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FEATURE

STATINS

Rosuvastatin: winner in the statin wars, patients' health notwithstanding

More is spent in the US on rosuvastatin than any other statin. Yet the evidence of its health benefits has always been weak and there is growing evidence of harmful side effects. **Sidney Wolfe** explains why he thinks the drug should have been withdrawn and why it should not be used

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Last year, rosuvastatin (Crestor) was the most prescribed brand name drug in the US, with 22.3 million prescriptions filled and $5.8bn (£3.9bn; €5.5bn) in sales.[1] Worldwide 2013 sales were $8.2bn, the third highest for any branded drug.[2] Given the longstanding, continuing evidence of rosuvastatin's comparative lack of clinical benefits and increasing evidence of risks, how did this happen? The short answer is that of statins still on the market, the milligram for milligram cholesterol lowering potency of rosuvastatin exceeds all others, a fact exploited in advertising campaigns. But what about actually improving health, preventing heart attacks and strokes?

Less evidence of clinical benefit since approval

When rosuvastatin was approved in the US in 2003 for lowering cholesterol, three other statins—simvastatin, pravastatin, and lovastatin—had already obtained additional Food and Drug Administration approval for use to reduce cardiovascular risk, and a fourth, atorvastatin, was found to have such clinical benefit in 2004.[3]

But rosuvastatin did not gain approval for cardiovascular risk until 2010, and then only for primary prevention of heart attacks and strokes. Approval was based on the results of the JUPITER study, which included only patients with both low density lipoprotein (LDL) cholesterol <130 mg/dL (3.4 mmol/L) and C reactive protein ≥ 2 mg/L (19 nmol/L)[4] and thus has limited generalizability.

Other criticisms of the study include concern that the size of the treatment benefit could have been exaggerated because the study was stopped early.[5] Simulations show that trials stopped early will consistently overestimate treatment effects. This is supported by a study comparing the size of the benefits in 91 randomized controlled trials that were stopped early or truncated with those in 424 non-truncated trials, matched for the same disease research questions. The pooled results showed that trials stopped early for benefit "systematically overestimate treatment effects for the outcome that precipitated early stopping," especially with studies stopped with fewer than 500 clinical events.[6] When JUPITER was stopped early because of benefit, the accrued number of clinical events was 393.[2] The relatively larger effect seen in JUPITER than other statin trials is almost certainly at least partly because it was stopped early. A reduced benefit might be outweighed by the risks of rosuvastatin.

By the time rosuvastatin was approved for primary prevention in 2010, the three most prescribed statins had been approved for both primary and secondary prevention after multiple trials, including in patients with raised LDL cholesterol, had shown benefit (atorvastatin, four trials; pravastatin, three trials; and simvastatin, two trials).[3]

More evidence of risks

In addition to the evidence of clinical benefits for rosuvastatin being substantially less robust than for these three statins, there is increasing evidence that the drug also carries a higher risk of serious adverse effects. Prespecified outcomes in the JUPITER study[2] included not only cardiovascular endpoints but also new onset diabetes. Ironically, the reason for including this "hopeful" endpoint was that an earlier study had found that pravastatin decreased new onset diabetes.[7 8] In JUPITER, however, there was a significantly higher incidence (26%) of new onset diabetes in the rosuvastatin group compared with the placebo group.

A recent review of 17 randomized trials involving 113 394 patients comparing the risk of new onset diabetes for various statins corroborated this finding.[9] Treatment with rosuvastatin, compared with placebo, was associated with a 25% relative increase in the risk of developing diabetes; pravastatin was associated with the lowest risk, a 7% increase. An earlier, observational study of 240 000 patients beginning statin treatment also found that rosuvastatin was associated with the highest increased risk of diabetes and pravastatin the lowest.[10]

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The differences in new onset diabetes are probably caused by the differing metabolic effects of rosuvastatin and pravastatin. In another randomized study of patients with raised cholesterol, rosuvastatin significantly increased glycated hemoglobin (HbA_{1C}) and fasting insulin levels, and decreased insulin sensitivity, whereas pravastatin significantly lowered HbA_{1C} and fasting insulin levels, and increased insulin sensitivity.[11] Further evidence of differing metabolic effects among statins has been recently reviewed.[12]

Rosuvastatin's FDA approved labeling now says: "In JUPITER, there was a significantly higher frequency of diabetes mellitus reported in patients taking rosuvastatin (2.8%) versus patients taking placebo (2.3%)."[13] The labeling for other statins merely states that "Increases in HbA1c and fasting serum glucose levels have been reported with HMG-CoA reductase inhibitors."

Other serious problems were identified before rosuvastatin's approval. Public Citizen opposed approval of rosuvastatin in 2003,[14] and in 2004 it asked the FDA to ban the drug because of two serious adverse reactions.[15] The first was rhabdomyolysis. Rosuvastatin is the only statin in which rhabdomyolysis was detected in randomized controlled clinical trials before the drug was approved. Even with cerivastatin, eventually banned because of rhabdomyolysis, no cases had occurred in the clinical trials before its approval. In a recent study of 641 703 patients in the UK prescribed different statins, those taking rosuvastatin had a significantly higher risk of an abnormally raised creatine phosphokinase activity than patients on large daily doses of other statins (simvastatin, pravastatin, or atorvastatin).[16]

The second serious concern seen during preapproval trials was renal problems. At the time, rosuvastatin was the only statin to have been associated with proteinuria and hematuria. According to FDA documents "in the subgroup of patients with dipstick [protein and blood] positive urine, 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."[17]

Although the FDA rejected our petition to ban rosuvastatin in 2005, the agency agreed that: "In addition, urine abnormalities, specifically proteinuria and hematuria, not previously noted in the review of other statin drug applications and not known to occur with this class, were observed sporadically in a small percentage of rosuvastatin-treated patients, with the highest incidence occurring at the 80-mg dose."[18]

Further concerns about rosuvastatin's renal effects were seen in an AstraZeneca funded randomized study comparing high dose rosuvastatin with atorvastatin in diabetic patients with progressive kidney disease.[19] Although rosuvastatin lowered plasma lipid concentrations to a greater extent than atorvastatin, the study reported that "atorvastatin seems to have more renoprotective effects." Urinary protein excretion was reduced during one year of treatment with atorvastatin 80 mg, with no significant changes in estimated glomerular filtration rate (eGFR). In patients given rosuvastatin 40 mg, however, "urinary protein excretion was not significantly different from baseline, but the patients did have a significant decrease from baseline in eGFR, and doubling of serum creatinine and acute renal failure were more common in this group."[19]

Why the drug remains popular

Given the evidence of more serious risks and less clinical benefit than other statins how has the drug fared so well for so long? A prescient answer can be found in an October 2003 *Lancet* editorial, "The statin wars: why AstraZeneca must retreat."[20] It stated that AstraZeneca's chief executive, Tom McKillop, "has pledged to do whatever it takes to persuade doctors to prescribe rosuvastatin, including launching an estimated $1 billion first-year promotional campaign. 'We've got to drive the momentum', he [McKillop] said at a recent investors meeting. 'You get one shot at launching a major new product. This is our shot.'" The editorial concluded, "Physicians must tell their patients the truth about rosuvastatin—that compared with its competitors, rosuvastatin has an inferior [clinical] evidence base supporting its safe use. AstraZeneca has pushed its marketing machine too hard and too fast. It is time for McKillop to desist from this unprincipled campaign."

McKillop promptly responded, accusing the journal of not telling the truth, then stating "Crestor is an extensively studied and well tolerated drug with a safety profile comparable to other marketed statins combined with a greater ability to get patients to their cholesterol goals than any other single product." Referring to the unmet need for adequate treatment with lipid lowering treatment, McKillop stated that "With this compelling medical need, it is unthinkable that we should desist from our efforts to make this medicine more widely available to physicians and patients."[21]

Barely more than a year later, in December 2004 the US FDA had to send a letter to AstraZeneca demanding that it immediately stop an advertisement in the *Washington Post* containing false and misleading information about Crestor's risks. The advert stated that "The scientists at the FDA who are responsible for the approval and ongoing review of CRESTOR have, as recently as last Friday, publicly confirmed that CRESTOR is safe and effective; and that the concerns that have been raised have no medical or scientific basis," citing the FDA website, which actually contained no such information.[22]

The advert was in response to a *Washington Post* article about Public Citizen's campaign against the drug, discussing the safety concerns shared by us and the FDA.[23] In the article Steven Galson, acting director of the FDA's Center for Drug Evaluation and Research, stated that the FDA "has been very concerned about Crestor since the day it was approved, and we've been watching it very carefully." He further stated the agency is "concerned about the same issues with Crestor as Public Citizen."

The FDA's letter to AstraZeneca said, "The 'patient safety' print ad makes false or misleading safety claims that minimize the risks associated with Crestor, thereby suggesting that Crestor is safer than has been demonstrated by substantial evidence or substantial clinical experience." The agency wrote to the company again the following year about "misleading superiority claims" for Crestor in other promotional materials.[24]

When patents expired for simvastatin, pravastatin, and atorvastatin, the rise in generic prescriptions quickly equaled or exceeded the sharp decreases in brand name prescriptions (IMS Health data). The patent for rosuvastatin expires in 2016, and with it AstraZeneca's need to promote it. But for the sake of the public's health, we must hope that the drug's disadvantages will lead to a sharp decline in its use before next year.

Competing interests: I have read and understood BMJ policy on declaration of interests and declare I am the founder of Public Citizen.

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