CORRESPONDENCE

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Dangers of rosuvastatin identified before and after FDA approval

Sir—The lipid-lowering drug rosuvastatin is currently in the midst of the most heavily financed launch of a prescription drug ever. Here I present premarketing and postmarketing evidence of the dangers of the drug, and call for its removal from the market.

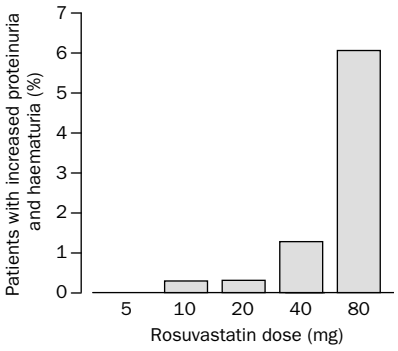
Detailed briefing documents including unpublished reviews of safety and efficacy data from clinical trials are now made public on the internet before all Food and Drug Administration (FDA) advisory committee meetings discussing the approval of a new drug. Documents for the July 9, 2003, meeting on rosuvastatin,[1] and the transcript of that meeting,[2] were the source of the preapproval data I present. FDA adverse event reporting system (AERS) reports up to April 13, 2004, obtained through the Federal Freedom of Information Act were the source of postmarketing data.

The preapproval documents state that "The data. . . show, for the first time, the development of severe myopathy and rhabdomyolysis in clinical trials submitted for the original approval of a new statin. This risk is clearly increased at the highest dose studied (80 mg), which has subsequently been discontinued from development. While the risks of myopathy at lower doses appear comparable to other marketed statins, these risks may increase in special populations in which patients are exposed to higher levels of drug (drug-drug interactions, renal impairment, Japanese descent)." There were eight cases of rhabdomyolysis, seven at 80 mg and one at 10 mg, in clinical trials.[1]

The preapproval documents also state that "80 mg of rosuvastatin has a high frequency of [creatine kinase] elevations (CK>10×ULN=1·9%), between what was seen in clinical trials for cerivastatin doses of 0·4 mg (1·55%) and 0·8 mg (2·1%) and higher than seen for all other currently approved statins" and that "there is a higher incidence of myopathy (1·0%) and rhabdomyolysis (0·4%) observed in the clinical trials with 80 mg of rosuvastatin than reported in the original NDA or current labels for any of the currently approved statins."[1]

The FDA stated at the meeting that "since safe and effective statins with a low risk for the development of rhabdomyolysis are already currently available, any future statins which would be approved need to have a comparable or lower risk for this adverse event".[2] However, rosuvastatin was approved under the belief that doses lower than 80 mg would be much safer.

". . . rosuvastatin was also associated with renal findings not previously reported with other statins. A small percentage of patients exposed primarily to the 80 mg dose of rosuvastatin had an increased frequency of persistent proteinuria and hematuria, which in some patients was also associated with an increase in serum creatinine." The figure, based on the documents,[1] shows a dose-related increase in haematuria and proteinuria, beginning with 1·3% of patients at 40 mg. None of the other statins showed any dose-related increase. "Out of all the patients enrolled in these trials only 3% had an increase in serum creatinine of >30% above baseline. . . However, in the subgroup of patients with dipstick-positive urine (⩾++ protein and ⩾+ blood), the percentage of patients with an increase of serum creatinine of 30% over baseline was 14%, 16%, 24%, 33%, and 41% for 5 mg, 10 mg, 20 mg, 40 mg and 80 mg of rosuvastatin, respectively. . . These data suggest that some patients with greater levels of proteinuria and hematuria may progress to clinically relevant renal disease".[1]



Increased proteinuria and haematuria with increased rosuvastatin dose
Drawn from data in reference 1.

Three cases of renal insufficiency or renal failure during the trials in people using 80 mg were "of concern because they present with a clinical pattern, which is similar to the renal disease seen with rosuvastatin in these clinical trials. There is mild proteinuria associated with hematuria and the suggestion of tubular inflammation or necrosis. . . However, if they [proteinuria and hematuria] are the signals for the potential progression to renal failure in a small number of patients, this may represent an unacceptable risk since currently approved statins do not have similar renal effects".[1]

A statistical review of the efficacy of rosuvastatin compared with higher doses of another statin found that there was no significant difference in the percentage LDL change from baseline between 5, 10, or 20 mg of rosuvastatin and four times as much atorvastatin (20, 40, or 80 mg, respectively).[3]

Since marketing began, there have been 18 additional cases of rhabdomyolysis, including 11 in the USA, even though the drug had only been on the market in that country for 7 months as of the April 13 date of the AERS data from the FDA. All of the latest ten US cases had been reported in the 6 weeks before April 13. Two of the 18 patients were using 40 mg, five were using 20 mg, and 11 were using 10 mg. An FDA review of reports of rhabdomyolysis in other currently marketed statins found that the rate of reports per million US prescriptions ranged from none for fluvastatin to 1·2 per million for lovastatin, the next highest being 0·8 for simvastatin, then 0·3 for atorvastatin.[4]

If the majority of the 11 US postmarketing reports of rhabdomyolysis meet the case definition used in the FDA paper[4] (ie, creatine phosphokinase concentration ⩾10 000 IU/L), as did 62% of the eight premarketing cases, and using the FDA estimate of one million prescriptions for

rosuvastatin in the USA,[5] the rate of rhabdomyolysis reports for rosuvastatin is probably higher than the highest of any other currently marketed statin, predictable from preapproval trial data. Only cerivastatin, now banned, was higher at 18·1 per million.

There have been eight reported cases of acute renal failure and four of renal insufficiency in patients using rosuvastatin since marketing began. Of these 12 cases, the dose was known in 11: nine were using the 10 mg dose, the other two 40 and 80 mg.

By now, the number of reported cases of rhabdomyolysis and renal insufficiency or renal failure—20 of which have occurred in people using 10 mg—is certain to have increased substantially from the number filed by April 13, 2004. The renal toxicity, high rate of cases of rhabdomyolysis compared with other statins, and lack of unique benefit are compelling reasons to remove rosuvastatin from the market before additional patients are injured or killed. To allow AstraZeneca to continue desperately seeking a piece of the estimated $20 billion a year statin market hardly justifies governments allowing this ultimately doomed drug to stay on the market.

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1 Food and Drug Administration Center for Drug Evaluation and Research (CDER). Endocrinologic and Metabolic Drugs Advisory Committee Meeting, July 9, 2003. Briefing information: Crestor: indicated for the treatment of hypercholesterolemia and mixed dyslipidemia. http://www.fda.gov/ohrms/dockets/ac/03/briefing/3968b1.htm (accessed June 1, 2004).

2 Department of Health and Human Services, Food and Drug Administration Center for Drug Evaluation and Research Endocrinologic and Metabolic Drugs Advisory Committee. July 9, 2003, Bethesda, MD, USA. http://www.fda.gov/ohrms/dockets/ac/03/transcripts/3968T1.htm (accessed June 1, 2004).

3 Mele J. Crestor (ZD4522, rosuvastatin calcium) tablets: comments on efficacy. http://www.fda.gov/ohrms/dockets/ac/03/slides/3968S1_02_FDA-Mele.ppt#8 (accessed June 10, 2004).

4 Chang JT, Staffa JA, Parks M, Green L. Rhabdomyolysis with HMG-CoA reductase inhibitors and gemfibrozil combination therapy. *Pharmacoepidemiol Drug Safety* 2004; **13:** 417–26. http://interscience.wiley.com DOI: 10.1002/pds.977

5 Gardner A. Group seeks ban on cholesterol drug. http://www.medicinenet.com/script/main/art.asp?articlekey=32678 (accessed June 1, 2004).

World situation and WHO

Sir—It is not the case, as Vicente Navarro claims (Apr 17, p 1321),[1] that Canada has been forced to dismantle any aspect of its public-health insurance systems by international trade agreements or World Trade Organization strategies. If the doctoral dissertation he cites as authority for this statement actually makes such a claim, it should not have been accepted by the university's examiners.

In the future, a revised General Agreement on Trade in Services (GATS) might have such an effect in Canada,[2] as elsewhere.[3] For the moment, however, the threat to Canada's public-health insurance is a retreat from progressive taxation, which has created serious revenue constraints.[4,5] This retreat is attributable to interaction between the global spread of neoliberal ideas and Canada's changing domestic class structure, not to trade law and policy. Canadian governments could afford to rescue publicly financed health care from its current crisis; they have chosen not to do so.

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1 Navarro V. The world situation and WHO. *Lancet* 2004; **363:** 1321–23.

2 Campbell B, Blouin C, Foster J, et al, for the Canadian Centre for Policy Alternatives. Putting health first: Canadian health care reform, trade treaties and foreign policy. Ottawa: Commission on the Future of Health Care in Canada, 2002. http://www.policyalternatives.ca/publications/putting-health-first.pdf (accessed May 26, 2004)

3 Woodward D. Trading health for profit: the implications of the GATS and trade in health services for health in developing countries. London: UK Partnership for Global Health, 2003. http://www.ukglobalhealth.org/content/Text/GATS_Woodward.pdf (accessed May 26, 2004).

4 Schrecker T. Private health care for Canada: north of the border, an idea whose time shouldn't come? *J Law Med Ethics* 1998; **26:** 138–48.

5 Evans RG. Getting to the roots: health care financing and the inegalitarian agenda in Canada, HPRU 02:7D. Vancouver: Centre for Health Services and Policy Research, University of British Columbia, 2002. http://www.chspr.ubc.ca/ hpru/pdf/hpru02-07D.pdf (accessed May 26, 2004).

Author's reply

Sir—The World Trade Organization (WTO) is indeed contributing to the global spread of neoliberal ideas that undermine the Canadian Health Program. Even though the Canadian government has taken a waiver not to liberalise the provision of health services, health insurance is not covered by this waiver, thus the Canadian Health Program is not fully protected.

Private insurance companies in Canada have long insured services deemed not to be "medically necessary" by the public sector and are eager to expand their market share. The reality is that commercial health insurance companies are aggressively marketing to the rich sectors of the population who feel they need not rely on provincial health programmes, thus weakening support for such public programmes. Also, the liberalisation of specialty-care providers is facilitating the sub-contracting of care to commercial providers. Rather than sufficiently investing in the public sector, provincial governments are increasingly subcontracting to the private sector, which again weakens the public health-care programme.

A revised GATS might indeed further pressure Canada to dismantle its public health insurance system, but the current promotion of neoliberal ideas by the WTO is already undermining public health insurance models.

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Language use in public health

Sir—Vicente Navarro (Apr 17, p 1321)[1] observes that WHO reproduces, in many of its documents, the ideology predominant in the political and health establishments of the USA since the 1980s. He mentions in passing that this is also associated with a change in the use of language. For example, "hunger" is replaced by the ostensibly more neutral term "underweight", thereby disregarding existing realities and their causes.

We believe that the way in which language is used in public health deserves more attention. The deliberately euphemistic, ambiguous language described by Navarro is common in public health. Frequently we fail to even notice it because we have become so used to it. Language that expresses a simultaneous belief in contradictory ideas is even more obfuscating; for this type of misuse