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Detailed briefing documents including unpublished reviews of safety and efficacy data from clinical trials are now made public on the internet before all Food and Drug Administration (FDA) advisory committee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, and the transcript of that meeting, 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 NDA or current labels for any of the currently approved statins.” 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”. 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, 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

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).1

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 (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
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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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 contradiction ideas is even more obfuscating; for this type of misuse

Registering clinical trials

Sir—I share the view of Timothy Evans and colleagues (May 1, p 1413) that much research is wasted because some important studies are not published. Evans and co-workers are also concerned that researchers in developing countries whose first language is not English might experience difficulty publishing in international indexed journals. However, the notion that WHO leading universal registration of studies in developing countries will allow equitable access to the results of relevant research might not happen in practice.

Like many international agencies, including the International Monetary Fund, World Bank, and the World Trade Organization, WHO has been hijacked by the alliance of dominant classes in dictating its policies and practices. One example was the failure of the WHO Global Outbreak Alert and Response Network (GOARN) in responding to the severe acute respiratory syndrome (SARS) outbreak in China.

SARS is a timely reminder of the growing threat to humanity from infectious diseases. WHO set up GOARN to maintain global-health security, but it was frustrated by the influence of dominant nations; in this instance, China managed to delay everything that WHO aimed to do. Moreover, since the 23 million people of Taiwan are excluded from WHO, there is a serious gap in the GOARN network.

Outside WHO, my friends and colleagues in Taiwan are compromised in matters of global-health policy discussions, technical connections, and disease control and prevention. Scholars in Taiwan are inhibited in developing public-health policy and promoting good practice owing to lack of support. They were barred from attending the WHO influenza symposium in March—an example that contradicts the spirit behind universal access to health-related knowledge for health improvement.

For the universal registration of controlled trials to succeed, I agree with Vicente Navarro that WHO should be faithful to its constitution and charters, which state that health is one of the fundamental human rights of every human being, and that it should stop ostracising the people of Taiwan.

Many parliamentarians from the UK, the USA, Canada, Australia, and the European Parliament, together with the British Medical Association and the World Medical Association, have recognised the dangers and pitfalls of allowing China to hold WHO ransom in matters of global health. The Lancet Editorial echoed the difficulty of China’s weak commitments to international human-rights agreements. I hope that the initiative of universal sharing of health-related knowledge for health improvement will allow WHO to turn a new page and succeed in their essential role.

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Global human resources crisis

Sir—We agree with Vasant Narasimhan and colleagues (May 1, p 1469) that in many developing countries, international players have substantial influence over the agenda-setting and policy-making with respect to human resources for health. The joint poverty-reduction strategy paper and debt initiative for heavily indebted poor countries (PRSP-HIPC) is a prime example of an interface between international actors and national decision-makers with real clout. Unfortunately, human resources for health often do not even figure on its agenda. A review of the PRSP in six selected African countries by the UK’s Department for International Development Health Systems Resource Centre indeed shows that, at best, the human resources crisis is merely acknowledged, and that an in-depth analysis of the issue and how it relates to civil service conditions is conspicuously absent in most papers.

Cynics might say that these findings simply confirm the worrying tendency among both national and international policy-makers to skirt the very problems that will undermine any attempt to improve health and social services, let alone poverty reduction.

George Orwell coined the term “doublethink”. Doublethink can mislead even experienced public-health practitioners. An example is the term “post-eradication immunization policy” for poliomyelitis. It describes preventive strategies, such as routine immunization with inactivated polio vaccine in low-income and middle-income countries, which will have to be implemented once the eradication of poliomyelitis has been achieved. “Eradication”, as defined by WHO, is the “achievement of a status whereby no further cases of a disease occur anywhere, and continued control measures are unnecessary”. By definition, in a post-eradication scenario, there will be no further need for any strategy against either poliomyelitis or poliovirus. In short, for any strategy against either scenario, there will be no further need for any control measures such as vaccination.

Confusing and unclear language of this kind should be avoided in a scientific approach to public health.

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efforts. But the extent of the human resource crisis in Africa in general and particularly in the countries with a high HIV/AIDS prevalence, forces us to act decisively. We believe that we need to reconsider approaches that used to be politically incorrect. If not, the current staff deficits will continue to undermine the absorption capacity to act decisively. We believe that we need to reconsider the human resources for health plan should be part of any PRSP as a condition for approval. Moreover, the recruitment ceilings imposed under the structural adjustment programmes represent a relic from the past and need to be removed. International actors should no longer shun the funding of recurrent expenditure with the excuse that this amounts to unsustainable interventions. For example, international development agencies need to reconsider contributing to funding salaries and wages in the new recruitment drives. Also bilateral agencies need to critically review their policies. Sending out expatriate medical personnel as a short-term measure or hiring medical professionals from the brain drain diaspora are options.

In short, the context and the challenges besetting health systems in developing countries have changed dramatically and paradigm shifts are called for to come up with effective strategies.

Risk of cancer from diagnostic X-rays

Sir—In their otherwise balanced commentary on cancer risks from diagnostic X-rays, Peter Herzog and Christina Rieger (Jan 31, p 340) did not mention that the radiation dose used in diagnostic X-rays does induce cancer. This statement is a central issue because, if true, the risks of diagnostic X-rays would be at most hypothetical, dependent on the substantial uncertainties associated with low-dose radiation-risk extrapolation—and not something for the practising physician to be overly concerned about. For adults, however, their statement is probably not correct, as for children it is almost certainly incorrect.

To take the common adult CT examinations as an example, depending on the machine settings, typical equivalent doses in examined organs are in the range of 20–30 mSv for a single examination; the average number of CT scans for a given medical problem for which CT is used is about two, giving an average total dose of 40–60 mSv. Is there direct evidence of increased cancer risk in this dose range?

The individuals in the lowest dose group of atomic-bomb survivors that showed a significant rise in cancer incidence, received doses in the range of 5–100 mSv (mean 29 mSv). The corresponding lowest dose group that showed significantly increased cancer mortality was very similar (5–125 mSv, mean 34 mSv). Thus, there are reliable data showing increased cancer risk at the doses (40–60 mSv) used in adult diagnostic CT.

The situation is still clearer for paediatric CT for which, depending on the age and settings used, the doses for the same examinations are up to four times higher than in adults. Additionally, depending on their age, children are three to five times more sensitive than adults to radiation-induced cancer. Therefore, there can be little doubt that diagnostic CT examinations in children result in an increased cancer risk. Although the individual risk is small, use of paediatric CT is increasing; therefore the public-health risk is not negligible.

Are the atomic-bomb exposures relevant to radiological examinations? The major differences are (1) radiological exposures are less uniform, so fewer organs are effectively at risk; and (2) radiological examinations use lower-energy X-rays, which, since they are more densely ionising, are more carcinogenic than the high-energy γ rays to which atomic-bomb survivors were exposed. Therefore, atomic-bomb exposures are relevant to radiological examinations, but there is also direct evidence from in-utero radiological examinations, where the increased sensitivity of the developing embryo and fetus allows significantly increased cancer risks to be seen at doses as low as 6 mSv. We applaud the recommendations of Herzog and Rieger that physicians should carefully consider the risks and benefits before ordering radiological examinations. However, particularly for CT examinations, which increasingly dominate the radiologically related population dose, we would add that the radiation risks have a much firmer scientific basis than Herzog and Rieger imply.

* Authors’ reply

Sir—David Brenner and Eric Hall make the assumption that our statement regarding the probable impreciseness of the estimate of cancer risk from diagnostic radiological exposure, from Berrington de Gonzalez and Darby’s work, is incorrect.

Brenner and Hall disregard the different quality of radiation derived from X-ray tubes and detonation of nuclear devices. The atomic-bomb survivors were not only directly exposed to γ rays emitted from radionuclides—which would be comparable to X-ray radiation—but also to neutron radiation from the bomb detonations and, most importantly, to radionuclides, from contaminated food, water, and air (dust), emitting γ, β, and high-energy α radiation. Some of these radionuclides have a long half-life and are embedded into bone metabolism and stored there for almost the whole life of the individual. This additional exposure is not apparent in patients undergoing radiological examinations, but it contributes to the morbidity and mortality of the atomic-bomb survivors. Different radiation qualities are only poorly accounted for by use of weighting factors. The difference between incorporated radionuclides and short-time external radiation sources is not accounted for at all. Additionally, the γ rays the atomic-bomb survivors were exposed to were of a different...
energy spectrum than the ones used for diagnostic X-rays. On the basis of these considerations, we still think that the cancer risk is overestimated with these data, although we acknowledge the fact that there are probably no better data showing the effect of ionising radiation exposure in such a large population.

Furthermore, Brenner and Hall claim that typical equivalent doses derived from a single CT scan in adults were comparable to a group of atomic-bomb survivors exposed to doses from 5 to 100 mSv with a mean dose of 29 mSv. At least in our department, adults are exposed to a substantially lower mean radiation dose when undergoing CT examinations—eg, average doses in men are 4·0 mSv (scan length 27 cm) for a thoracic CT examination, 7·0 mSv (42 cm) for an abdominal scan including the pelvis in males (120 kVp, 120 mAs eff, Coll 4/5 mm, CTDIv 8·28 mSv, effective doses estimated with CT-EXPO version 1·0 Software). Average exposures ranging from 20 to 30 mSv in one single CT examination, as stated in Brenner and Hall’s letter, should be easily reduced. Indeed, we also believe that the individual risk of cancer from diagnostic X-rays is small but not at all negligible—especially in children—although in our Commentary we did not address paediatric CT.

Of course, there is no doubt that CT examination in children results in a heightened cancer risk due to an increased cell division rate. We want to stress that our above-mentioned estimates are not applicable for examinations in children. We were very surprised that Brenner and Hall referred so strongly to children’s examinations, especially since they were not so much the point in Berrington de Gonzalez and Darby’s article nor in our Commentary. We can certainly only agree with their statements that CT examinations in children and in adults should be carefully indicated and exposure parameters should be chosen meticulously.

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**Autologous salvaged blood and natural-killer cell frequency**

Sir—According to a report by Ahmad Gharehbaghian and colleagues (Mar 27, p 1025),1 autologous salvaged blood containing wound drainage fluid is invariably associated with an increased frequency of natural-killer cell precursors (NKp) and synthesis of interferon γ 5 days after joint replacement surgery. However, the authors do not speculate what the key factors were that heightened the frequency of NKp and interferon γ.

Bottner and colleagues measured various cytokine concentrations after transfusion of washed wound drainage in knee arthroplasty.2 They showed that washed wound drainage contained significantly more interleukin 6 and interleukin 8 than predonated autologous blood. No significant difference was shown for interleukin 1β and tumour necrosis factor α. Bottner and co-workers concluded that the rise in interleukin 6 and interleukin 8 after transfusion might be related to the surgical trauma response. However, they did not report an association between interleukin 6 or interleukin 8 and natural killer cell differentiation and interferon γ synthesis. Activated natural killer cells secrete interferon γ.

Shibuya noted, in his review, that interleukin 15 had a crucial role differentiation and maturation of natural killer progenitors into functional natural killer cells.3 However, neither Gharehbaghian and others nor Bottner and co-workers measured concentrations of interleukin 15. Moreover, did Gharehbaghian and colleagues estimate the concentration of several cytokines included in autologous salvaged blood? Did increased frequency of NKp or synthesis of interferon γ actually reduce the infectious complications after joint replacement surgery?

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**Authors’ reply**

Sir—Washing salvaged erythrocytes might remove some of the factors that cause immunostimulation after reinfusion of autologous salvaged blood. However, as Yujiro Kida points out, washed salvaged blood leads to increased concentrations of interleukin 6 and interleukin 8 in the patient’s blood within hours of transfusion, and the same occurs in patients receiving autologous predespoded blood. The cohort treated with autologous predespoded blood that we studied showed no immunostimulation, ruling out these two cytokines as key factors.

We postulate that interleukin 12 could be a key factor. This is a natural-killer chemokine that upregulates the cell-surface receptor for interleukin 18 and synergises with it to induce proliferation of early natural-killer cells and subsequent synthesis of interferon gamma.4 Kida suggests that interleukin 15 in the salvaged blood could have been a key factor; this is possible, but unlikely because it acts at a later stage in natural-killer cell differentiation.5 Nonetheless, we have yet to measure concentrations of cytokines in our salvaged blood.

Why do these key factors accumulate in the wound space? Could they be attributes of the synthetic materials implanted by the surgeon? If the key factors have a cellular origin, could they be transferred by dendritic cells (interleukin 12), macrophages (interleukin 18), or stromal cells (interleukin 15)? Did the natural-killer cell precursors originate from bone marrow cells drawn into the wound space by negative pressure exerted by the salvage pump?

Irrespective of the nature of the key factors, Kida’s most important question is whether autologous-salvaged blood led to a decreased risk of postoperative infection. A meta-analysis failed to show any significant reduction in infection.6 However, we feel this all-inclusive analysis should not be regarded as conclusive since the analysis did not take into account different techniques used for cell salvage, which is crucial. Hence, a randomised prospective controlled trial is urgently needed to address this issue.

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Kinship structure and health-care improvement in sub-Saharan Africa

Sir—In sub-Saharan Africa, inadequate resources, poor planning and management, and high poverty levels are so pervasive that apathy is almost the order of the day. Public-health indices from Africa attest to this.1–3 Even where success has been achieved, its sustainability has not been assured.

Our experience shows that the traditional kinship system can be instrumental in involving both men and women in caring for vulnerable groups such as children, teenagers, the elderly, and the disabled. It provides a mechanism for receiving, retaining, and acting on health education messages; for insuring its members; for preventing risky behaviour; for involving all its members in collective decision-making; and for taking responsibility for their own health and security. This provision ensures trust, equity, and quality of health-care delivery at the community level.4

The onchocerciasis control programme in Uganda has used the kinship system to stunning success. This approach helped to eliminate the demand for monetary incentives by community-directed health workers.4 Health education levels have been raised and maintained at more than 67% of the total population. For at least 6 years, the programme has achieved annual treatment coverage of at least 90% of eligible individuals. This success was achieved by getting a large number of community members to select as many community-directed health workers as practical through their own kinships. Government-employed health workers then trained them to educate and treat their own relatives and neighbours. The communities were able to assess their own success and weaknes, and make adjustments in their health-care programme. The communities at the kinship level used community-directed health workers to bring more health and development programmes to their communities. Where government health workers were few and unable to handle as many community-directed health workers, communities selected their own supervisors, who were themselves trained by health workers to train and supervise community-directed health workers.

In addition to onchocerciasis control, the kinships have also embraced programmes for HIV/AIDS control and prevention, malaria control, tuberculosis control, reproductive health, immunisation, and other development challenges. The gap between the health-care system and how the communities has been filled, and community knowledge on how government systems work increased. This success has motivated communities to pose the right questions to the right people when they have specific needs. This community participation has precipitated a large-scale lobby for quality health-care delivery, which health-care decision-makers, programme directors, politicians, and administrators can no longer ignore. It is what the Alma Ata conference set out to achieve more than 25 years ago.1

This model could be adapted in other sub-Saharan countries. Where kinship systems are weak or non-existent—eg, in urban areas—neighbourhood zones might provide a better option.

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