

NEW DRUG REVIEW

Infliximab in Pediatric Crohn's Disease Patients

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The US Food and Drug Administration (FDA) recently approved an expanded indication for infliximab (Remicade, Centocor) to include a labeled use in pediatric patients for the treatment of Crohn's disease. Beyond antibiotics, virtually none of the medical therapies used to treat inflammatory bowel disease (IBD) have had a pediatric indication up until now and therapy for this population has been conducted largely off-label. This ruling sets a precedent, at least among biologic agents, that will foster new research in pediatric patients and set an example for the pharmaceutical industry, in terms of demonstrating efficacy and safety, to achieve FDA approval. FDA approval is also important in that it promotes acceptance and payment among insurers, allowing for greater patient access to helpful medications.

Clinical trials in pediatric patients pose several problems. They are largely conducted with drugs that are already marketed and are thus more difficult to recruit. In addition, they present an ethical dilemma in terms of achieving informed consent from young people, which makes placebo control a difficult issue. The phase III REACH (Randomized Multicenter Open-label Study to Evaluate the Safety and Efficacy of Anti-TNF Monoclonal Antibody Remicade in Pediatric Subjects with Moderate to Severe Crohn's Disease) was designed to address these problems while still testing the efficacy of infliximab in pediatric patients.

REACH was an open-label trial of 112 patients age 6–17 with moderate to severely active Crohn's Disease who had failed treatment with immunomodulators, either with or without steroidal cotherapy. All patients were administered standard-dose (5 mg/kg) infliximab at weeks 0, 2, and 6 and clinical response was achieved in 88.4%. Responders were then randomized to maintenance therapy of standard dosing once every 8 weeks



(q8) or once every 12 weeks (q12). After 1 year, 56% of the q8 maintenance patients were in clinical remission as were 24% of the q12 patients. Nonresponders in the q12 group were stepped up to q8 therapy and achieved similar results.

REACH was not powered to definitively test the safety of one dose over the other, though there were two cases of herpes zoster in the q8 group and none in the q12 group. The main safety concern with this expanded indication is the FDA's ruling to add a black box warning label regarding isolated cases of hepatosplenic T-cell lymphoma that have been reported in adolescent and young adult patients. Because infliximab is prescribed in pediatric cases as last-line therapy in combination with immunomodulators, and because there have been cases of lymphoma reported in Crohn's patients not on infliximab, more research is necessary to determine what drug, or combination of drugs, is at the root of this rare adverse event. FDA is requiring the manufacturer to conduct a postmarketing longitudinal study of 2,000 pediatric patients on infliximab to get a better understanding of this problem. Until the cause is determined, patient education about possible risks will be the most important precaution for prescribing physicians.

Results of the REACH study have been out for several years and physicians are already comfortable with the use of infliximab in pediatric patients. However, the FDA encourages pediatric labels and now, with biologic agents, a benchmark has been achieved that will make labeled indication the expected norm. I think this is an exciting development that will allow researchers to start asking important questions about how these drugs impact on pediatric growth and development.