The switch to biosimilar infliximab as a cause of treatment cessation in 3 paediatric patients with Crohn's disease

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Abstract

Discontinuation of treatment in children with inflammatory bowel disease (IBD) in long-term remission remains debatable. The risk of relapse is one of the main concerns in the consideration of reduction or cessation of treatment. In 2017 all paediatric IBD patients treated with originator infliximab at the Department of Paediatric Gastroenterology, Ghent University Hospital, were switched to biosimilar Remsima®. Faecal calprotectin, infliximab through levels and antibodies, white cell count, haemoglobin and C-reactive protein were measured before and after switching to biosimilar. In total 21 IBD patients (3 Ulcerative Colitis – 19 CD) between 7 and 15 years old were switched. Three (14%) patients with CD in clinical, biochemical and histological remission had an unmeasurable through level and antibodies for infliximab, after 22 to 82 months of use. Switching to another treatment or cessation was discussed with patients and parents, all 3 patients decided to stop treatment. All 3 are still in clinical remission 21 to 24 months after treatment stop. Six-monthly follow-up is foreseen. (Acta gastroenterol. belg., **2020**, 83, **657-659**).

Key words : paediatrics, Crohn's disease, stop treatment

Introduction

The risks and benefits of treatment discontinuation in patients with inflammatory bowel disease (IBD) remain poorly investigated. In 3 paediatric patients with Crohn's disease (CD) in stable remission, antibodies for infliximab were detected. Cessation of treatment was discussed with patients and parents. We here present the clinical, and biochemical data of these patients before and after stopping treatment.

Case series

In 2017 the Belgian government firmly suggested to switch from originator infliximab to a biosimilar. Between October 2017 and February 2018, 21 paediatric IBD patients (3 ulcerative colitis, 19 CD) were switched from originator infliximab to biosimilar, Remsima® (CT-P13). BIRD recommendations support the use of Remsima® in IBD (1). Our centre used a reactive approach concerning through level measurement (2 out of 3 patients never had a through level, 1 in 3 had a trough level of 1.7 µg/ml 15 months before detecting antibodies) in biological use but switching to biosimilar was considered as a moment of precaution.

Faecal calprotectin (FCP), infliximab trough levels and antibodies, white blood cell count (WBC), haemoglobin (Hb) and C-reactive protein (CRP) were checked before and after switching from originator infliximab to biosimilar in our paediatric cohort.

In 3/21 (14%) IBD patients antibodies for infliximab were found. Table 1 shows clinical and biochemical data in all 3 patients with Crohn's disease (CD)(2). All were on monotherapy infliximab. In these 3 patients azathioprine was stopped 6 months after achieving clinical and biochemical remission with infliximab as a step-down strategy. None of the patients had previous surgery. Colonoscopy was performed with normal macroscopic view (Crohn's Disease Endoscopic Index of Severity (CDEIS) score of 0)(3) and confirmed histological remission in all. After discussing risks and benefits with patients and parents, all decided to stop treatment. The patients remained under six-monthly clinical and biochemical (Hb, CRP and faecal calprotectin) follow up, up till now without any clinical recurrence of disease.

Discussion

In 2018 ECCO published exit strategies in IBD as a guidance for clinical practice in order to make informed decisions in partnership with patients and parents (4). There are some general considerations before treatment cessation, and others are more specifically related to withdrawal of anti-TNF agents. In general, an appropriate evaluation of disease activity, patient preference and clinical follow-up after treatment withdrawal is advised. Gisbert et al systematically reviewed the risk of relapse after withdrawal of anti-TNF in IBD (5). In CD, the relapse rate was 38% at 6 months, 40% at 12 months and 49% > 25 months. The overall risk was 44% in 912 CD patients if only clinical remission was required before treatment stop, however when an endoscopic remission was the stop criterion, the relapse risk decreased to 26% (5). Only 3 exclusively paediatric studies on 62 patients were included in this review. They all used only clinical remission as stop criterion resulting in a comparable relapse rate as in adults (25/62 (40%) after 12 months) (6-8). One study including 11 children continued treatment with an immunomodulator after stop infliximab (8).

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Table 1. — **Characteristics, clinical and biochemical data at baseline and at follow up**

Characteristics	Girl, 16 y	Boy, 13 y	Boy, 15 y
Paris classification (1)	A1a L3 B1p G1	A1a L2 B1 G0	A1b L3 B1 G0
Time on infliximab	82 months	22 months	47 months
Trough level (mcg/ml)	negative	negative	negative
Antibodies (ng/ml)	41.2	64.3	24.2
At baseline			
Faecal Calprotectin (mg/kg)	16	46	19
CRP (mg/L)	< 0.6	< 0.6	0.7
Hb (g/dl)	12.6	12.6	14.7
WBC	5.85	6.61	5.79
BMI z score	-0.6	0.1	0.4
Height z score	-0.5	0.3	0.2
At follow up	21 months	24 months	23 months
Faecal calprotectin	29	78	226
CRP	< 0.6	2.0	7.2
Hb	12.5	13.1	14.3
WBC 10E3/µl	7.54	10.01	6.03
BMI z score	-0.3	0.2	0.2
Height z score	-0.6	0.5	0.3
STORI criteria score at baseline	2 Absence of surgery - Hb	4 Absence of surgery - Hb - Male - WBC	3 Absence of surgery – Male - CRP

Legend : CRP : C-reactive protein ; Hb : haemoglobin ; WBC : white blood cell count ; BMI : body mass index.

Although the review included studies combining adult and paediatric results, it was not possible to refine the outcomes of the children (9-10). Notice that the paediatric studies are almost 10 years old and include small groups, making an informed decision on the risks of stopping treatment difficult. Studies describing relapse in paediatric settings are very limited, therefore the presentations of these 3 cases with a longer follow-up period seems interesting.

In face of the switch of the originator to a biosimilar, a safety procedure was installed at our centre including clinical and laboratory tests. This procedure revealed 3 patients seemingly in remission with unmeasurable trough levels and antibodies to infliximab. Confronted with development of antibodies against infliximab, continuing current treatment made no sense. To have a balanced discussion with the patients and their parents the availability of relapse risk factors would have helped. Although mucosal healing is often perceived as a key element to lower relapse rates, probably a combination of markers will be needed to identify patients with a low risk of relapse. Using multivariable analysis, the STORI trial revealed several risk factors associated with high risk of relapse after discontinuation of infliximab while on an antimetabolite treatment (corticosteroid use 12 to 6 months before baseline, absence of surgery, male sex, haemoglobin level ≤ 145 g/L, leukocyte count > $6x10^9$/L, no mucosal healing, high CRP, FCP ≥ 300 µg/L, infliximab through levels ≥ 2 mg/L) (11). Patients positive for 3 factors or less, had a lower relapse risk. If the STORI criteria score was applied to our 3 paediatric patients (table 1), the score varied between 2 and 4. However, the cut-off for low haemoglobin of 145 g/l is not applicable to children, who have lower normal values. Also normal haemoglobin levels differ between males and females (12). Hence, it is questionable whether the same score is applicable in children.

Why do these 3 children with CD stay in clinical remission 2 years after infliximab treatment stop? Ben-Horin et al described 48 patients stopping their anti-TNF treatment. Of these patients 42/48 had remission confirmation through endoscopy or magnetic resonance and 6 had only clinical remission. The relapse rate after 12 months differed according to the detection of through levels (16/20 (80%) with and 9/28 (32%) without detectable through levels relapsed) (13). Despite the absence of an explanation they concluded that patients in a long-lasting deep remission with absent anti-TNF drug levels (independent of the presence or absence of antibodies) are a unique subset with low risk of disease relapse upon drug discontinuation (13). Furthermore, in their cohort the presence of a very low to normal FCP (≤ 50 µg/g) was even for patients with mucosal healing, a discriminatory predictive factor for low risk of future relapse.

There remain questions concerning the necessary type of monitoring and monitoring frequency after treatment stop. The ECCO guideline for exit strategies proposes a more intensive follow-up during the first year by clinical evaluation, CRP and FCP as an elevation of FCP and/or CRP usually occurs a few months before symptomatic relapse (4). The cut-off level of FCP used as a STORI criterion was ≥ 300 µg/g (10) however, more recent studies used FCP based remission with levels < 100 µg/g (13) or even levels ≤ 50 µg/g (13). Elevation of a marker should trigger re-testing and if confirmed, careful

reassessment of the patients preferable with endoscopy is needed (4). Six-monthly clinical and biochemical follow up has been performed in our 3 patients until now. Patient 3 is having higher levels of FCP, thus will be retested in 3 months.

Conclusion

We present 3 paediatric patients with Crohn's disease and a 2-year medication-free survival after stopping infliximab. Now a proactive approach in measuring through levels is used in our centre, hoping to lead to a better outcome for patients, but also to detect antibodies. There is a place for treatment discontinuation as has been shown with these 3 paediatric patients. Long term follow-up data are however needed, especially in children. Factors predicting relapse, optimal monitoring strategy following withdrawal must be further elucidated specifically for children and cannot be simply copied from adult care.

Conflict of interest

Authors have no conflict of interest and no funding to declare

References

1. FRANCHIMONT D., FERRANTE M., LOUIS E., *et al*. Belgian IBD research group (BIRD) position statement 2017 on the use of biosimilars in inflammatory bowel disease (IBD). *Acta Gastroenterol. Belg*., 2018, **81** : 49-53.
2. LEVINE A., GRIFFITHS A., MARKOWITZ J., *et al*. Pediatric modification of the Montreal classification for inflammatory bowel disease : the Paris classification. *Inflamm. Bowel Dis*., 2011, **17(6)** : 1314-21.
3. MARY JY., MODIGLIANI R. Development and validation of an endoscopic index of the severity for Crohn's disease : a prospective multicenter study. *Gut*, 1989, **30(7)** : 983-89.
4. DOHERTY G., KATSANOS KH., BURISH J., *et al*. European Crohn's and colitis organization topical review on treatment withdrawal [exit strategies] in inflammatory bowel disease. *J. Crohns Colitis*, 2018, **12(1)** : 17-31.
5. GISBERT JP., MARIN AC., CHAPARRO M. The risk of relapse after anti-TNF discontinuation in inflammatory bowel disease : systematic review and meta-analysis. A*m. J. Gastroenterol*., 2016, **111(5)** : 632-47. doi : 10.1038/ajg.2016.54.
6. CROMBE V., SALLERON J., SAVOYE G., *et al*. Long-term outcome of treatment with infliximab in pediatric-onset Crohn's disease : a population-based study. *Inflamm. Bowel Dis*., 2011, **17** : 2144-53.
7. NUTI F., CONTE F., CAVALLARI N., *et al*. Long term efficacy of infliximab in inflammatory bowel disease at a single tertiairy center. *Dig. Liver Dis*., 2010, **42** : S326-7.
8. WYNANDS J., BELBOUAB R., CANDON S., *et al*. 12-month follow-up after successful infliximab therapy in pediatric crohn disease. *JPGN*, 2008, **46** : 293-8.
9. DAI C., LIU WX., JIANG M., *et al*. Mucosal healing did not predict sustained clinical remission in patients with IBD after discontinuation of one-year infliximab therapy. *PLoS One*, 2014, **9** : e1 10797.
10. CASANOVA MJ., CHAPARRO M., GARCIA-SANCHEZ V., *et al*. Evolution after anti-TNF discontinuation in patients with inflammatory bowel disease : a multi-center long-term follow-up study. *Am. J. Gastroenterol*., 2017, **112** : 120-31.
11. LOUIS E., MARY JY., VERNIER-MASSOUILLE G., *et al*. Maintenance of remission among patients with Crohn's disease on antimetabolite therapy after infliximab is stopped. *Gastroenterology*, 2012, **142** : 63-70.
12. NATHAN DG. Hemoglobin reference values for females/males per age group. In : Nathan DG, Orkin SH, Look AT, Ginsburg D, eds. Nathan and Oski's Hematology of Infancy and Childhood, 6th edn. Philadelphia : Saunders, 2003 : appendix 2.
13. BEN-HORIN S., CHOWERS Y., UNGAR B., *et al*. Undetectable anti-TNF drug levels in patients with long-term remission predict successful drug withdrawal. *Aliment. Pharmacol. Ther.*, 2015, **42**(3) : 356-64.
14. MOLANDER P., FÄRKKILÄ M., RISTIMÄKI A., *et al*. Does fecal calprotectin predict short-term relapse after stopping TNFα-blocking agents in inflammatory bowel disease patients in deep remission? *J. Crohn Colitis*, 2015, **9** : 33-40.