Editorial

The Rosiglitazone Controversy : The Indian Perspective

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In this era of evidence based medicine and drug discovery we are fortunate to get new molecules as treatment options but they are under continuous pharmacovigilance.The arrival of the thiazolidione compounds (also known as 'glitazones') with the introduction of troglitazone for treatment of type 2 diabetes heralded a new era in the management of type 2 diabetes. For the first time, a class of drugs to address the main pathophysiological defect in type 2 diabetes namely, impaired insulin action (or insulin resistance) had become available.[1] Hardly had the euphoria regarding troglitazone settled with sales in excess of 2.1 billion dollars, when the drug had to be abruptly withdrawn following its hepatotoxic effects leading to 63 deaths in the United States.[2] The introduction of the two subsequent drugs in this class namely rosiglitazone and pioglitazone was therefore viewed with great suspicion with the Food and Drug Administration (FDA) initially recommending mandatory liver function tests.[3] It soon became apparent that these two classes of drugs were not hepatotoxic and liver function tests were soon declared unnecessary. However, they were not without side effects. Weight gain, pedal edema, a mild drop in haematocrit and fluid overload had been reported from studies abroad[4] and from India.[5] A slight increase in risk of cardiac failure has also been documented with both rosiglitazone[6] and pioglitazone[7] and these side effects appear to be a class effect. Meanwhile, there were also exciting positive developments. The ADOPT study showed that rosiglitazone scored over both Metformin and Glyburide (Glibenclamide) with respect to slowing down of monotherapy failure in newly diagnosed type 2 diabetic subjects.[8] Going a step further, the "DREAM" study showed a 62% risk reduction in development of diabetes in subjects with pre-diabetes,[6] albeit, the effect being sustained only as long as the drug is taken.[9] These two studies thus raised the possibility for the first time of using this class of drugs as first line therapy in type 2 diabetic subjects, or indeed even at the stage of pre-diabetes, if lifestyle measures failed. It is against this background that the recent rosiglitazone controversy which has shaken the medical world via lay media should be viewed.

The whole controversy erupted after a statistical tool called meta-analysis was published in a leading medical journal. In this era of evidence based medicine clinicians have to rely on mathematical tools and biostatisticians. Variability is an inherent characteristic of the biological world .Human biology usually follows Gaussian (normal) distribution and at best we rely on 95% confidence intervals. When sufficient numbers are not available to get a 95% confidence intervals then biostatisticians pool data and do a meta-analysis of a well recognized databases like Medline etc. Such database search small studies which can be collated and need to be homogenous both in design and study pattern. The current controversy shows us how such meta-analytical tools can be misleading and lead to even inaccurate conclusions. Nevertheless when doubts are created in suspicious human clinical minds it can significantly impact a trend. India is the epicenter of Diabetes epidemic with 42 million Indians being diabetic.[10] The Asian Indian community both native and migrant is particularly vulnerable and susceptible to cardiovascular disease .Thus such doubt however small must be clarified from the Indian perspective

A recent meta analysis published in the New England Journal of Medicine (NEJM) by Nissen et al[11] has raised concerns regarding the increased risk of coronary artery disease among subjects on rosiglitazone treatment. Analysis of 42 trials showed the risk for myocardial infarction to be 1.43 times higher, and death due to cardiovascular causes to be 1.6 times higher, in subjects on rosiglitazone treatment compared to the control group.[11] In other words, rosiglitazone was associated with a 43% increase in risk of myocardial infarction which was statistically significant and 64% increase in

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death from cardiovascular causes which however was not statistically significant. Analyses of the 42 studies showed that 40 of them were small and all these put together did not yield statistically significant difference for myocardial infarction (MI) between groups. Of the 42 studies included 30 were unpublished and none of them were designed to address Myocardial Infarction as either primary or secondary endpoint. Medline or standard database search was excluded and the manufacturer's website was the source. Several studies in published literature which addressed specifically cardiovascular issues were excluded. Thus it was a weak and flawed metaanalysis. In contrast, combining ADOPT and DREAM, the two large studies showed a significant difference in MI between the study groups although either study alone did not show a statistically significant risk of coronary artery disease. A major limitation of this meta-analysis is that it was confined to summary data and was not extrapolated to the actual data sets where time to events would have added valuable information. An accompanying NEJM editorial admits these serious limitations in the metaanalysis and states "the weakness which are largely related to the quality of the available data, are nonetheless substantial. A few events either way might have changed the findings for myocardial infarction or for death from cardiovascular causes. In this setting, the possibility that the findings were due to chance cannot be excluded".[12]

An independent analysis by GlaxoSmithKline published by Ronald L Krall in the Lancet Online May 30, 2007 showed the incidence of the composite cardiovascular endpoints was 1.75 events per 100 patient- years for the rosiglitazone containing regimen and 1.76 events per 100 patient-years for the non-rosiglitazone containing regimen (hazard ratio 0.93, 95% CI : 0.80 – 1.10).[13] Responding quickly to the metaanalysis by Nissen et al [10], the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes (RECORD) study investigators did an unplanned interim analysis of their results two years before the study was scheduled to conclude.[14] The RECORD study focused on comparing the hospitalization or death from cardiovascular causes in subjects receiving metformin or sulfonylurea [n=2220] with add-on rosiglitazone (rosiglitazone group), against combination of metformin plus sulfonylurea (control group) [n=2227]. The results indicated no statistically significant differences in the overall risk of hospitalization or death from cardiovascular causes between the study groups.[14] The results were (not surprisingly) inconclusive as this is an interim analysis after 3.75 years of median follow up and thus lacked adequate power as the original analysis was planned to be done after 6 years of median follow up.

A series of three editorials in NEJM[15-17] subsequently discussed the rosiglitazone controversy at length, which thanks to media hype, political interference and other non-scientific reasons has snowballed into a veritable medical storm, the like of which has not been witnessed in recent times.

From a purely statistical perspective, these results would indicate a slight increase in risk for MI / coronary artery disease among subjects on rosiglitazone. However, a closer analysis of these data would indicate that the presently available data are not conclusive as none of the studies had cardiovascular disease (CVD) as primary end-points except RECORD. In the RECORD study, only an interim analysis was published which had inadequate power to assess CVD outcomes. Neither ADOPT nor DREAM had CVD as primary end-points and neither showed a significant increase in CVD risk by themselves. Adding up studies which individually show no risk and ending up with a result that shows risk may be statistically acceptable, but is it clinically relevant? Several Societies like the American Diabetes Association, Endocrine Society in the US, American Association of Clinical Endocrinologists have come out with statements urging physicians and patients not to panic and stop the medication but to undergo a reevaluation by their treating physicians and make decisions with them. Also they all again emphasize the relevance of good glycemic control. Even the US FDA has not withdrawn the drug but asked for strict review and some changes have been made on the prescription label. The US FDA website is periodically updated and it is worthwhile keeping updated. The EU regulatory agencies have also not withdrawn the drug.

What stance should we as physicians in India take at the present moment with respect to Glitazones in general and Rosiglitazone in particular?

This issue is of great importance with regard to Indians as it is well known that Indians are at high risk for both diabetes[18] and premature CVD.[19] According to the latest available prescription analysis by one of the agencies, rosiglitazone alone is used in 3.4% of patients and in combination with an additional OHA in 3.7% of patients (i.e. a total of 7.1% of type 2 diabetic patients in India are treated with rosiglitazone).

In our experience, whenever glitazones are withdrawn, the glucose control almost certainly worsens. In several cases, the good glycemic control obtained with glitazones has not been matched by any other class

of drugs, including in some cases, even by insulin. If rosiglitazone is withdrawn from the regime, a large number of these patients will need to go on to insulin injections. Indeed, the converse is also true. When these agents were introduced, several patients who were on insulin could go off injections altogether. Undoubtedly, patients' safety comes first and there should not be any compromise on this score. However, if the evidence is not 'black and white' but 'grey' zone, it is our duty as physicians and diabetologists to shift the chaff from the grain when reviewing the evidence. A recent commentary in correlation with a similar combination with respect to ACE / ARB treatment in hypertension discusses at length, the limitations of such metaanalyses and cautions us about their overinterpretation.[20]

At this juncture, we would recommend the following actions with respect to rosiglitazone while treating patients in India

1. Reassure patients and physicians that there is nothing to panic.
2. Advise patients not to abruptly stop their medications but discuss it with their physician and under medical supervision of experts decide on case to case basis a plan which meets patient's safety and therapy concerns.
3. Ensure that current glycemic control & non glycemic comorbid conditions are validated by not just fasting and postprandial blood glucose but do a glycosylated hemoglobin test, lipid profile,hematocrit and electrocardiogram(with or without an echocardiogram)
4. If they have established heart disease, it may be worthwhile to discuss with their physician / cardiologist about stopping the drug and appropriately adjusting their anti-diabetic medications.
5. If the physician is convinced about any concern then there are other options available in the same class, other class as well as Insulin. Both options need patient education and physician supervision to ensure patient safety risk as well as the glycemic control is well balanced as well as monitored periodically.
6. New patients with type 2 diabetes at risk of heart disease could probably be given alternate drug therapies until further evidence emerges with respect to the safety of this class of drugs.
7. Strict adherence to CVD risk reduction i.e. Aspirin (or Clopidrogel), Statin, ACE (or ARB) inhibitors, weight reduction, tighter glucose and BP control and stricter cardiac evaluation in all diabetic patients.
8. Individualized comprehensive evaluation and cardioprotective measures can be re-addressed and its an ideal opportunity for patient education to ensure that they are in control of their diabetes and vascular risk.

In India which is faced with the twin epidemic of Diabetes and Heart disease, it is mandatory that we follow standard guidelines which advocate routine co prescription of Aspirin (or Clopidrogel) and Statin with or without ACE (or ARB) for every diabetic adult patient especially above thirty years of age. It is time to routinely use the polypill concept of SAMTA in every case to ensure that the vulnerable at risk Asian Indian Diabetic is protected from the ravages of the vascular complications.[21]

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