

## **HMG-CoA-reductase inhibitors and hypersensitivity pulmonary reactions**

### **Introduction**

HMG-CoA reductase inhibitors are widely used for the treatment of hypercholesterolemia and prevention of related disorders, such as atherosclerosis and coronary heart disease. Their efficacy in several other disorders, for example Alzheimer's disease, is being investigated. The Summary of Product Characteristics of the HMG-CoA reductase inhibitors describes a hypersensitivity syndrome with several manifestations, such as angioneurotic oedema, lupus-like syndrome, polymyalgia rheumatica, dermatomyositis, vasculitis, thrombocytopenia, eosinophilia, fever, hepatitis, dyspnoea and urticaria [1-5]. However, pulmonary or pleural involvement is not mentioned.

### **Reports**

The Netherlands Pharmacovigilance Centre Lareb received six reports of pulmonary reactions associated with the use of HMG-CoA reductase inhibitors. Five reports mention pulmonary fibrosis, one report pleural effusion. Two patients had been using other statins in the past.

### **Other sources of information**

#### *Literature*

Hypersensitivity pulmonary reactions are known adverse reactions of HMG-CoA reductase inhibitors. A Medline search revealed several case reports of hypersensitivity pulmonary reactions associated with the use of HMG-CoA reductase inhibitors [6-9].

#### *Databases*

The database of the Uppsala Monitoring Centre (WHO) contains 42 reports of pulmonary infiltration, 57 reports of pleural effusion and 17 reports of pneumonitis associated with the use of HMG-CoA reductase inhibitors. However, with the exception of the association of pulmonary infiltration associated with the use of simvastatin (ROR 1.45; 95% CI 1.0-2.2), none of these associations were disproportionately present in the database of the Uppsala Monitoring Centre (WHO).

#### *Mechanism*

Hypersensitivity pulmonary reactions are immunologically mediated, which is supported by the slight eosinophilia in one patient. Histological analysis shows a classical, patchy distribution of the alveolitis with an early granuloma formation, and a diffuse fibrosis of the alveolar wall [9].

#### *Prescription data*

Total number of prescriptions of HMG-CoA reductase inhibitors are shown in table 2.

Table 2. Total number of prescriptions of HMG-CoA reductase inhibitors per year since 1999 (Source: GIP College voor Zorgverzekeringen, Diemen).

	1999	2000	2001	2002	2003
C10AA01 Simvastatine	1.301.000	1.359.000	1.415.000	1.499.000	1.581.000
C10AA03 Pravastatine	292.000	354.000	486.000	632.000	725.000
C10AA04 Fluvastatine	140.000	129.000	127.000	134.000	137.000
C10AA05 Atorvastatine	511.000	648.000	798.000	934.000	1.102.000
C10AA06 Cerivastatine	31.000	42.500	49.100	.	.
C10AA07 Rosuvastatine	.	.	.	.	176.000
<b>Totaal</b>	<b>2.275.000</b>	<b>2.532.500</b>	<b>2.875.100</b>	<b>3.199.000</b>	<b>3.721.000</b>

### Conclusion

Six cases of potential hypersensitivity pulmonary reactions during the use of HMG-CoA reductase inhibitors are reported to the Netherlands Pharmacovigilance Centre Lareb. The presence of eosinophilia in one patient and the recovery of three patients after discontinuation of the used HMG-CoA reductase inhibitor support a causal relationship. Despite of lacking disproportionality, the number of reports in the database of the Uppsala Monitoring Centre (WHO) and several case reports described in literature contribute to the strength of the association. Hypersensitivity pulmonary reactions should be mentioned in the SPC's of HMG-CoA reductase inhibitors.

### References

1. Dutch SPC Zocor<sup>®</sup>. (version date 9-9-2004) <http://www.cbg-meb.nl/IB-teksten/13192-13193-13194-13195-23457.PDF>.
2. Dutch SPC Lescol<sup>®</sup>. (version date 16-2-2004) <http://www.cbg-meb.nl/IB-teksten/18719-18720.PDF>.
3. Dutch SPC Selektine<sup>®</sup>. (version date 24-9-2004) <http://www.cbg-meb.nl/IB-teksten/13755-13756-20665.PDF>.
4. Dutch SPC Lipitor<sup>®</sup>. (version date 26-9-2003) <http://www.cbg-meb.nl/IB-teksten/21081.PDF>.
5. Dutch SPC Crestor<sup>®</sup>. (version date 20-7-2004) <http://www.cbg-meb.nl/IB-teksten/26872-26873-26874-30823.pdf>.
6. Liebhaber MI, Wright RS, Gelberg HJ, Dyer Z, Kupperman JL. Polymyalgia, hypersensitivity pneumonitis and other reactions in patients receiving HMG-CoA reductase inhibitors. *Chest* 1999;115:886-9.
7. De Groot REB, Willem LNA, Dijkman JH. Interstitial lung disease with pleural effusion caused by simvastatin. *J Intern Med* 1999;239:361-3.
8. Hill C, Zeitz C, Kirkham B. Dermatomyositis with lung involvement in a patient treated with simvastatin. *Aust NZ J Med* 1995;25:745-6.
9. Lantuejoul S, Brambilla E, Brambilla C, Devouassoux G. Statin-induced fibrotic non-specific interstitial pneumonia. *Eur Respir J* 2002;19:577-580.