvastatin 10 mg once daily and pravastatin 10 mg once daily- it is not clear if these were used simultaneously or in sequence. One month later the treatment with statin was discontinued and patient recovered.

Patient M discontinued pravastatin because of double vison, headache and pain of the eyeball and switched back to former medication NOS. Patient was recovering at the moment of notification.

Patient N experienced the adverse reactions also before in association with pravastatin.

The information regarding patient P was reported by the marketing authorization holder; no additional information is available

Patient Q experienced diplopia in association with another statin, 2 years before. Because of diplopia, patient uses glasses with a prism. Since the use of simvastatin complaints of diplopia have worsened.

Other sources of information

SmPC
The SmPC of pravastatin describes diplopia as adverse reaction [1]. Diplopia is not mentioned in the SmPCs of atorvastatin, fluvastatin, rosuvastatin, simvastatin and pitavastatin [3-7]. The US SmPCs of both pravastatin and simvastatin mention impairment of extraocular movement. [8,9]. The US SmPC of pravastatin describes also diplopia as adverse reaction [9].

Literature
Fraunfelder [10] studied two hundred fifty-six case reports of ptosis, diplopia, and ophthalmoplegia associated with statins from the National Registry of Drug-Induced Ocular Side Effects, the World Health Organization (WHO), and the Food and Drug Administration. Average time from beginning of therapy to appearance of the ADR was 8.3+/-1.5 months, median 3.5 months (range, 1 day-84 months). A total of 23 case reports described total ophthalmoplegia. Ptosis was reported alone 8 times and in conjunction with diplopia 18 times. There were 62 positive de-challenge and 14 positive re-challenge case reports. Confounding was only suggested in one patient out of these 14 re-challenges, having diabetes mellitus, possibly leading to cranial nerve palsy. 108 patients were not taking other medications except the statin Five patients were taking gemfibrozoil as concomitant medication. Myositis associated with statins occur in approximately 0.1 % of patients, which is increased to 0.5-2.5 % if gemfibrozil is administered at the same time. According to WHO criteria, the relationship between statin therapy and diplopia, ptosis, or ophthalmoplegia is possible.

This causality assessment is based on the time relationship of drug administration and ADR development, the multiple positive de-challenge and re-challenge reports, and a plausible mechanism.

A 60-year-old woman experienced horizontal diplopia, blurred vision, vertigo and paresthesias of both upper extremities, 2.5 months after starting atorvastatin 10 mg daily. There was ptosis of the right and left upper eyelids. External ophthalmoplegia was observed: Eye movements were limited for upwards and sideward movements. Anti-AchR antibodies were ten times the upper limit. Myasthenia gravis was excluded by a negative tensilon test and a negative repetitive stimulation test on electromyography. Two days after discontinuation of atorvastatin symptoms improved and after ten weeks almost completely disappeared. Anti-AchR antibodies had normalized [11].
A 67-year-old woman experienced bilateral blepharoptosis, intermittent diplopia and symmetrical proximal muscle weakness three months after starting atorvastatin for hypercholesteremia. She recovered six weeks after discontinuation of atorvastatin. Because of high lipid concentrations, she received sequentially fluvastatin, simvastatin and benzafibrate. With each agent the muscle weakness recurred after two to three months. A myogenic ptosis with ocular myasthenia was observed with moderate proximal limb-girdle weakness. No acetylcholine-receptor antibodies or striated-muscle antibodies were detected - patient was euthyroid. Symptoms subsided two months after discontinuation [12].

Databases

Table 2. Reports of diplopia with statins in the databases of the Netherlands Pharmacovigilance Centre Lareb, the WHO- and Eudravigilance (EMA) database [13,14]

Database	Preferred Terms	Number of reports	ROR (95% CI)
Lareb	diplopia	17	1.6 (1.0-2.5)
WHO	diplopia	409	1.4 (1.3-1.5)
Eudravigilance	diplopia	150	1.1 (0.9 – 1.3)

Prescription data

Table 3. Number of patients using statins in the Netherlands between 2010 and 2014 [15]

Drug	2010	2011	2012	2013	2014
simvastatin	930,700	980,250	1,043,000	1,065,000	1,085,000
pravastatin	170,080	169,640	170,580	168,620	166,660
fluvastatin	22,181	21,667	21,453	20,582	19,751
atorvastatin	375,810	364,900	383,280	405,180	438,990
rosuvastatin	181,230	191,890	209,330	217,410	228,570
Total	1,594,000	1,662,000	1,750,000	1,793,000	1,849,000

Mechanism
In the study of Fraunfelder [10] two hundred fifty-six case reports of ptosis, diplopia, and ophthalmoplegia associated with statins were investigated. He suggested as mechanism by which diplopia, ptosis, or ophthalmoplegia may occur: myositis of the extraocular muscles, the levator palpebrae superioris muscles, or both. In a published case of ptosis related to statin therapy, magnetic resonance imaging showed an enlarged right levator muscle. Enhanced with gadolinium, these images suggest myositis [16]. Muscle biopsies of patients with statin induced myopathy have revealed evidence of mitochondrial dysfunction, abnormally increased lipid stores in the mitochondria, muscle fibers that do not stain for cytochrome oxidase activity, and ragged red fibers [17]. Hargreaves suggests that statins reduce endogenous coenzyme Q_{10} concentrations, resulting in severe deficit in

mitochondrial energy metabolism and consequent myopathy [18]. These findings are reversible on discontinuation of the offending statin. Creatinin kinase levels usually are elevated, but may be normal in statin- associated myositis [19]. It is unknown if neuropathy contributed to the diplopia, ptosis or ophthalmoplegia reported [10]. In some cases with reversible ophthalmoplegia by statins, elevated anti-AchR antibodies are found. It is suggested that there is a systemic immune reaction with mitochondrial dysfunction [20].

Discussion and conclusion

Lareb has received 17 reports of diplopia in association with statins. In more than half of the reports recovery took place after discontinuation of the statin. In six patients antihypertensive drugs were used, which could play a role in diplopia [21]. In three of these patients however, patients recovered after dose reduction or discontinuation of the statin. Eleven patients were older than 65 years. Diplopia is more often observed in older patients, with risk factors as hypertension, atherosclerosis or diabetes for cerebrovascular diseases affecting the pons or midbrain. However, recovery after discontinuation of the suspected drug was observed in eight of these older patients, pointing into the direction of an association with statins.

The association was supported by the WHO- data and by several publications. In several of these publications diplopia developed together with ptosis or myasthenic symptoms, with susceptibility for ocular symptoms [10-12,22,23]. Extra-ocular muscles differ from limb muscles as an embryonic isoform of AchR subunit is highly expressed [22,24]. In several publications an increase in anti-AchR antibodies was found, which decreased as ocular symptoms subsided [11,22].

Beside reports of diplopia, also publications of mere ptosis in relation to statins are found in the literature. A case of unilateral ptosis, worsening over one week, after two years of 10 mg atorvastatin treatment was presented by Ertas [16]. Within four days of discontinuing atorvastatin, blepharoptosis completely resolved and had not recurred in 10- months of follow up.
Elsais reports upon a 43-year- old male, who experienced myalgia and bilateral ptosis, soon after starting atorvastatin 20 mg daily, initiated after a myocardial infarction (MI). He was surgically treated without lasting effect. One year later, after another MI, atorvastatin was increased to 40 mg daily Within 2 weeks the ptosis worsened and he developed diplopia. Myasthenia gravis (MG) was suspected. Edrophonium chloride however improved the ptosis, but not the diplopia. Acetylcholine receptor antibodies were elevated (20-fould). No effect of pyridostigmin, azathioprine, iv immunoglobulin and plasma exchange was observed. De-challenge of atorvastatin took place two years later, resulting in a rapid recovery form myalgia and ptosis in a couple of days, but diplopia remained unchanged. Anti-AchR levels became only slightly elevated in the following 18 months. Another initiation of a statin (pravastatin) took place one year later, after another MI, and again ptosis recurred. After a positive de-challenge, re-challenge resulted in ptosis and diplopia. Finally he received no statins anymore, but ezetimib: ptosis resolved but diplopia remained. Because of the slightly elevated Anti-AchR levels, MG was suspected, but he showed no myasthenic symptoms in the subsequent three years [22].
Lareb has also two reports of solitary eyelid ptosis in association with statins. In the first case, a 67-year-old man experienced ptosis of the left eyelid, accommodation disorder, mydriasis and myalgia two days after start of rosuvastatin. As concomitant medication ciprofibrate, acetyl salicylic acid and fluticason nasal drips were used. Symptoms resolved after discontinuation of rosuvastatin. The second case regarding a male patient, aged 74, was reported by an ophthalmologist . The patient had a ptosis, with a latency of months after starting rosuvastatin. Concomitant medications were timolol and carbasalate calcium. One year later this rosuvastatin was discontinued. Patient recovered within two to three weeks. In this patient, myasthenia gravis was excluded as possible cause of ptosis.

Also solitary aggravation of myasthenia gravis was reported twice to Lareb. A male aged 62 years experienced worsening of his myasthenia four weeks after starting simvastatin. Recently he was vaccinated for influenza and received local anesthesia for a dental treatment. After discontinuation of simvastatin however, he recovered within three weeks. The other report concerned a 65-year-old male with aggravated ocular myasthenia within days after starting simvastatin. Months later simvastatin was discontinued- the outcome was unknown, at the day of reporting, which was approximately two weeks later. This patient experienced the same ocular myasthenic symptoms, when he used pravastatin in the past.
Purvin reports upon four patients who developed symptoms of myasthenia gravis within two weeks of starting treatment with a statin drug. In one case the drug

appears to have exacerbated underlying myasthenic weakness, whereas in the other three cases, de novo antibody formation appears to be most likely. Acetylcholine receptor (AChR) binding antibodies were elevated in three of the four cases (0.06 to 17.5 nanomoles/L) and single fiber electromyogram in two patients displayed increased jitter. In each case, some degree of recovery followed discontinuation of the statin medication. In one of the patients, who was on simvastatin, a re-challenge with pravastatin caused a recurrence of myasthenic symptoms [23].

It is of importance to acknowledge the possible role of statins in a patient with (binocular) diplopia. Diplopia is a symptom for which the underlying cause should be investigated in order to rule out serious conditions and find an appropriate treatment. Binocular diplopia, but also ptosis, might be due to external opthalmoplegia related to a drug-related myasthenia gravis; determination of anti- AchR antibodies is recommended. Discontinuation of statins might result in a substantial improvement in symptoms.

- Further investigation upon the information of the marketing authorization holders and other national centres is needed to evaluate the signal of binocular diplopia in association with statins in order to obtain more insight in the underlying pathogenesis

References

1. Dutch SmPC Selektine®. (version date: 17-4-2015, access date: 20-7-2015) http://db.cbg-meb.nl/IB-teksten/h13755.pdf.
2. Merck Manuals. (version date: 2014, access date: 20-7-2015) http://www.merckmanuals.com/professional/eye-disorders/symptoms-of-ophthalmologic-disorders/diplopia.
3. Dutch SmPC Lipitor®. (version date: 24-3-2015, access date: 20-7-2015) http://db.cbg-meb.nl/IB-teksten/h21081.pdf.
4. Dutch SmPC Lescol®. (version date: 13-6-2015, access date: 20-7-2015) http://db.cbg-meb.nl/IB-teksten/h18719.pdf.
5. Dutch SmPC Zocor®. (version date: 22-6-2015, access date: 20-7-2015) http://db.cbg-meb.nl/IB-teksten/h13193.pdf.
6. Dutch SmPC Livazo®. (version date: 20-2-2015, access date: 20-7-2015) http://db.cbg-meb.nl/IB-teksten/h106928.pdf.
7. Dutch SmPC Crestor®. (version date: 27-2-2015, access date: 5-8-2015) http://db.cbg-meb.nl/IB-teksten/h26872.pdf.
8. US SmPC simvastatin. (version date: 2015, access date: 5-10-2015) http://www.accessdata.fda.gov/drugsatfda_docs/label/2007/021961lbl.pdf.
9. US SmPC pravastatin. (version date: 2015, access date: 5-10-2015) http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/019898s063s064lbl.pdf.
10. Fraunfelder FW, Richards AB. Diplopia, blepharoptosis, and ophthalmoplegia and 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitor use. Ophthalmology. 2008;115(12):2282-5.
11. Negevesky GJ, Kolsky MP, Laureno R, Yau TH. Reversible atorvastatin-associated external ophthalmoplegia, anti-acetylcholine receptor antibodies, and ataxia. Arch.Ophthalmol. 2000;118(3):427-8.
12. Parmar B, Francis PJ, Ragge NK. Statins, fibrates, and ocular myasthenia. Lancet 2002;360(9334):717
13. WHO Global Individual Case Safety Reports database (Vigibase). (version date: 2015, access date: 20-7-2015) https://tools.who-umc.org/webroot/ (access restricted).
14. Eudravigilance database. (version date: 2015, access date: 3-8-2015) http://bi.eudra.org (access restricted).
15. GIP database - Drug Information System of the Dutch Health Care Insurance Board. (version date: 21-4-2015, access date: 20-7-2015) http://www.gipdatabank.nl/.
16. Ertas FS, Ertas NM, Gulec S, Atmaca Y, Tanju S, Sener C, Erol C. Unrecognized side effect of statin treatment: unilateral blepharoptosis. Ophthal.Plast.Reconstr.Surg. 2006;22(3):222-4.
17. Draeger A, Monastyrskaya K, Mohaupt M, Hoppeler H, Savolainen H, Allemann C, Babiychuk EB. Statin therapy induces ultrastructural damage in skeletal muscle in patients without myalgia. J Pathol. 2006;210(1):94-102.
18. Hargreaves IP, Heales S. Statins and myopathy. Lancet 2002;359(9307):711-2.
19. Phillips PS, Haas RH, Bannykh S, Hathaway S, Gray NL, Kimura BJ, Vladutiu GD, England JD. Statin-associated myopathy with normal creatine kinase levels. Ann.Intern.Med 2002;137(7):581-5.
20. Rudski L, Rabinovitch MA, Danoff D. Systemic immune reactions to HMG-CoA reductase inhibitors. Report of 4 cases and review of the literature. Medicine.(Baltimore.) 1998;77(6):378-83.
21. Stilma. Bijwerkingen van geneesmiddelen in de oogheelkunde. 1993.
22. Elsais A, Lund C, Kerty E. Ptosis, diplopia and statins: an association? Eur J Neurol 2008;15(10):e92-e93
23. Purvin V, Kawasaki A, Smith KH, Kesler A. Statin-associated myasthenia gravis: report of 4 cases and review of the literature. Medicine.(Baltimore.) 2006;85(2):82-5.
24. Kaminski HJ, Li Z, Richmonds C, Ruff RL, Kusner L. Susceptibility of ocular tissues to autoimmune diseases. Ann.N Y.Acad.Sci. 2003;998:362-74.

This signal has been raised on January 2016. 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