

# **Subtherapeutic infliximab trough levels and complete mucosal healing are associated with sustained clinical remission after infliximab cessation in paediatric-onset Crohn's disease patients treated with combined immunosuppressive therapy**

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**Short title:** Infliximab cessation in paediatric-onset Crohn's disease

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**List of abbreviations:** ADL, adalimumab; ATI, antibody to infliximab; AZA, azathioprine; CD, Crohn's disease; CI, confidence interval; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FC, faecal calprotectin; GI, gastrointestinal; HR, hazard ratio; IBD, inflammatory bowel disease; IFX, infliximab; IQR, interquartile range; MH, mucosal healing; MRE, magnetic resonance enterography; PCDAI, Pediatric Crohn's Disease Activity Index; RBC, red blood cell; SES-CD, Simple Endoscopic Score for Crohn's Disease; 6-TGN, 6-thioguanine nucleotides; TL, trough level; TNF, tumour necrosis factor

## ABSTRACT

**Background and aims.** We aimed to investigate the outcome in paediatric-onset Crohn's disease patients who had discontinued infliximab after maintaining clinical remission with combined immunosuppression, and to determine factors associated with clinical relapse.

**Methods.** We conducted a retrospective observational study of 63 paediatric-onset Crohn's disease patients who had stopped scheduled infliximab during sustained corticosteroid-free clinical remission for at least 1 year with infliximab and azathioprine, and were followed up for at least 1 year thereafter. Cumulative relapse rates and the median time to relapse were estimated statistically. Factors at cessation were also evaluated for their association with clinical relapse.

**Results.** After a median follow-up period of 4.3 years (range, 1–7.5 years), 60.3% (38/63) of patients had experienced clinical relapse. According to Kaplan–Meier survival analysis, the estimated cumulative relapse rates at 1, 4, and 6 years were 19.0%, 62.2%, and 75.2%, respectively, and the median relapse time was 3.3 years from infliximab cessation. According to multivariate Cox proportional hazard regression analysis, infliximab trough levels of  $\geq 2.5$   $\mu\text{g/mL}$  and incomplete mucosal healing were associated with clinical relapse (HR=7.199, 95% CI=1.641–31.571,  $p=0.009$  and HR=3.628, 95% CI=1.608–8.185,  $p=0.002$ , respectively). Although retreatment with infliximab was effective in 90.9% (30/33) of patients, 7.9% (3/38) eventually underwent surgery within 1 year of relapse.

**Conclusions.** Considering the high cumulative relapse rates in the long term and cases of severe relapse requiring surgery, discontinuing infliximab in paediatric-onset Crohn's disease patients is currently inadvisable. However, there may be a subgroup of patients who are good candidates for infliximab withdrawal.

**KEYWORDS:** Infliximab, pharmacokinetics, mucosal healing

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