1.1. HMG-CoA-reductase inhibitors and tendinitis or tendon rupture

Introduction

HMG-CoA-reductase inhibitors are widely used for *treatment of primary hypercholesterolemia or mixed dyslipidemia* and for *treatment of homozygote familiar hypercholesterolemia* [1-5]. HMG-CoA-reductase inhibitors available in the Netherlands are: atorvastatin (Lipitor®), fluvastatin (Lescol®), pravastatin (Selektine®), rosuvastatin (Crestor®) and simvastatin (Zocor®).
In tendinitis, the normally tightly-packed collagen fibers are in a state of disrepair, with proliferation and chronic irritation of neurovascular repair tissue in the tendon and its linings (paratendon and endotendon) [6]. Tendinitis most commonly occurs as a result of injury. It can also occur as a result of an underlying inflammatory rheumatic disease, such as reactive arthritis or gout. Furthermore, tendinitis has been described as an adverse drug reaction of, for example, fluoroquinolones. Tendon rupture is a condition where the tendon is torn. It may occur without any preceding tendon problems, or it may be a result of tendinitis.
In the SmPCs of most of the forenamed HMG-CoA-reductase inhibitors tendinitis or tendon rupture is not mentioned. Only the SmPC of pravastatin mentions *tendon disorder, sometimes complicated by rupture* in section 4.8 [4]. The SmPC of atorvastatin mentions tendon rupture as a potential adverse drug reaction (ADR) [2].

Reports

Up to January 29, 2010 Lareb received 11 reports from health professionals and consumers in which tendinitis was suspected to be caused by HMG-CoA-reductase inhibitors. For characteristics of these reports see table 1.
Up to January 29, 2010 Lareb received 10 reports from health professionals and consumers in which tendon rupture was suspected to be caused by HMG-CoA-reductase inhibitors. For characteristics of these reports see table 2. Patient J in table 1 is the same person as patient I in table 2.

Table 1. Reports of tendinitis in which a HMG-CoA-reductase inhibitor was the suspect drug

Patient, Number, Sex, Age	Drug, daily dose Indication for use	Concomitant Medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
A 11311 M, 61 – 70 years	simvastatin 1dd 20mg unknown	carbasalate calcium	tendinitis	3 weeks discontinued not reported
B 36798 M, 51 – 60 years	pravastatin 1dd 40mg familiar hypercholesterolaemia	naproxen meloxicam	tendinitis	not reported discontinued not recovered
C 38382 F, 61 – 70 years	simvastatin 1dd 20mg hypercholesterolaemia	budesonide prednisolone* ipratropium diltiazem hydrochlorothiazide sodium chloride/urea cream lisinopril	tendinitis, peripheral oedema	not reported no change not reported
D 38951 M, 51 – 60 years	simvastatin 1dd 20mg	atenolol lisinopril acetylsalicylic acid	tendinitis	3 years no change not recovered
E 39584 F, 51 – 60 years	atorvastatin 10mg hypercholesterolaemia	not reported	tendinitis	week unknown not recovered
F 43569 F, 51 – 60 years	rosuvastatin 1dd 20mg hypercholesterolaemia	fosinopril acenocoumarol bisoprolol	tendinitis, myalgia	1 week discontinued not yet recovered

G 52108 M, 61 – 70 years	simvastatin 1dd 20mg hypercholesterolaemia perindopril 1dd 4mg hypertension	not reported	tendinitis, arthritis	14 days discontinued not recovered
H 60814 F, 61 – 70 years	rosuvastatin 5mg not reported	atorvastatin telmisartan	tendinitis, malaise, dizziness, myalgia, eye disorder	11 days discontinued not recovered
I 64366 M, 51 – 60 years	simvastatin 1dd 20mg hypercholesterolaemia	not reported	tendinitis, bursitis, myalgia	15 months discontinued not yet recovered
J 82397 M, 70 years and older	pravastatin 1dd 40mg	tolbutamide metformin acetylsalicylic acid temazepam	tendinitis, tendon rupture	2 years discontinued unknown
K 91826 M, 61 – 70 years	simvastatin ezetimibe	not reported	tendinitis	not reported discontinued unknown

* also known as a cause of tendinopathy

Table 2. Reports of tendon rupture in which a HMG-CoA-reductase inhibitor was the suspect drug

Patient, Number, Sex, Age	**Drug, daily dose Indication for use**	**Concomitant Medication**	**Suspected adverse drug reaction**	**Time to onset, Action with drug outcome**
A 33374 M, 61 – 70 years	atorvastatin 1dd 40mg hypercholesterolaemia	gliclazide verapamil	tendon rupture	7 weeks discontinued not yet recovered
B 34817 M, 51 – 60 years	pravastatin 1dd 40mg hypercholesterolaemia	ciprofibrate candesartan	tendon rupture myalgia	1 month no change not recovered
C 39491 M, 31 – 40 years	atorvastatin 1dd 60mg hypercholesterolaemia	not reported	increased creatine phospho-kinase tendon rupture myalgia	not reported discontinued not recovered
D 53639 M, 51 – 60 years	atorvastatin 1dd 10mg	not reported	tendon rupture	1 month no change recovered with sequelae
E 54193 M, 61 – 70 years	atorvastatin 1dd 40mg	acenocoumarol allopurinol metoprolol	arthralgia, tendon rupture	2.5 years discontinued recovered
F 55786 M, 61 – 70 years	fluvastatin hypercholesterolaemia diltiazem 2dd 120mg coronary artery disease	quinapril acetylsalicylic acid	tendon rupture	5 years discontinued unknown
G 57406 F, 70 years and older	simvastatin 2dd 20mg	amiloride/ hydrochlorothiazide atenolol acetylsalicylic acid omeprazol diclofenac levothyroxine	tendon rupture	not reported discontinued recovered
H 74878 M, 51 – 60 years	atorvastatin 1dd 40mg hypercholesteraemia	not reported	tendon rupture	10 years discontinued unknown
I 82397 M, 70 years and older	pravastatin 1dd 40mg	tolbutamide metformin acetylsalicylic acid temazepam	tendon rupture, tendinitis	2 years discontinued unknown
J 86755	atorvastatin 1dd 10mg	not reported	tendon rupture	3 months

M, 51 – 60 years	hypercholesteraemia	discontinued recovered with sequelae

Other sources of information

Literature

Tendinitis and tendon rupture in association with HMG-CoA-reductase inhibitor use has been described anecdotally until the retrospective studies of Marie *et al* [7,8]. In this study tendinitis and tendon rupture were observed in 96 patients (median age 56 years old) who were treated with HMG-CoA-reductase inhibitors during the period 1990 through 2005, according to a retrospective analysis of data collected through 31 French Pharmacovigilance Centres. The median time to onset of symptoms was 243 days (range, 0 to 5,659 days); with 59% of the cases appearing in the first year after the HMG-CoA-reductase inhibitor was initiated. All patients were receiving dosages within the standard range. The specific drugs involved were atorvastatin (37% of patients), simvastatin (31% of patients), pravastatin (22%), fluvastatin (5%), and rosuvastatin (5%). Tendinitis was reported in 63 patients, tendinitis followed by tendon rupture occurred in 12, and de novo tendon rupture was reported in 21, with Achilles tendon disorders being the most common (52.1% of cases). HMG-CoA-reductase inhibitor treatment was reinitiated in 7 of the patients, resulting in a 100% recurrence of tendon complications. Predisposing factors included hyperuricemia in 5 patients, sport practice in 15 patients, diabetes in 11, and history of tendinopathy in 11. Regression of symptoms occurred after a median of 23 days following discontinuing the HMG-CoA-reductase inhibitor [7,8].
Clarke and Hill describe a Vigibase search, in which 119 reports of tendon rupture following the use of one or more HMG-CoA-reductase inhibitors were present. They excluded reports describing fluorquinolone use, irrespective its classification as a suspect or a concomitant drug [9].

Databases

On January 29, 2010 the Netherlands Pharmacovigilance Centre Lareb had received 11 reports on tendinitis in association with the HMG-CoA-reductase inhibitors. The reporting odds ratio (ROR) is 1.1 (95% confidence interval [CI] 0.6 – 2.0). The ROR in the WHO database is shown in table 3. Tendinitis in association with pravastatin and rosuvastatin was not present in the WHO database.
The Lareb database contained, at the same date, 10 reports of tendon rupture in association with the HMG-CoA-reductase inhibitors. The reporting odds ratio (ROR) is 4.0 (95% confidence interval [CI] 2.1 – 7.9). The ROR in the WHO database is shown in table 4. Tendon rupture in association with simvastatin was not present in the WHO database.

Table 3. number of reports in the WHO database and ROR of tendinitis in association with the HMG-CoA-reductase inhibitors

Drug	Number of reports	ROR (95% CI)
atorvastatin	72	3.5 (2.8-4.4)
fluvastatin	5	1.3 (0.6-3.2)
simvastatin	64	2.7 (2.1-3.5)

Table 4. number of reports and ROR of tendon rupture in association with the HMG-CoA-reductase inhibitors

Drug	Number of reports	ROR (95% CI)
atorvastatin	43	6.5 (4.8-8.9)

Drug	Number of reports	ROR (95% CI)
fluvastatin	8	7.0 (3.5-14.0)
pravastatin	11	3.9 (2.1-7.0)

On February 3, 2010 the Eudravigilance database contained 143 reports of HMG-CoA-reductase inhibitors associated tendon rupture. Fifteen female and 125 male patients were involved (non-specified sex in three cases). Ages ranged from 32 to 84 years. Four patients used concomitant fluorquinolones. One patient used systemic corticosteroids, two other patients an inhalation corticosteroid. In 48 cases, the reported rupture concerned the Achilles tendon, in ten cases the biceps tendon, in six cases the quadriceps tendon and in one case the patellar tendon. All but two cases were reported as serious. In 36 cases the rupture led to disability, in 63 cases to a hospital admission. In 76 cases seriousness was reported as caused by other non-specified causes. None of the reported reactions was part of a life-threatening event.
In an additional 94 cases tendonitis was reported in association with statin use.

Prescription data

The number of patients using HMG-coA-reductase inhibitors has increased over the years. The number of patients using HMG-coA-reductase inhibitors in the Netherlands is shown in table 5.

Table 5. Number of patients using HMG-coA-reductase inhibitors in the Netherlands between 2004 and 2008 [10]

	2004	2005	2006	2007	2008
simvastatine	418.070	462.830	612.620	648.700	719.280
pravastatine	187.510	176.830	182.680	168.710	169.530
flluvastatine	31.566	29.384	32.018	29.667	28.931
atorvastatine	332.370	382.390	447.310	446.410	464.680
rosuvastatine	104.950	129.030	166.960	184.090	198.540

Mechanism

Theories on the association are based on the associated skeletal muscle toxicity, as *Marie et al.* propose. Firstly, cholesterol is an important component of tendon cell membranes. Lowering the cholesterol level might result in frailty of the membrane. Secondly, reduced levels of regulatory proteins involved in the maintenance of tendon cells may be responsible for tendon injury. Finally, apoptosis produced by HMG-CoA-reductase inhibitors reduces vascular smooth muscle cell proliferation; apoptosis of tendon cells could also lead to tendon damage [6]. This last hypothesis considers HMG-CoA-reductase inhibitors as matrix metalloproteinase (MMP) inhibitors. This has been postulated before by *Pullatt et al*, who speculated that the inhibition of MMP-9 and augmentation of tissue inhibitor of metalloproteinase 1 (TMP-1) in macrophages by HMG-CoA-reductase inhibitors could impair tendon remodelling and contribute to tendinopathy [11]. However, in ruptured Achilles tendon samples MMP-9 levels were increased compared with normal tendons [12].
In conclusion, although some possible mechanisms have been proposed, the mechanism by which HMG-CoA-reductase inhibitors cause tendinitis or tendon rupture remains to be elucidated.

Discussion

Tendinitis and tendon rupture are recognized adverse reactions of HMG-CoA-reductase inhibitors. The SmPC of pravastatin and atorvastatin partly mention these effects. A shortcoming is that in a majority of the reactions reported to Lareb the reaction outcome was unknown or ‘not recovered’. It means that at the moment of reporting the tendinitis or tendon rupture had not recovered. Follow-up information was not received.

The time to onset varies between the reports from several weeks to years. Additional factors may be needed to elicit the ADR like exercise. In the reports it was not explicitly mentioned that the tendon ruptures were caused by sports injuries.
The number of reports in the WHO database is strikingly low considering the reports to Lareb and the French pharmacovigilance centres, which all send their reports to the WHO database.
Although concomitant factors like diabetes and (sports) exercise theoretically could have influenced the height of the Reporting Odds Ratio, unfortunately these data were not available in the database of the WHO.

Conclusion

Lareb received 11 reports of tendinitis and 10 reports of tendon rupture in association with HMG-CoA-reductase inhibitors. These associations are described in literature as well. This is supported by reports in the Lareb and the WHO databases, in which the associations are disproportionally present for most HMG-CoA-reductase inhibitors. Because of the clinical relevance and the large number of precriptions of statins, it should be considered to mention tendinitis and tendon rupture in all SmPCs of the HMG-CoA-reductase inhibitors.

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References

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This signal has been raised on June 2010. It is possible that in the meantime other information became available. For the latest information please refer to the website of the MEB www.cbgmeb.nl/cbg/en/default.htm or the responsible marketing authorization holder(s).