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Reception date: October 10, 2017 • **Acceptance date:** October 13, 2017
Publication date: October 18, 2017

Evid Pediatr. 2017;13:60.

HOW TO CITE THIS ARTICLE

Navas López VM. Biologics, thiopurines and risk of malignancy development: is it time to change our clinical practice? Evid Pediatr. 2017;13:60.

This article is available at http://www.evidenciasenpediatria.es/EnlaceArticulo?ref=2017;13:60
 • ISSN: 1885-7388

Biologics, thiopurines and risk of malignancy development: is it time to change our clinical practice?

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The incidence of inflammatory bowel disease (IBD) has increased in recent decades in both adults and children. In the paediatric population, this increase has been marked and significant in children aged less than 10 years, who are characterised by presenting with more aggressive and extensive forms and a longer duration of disease. The goals of treatment in paediatric IBD are control of inflammation, mucosal healing, disease modification, prevention of adverse effects of treatment, and guaranteeing adequate growth and development.

The identification of factors predictive of a poor outcome at the time of diagnosis has become a priority of the initial evaluation of the patient.[1] The addition of biologic agents to the therapeutic armamentarium of paediatric IBD has contributed to the modification of the course of disease and an improved prognosis in these patients. The recently published results of a multicentre study with early introduction (within 90 days from diagnosis) of anti-tumour necrosis factor (anti-TNF) showed that this was associated with a decreased incidence of fistulising complications in the subsequent 3 years of followup.[2] A widespread approach is combination therapy with anti-TNF and azathioprine, which aims at improving remission rates and decreasing the formation of anti-TNF antibodies and the subsequent loss of response due to the immunogenicity of these components, especially in chimeric preparations.[3]

Before starting treatment, the benefits and risks of this therapeutic modality must be explained to the patient and the family, with particular emphasis on individual risk based on the characteristics of the patient. The potential consequences of not initiating the proposed treatment must also be explained. The overall risk of developing malignant disease in patients with inflammatory bowel disease that can be attributed to the prescribed medication is low, although there is evidence of increased susceptibility in specific patient subsets.[4] The article subject of this commentary concludes, within the methodological limitations already stated by the authors themselves as well as the reviewers, that exposure to infliximab is not associated with an increased risk of malignancy or haemophagocytic lymphohistiocytosis in children with inflammatory bowel disease, although such an association was found for thiopurines. These results do not support the current trend in some countries of not prescribing thiopurines in these patients, although it seems that the appropriateness of their use should be considered in patients without primary Epstein-Barr virus infection.[1] Table 1 presents the types of lymphoma that may develop during treatment with thiopurines, their risk factors and possible preventive measures.[4,5]

The chief conclusions are:

1. The overall risk of malignant complications in children with inflammatory bowel disease receiving thiopurines ± anti-TNF is low.

2. The use of thiopurines in patients without primary infection by Epstein-Barr virus has been associated with an increased risk of developing haemophagocytic lymphohistiocytosis, while no such case has been observed in patients treated with methotrexate, so the latter may be a valid and safe alternative in this subset of patients.

TABLE 1. FRISK FACTORS FOR LYMPHOMA AND HAEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS DURING THIOPURINE TREATMENT[4,5]

	Risk factors	Association with EBV	Preventive measure
Post-transplant-like lymphoma	Serology + EBV > age > risk	Yes	Sequential EBV loads. Same as in transplant patients Discontinue thiopurines after prolonged remission with low risk of recurrence
Early post-mononucleosis lymphomas	< 35 years, male sex Serology - EBV	Yes	Do not use AZA/6MP. MTX as alternative to thiopurines
Hepatosplenic T-cell lymphoma	< 35 years. Male sex AZA + Anti-TNF > 2 years	No	Reduce duration of combined therapy. MTX as alternative to thiopurines
Haemophagocytic lymphohistiocytosis	Serology - EBV Serology - CMV	Yes	Do not use AZA/6MP. MTX as alternative to thiopurines

6MP: mercaptopurine; **AZA:** azathioprine; **CMV:** cytomegalovirus; **EBV:** Epstein-Barr virus; **MTX:** methotrexate.

3. Combined treatment must be used for the shortest possible time, and only in clinical situations in which it has been proven to be efficacious.

4. These patients must be monitored closely for the early detection of these complications.

5. Patients at risk of developing complications within the next few months must be identified for the early initiation of anti-TNF therapy.

6. The risks and benefits of treatments must be explained in detail to the patient and his or her family.

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