

## Was Risk Properly Assessed in Carter, *et al*'s Safety Assessment of Tumor Necrosis Factor Antagonists During Pregnancy?

To the Editor:

We read with great interest the article by Carter, *et al*<sup>1</sup>, which is the first to suggest that women exposed to tumor necrosis factor- $\alpha$  (TNF) antagonists during pregnancy may experience an increased risk of congenital anomalies. Thus this report may have a chilling effect on utilization of these medications in women of child-bearing age suffering conditions that might benefit from their use. Moreover, these drugs are currently being investigated for their use prior to pregnancy. We applaud the authors for recognizing "limitations" that might compromise the reliability of their findings. However, the limitations listed in the Discussion<sup>1</sup> are not reflected in the data analysis found in the Results<sup>1</sup>.

The article follows an abstract presented at the 2007 American College of Rheumatology/Association of Rheumatology Health Professionals meeting<sup>2</sup>. We are aware of 2 commentaries. Each broaches important questions regarding the article's conclusions. The first is a Powerpoint presentation that discusses limitations to the interpretation of the US Food and Drug Administration (FDA) database<sup>3</sup>. The second is a commentary placed on the Johns Hopkins website that makes several critical observations<sup>4</sup>.

First, it was noted that the data collected were voluntary and, therefore, may not represent the true number of congenital anomalies within the population. Second, the data reviewed did not support the calculation of a denominator necessary for the calculation of incidence. Third, there is little discussion about coexisting risk factors likely to be present in an atypical obstetrical population that might benefit from TNF- $\alpha$  antagonist therapy. Women who continue TNF- $\alpha$  antagonists into pregnancy are likely to have more active disease associated with adverse outcome, independent of the medication being taken. In addition, individuals prescribed TNF- $\alpha$  antagonists are often given the known teratogens methotrexate and leflunomide concomitantly. A sensitivity analysis should have been performed excluding these patients on concurrent teratogenic medications to see if the Poisson probabilities they calculated were still valid. The review states that these factors make the "connection between exposure and outcome difficult to support." Finally, the congenital anomalies reported in this study tend to be the most common in the population, further compromising any correlation between drug exposure and specific anomaly incidence. The analysis in the Results<sup>1</sup> does not address these limitations.

Carter, *et al* conclude their article with the suggestion that there is an excess of anomalies of the VACTERL association. The VACTERL association is a constellation of 7 anomalies. For a diagnosis, at least 3 of these anomalies must be identified in a single patient. According to this criterion, no patient reported in this study qualifies for the diagnosis. Therefore the reported anomalies can be regarded only as sporadic and not as a manifestation of the VACTERL association. Conclusions suggesting an increase in VACTERL-associated anomalies are problematic.

The analysis performed by Carter, *et al* is inherently biased. They summarize their data in Table 2 with p values calculated in an admittedly flawed manner. Moreover, Table 2 appears to have been constructed ad hoc: the only anomalies reported in the table were those identified in an

incident report. This selection method ignores all anomalies not reported in an incident report. Anomalies that occurred at a reduced rate with TNF- $\alpha$  antagonist exposure, therefore, were not included. This creates a selection bias. In a more appropriate experimental design, where the list of possible anomalies is generated prior to data analysis, the table would include anomalies that both were and were not reported to the FDA. This would have prevented the positive sampling error observed at this stage of analysis.

Finally, the Carter, *et al* study may have made improper use of the FDA database: It is a review of data gathered by the FDA through their online Adverse Event Reporting System (AERS), which could be requested through their website. We reviewed the FDA's instructions. We found that the FDA prohibits the calculation of disease incidence as well as the association of disease with the use of any drug. "Accumulated reports cannot be used to calculate incidence (occurrence rates) or to estimate drug risk. Comparisons between drugs cannot be made from these data." Not only did Carter, *et al* utilize the data set precisely in the prohibited manner, they did not acknowledge the FDA prohibition in their article. While examination of AERS data has led to useful insights, the FDA has, nonetheless, placed explicit limitations on their use that clearly have anticipated the problems identified with this article<sup>5</sup>.

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