

# PULMONARY FIBROSIS REPORTED WITH STATINS

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## Objective

To assess spontaneously reported cases of PULMONARY FIBROSIS as a possible adverse reaction to HMG-CoA reductase inhibitors, statins.

## Method

The WHO ADR database, Vigibase, is a global source of over 3.7 million suspected spontaneous reports from 81 countries. A clinical review of case reports on the statins and the preferred term (WHO Adverse Reaction Terminology) 'pulmonary fibrosis' in Vigibase was performed. The case reports are heterogeneous regarding source, documentation and relationship likelihood.

## Results

Vigibase contains 59 reports (see table 1) on the preferred term PULMONARY FIBROSIS (total number: 3742) for different statins, reported from nine countries.

Table 1. Cases of pulmonary fibrosis reported with statins in Vigibase.

Drug	Total No. reports - any ADR	Total No. reports - of combination	No. of reporting countries	Fatal outcome
ATORVASTATIN	19464	12	6	1
CERIVASTATIN	14031	4	3	0
LOVASTATIN	12906	9	2	0
PRAVASTATIN	8459	12	4	0
ROSUVASTATIN	5270	2	2	0
SIMVASTATIN	22790	23	6	2
Total		59	9	3

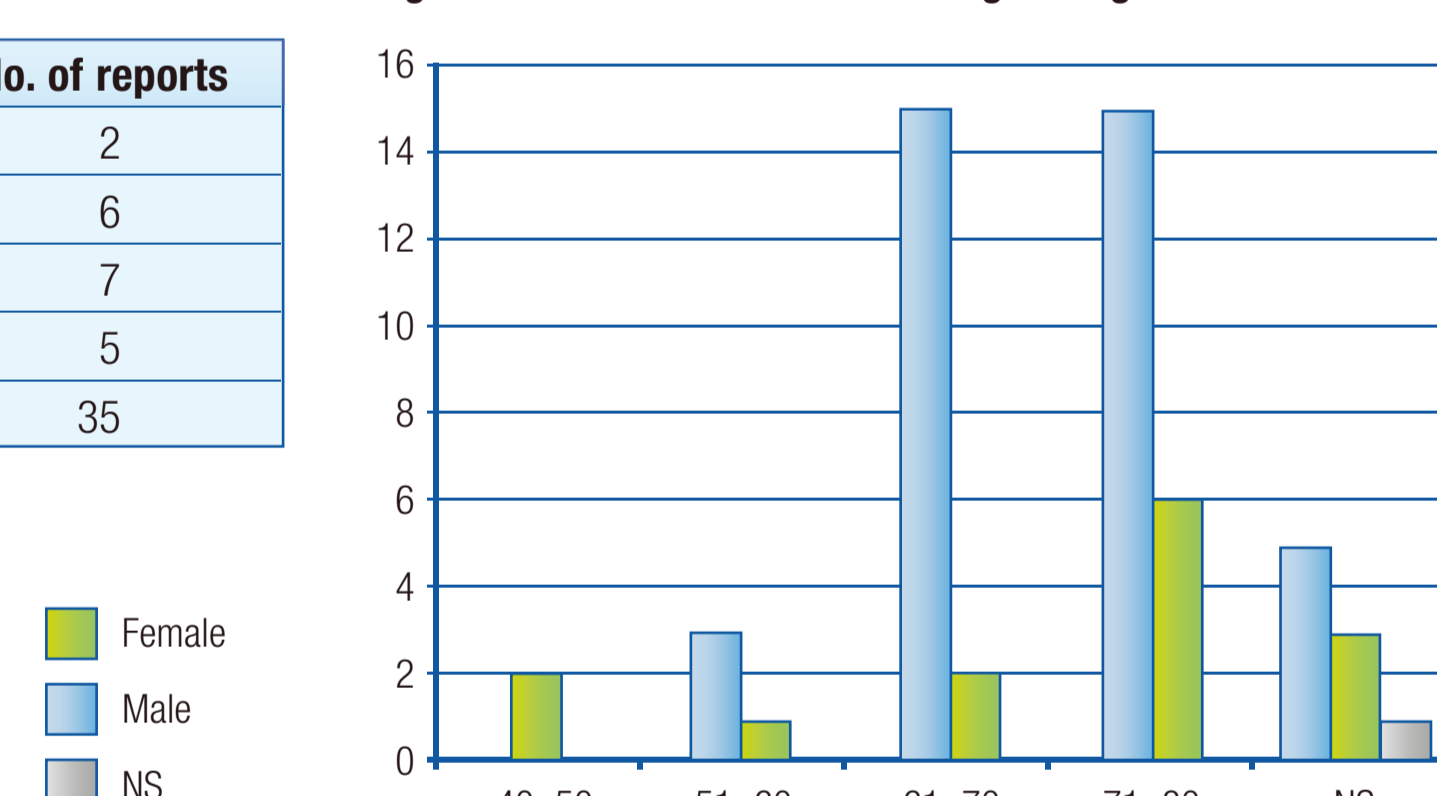
Four of the reports (two cases each of cerivastatin and simvastatin) were removed from this assessment due to suspicion of duplication. In the 55 reports assessed, the time to onset was inconclusive or not stated in the majority of the reports (see table 2). Patient demographics can be seen in figure 1.

Dosage (stated in 26 cases) was in normal ranges. Among the patients with known outcome, three patients died, two patients recovered, five patients recovered with sequelae and eighteen patients had not recovered at the time of reporting. The causality in six cases was assessed as 'Possible' by the National Centres. One case was assessed as 'Unlikely'.

Table 2. Time to onset.

Time to onset	No. of reports
6-10 days	2
1-4 months	6
10-16 months	7
2-6 years	5
Not stated or inconclusive	35

Figure 1. Patient distribution over age and gender.



## Co-reported Drugs

### Co-suspected

Co-suspected drugs were present in 19 reports, including some drugs that may have respiratory side effects such as pioglitazone, bosentan, bisoprolol (3), carbamazepine, moxifloxacin, nabumetone and mycophenolic acid.

Other drugs reported as co-suspected included clopidogrel (3), acetylsalicylic acid (2), diltiazem (2) and single occurrences of e.g. allopurinol, atenolol, colestyramine, fluoxetine, gatifloxacin, mercaptopurine, phenobarbital and Prunus Africana.

### Concomitant

Co-reported drugs reported as concomitant on three or more reports included e.g. acetylsalicylic acid (14), allopurinol (3), betablockers (8), azathioprine (3), diltiazem (5), furosemide (9), glyceryl trinitrate (5) and proton pump inhibitors (6).

## Case reports

One case related to each statin is presented below:

### Simvastatin

*The patient, a 67-year-old male, with hypertension, paroxysmal fibrillation and hyperuricaemia, had been a smoker for 38 years, but stopped in 1992. He was treated with simvastatin for hypercholesterolaemia since August 2003. During 2004 he experienced increased mucus formation and coughing, and since middle of July 2004, bloody expectorations and bloody mucus almost every day. The pathological anatomical diagnostic investigation of the tissue showed an atypical pulmonary fibrosis. Concomitant drugs included losartan, warfarin, allopurinol and sotalol, but the reporting physician strongly suspected a drug induced pulmonary fibrosis related to simvastatin. Causality was assessed as 'possible'.*

### Atorvastatin

*A male patient of 65 years of age, with asthenia and angina pectoris, developed pulmonary fibrosis after taking atorvastatin 20 mg daily for 10 months. The report was considered serious and determined to be unexpected. The physician indicated that the patient, who had no previous pulmonary problems, acutely developed respiratory insufficiency due to massive pulmonary fibrosis. Cultures from bronchial fluid and hemocultures were negative for bacteria, fungi or parasites. Concomitant medications included molsidomine, atenolol and acetylsalicylic acid. The patient died. The causality was recorded as 'possible'.*

### Lovastatin

*A 60-year-old female was diagnosed with pulmonary fibrosis after therapy of 20 mg of lovastatin per day for 30 days for pure hypercholesterolaemia. Colestyramine was reported as a concomitant medication. She had not yet recovered at the time of reporting. The causality was assessed as 'possible'.*

### Pravastatin

*A male (age not provided) developed pulmonary fibrosis while taking pravastatin (onset date of the event was not reported). Duration of therapy was "a few years". The physician stated that the patient had no family history of pulmonary fibrosis and did not smoke. Concomitant medications included acetylsalicylic acid and metoprolol. The patient was treated with cyclophosphamide and steroids, but the fibrosis did not improve and the pravastatin therapy was stopped. Prior to the event, the patient was in good health. The patient has now recovered with sequelae since he has to use a wheelchair.*

### Rosuvastatin

*A 58-year-old male developed interstitial lung fibrosis and pneumonitis after receiving 10 mg of rosuvastatin for over one year. The physician reported that the patient had not recovered at the time of the reporting.*

### Cerivastatin

*A 72-year-old male had recovered with sequelae from pulmonary fibrosis after use of cerivastatin. Co-suspected drugs were carbamazepine, colestyramine, Prunus Africana and a combination product containing phenobarbital, caffeine and atropa belladonna extract.*

## Co-reported Terms

Table 3. A selection of reported terms.

System Organ Class	Frequency (No. of reports)	Reported term
Pulmonary	29 out of 55 reports	Pulmonary fibrosis as the only reported term
Pulmonary	4	Pneumonia
Pulmonary	2	Bronchitis, Atelectasis (i.e. collapsed or airless condition of the lung)
Pulmonary	1	Pulmonary oedema, Chronic obstructive airways disease, Apnoea, Bronchospasm, Pleurisy, Pneumonitis, Pulmonary oedema, Respiratory disease, Respiratory failure
Autoimmune	2	Antinuclear factor test positive, LE syndrome
Musculoskeletal system	1-2	Collagenosis/dermatomyositis (2), Myopathy, Peripheral neuropathy, Arthritis, Arthralgia
Cardiovascular system	1-2	Cardiomegaly, ECG abnormal (2), Pulmonary hypertension, Vascular disorder, Atherosclerosis, Cerebral infarction, Myocardial infarction
Haematology	1-2	Pancytopenia, Anaemia (2), Microcytic anaemia, Monocytosis

## Discussion

Chronic diffuse infiltrative lung disease affects approximately 70 per 100,000 in the population, and post-inflammatory pulmonary fibrosis and idiopathic pulmonary fibrosis (IPF) are the most common diagnoses.<sup>1,2</sup> Approximately 3% of infiltrative lung disease is considered drug-induced, but few drugs, e.g. busulfan and bromocriptine, are established major causes of pulmonary fibrosis.<sup>3,4,5</sup>

Pulmonary ADRs are not listed in the European SPCs, but lupus erythematosus-like and hypersensitivity syndromes, with features like angioedema, polymyalgia rheumatica, dermatomyositis, vasculitis, arthritis, fever and dyspnoea, have rarely been reported post marketing for most of the statins.<sup>5,6</sup> Cough, dyspnoea, pneumonia and upper respiratory infections have been reported for some of the statins listed in Physicians Desk Reference.<sup>7</sup>

Some statins are suggested to have immuno-modulatory and anti-fibrogenic properties<sup>8,9</sup>, one case report was however published in 2002 describing a statin-induced fibrotic non-specific interstitial pneumonia with recurrence of the reaction after rechallenge with the drug.<sup>10</sup>

New reports have been entered into Vigibase since this topic was signaled<sup>11</sup> in May 2005. These reports, although the connection is uncertain in individual cases, raise a suspicion that needs further monitoring and investigation. This would need a compatible clinico-pathologic picture and eliminating other causes of diffuse disease, e.g. asbestos, chemotherapy or collagen vascular disorders. In some of the cases, the co-reported drugs might be alternative or additional factors, and since most HMG-CoA reductase inhibitors are metabolised by cytochrome P450 3A4, interactions might be of importance.

## Conclusion

A number of cases of pulmonary fibrosis associated with statin use have been reported to the WHO international pharmacovigilance system. In order to verify if this is a very rare but true drug safety problem for the statins, further investigations are needed.

## References

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