

# Biologics Tied to Greater Risk of Adverse Events

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FROM THE COCHRANE COLLABORATION

**B** biologics appear to be associated with a significantly greater rate of total adverse events, withdrawals due to adverse events, and an increased risk of tuberculosis reactivation compared with control agents, based on a meta-analysis involving more than 60,000 patients.

However, there were no significant differences in the rates of serious adverse events, serious infections, lymphoma, and congestive heart failure between biologics and control agents, wrote Dr. Jasvinder A. Singh and his coauthors (Cochrane Database Syst. Rev. 2011 [doi: 10.1002/14651858.CD008794.pub2]); <http://www2.cochrane.org/reviews/en/ab008794.html>.

The results come from a network meta-analysis and Cochrane overview of the adverse effects of biologic drugs that are approved for the treatment of rheumatoid arthritis and other conditions in Europe, the United Kingdom, the United States, Canada, and Australia.

The investigators included randomized controlled trials (RCTs), controlled clinical trials, and open-label extension studies that involved one of the nine biologics for

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**Major Finding:** In the short term, biologics as a group were associated with a significantly greater rate of total adverse events (odds ratio 1.19), and withdrawals due to adverse events (OR 1.32), as well as an increased risk of TB reactivation (OR 4.68), compared with control agents.

**Data Source:** A meta-analysis of data from 163 randomized controlled trials with 50,010 adult participants and 46 extension studies with 11,954 adult participants.

**Disclosures:** Dr. Singh and several of his coauthors reported that they have significant financial relationships with several pharmaceutical companies.

use in any indication and that reported this study's prespecified adverse outcomes. The researchers did not include studies on biologics for the treatment of HIV/AIDS. The nine biologics investigated were abatacept (Orencia), adalimumab (Humira), anakinra (Kineret), certolizumab pegol (Cimzia), etanercept (Enbrel), golimumab (Simponi), infliximab (Remicade), rituximab (Rituxan/MabThera), and tocilizumab (Actemra). They searched the Cochrane Library, Medline, and Embase (through January 2010).

The investigators performed mixed-effects logistic regression using an arm-based, random-effects model within an empirical Bayes framework for the network meta-analysis.

In all, included in the analysis were 163 RCTs with 50,010 adult participants and 46 extension studies with 11,954 adult

participants. The median duration was 6 months for the RCTs and 13 months for the extension studies. Given the short duration of the RCTs, all the results should be interpreted as applying to a fairly short time frame.

After the analysis was adjusted for dose, biologics as a group were associated with a significantly greater rate of total adverse events (odds ratio 1.19) and withdrawals due to adverse events (OR 1.32), as well as an increased risk of TB reactivation (OR 4.68), compared with control agents.

Certolizumab pegol was associated with a significantly greater risk of serious infections than was control treatment (OR 3.51), according to the report. Infliximab was associated with a significantly greater risk of withdrawals due to adverse events compared with the control (OR 2.04).

Heart failure and cancer have been of particular concern with the use of biologic drugs.

There appears to be little or no difference in the number of people who experienced heart failure or cancer taking any biologic compared with people who took placebo. However, there were not many cases of congestive heart failure or cancer, so confidence in these results is low.

The researchers also were able to indirectly compare individual biologics.

These analyses revealed that abatacept and anakinra were associated with a significantly lower risk of serious adverse events than were most other biologics. In addition, certolizumab pegol was associated with significantly greater odds of serious infections than were etanercept, adalimumab, abatacept, anakinra, golimumab, infliximab, and rituximab. Abatacept was significantly less likely than infliximab and tocilizumab to be associated with serious infections; abatacept, adalimumab, etanercept, and golimumab were significantly less likely than infliximab to result in withdrawals due to adverse events.

"There is an urgent need for more research regarding the long-term safety of biologics and the comparative safety of different biologics," they concluded. ■

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