EVIDENCIAS EN PEDIATRÍA
Toma de decisiones clínicas basadas en las mejores pruebas científicas
www.evidenciasenpediatria.es

Critically Appraised Articles

Infliximab treatment in inflammatory bowel disease does not increase the risk of malignancy

Pérez-Moneo Agapito B[1], Molina Arias M[2]
[1]Hospital Universitario Infanta Leonor. Madrid. Spain.
[2]Department of Gastroenterology. Hospital Infantil Universitario La Paz. Madrid. Spain.

Correspondence: Begoña Pérez-Moneo Agapito, begona.perezm@salud.madrid.org

English key words: tumor necrosis factor antagonist, inflammatory bowel disease, cancer risk, hemophagocytic lymphohistiocytoses.
Spanish key words: factor de necrosis tumoral alfa/antagonistas e inhibidores, enfermedad inflamatoria intestinal, riesgo de malignización, linfohistiocitosis hemofagocítica.

Reception date: October 9, 2017 • **Acceptance date:** October 13, 2017
Publication date: October 18, 2017

Evid Pediatr. 2017;13:51.

HOW TO CITE THIS ARTICLE

Pérez-Moneo Agapito B, Molina Arias M. Infliximab treatment in inflammatory bowel disease does not increase the risk of malignancy. Evid Pediatr. 2017;13:51.

This article is available at http://www.evidenciasenpediatria.es/EnlaceArticulo?ref=2017;13:51
 • ISSN: 1885-7388

Infliximab treatment in inflammatory bowel disease does not increase the risk of malignancy

Pérez-Moneo Agapito B[1], Molina Arias M[2]
[1]*Hospital Universitario Infanta Leonor. Madrid. Spain.*
[2]*Department of Gastroenterology. Hospital Infantil Universitario La Paz. Madrid. Spain.*

Correspondence: Begoña Pérez-Moneo Agapito, begona.perezm@salud.madrid.org

Artículo original: Hyams JS, Dubinsky MC, Baldassano RN, Colletti RB, Cucchiara S, Escher J, *et al*. Infliximab is not associated with increased risk of malignancy or hemophagocytic lymphohistiocytosis in pediatric patients with inflammatory bowel disease. Gastroenterology.2017;152;1901-14.

Abstract

Authors' conclusions: exposure to infliximab is not associated with an increased risk of malignancy or hemophagocytic syndrome in children with inflammatory bowel disease. Exposure to thiopurines is an important antecedent for the development of these complications.

Reviewers' commentary: the use of infliximab and other biological therapies does not seem to increase the risk of onset of tumors in the medium term, although it would be advisable to prolong the follow-up time. Primary and secondary prevention measures should be recommended, especially if patients are treated with thiopurines and have not had primoinfection by Epstein-Barr virus.

Key words: tumor necrosis factor antagonist, inflammatory bowel disease, cancer risk, hemophagocytic lymphohistiocytoses.

El tratamiento con infliximab en la enfermedad inflamatoria intestinal no aumenta el riesgo de tumores

Resumen

Conclusiones de los autores del estudio: la exposición a infliximab no se asocia a un mayor riesgo de malignidad o síndrome hemofagocítico en niños con enfermedad inflamatoria intestinal. La exposición a tiopurinas sí es un antecedente importante para el desarrollo de estas complicaciones.

Comentario de los revisores: el uso de infliximab y otras terapias biológicas no parece aumentar el riesgo de aparición de tumores a medio plazo, aunque sería conveniente ampliar el tiempo de seguimiento. Se deben recomendar medidas de prevención primaria y secundaria, especialmente si están tomando tiopurinas y no han tenido primoinfección por virus de Epstein-Barr.

Palabras clave: factor de necrosis tumoral alfa/antagonistas e inhibidores, enfermedad inflamatoria intestinal, riesgo de malignización, linfohistiocitosis hemofagocítica.

STRUCTURED ABSTRACT

Objective: to compare the incidence of malignancy in patients with inflammatory bowel disease (IBD) exposed and not exposed to biologic therapy (infliximab).

Design: multicentre prospective cohort study.

Setting: 82 paediatric gastroenterology units in the United States (56) and the European Union (EU) (26).

Study population: 5766 patients managed over a period of 9 years, with a confirmed diagnosis of IBD, aged less than 17 years in the United States and between 6 and 17 years in the EU. Patients were compared with a United States population database (SEER). The planned duration of followup is 20 years.

Risk factor assessment: the study population was divided in three cohorts: 2824 patients exposed to biologic therapy (anti-tumour necrosis factor [anti-TNF] or other), 2396 exposed to infliximab (IFX) (a subset of the biologics cohort) and 2942 exposed to non-biologic agents (aminosalicylates, corticosteroids, thiopurines [TP], methotrexate or antibiotics).

All study cohorts were stratified by TP or methotrexate exposure.

Outcome measurement: the authors calculated the rates of malignancy and haemophagocytic lymphohistiocytosis (HLH) per 1000 patient-years of followup for each cohort, as the quotient of the total number of malignancy events and cumulative patient-years of exposure multiplied by 1000. Results were expressed with the corresponding 95% confidence intervals (95 CI). The rates were stratified by TP or methotrexate exposure, so that single participants could contribute to more than one cohort in patient-years of followup based on the received treatments.

The authors assessed the risk relative to that of the general population by means of the standardised incidence ratio (SIR), calculated as the quotient of the number of events observed in each cohort and the expected number of events in the reference population. The SIRs and their corresponding 95 CIs were adjusted for sex, age and race.

Main results: the mean duration of followup was 4.7 years, with a total of 24 543 patient-years of followup. Fifteen tumours were detected (8 of them leukaemia/lymphoma), 10 in patients exposed to IFX (9 of who were also exposed to a TP). In all, 13 de los 15 tumours were associated with exposure to TP.

There were 5 cases of HLH, all in patients exposed to TP and none in those exposed to anti-TNF. Four were associated with primary infection by Epstein-Barr virus and one with infection by cytomegalovirus.

The unadjusted incidence rates in the cohort exposed to IFX showed no increase in the risk of malignancy (0.46/1000 patients-year) or of HLH (0/1000 patient-years) compared to patients not exposed to biologics (malignancy, 0.56/1000 patient-years, HLH 0.2/1000 patient-years).

The comparison with the reference population did not show any increase in the risk of malignancy in patients exposed to IFX (SIR: 1.69, 95 CI: 0.46 to 4.32) compared to patients not exposed to it (SIR: 2.17, 95 CI: 0.59 to 5.56), even in the analysis in which the data were stratified by TP exposure.

Conclusion: exposure to IFX is not associated with an increased risk of malignancy or HLH in children with IBD, while TP exposure is an important risk factor for the development of these complications.

Conflicts of interest: the study sponsor was involved in the study design, analysis and interpretation of results, and writing the primary manuscript.

Funding source: Janssen Scientific Affairs.

COMMENTARY

Justification: the association between IBD and tumour development has been investigated for years.[1,2] Sustained inflammation is one of the causes that has been proposed, so more recent treatments are geared toward histologic or deep remission to limit its impact. These biologic therapies act on different parts of the immune system, so it is important to assess whether they can increase the risk of tumours by reducing "immunologic surveillance" in a population that is already more vulnerable.

Internal validity: the study population was clearly defined. Patients were enrolled consecutively, but the authors ensured that there were patients in each treatment group, without explaining how they did it, so we cannot exclude the possibility of selection bias. Exposure to pharmaceutical agents was measured in patient-years. The effect was measured in terms of the development of a tumour or HLH, taking into account the temporal association between the effect and the most recent treatment in the cases of participants that contributed to more than one cohort.

At the time of enrolment in the study, the biologic treatment cohorts had greater disease duration and severity. They had longer duration of followup, contributed more patients, and therefore more patient-years of followup. This could increase the frequency of the association between exposure and effect, a fact that is not noted in the study.

Authors controlled for potential confounders, stratifying participants by TP exposure and adjusting the analysis by age, sex and race, although performance of a multivariate analysis would have been of interest. Based on current guidelines, it is very likely that all patients treated with IFX have been treated with TPs at some point, so it would be interesting to document the time spent free of TP treatment.

Clinical relevance: the study found no increase in the risk of malignancy in the group treated with IFX compared to the population reference (SIR of 1.69 [95 CI: 0.46 to 4.32]). It also did not find a difference in comparison with the group not treated with biologics adjusted for the use of TP (0.53 versus 0.69 with TP, compared to 0.31 versus 0.32 without TP). The data showed a tendency toward an increased risk in every group treated with TPs, although the difference was not statistically significant, probably because the effect under study is rare. None of the patients with HLH had received IFX.

The absence of an association with tumour development is an important finding, as this is a very clinically relevant complication. For this reason, the duration of followup could be considered short.

Previous studies had already pointed at this outcome. The development of lymphoproliferative disorders and skin cancers is associated mainly with the use of TP and primary infection by Epstein-Barr virus.[3,4] There is also no evidence of an

increase in malignancy associated with the use of IFX in adults.[5]

The dilemma that arises is that there are clinical situations in which the use of TP as an adjuvant therapy is indicated (prevention of immunogenicity of biologic therapy, steroid sparing, etc). Such situations would require the establishment of the duration of treatment or consideration of the use of methotrexate, which in this study did not seem to be associated with malignancy.

Applicability to clinical practice: the use of infliximab and other biologic agents does not seem to increase the risk of tumour development in the medium term, although a longer duration of followup would be advisable. Nevertheless, IBD seems to increase the risk of certain tumours and HLH. Primary and secondary prevention measures need to be recommended, especially in patients receiving TP therapy and without a history of primary infection by Epstein-Barr virus.

REFERENCES

1. Kappelman MD, Farkas DK, Long MD, Erichsen R, Sandler RS, Sørensen HT, *et al.* Risk of cancer in patients with inflammatory bowel diseases: a nationwide population-based cohort study with 30 years of follow-up evaluation. Clin Gastroenterol Hepatol. 2014;12:265-73.e1.
2. Biank VF, Sheth MK, Talano J, Margolis D, Simpson P, Kugathasan S, *et al.* Association of Crohn's disease, thiopurines, and primary Epstein-Barr virus infection with hemophagocytic lymphohistiocytosis. J Pediatr. 2011;159:808-12.
3. Beaugerie L, Brousse N, Bouvier AM, Colombel JF, Lémann M, Cosnes J, *et al.* Lymphoproliferative disorders in patients receiving thiopurines for inflammatory bowel disease: a prospective observational cohort study. Lancet. 2009;374:1617-25.
4. Peyrin-Biroulet L, Khosrotehrani K, Carrat F, Bouvier AM, Chevaux JB, Simon T, et al. Increased risk for non-melanoma skin cancers in patients who receive thiopurines for inflammatory bowel disease. Gastroenterol. 2011; z141:1621-8.
5. Dulai PS, Siegel CA. The risk of malignancy associated with the use of biological agents in patients with inflammatory bowel disease. Gastroenterol Clin N Am. 2014;43:525-41.