Goodbye Avandia!

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The anti-diabetes drug rosiglitazone (Avandia® [Av]) has been "sick" for many years now, but it has only recently been declared "terminally ill and possibly dying". The grim prognosis was announced simultaneously on 23rd September by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA),[1,2] whereby, the FDA decided to impose heavy restrictions on the use of Av (to the point that the drug can now hardly be used in clinical practice), while for its part, EMA called for a complete suspension of Av across Europe. In this regard, the end is now near for a drug that has been a source of endless debate and controversy, and long been suspected of serious side effects. Yet, only 6 months earlier (and for many years before), both the FDA and EMA believed Av was a safe medication to keep on the market, dismissing all pleas made at the time to have it suspended. What happened in the preceding few months to prompt both agencies to change their mind so dramatically regarding Av? An intriguing mixture of science and politics can be delicately traced. This Editorial therefore, attempts to shed light on the events surrounding the rise and fall of Av, and identify appropriate lessons that can be learned.

Since its birth (into the market) in 1999, Av has been marred in scientific controversy and political debate. There had always been the odd symptom and sign indicating something was wrong with Av, but nothing substantial to warrant serious attention until 2007. A detailed report (meta-analysis) carried out by Nissen and Wolski,[3] and published in the New England Journal of Medicine in May 2007 showed a disturbing link between the use of Av and development of cardiovascular complications (heart attacks). The article caused public uproar, as well as medical confusion. An intense and acrimonious debate erupted, and the medical community became "split" between those alarmed by the deadly side effects of the drug and so wanted it stopped instantly, and those in the other camp (spearheaded by the manufacturer of Av, GlaxoSmithKline, [GSK]) who disputed the findings of the study, and argued vehemently that Av was a safe drug, and they were, therefore determined to fight for it until the end. Public confidence was nevertheless irrevocably shaken, and prescriptions of Av progressively dropped. A public enquiry was called for, and uncertainties on the safety of Av were subsequently addressed by a series of scientific studies and publications. As evidence mounted up however, the case against Av grew bigger and more sinister both scientifically and politically.

The second major setback in the turbulent history of Av came in February 2010 with the publication of the US Senate investigation into the safety of Av and the conduct of GSK.[4] The enquiry took 2 years to complete and included review of hundreds of thousands of pages of internal GSK documents. Investigators uncovered essentially 3 things: the scientific evidence against Av was substantial if not overwhelming, the tactics employed by GSK to keep the drug on the market were grossly unprofessional, if not unethical (such as, withholding important information from regulatory bodies and the public), and investigators also found serious flaws within the FDA organizational structure, which may have biased outcomes in favor of Av. In response, the FDA promptly organized a public hearing and assembled an advisory team of experts to address the issue. A meeting was subsequently held in July 2010. The verdict of the advisory committee came out as follows: one-third of panelists voted for keeping Av on the market without change (with black box label warning), whereas two-thirds of panelists were unhappy to continue the same, and were divided equally between those who wanted (even) greater restrictions, and those who wanted Av totally banned from the market.[5] The last word, however, was left for the FDA itself to make. Meantime, over the summer, 2 more studies with large numbers of patients recruited published their findings. Both showed evidence of increased cardiovascular risk with the use of Av, calling for its withdrawal.[6,7] The long awaited verdict of the FDA came out on 23 September; the agency had officially decided to keep Av on the market, albeit with tighter regulations.

Many of us in the medical community were surprised and baffled by the FDA's decision. If the safety of a drug

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was hotly contested, if the suspected side effects were as serious as heart attacks and strokes, if there was an alternative therapy available, and if a sizable proportion of the agency's own experts believed the drug unsafe to use, why would you still want to keep the drug on the market? Did the FDA expect 100% proof that a drug was unsafe before it would consider withdrawing it from the market? According to the FDA's new regulations, Av still had a place in clinical practice. It identified 2 clinical situations whereby Av can be prescribed to new patients: first, when all other medications have been tried and failed to control blood glucose, however, to implement this means a physician would have to exhaust all the other 6 classes of anti-diabetic agents first before considering using Av. How feasible is this to do in everyday clinical practice? The second indication advocated by the FDA was that Av could be used as a substitute for Pioglitazone (Actos, a safer and less controversial sister drug of Av) in patients who are unable to take the latter drug, however, patients who cannot take Pioglitazone (such as because of heart disease or heart failure) are typically those who would not be able to take Av in the first place anyway. It is, therefore, hard to understand the rationale behind the FDA decision of keeping Av on market, a drug with a dubious safety record, and no clear way of using it clinically. In fact, the situation as it stands may encourage abuse of Av by misinformed doctors and unsuspecting diabetic patients. The European approach to the debate on Av was entirely different from that adopted by the FDA and unfortunately, far less desirable.[8] No public hearing of any kind was organized. No scientific investigation was sought or debated. Decisions at the EMA are strictly made behind closed doors. It appears that the decision to keep Av on the market was based largely on the issue of "trust" on the claims made by GSK, rather than on a thorough examination of the scientific evidence, for and against the drug. No wonder why EMA approved a 5-year extension of the marketing license of Av in March, only to scramble to have Av totally banned in September.

One of the lessons to be learned out of the whole Av affair is that the FDA and EMA are not invincible organizations, as we always believed. They are "human" after all; they can make mistakes and will always be vulnerable to the mighty reach of the media, the industry, and local politics. Nonetheless, a number of positive steps have taken place as a direct result of the Av debate. For instance, the FDA now insists on documentation of improvements in cardiovascular outcomes with all new oral hypoglycemic agents (otherwise, what's the point of lowering blood sugar with an anti-diabetes agent if this was to be made at the expense of raising cardiovascular risk?). The general public and the medical community demand better evaluation and greater safety surveillance of new drugs. Existing flaws have been identified and regulatory organizations are expected to rise from the ashes of Av much stronger, more transparent and fiercely independent than before to successfully serve us all in the future.

Finally, a word of praise for the Saudi FDA who in March 2010 was first in the world to suspend Av.[9] They were obviously convinced of the scientific evidence stacked against Av, and so decided not to sit on the fence, or wait for others to take action. Politically, it must have been an extremely unpopular decision to make at the time, however, they must have felt science was fully on their side, and that itself was a good enough reason for them not to concede to outside pressure.

Disclosure. This editorial has no conflicting interests and has not received support or funding from any drug company.

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