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Atorvastatin
A Safety and Tolerability Profile

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Abstract

Extensive data are available on the safety of atorvastatin from randomised clinical trials, postmarketing analyses and reports to regulatory agencies. Atorvastatin is generally well tolerated across the range of therapeutic dosages, with the exception of a slightly higher rate of liver enzyme elevations with atorvastatin 80 mg/day which does not appear to confer an increased risk of clinically important adverse events. Unlike simvastatin, atorvastatin is associated with a low incidence of muscular toxicity. It is not associated with neurological, cognitive or renal adverse effects and does not require dosage adjustment in patients with renal dysfunction, due to its favourable pharmacokinetic profile, which is unique among the statins. In patients aged ≥65 years, atorvastatin is well tolerated with no dose-dependent increase in adverse events up to the maximum daily dosage of 80 mg/day. Thus, atorvastatin is a safe and well tolerated statin for use in a wide range of patients.

The 3-hydroxy-3-methylglutaryl coenzyme-A (HMG-CoA) reductase inhibitors, or statins, have been the mainstay of lipid-lowering therapy for 20 years because of their well established efficacy for a reduction in coronary artery disease (CAD) morbidity and mortality in various at-risk populations. Historically, statin therapy was associated with rare occurrences of serious adverse events.[1] However, the withdrawal of cerivastatin from the market in 2001 because of reports of fatal rhabdomyolysis led to an increased focus on the safety and tolerability of all statins in terms of muscular effects, particularly with regard to high-dose statin therapy such as that used for aggressive lipid lowering.[2,3] Although muscular toxicity is a class effect pertaining to all the statins,[4] it is rare and the degree of risk varies between different agents. Distinction must be made between various agents regarding specific safety issues.

Atorvastatin is one of the most widely used statins worldwide. There are a wealth of data available on the tolerability of atorvastatin: over 400 randomised clinical trials have been conducted to evaluate the efficacy and safety of this agent.[5] It is also important to consider the use of the agent in daily clinical practice when evaluating the tolerability profile of a drug and, consequently, data from postmarketing analyses and reports to regulatory agencies are also valuable sources of safety information.

This article reviews the safety and tolerability profile of atorvastatin at therapeutic dosages of up to 80 mg/day based on data from large postmarketing analyses and meta-analyses of randomised clinical studies. The comparative tolerability of atorvastatin versus other statins and the safety of the use of this agent in specific patient populations, such as the elderly, are discussed.

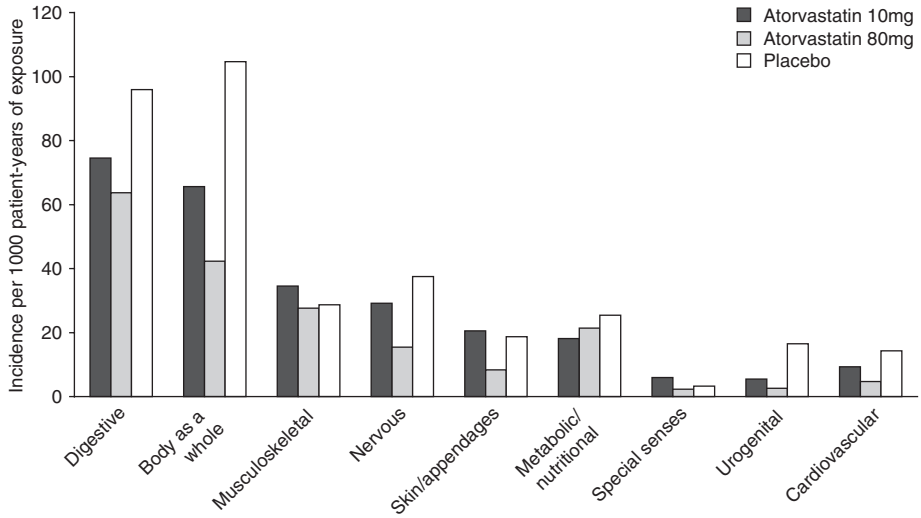

Fig. 1. Incidence of treatment-related adverse events by body system. Data are from a pooled analysis of results from 49 placebo-controlled clinical trials in a total of 14 236 patients treated with atorvastatin 10mg (n = 7258), atorvastatin 80mg (n = 4798) or placebo (n = 2180) for up to 1 year.[7]

1. Atorvastatin Tolerability Profile: Overview

Data from a meta-analysis of 44 clinical studies conducted in >9000 patients receiving atorvastatin demonstrated that the incidence of adverse events is not dose-dependent with the atorvastatin 10–80 mg/day range.[6] Myalgia is the most commonly occurring treatment-related adverse event, occurring in 1.3%, 1.7%, 2.7% and 1.3% of patients receiving atorvastatin 10, 20, 40 and 80 mg/day, respectively; the incidence of myalgia with placebo was 0.8%.[6] The lack of dose-dependent tolerability was confirmed in a recent meta-analysis of 49 studies involving >14 000 patients treated with atorvastatin 10 or 80 mg/day.[7] As shown in figure 1, the overall adverse event profiles were similar with both dosages of atorvastatin and placebo.[7]

In a real-world setting, atorvastatin has shown excellent safety compared with 'usual care'.[8,9] No increases in adverse effects occurred with atorvastatin versus 'usual care' in the GREACE (GREek Atorvastatin and Coronary heart disease Evaluation) study[8] or ALLIANCE (Aggressive Lipid-Lowering Initiation Abates New Cardiac Events) study.[9] Similarly, atorvastatin is generally well tolerated compared with other statins;[10,11] analysis of adverse event reports (AERs) and serious AERs made to the US FDA for each statin between 1999 and March 2005 show that atorvastatin is at least as well tolerated as simvastatin, pravastatin, lovastatin or the combination of lovastatin plus extended-release niacin.[10]

2. Musculoskeletal Effects

A report by the FDA in 2002 summarising the incidence of fatal rhabdomyolysis associated with various statins highlighted the existence of a class effect on muscular toxicity, with varying risk with the individual agent.[2] The rate of fatal rhabdomyolysis with atorvastatin was approximately one-quarter of that reported for all statins (0.04 vs 0.15 cases per million prescriptions), and was among the lowest in the statin drug class (figure 2).[2] Another survey, which complied with the FDA adverse event reporting system, and which reported the rates of fatal rhabdomyolysis with statin monotherapy or statin plus gemfibrozil combination therapy since mid-2001, documented the following rates per 100 000 prescriptions: all statins <1; atorvastatin 0.03; fluvastatin ≈0.0; lovastatin 0.18; and cerivastatin 4.29.[12] The rate of rhabdomyolysis AERs re-

ported to the FDA between 1999 and March 2005 per million statin prescriptions was 2.3 with atorvastatin; corresponding rates with lovastatin, pravastatin and simvastatin were 2.9, 2.1 and 7.8, respectively (figure 3).[10]

Unlike simvastatin, which is associated with an increased incidence of myopathy at a high dose (80 mg/day),[13] atorvastatin does not appear to confer a dose-dependent risk of rhabdomyolysis.[7] Notably, there were no cases of myopathy or rhabdomyolysis among 2100 acute coronary syndrome patients who received atorvastatin 80 mg/day for 2 years in the PROVE-IT TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22) study.[14]

Various risk factors increase the likelihood of developing myopathy or rhabdomyolysis, including advanced age (see section 6),[15] small body frame, alcohol abuse, and the presence of other systemic diseases.[16] Risk is also enhanced with the use of combination statin-fibrate therapy[12] and the concomitant use of agents that inhibit the cytochrome (CYP) 3A4 enzyme, thereby blocking the oxidative metabolism of atorvastatin (and also lovastatin and simvastatin) and increasing drug plasma concentrations.[17] The risk of serious myopathy and rhabdomyolysis can be minimised or prevented with consideration of these factors.

Consideration must also be given to the risk of severe or life-threatening rhabdomyolysis with statin therapy in light of the treatment benefits.[18] The risk of mortality associated with rhabdomyolysis in patients receiving atorvastatin, fluvastatin, lovastatin, pravastatin or simvastatin was 0.3 per 100 000 person-years, according to a review of data from cohort studies, randomised trials, published case reports and voluntary notifications to voluntary regulatory authorities.[17] The US National Lipid Association (NLA) Muscle Safety Expert Panel concluded in 2005 that, on the basis of the available evidence, for every 15 million statin prescriptions there is only one occurrence of severe muscle damage, and the health benefits of statins outweigh their risks.[4]

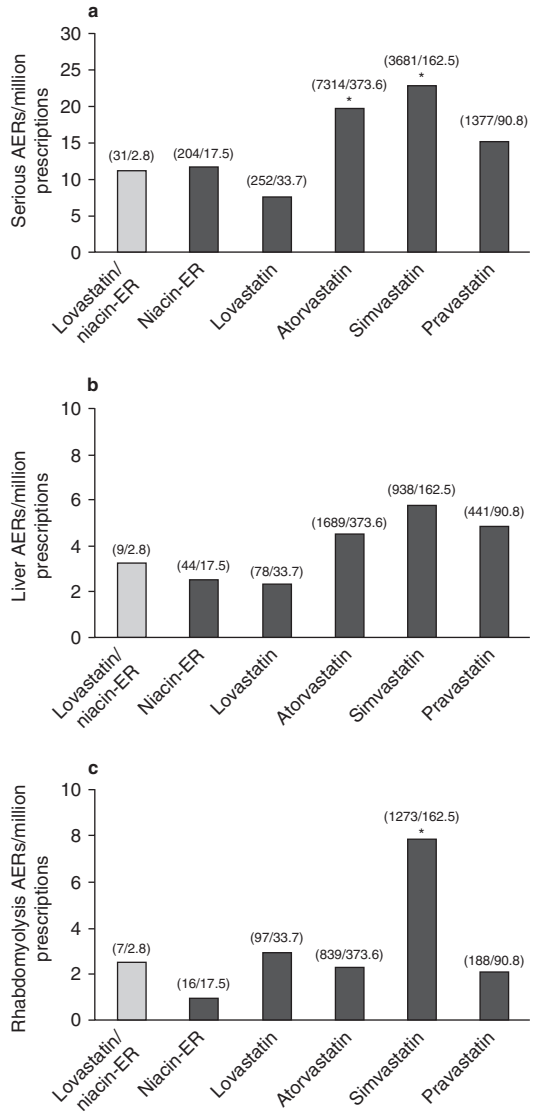

Fig. 3. Rates of adverse events reports (AERs) to the US FDA per 1 million prescriptions for statins between 1999 and March 2005, for which one of the statins was listed as suspect: (**a**) serious AERs; (**b**) liver AERs; (**c**) rhabdomyolysis AERs. Numbers above the bars represent the number of AERs/number of prescriptions in millions during the study period. The vertical axes use different scales (reproduced from Alsheikh-Ali and Karas,[10] with permission). * $p < 0.01$ vs lovastatin/niacin-extended release (ER).

3. Renal Effects

Although high-dose rosuvastatin (80 mg/day) has been associated with an increased incidence of pro-

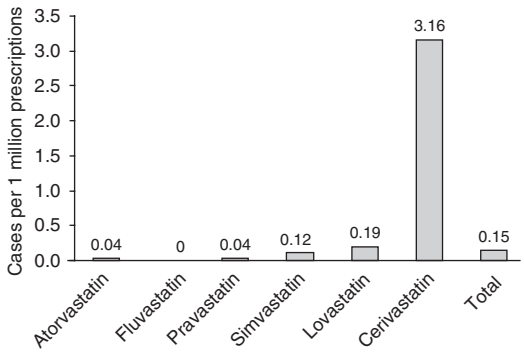

Fig. 2. Rates of fatal rhabdomyolysis with statin therapy. Data are based on the number of cases reported to the US FDA before 26 June 2001.[2]

teinuria,[19,20] there is no evidence that other statins or lower doses of rosuvastatin cause acute renal insufficiency, proteinuria, haematuria, chronic kidney disease or renal tubular or glomerular damage not associated with rhabdomyolysis.[21] Atorvastatin is the only statin that undergoes only 2% of total excretion via the kidney and, unlike other statins, no adjustment of the atorvastatin dosage is required in patients with renal insufficiency.[5] A recent analysis of data from four long-term studies (n = 9394) found that atorvastatin 10–80 mg/day and placebo were associated with similar rates of albuminuria (1.3% and 1.8%) and haematuria (1.7% and 1.8%).[22]

4. Hepatic Effects

Increased levels of hepatic alanine aminotransferase[23] and aspartate aminotransferase[16] to >3-fold greater than the upper limit of normal (ULN) generally occur in <1% of all statin recipients.[24] Similar rates of liver AERs per million prescriptions for atorvastatin, simvastatin and pravastatin were reported to the FDA between 1999 and March 2005 (figure 3).[10] The incidence appears to be slightly increased with atorvastatin 80 mg/day; persistent elevations in ALT and AST to >3-fold greater than the ULN were observed in 0.6% of patients receiving atorvastatin 80 mg/day, with baseline values <1.5-fold greater than the ULN versus ≤0.2% of atorvastatin 10 mg/day or placebo recipients.[7] However, the very low incidence of serious hepatobiliary adverse events with both dosages of atorvastatin in this analysis (<0.5%) confirm previous data showing that statin-associated elevations in hepatic liver enzyme levels are usually asymptomatic; the incidence of statin-associated liver failure is estimated at ≈1 per million person-years of use, and is similar to that observed among the general population.[17]

5. Neurological Effects

Although peripheral neuropathy has been reported in patients receiving statin therapy,[25] the incidence is extremely low (estimated at 12 cases per 100 000 person-years) and should not limit the use of statins.[17] Speculation about a potential association between statins and the development of amyotrophic lateral sclerosis (ALS; Lou Gehrig's disease)[26] resulted in lay media alarm about the neurological safety of statins without well established evidence of any grounds for concern.[27] A soon-to-be-published FDA analysis of >120 000 statin-treated patients has revealed no such association.[28]

Cognitive dysfunction is extremely rare in statin recipients and there appears to be no causative association.[17] Cognitive function was unaffected by treatment with atorvastatin 10 mg/day in patients in the LORD (Lipid Lowering and Onset of Renal Disease) study.[29]

6. Safety in Elderly Patients

Elderly patients are at increased risk of treatment-related muscular toxicity with statin therapy; a recent analysis of 252 460 statin recipients in the US found that patients aged ≥65 years were at the highest risk of hospitalisation for statin-associated rhabdomyolysis (odds ratio [OR] 4.36 vs patients aged <65 years; 95% CI 1.5, 14.1).[15]

However, this increased risk does not appear to extend to other adverse events and, despite atorvastatin plasma concentrations being increased by up to 40% in healthy adults aged ≥65 years,[5] atorvastatin appears to be well tolerated in elderly patients. Data collected from >50 randomised controlled trials were analysed retrospectively with a view to clarifying any potential association between increasing atorvastatin dosage and an increased incidence of

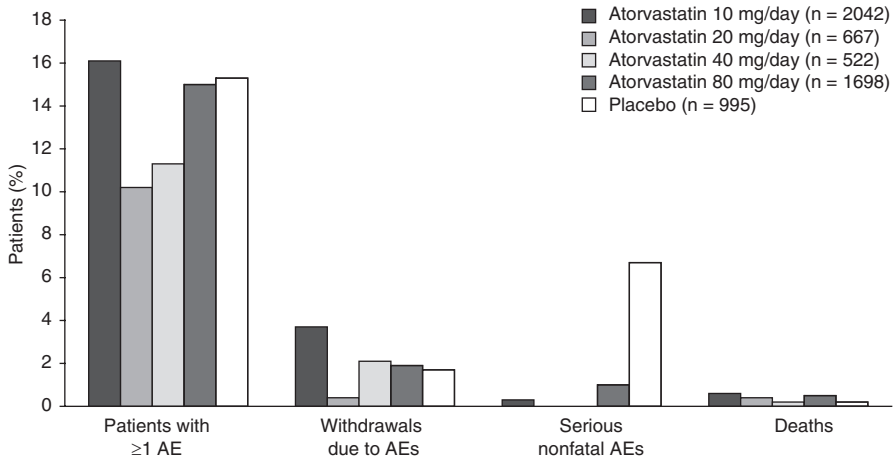

Fig. 4. Prevalence of treatment-related adverse events (AEs) in elderly patients aged ≥65 years receiving atorvastatin or placebo.[30]

adverse events in elderly patients (aged >65 years).[30] Overall, no amplification of adverse events was noted with increasing atorvastatin dosage (10–80 mg/day), and the rates of adverse events appeared similar to those attained with placebo. For instance, the proportion of patients with ≥1 treatment-related adverse event was 16.1% in the low-dosage atorvastatin group, 15.0% in the high-dosage atorvastatin group, and 15.3% in the placebo group (figure 4).[30] The lack of a dose effect on the incidence of treatment-related adverse events with atorvastatin 10–80 mg/day was confirmed in a small study of 72 coronary heart disease patients aged ≥65 years.[31] Furthermore, a pooled analysis of data from 2128 patients aged ≥75 years in 54 randomised trials of atorvastatin 10, 20, 40 or 80 mg/day versus placebo found a similar incidence of adverse events in all treatment groups and a low overall incidence of treatment-related myalgia (<2.5%).[32]

High-dose atorvastatin therapy (80 mg/day) was well tolerated in elderly patients with acute coronary syndrome, according to a *post hoc* analysis of data from the MIRACL (Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering) study.[33] The incidence of liver enzyme elevations was similar in patients aged <65 and those aged ≥65 years, while that of seriuos adverse events, although low overall, appeared higher in patients aged >65 years than in those aged <65 years (table I).[33] Moreover, high-dose atorvastatin was as well tolerated as standard-dose pravastatin in 893 elderly patients with CAD in the SAGE (Study Assessing Goals in the

Table I. Incidence of treatment-related adverse events and liver enzyme increases in patients aged <65 and ≥65 years receiving atorvastatin 80 mg/day or placebo in the MIRACL (Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering) study (reproduced from Olsson et al.,[33] with permission)

	Patients <65 years old [n (%)]		Patients ≥65 years old [n (%)]	
	atorvastatin (n = 689)	placebo (n = 725)	atorvastatin (n = 849)	placebo (n = 823)
Discontinuations due to adverse events[a]	24 (3.5%)	21 (2.9%)	45 (5.3%)	22 (2.7%)
Serious adverse events[a]	4 (0.6%)	5 (0.7%)	11 (1.3%)	2 (0.2%)
Alanine transaminase[b] ≥3 × upper limit of normal	13/390 (3.3%)	1/418 (0.2%)	19/590 (3.2%)	3/560 (0.5%)
Aspartate transaminase[b] ≥3 × upper limit of normal	8/297 (2.7%)	0/322 (0.0%)	9/403 (2.2%)	2/393 (0.5%)

a Creatine phosphokinase data were not collected systematically during the study.

b Numbers of patients with baseline laboratory measurements after acute coronary syndrome were used as denominators.

Elderly) study.[34] Similar proportions of patients receiving atorvastatin 80 mg/day and pravastatin 40 mg/day experienced ≥1 adverse event (61% and 65%, respectively) and serious adverse events occurred in 20% and 23% of patients in each treatment group, respectively.[34]

7. Conclusions

Extensive data from randomised clinical trials, postmarketing analyses and reports to regulatory agencies demonstrate the safety of atorvastatin in a large number of patients with a variety of indications. With the exception of a slightly higher rate of liver enzyme elevations with atorvastatin 80 mg/day, which does not appear to confer an increased risk of clinically important adverse events, atorvastatin is notable for its lack of dose-dependent tolerability. Unlike simvastatin, atorvastatin is associated with a low incidence of muscular toxicity at all therapeutic dosages. It is not associated with neurological or cognitive adverse effects, and has a placebo-like effect on the kidney as a result of its favourable pharmacokinetic profile, which is unique among the statins. Atorvastatin is generally well tolerated in elderly patients, with no dose-dependent increase in adverse events up to the maximum daily dosage of 80 mg/day. Thus, atorvastatin is a safe and well tolerated agent for use in patients requiring lipid-lowering therapy.

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