

TNF blockers may increase the risk of malignancy in children

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The Food and Drug Administration (FDA) received reports of malignancies in children using tumor necrosis factor a (TNF) blockers, raising concerns of an associated risk and prompting an investigation. Researchers from the FDA set out to identify all reports of malignancy in children using infliximab, etanercept, and adalimumab and their report is published in the August issue of *Arthritis & Rheumatism*, a journal of the American College of Rheumatology.

The FDA has approved 3 TNF blockers for use in children: Etanercept to treat juvenile idiopathic [arthritis](#) (JIA); infliximab to treat Crohn's disease; and adalimumab to treat JIA. Data suggest that certain adult populations may be at an increased risk of [malignancy](#) with TNF blocker therapy. The immunosuppressive properties of TNF blockers may also increase the risk of malignancy in children, but to what extent is unclear.

Cancer is very rare in children. According to the National Cancer Institute's Surveillance, Epidemiology, and End-Results (SEER) database, the U.S. annual incidence rate for all cancers in children ages 0-17 years was 16.8/100,000 compared with the rate of 469.7/100,000 for all cancers in adults, age adjusted to the year 2000 U.S. population. When 48 incidences of malignancy were identified among pediatric patients treated with TNF blockers, there was cause for concern. Study leader Peter Diak, Pharm.D., explains. "The number and rare types of malignancies reported in these cases are worrisome given the underreporting of adverse events in the Adverse Event Reporting System

(AERS) database, the long latency period of malignancy, and the relatively small number of pediatric patients treated with TNF blockers."

The study team searched the AERS database for all reports of malignancy in children using infliximab, etanercept, and adalimumab who initiated therapy between the ages of 0 and 18 years. The 48 cases identified included 31 following infliximab use, 15 following etanercept use, and 2 following adalimumab use. The reporting rates for infliximab and etanercept were compared with the background cancer rate in the general pediatric population. Reporting rates were not calculated for adalimumab because only 2 cases were reported, and previous use of other TNF blockers was reported in both cases. Most of the children evaluated received TNF blocker therapy for a prolonged period—a median of 30 months—suggesting these cases were not preexisting malignancies that were misdiagnosed as a rheumatic condition.

The analysis showed the reporting rate for U.S. cases of malignancy in children for infliximab was 66 per 100,000 patient years, 4 times the estimated background rate for the general U.S. pediatric population. For lymphomas in children, the reporting rate was 44 per 100,000 patient years, 18 times the background rate. If cases of hepatosplenic T cell lymphoma are excluded from the calculation, the reporting rate for lymphomas with [infliximab](#) drops to 22 per 100,000 patient years but still exceeds the background rate by 9 times. For etanercept, the reporting rate for U.S. cases of malignancy in children was 22 per 100,000 patient years and approximated the background rate. However, for lymphomas, the reporting rate with etanercept was 11 per 100,000 patient years, 5 times the background rate for lymphomas in children.

The team concludes that the risk of malignancy should be considered prior to initiating TNF blockers in children, particularly as some of the reported cases involved types of cancers not commonly seen in children

and that are usually associated with immunosuppression. Further, they suggest that the true incidence rate for these events in the pediatric population may be even higher due to substantial under-reporting to FDA's MedWatch program. Another concern is that the latency period of malignancy indicates there may be an extensive interval between the onset of TNF blocker treatment and the diagnosis of malignancy. Dr. Diak comments, "The number of reported cases of malignancy in children using TNF blockers is likely to increase as the usage and duration of therapy with TNF blockers increases."

He cautions, however, that the cases were confounded by the potential underlying risk of malignancy in patients with autoimmune disease and the use of concomitant immunosuppressants, preventing a clear causal relationship from being established.

The paper is accompanied by an editorial which points out that while the study raises a key concern, it is important to recognize that 25 of the 48 cases of malignancies occurred in children with inflammatory bowel disease who were also receiving immunosuppressants and thus the study findings are not directly relevant to children with JIA. The editorial, written by Thomas Lehman, M.D., from the Hospital for Special Surgery and Weill Medical College at Cornell University in New York, also highlights that there is no convincing evidence that the use of TNF blockers in children with JIA is associated with an increased risk of [malignancy](#) beyond that due to the disease alone or the disease when treated with methotrexate.

More information: "Malignancy in Children and Tumor Necrosis Factor a Blockers: Forty-Eight Cases Reported to the Food and Drug Administration." Peter Diak, Jeffrey Siegel, Lois La Grenade, Lauren Choi, Steven Lemery, and Ann McMahon. *Arthritis & Rheumatism*; Published Online: April 13, 2010 ([DOI: 10.1002/art.27511](https://doi.org/10.1002/art.27511)); Print Issue Date: August 2010.

"Should the Food and Drug Administration Warning of Malignancy in Children Receiving Tumor Necrosis Factor a Blockers Change the Way We Treat Children With Juvenile Idiopathic Arthritis?" Thomas J. A. Lehman. *Arthritis & Rheumatism*; Published Online: April 13, 2010 ([DOI: 10.1002/10.1002/art.27506](https://doi.org/10.1002/10.1002/art.27506)); Print Issue Date: August 2010.

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