HMG-CoA-reductase inhibitors and interstitial lung disease / pulmonary fibrosis – an update

Introduction

HMG-CoA-reductase inhibitors are widely used for the treatment of hypercholesterolemia and prevention of related disorders, such as atherosclerosis and coronary artery disease. The HMG-CoA-reductase inhibitors available in the Netherlands are: atorvastatin, fluvastatin, pravastatin, rosuvastatin and simvastatin. The Summaries of Product Characteristics (SmPCs) of all these products do not mention respiratory adverse reactions, some do mention hypersensitivity reactions but without any pulmonary localization; the SmPC of simvastatin mentions hypersensitivity with dyspnea, amongst other symptoms. [1]
In a previous quarterly report we discussed six reports of hypersensitivity pulmonary reactions associated with the use of HMG-CoA-reductase inhibitors (five pulmonary fibrosis, one pleural effusion). [2] Because since then additional well documented specialist reports were received, an update on the association between the use of HMG-CoA-reductase inhibitors and pulmonary fibrosis is given.

Reports

On May 21, 2008, the Netherlands Pharmacovigilance Centre Lareb contained eight reports on “pulmonary fibrosis” or “interstitial lung disease” in association with the use of HMG-CoA-reductase inhibitors (Table 1). An additional four reports were received on possibly pathophysiologically related disorders (Table 2). Some reporters actually mentioned their concern of a role for HMG-CoA-reductase inhibitors.

Table 1. Reports of pulmonary fibrosis or interstitial lung disease associated with the use of HMG-CoA-reductase inhibitors.

Patient, Sex, age	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, action with drug, outcome
A F, 78 27722#	atorvastatin 10 mg od* hypercholesterolemia	-	pulmonary fibrosis	20 months; dose not changed; not recovered
B F, 69 36867#	atorvastatin 40 mg od* unknown	propafenon rofecoxib verapamil	lung fibrosis interstitial	8 months; withdrawn 11 months after diagnosis; outcome unknown
C M, 67 43187#	simvastatin 20 mg od unknown	enalapril colchicine carb.-calcium dipyridamol	interstitial lung disease	1 month; withdrawn 6 months after reaction startdate; recovery after 11 months
D M, 76 47606#	simvastatin 20 mg od hypercholesterolemia	paroxetine omeprazol	pulmonary fibrosis dermatomyositis	2.5 years; withdrawn 7 weeks after diagnosis; immunosuppressive treatment; fatal

Patient, Sex, age	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, action with drug, outcome
E M, 58 55896	rosuvastatin 10 mg od hypercholesterolemia	-	severe interstitial pneumonitis lung fibrosis	18 months; immediately withdrawn; immunosuppressive therapy, mechanical ventilation; possibly fatal
F M, 74 56428	pravastatin 40 mg od angina pectoris unstable	acetylsal.acid metoprolol amlodipin amoxicillin/clavulanic acid ferrofumarate paracetamol	interstitial lung disease	3 months; withdrawn after 3 months; immunosuppressive therapy; recovering
G M, 71 64948 65143	atorvastatin 10 mg od prevention	metformin	pulmonary fibrosis	6 months; immediately withdrawn; recovering; life expectancy 3 years
H M, 64 73687	simvastatin 20 mg od	acetylsal.acid amlodipin	pulmonary fibrosis	18 months; not withdrawn; not recovered

reports previously discussed in quarterly report 2005-2.
*patient used other HMG-CoA-reductase inhibitor prior to the mentioned suspected drug.

Table 2. Additional reports of other interstitial pulmonary disorders associated with the use of HMG-CoA-reductase inhibitors.

Patient, Sex, age	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, action with drug, outcome
I M, 59 42314#	simvastatin 5 mg od	-	pleuritis	unknown; withdrawn, recovered with adhesions
J M, 68 60519	simvastatin 20 mg od perindopril 4 mg od metoprolol 50 mg od	-	pleuritis fibrinous	1-2 years; only simvastatin withdrawn; immunosuppressive therapy; recovering
K M, 70 65863	pravastatin 20 mg bd	sotalol flecainide carb.-calcium	BOOP (bronchiolitis obliterans with organizing pneumonia)	1-2 years; immunosuppressive therapy; recovering
L M, 77 67028	rosuvastatine 10 mg od	meformin insulin carb.-calcium metoprolol HCl-thiazide eprosartan	DAD (diffuse alveolar damage)	1 week; immunosuppressive therapy; fatal

reports previously discussed in quarterly report 2005-2.

Of the eight reports on pulmonary fibrosis, two were reported by a general practitioner (A, F) and one was received from the MAH (B); additional clinical information in patient A and B revealed that there was a firm diagnosis by a pulmonologist. Patient F was a farmer and bronchiolitis obliterans with organizing pneumonia (BOOP) was considered in the differential diagnosis.
One report (C) was reported by an internist, there was also eosinophilia, and positive auto-immune serology. A consultant rheumatologist did not find any connective tissue disease or vasculitis, although the possibility of sarcoidosis was raised. The patient recovered after withdrawal of simvastatin in months, information on additional treatment is not available. Patient E was reported by an intensivist: this concerned a man with a medical history of recent blunt thoracic trauma. He did not recover after withdrawal. The other three reports (D, G, H) were reported by pulmonologists.
Two reports (D, H) were reported by the same pulmonologist, who also reported three cases of possibly related disorders mentioned in Table 2 (I, J, K).
Diagnosis confirmation by CT-scan or HRCT-scan was reported in three cases (A, C, F). Histological confirmation was reported in two cases (G, H); confirmation by both CT and histology was reported in one case (D). Only two reports do not mention diagnostic procedures.
Latency varied from one month to 2.5 years or more, in some reports earlier use of a HMG-CoA-reductase inhibitor was mentioned. In patient H, already mild abnormalities were seen on pulmonary X-ray before start of simvastatin.
Of the eight reports, drug withdrawal was mentioned in six, but sometimes after a delay. Partial recovery was reported in only four cases, but this is consistent with the nature of this disease.
Since the reports from Table 2 are only possibly related, they are not extensively discussed here.

Other sources of information

Literature

Only three case-reports and one series of case-reports have been published on the association between HMG-CoA reductase inhibitors and pulmonary fibrosis.
In 1996, De Groot et al. described a male aged 61, who presented with non-productive cough, dyspnea and fatigue. He had used simvastatin for five months. Chest X-ray showed interstitial lung disease and pleural effusion. A bronchoalveolar lavage showed eosinophilia, a biopsy was non-conclusive. Drug-induced interstitial lung disease was suspected with simvastatin as most plausible cause. A few days after simvastatin discontinuation clinical improvement was seen and the eosinophilia in the BAL-fluid returned to normal. Further clinical improvement was only seen after prednisone treatment (40 mg od), with major improvement of previous restrictive lung function test abnormalities. The patient eventually died from another cause. [3]
Lantejoul et al. described a male aged 51, with type-2 diabetes mellitus and a history of myocardial infarction. He had been on a regimen of glibenclamide 10 mg/day, betaxolol 20 mg/day, and simvastatin 5 mg/day for six years. He presented with fever, polymyalgia, cough and dyspnea. Imaging of the chest showed diffuse, bilateral interstitial infiltrates and ground-glass opacities. Drug-induced pneumonitis was suspected, betaxolol and simvastatin were withdrawn,

and corticosteroid therapy was initiated. Fibrotic nonspecific interstitial pneumonia was diagnosed. Corticosteroid therapy over six months brought slow improvement. Inadvertently, pravastatin was started in this patient. Dyspnea, myalgia, and new infiltrates on chest radiography appeared. Pravastatin was rapidly stopped. Progressing clinical improvement was observed. [4]
Kalomenidis et al. described a male aged 60, who presented with bilateral pleural effusions following approximately one year of treatment with pravastatin 40 mg/day. The patient had no history of allergy or any deleterious exposure to the respiratory tract. His symptoms of several day's duration included persistent bilateral pleuritic chest pain and mild dyspnea, but no systemic symptoms or extrathoracic abnormalities. Small bilateral pleural effusions were seen on radiography and a CT scan elucidated effusions and bilateral pleural thickening. Biopsy showed fibrotic and nonspecific inflammatory changes of the thickened pleura. Approximately one month after presentation, when pleural effusions persisted, pravastatin was discontinued. Three months later the patient had resolution of signs and symptoms, with some residual pleural thickening. Six months later the patient was still asymptomatic with no re-accumulation of the pleural effusion. [5]
Walker et al. described seven patients seen in their clinic over a three year period, who were taking HMG-CoA-reductase inhibitors and who presented with interstitial pneumonitis. Clinical course varied, with the condition responding to prednisolone treatment and cessation of statins in three patients, and progressing slowly despite this management in another three, while one patient died of associated cardiac disease. Unfortunately, latency periods are not described. [6]

Databases

Reports of all HMG-CoA-reductase inhibitors available in the Netherlands except fluvastatin were associated with pulmonary fibrosis. This could be due to the limited use of fluvastatin, as is shown in Table 3. [7]
A search in the WHO database on May 26, 2008 resulted in a limited number of reports on pulmonary fibrosis: 19 associated with atorvastatin, 12 with pravastatin, one with rosuvastatin and 27 with simvastatin. Furthermore, fibrosing alveolitis was reported twice in association with fluvastatin. No disproportionality was found.
On June 8, 2008, the Eudravigilance database contained 218 reports of the five statins marketed in the Netherlands, associated with pulmonary fibrosis, acute interstitial pneumonitis or interstitial lung diseases. Patients were predominantly male, 140 male, 63 female, not specified in 15 cases. Most patients were in their sixties and seventies, only twenty were younger than sixty years, the youngest patient affected by a pulmonary interstitial disease was a 40 year old male.

Table 3. Number of users of HMG-CoA-reductase inhibitors in the Netherlands 2003-2007.

Generic name	2003	2004	2005	2006	2007
simvastatin	387,700	418,070	462,830	622,230	659,190
pravastatin	181,860	187,510	176,830	185,980	169,450
fluvastatin	32,804	31,566	29,384	32,170	29,364
atorvastatin	269,280	332,370	382,390	456,790	446,650
rosuvastatin	54,914	104,950	129,030	168,230	182,480

Mechanism

Pulmonary fibrosis is a type of interstitial lung disease that presents in mainly elderly patients (over 60 years) with progressive dyspnea, non-productive cough and fatigue. Lung function testing shows a restrictive pattern with abnormal diffusion. A high-resolution (HR)CT or lung biopsy is frequently needed for a firm diagnosis. Many times the cause is unknown, therefore the term idiopathic interstitial pneumonia is used, with five subgroups based on clinical presentation and histological findings, of which Usual Interstitial Pneumonia (UIP) is the most common. In idiopathic pulmonary fibrosis the outcome depends on the histological subgroup, treatment with immunosuppressive therapy is not always effective and fatal outcome is frequent; five-year survival for UIP is as bad as 20-55%. [8]
Pathophysiologically in UIP there seems to be a disturbance in the normal re-epithelialization of the alveoli after damage caused by viral infection, chemotherapy, inhalation of toxic agents or vascular collagen disease. An auto-immune mechanism is suspected. Treatment consists of immunosuppression and supportive therapy, although prevention of over-excessive epithelial recovery could be more adequate and effective. [9]
In the available case reports on HMG-CoA-reductase inhibitors induced pulmonary fibrosis, no information on a possible mechanism was found, although multiple immunomodulatory, vascular endothelial, anti-oxidant and other effects of statins are mentioned, that might play a role. [6]

Discussion

Although idiopathic pulmonary fibrosis is a diagnosis per exclusionem and often no causative mechanism can be proven, a pathophysiological role for HMG-CoA-reductase inhibitors is suspected. This is supported by several case reports in literature. Due to the nature of the disease, information on de- and rechallenge is of limited value, since progression to fatality is seen despite intervention in many cases and, apart from dechallenge, immunosuppressive therapy was started in most patients.

Conclusion

Since the presentation in a previous quarterly report on hypersensitivity pulmonary disorders in 2005, several well documented new reports of pulmonary fibrosis in association with HMG-CoA-reductase inhibitors were reported to Lareb. Although a firm causal relationship is difficult to prove in this specific illness, enough concern was raised to give an update and to appeal for additional research on this specific association.

References

1. Dutch SmPCs of HMG-CoA reductase inhibitors (access date: 2008-03-26) http://db.cbg-meb.nl/IB-teksten.
2. HMG-CoA-reductase inhibitors and hypersensitivity pulmonary reactions. Quarterly Report Netherlands Pharmacovigilance Centre Lareb 2005-2.
3. De Groot RE, Willems LN, Dijkman JH. Interstitial lung disease with pleural effusion caused by simvastin. J Intern Med 1996;239(4):361-3.
4. Lantejoul S, Brambilla E, Brambilla C, Devouassoux G. Statin-induced fibrotic nonspecific interstitial pneumonia. Eur Respir J 2002;19:577-80.
5. Kalomenidis I, Papiris S, Loukides S. Bilateral pleural effusions associated with pravastatin sodium treatment. Eur Respir J 2007;30(5):1022
6. Walker T, McCaffery J, Steinfort C. Potential link between HMG-CoA reductase inhibitor (statin) use and interstitial lung disease. Med J Aust 2007;186(2):91-4.

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7. GIP/College voor zorgverzekeringen (access data 2008-07-11) www.gipdatabank.nl.
8. Collard HR, King TE, Jr. Demystifying idiopathic interstitial pneumonia. Arch Intern Med 2003;163(1):17-29.
9. Lambrecht BN, Groot H. Immunopathogenese van longfibrose. Nederlands Tijdschrift voor Allergie 2008;8(1):17-22.

This signal has been raised on July 2008. It is possible that in the meantime other information became available. For the latest information please refer to the website of the MEB www.cbg-meb.nl/cbg/en/default.htm or the responsible marketing authorization holder(s).