



Rosiglitazone: the prescribing dilemma continues

From an editorial perspective it has been of considerable interest to observe the Pandora's Box phenomenon that has followed the now much publicised meta-analysis paper¹ in respect of rosiglitazone and possible increased risk of myocardial infarction. Sensation-seeking headlines have appeared within the popular press ('Is Avandia the next Vioxx?'),² whilst medical journals have provided prominent coverage in news sections ('Study links diabetes drug to heart deaths').³ The intensity of interest has largely obscured any easy interpretation of the issue, particularly as the debate is far from concluded with uncertainties of actual risk still to be established.⁴ Some prominent editorial leaders have attempted to maintain a measure of commonsense, arguing the need for a 'calmer and more considered approach'⁵ and cautioning against 'overreaction',⁶ whilst our own commissioned commentary favoured 'a pragmatic approach'.⁷

Key questions

Certainly, many questions remain unanswered, but it is salutary to note how the use of relative changes in effect (so favoured in drug trials when positive and in subsequent drug marketing) can work to disadvantage in this negative context, when in reality the much smaller dimension of absolute change may be more meaningful. Current outstanding key questions are whether the reported adverse effects with rosiglitazone, if proven, are drug specific or whether they might be a drug class effect with implications for the other current alternative thiazolidinedione (TZD), pioglitazone. So far the FDA has advised caution for both drugs, but this primarily rests on an increased heart failure risk known to be common to both.⁸ The real immediate question from patients and prescribers alike is 'what to do?': what are the real risks with TZDs; do the potential risks merit withdrawal of TZD prescribing; and, if so, what are the alternative therapeutic options? Not forgetting the importance of continued lifestyle attention, the tried and tested traditional therapies of metformin and second generation sulphonylureas still serve well in the oral treatment of type 2 diabetes, whilst the new DPP4 inhibitors, yet to be fully evaluated in clinical practice, are another consideration in the available drug armamentarium.

We believe guidelines on drug prescribing are important in supporting good clinical practice⁹ but recognise the need to revise recommendations in the light of new evidence. To determine definitive guidance on TZD prescribing just at this moment in time is very difficult, and professional bodies such as the Association of British Clinical Diabetologists will now no doubt wait until there is greater clarity. In the meantime, individual opinion will be held and championed such as by Bob Ryder, who has marshalled his arguments (see Personal Comment on page xxx) promoting a prescribing switch from rosiglitazone to pioglitazone on the basis of reported differences

between the two TZDs. Although new prescribing already may have shifted in the light of these recent reports, such a switch in existing usage takes the issue that one step further. A round-robin peer consensus enquiry suggests that not everyone is yet ready to take this step, but in the true spirit of open debate we feel that it is important to publish Bob Ryder's paper and will be interested to learn of readers' views on his recommendation.

The learning message

The whole episode will surely go down as a milestone in the way we introduce new drugs for diabetes. Issues concerning the adequacy of trial data provided for regulatory purposes and its relevance to the wider population post licensing have rightly been highlighted. Certainly, emphasising the ongoing need for careful surveillance of drug outcomes post marketing launch, both from further controlled studies as well as observation from open clinical practice, is essential. New treatments for diabetes are still much needed but perhaps the learning message from this experience is that new therapies, however welcome in principle, must be embraced with objective circumspection¹⁰ and a considered commitment to our patients' best interests. Ryder's reminder of 'primum non nocere' is appropriate.

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References

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