Safety and cost of infliximab for the treatment of belgian pediatric patients with Crohn's disease

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Abstract

Biologicals have become an important component in the treatment of Crohn's disease in children. Their increased and long term use raises safety concerns. We describe safety and cost of infliximab in Belgian pediatric Crohn's disease patients. All patients on infliximab as part of the present or past treatment for Crohn's Disease until January 1st 2011 were selected from an existing database. Information on disease phenotype, medication and adverse events were extracted. Adverse events occurred in 25.9% of patients exposed to infliximab of which 29.6% were severe. In total 31.7% of patients stopped infliximab therapy. The main reasons for discontinuation were adverse events in 45.4% and loss of response in 30.3%. No malignancies or lethal complications occurred over this 241 patient year observation period. Immunomodulators were concomitant medication in 75% of patients and were discontinued subsequently in 38.4% of them. The cost of infliximab infusions per treated patient per year in the Belgian health care setting is approximately 9 474 euro, including only medication and hospital related costs. Even though infliximab is relatively safe in pediatric CD on the short term, close follow-up and an increased awareness of the possible adverse reactions is highly recommended. Adverse reactions appeared in 25.9% of all patients and were the main reason for discontinuation. Treatment cost has to be balanced against efficacy and modifications in disease course. In the Belgian health care system, the medication is available to all patients with moderate to severe CD. (Acta gastroenterol. belg., **2012**, 75, **425-431**).

Key words : pediatric, Crohn's disease, biological treatment, safety, cost.

Abbreviations

Adverse events (AE)
Azathioprine (AZT)
Belgian IBD Research and Development Group (BIRD)
Belgian Society for Pediatric Gastroenterology, Hepatology and Nutrition (BESPGHAN)
Crohn's disease (CD)
Gastrointestinal (GI)
Immunomodulator (IM)
Inflammatory bowel disease (IBD)
Infliximab (IFX)
Methotrexate (MTX)
Pediatric Crohn's Disease Activity Index (PCDAI)
Physician's global assessment score (PGA)
Severe adverse events (SAE)
TB (Tuberculosis)
Tumor necrosis factor alpha (TNF-α)
6-Mercaptopurine (6-MP)

Introduction

Crohn's disease (CD) is a chronic relapsing and remitting disease with rising incidence throughout the western world (1). This condition is generally treated with a therapeutic 'step-up' approach : steroids or enteral nutrition as first line and immunomodulators (IM) as second line. Biological therapy is the next step for patients who became unresponsive to previous treatment or in severe fistulising disease. The anti- Tumor necrosis factor alpha (TNF) agent Infliximab (IFX) has been introduced with great success for the treatment of moderate to severe CD in adults and children (2,3). In Belgium, IFX has been used for children with CD in clinical trials or in a medical need program since 2000. Based on the results of the Reach study (3), reimbursement was obtained in August 2008 for all pediatric CD patients between 6-18 y fulfilling following criteria : moderate to severe CD ; unresponsive to conventional therapy with steroids, IM and/or enteral therapy for at least 3 months ; intolerance or contra-indications for the conventional therapy ; after exclusion of tuberculosis (TB). Another indication for reimbursement in childhood CD is severe fistulising disease.

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Submission date : 21/12/2011
Acceptance date : 06/07/2012

Concerns have been raised regarding short and long term safety and side effects of IFX treatment such as infections, lympoproliferative disease and malignancies (4-6). Several databases have been initiated to evaluate the risks of long-term severe immune suppression (3,7-10). In the Belgian Pediatric Crohn's Disease Registry (BELCRO) 256 newly and previously diagnosed CD patients under the age of 18 y were included between May 2008 and April 2010. We here present data from the IFX treated patients registered retrospectively and prospectively in the BELCRO database, until January 1st 2011.

Material and methods

Study Population

BELCRO was initiated in May 2008 based on a collaboration of the IBD working group of the Belgian Society for Pediatric Gastroenterology, Hepatology and Nutrition (BESPGHAN) and the Belgian IBD Research and Development Group (BIRD) to evaluate and follow Belgian pediatric (< 18 y) CD patients, recruited between May 2008 and May 2010, for a period of 5 years. All pediatric and adult centers were invited to register their pediatric CD patients, diagnosed according to the Porto criteria (11), retrospectively (diagnosed before 2008) and prospectively (diagnosed between 2008-2010) in the pediatric registry. In total, 256 patients were registered, in 23 centers. Data on demographics, disease phenotype, family and medical history, diagnostic modalities, treatment and disease evolution are recorded in a database at diagnosis, at inclusion in the registry and at a 3-montly basis for the first year after inclusion and at a yearly follow up thereafter. Data at diagnosis are retrospective for 156 patients diagnosed before 2008. This group and 100 newly diagnosed patients are followed prospectively. For this manuscript database closure was January 1th, 2011.

Data

Data were extracted from the database. The following variables were collected : demographics, medical and treatment data, disease location, disease behavior and severity. IFX dosage, infusion frequency, concomitant medication, duration of treatment, number of doses, age at start treatment, adverse events and reason for treatment discontinuation. No data on IFX efficiency was available in the database. All centers using IFX were requested to provide information on their policy regarding TB screening and prophylactic measures.

Statistics

Data were extracted from an Excel® database (Microsoft, Washington, USA). Descriptive statistics were derived (median, proportions) with corresponding 95% confidence interval and descriptives were expressed as median values with the adequate range. Non-parametric association tests were used to investigate relationships between variables of interest.

Results

Patient characteristics

IFX was prescribed to 104/256 (40.6%) BELCRO patients between diagnosis and January 1st, 2011. Median treatment duration is 22 m (range 1-87 m). The follow up for these patients represents 241 patient years. Not all centers in Belgium have experience with IFX use in children. Nineteen/23 centers, 10 pediatric and 9 adult, used IFX treatment in their registered patients ; 26/104 patients were newly diagnosed. Their data were collected prospectively. Considering reimbursement issues : 42/104 patients started on IFX prior to 2008 ; 62/104 patients were started on IFX between 2008 and end of 2010 after reimbursement was obtained for pediatric CD. Figure 1 shows the number of patients on IFX, starting IFX and stopping IFX each year for the period 2003-2010.

The majority of patients were male (65/104 (62.5%)). The median age at diagnosis for this subgroup was 13.2 y (range 1.6 y-17 y) and the median follow up until 1/1/2011 was 3 y 9 m (range 9 m-9 y 3 m). Disease location at diagnosis according to Montreal classification (12) was L1 in 10 patients (9.6%), L2 in 26 patients (25%) and L3 in 65 patients (62.5%). In 3 patients (2.9%) disease location could not be classified because of failed ileal intubation. In 69 patients (66%), lesions in the upper gastrointestinal (GI) tract were documented (L4). Following the Paris classification (13), upper GI involvement could be subdivided in 55% L4A and 37.2% L4B involvement. L4A and L4B were not evaluated in 5 and 10 patients respectively.

Data on disease severity at diagnosis, evaluated by the Pediatric Crohn's Disease Activity Index (PCDAI) in 60 (57.6%) patients and by physician global assessment score (PGA) in the remaining patients, showed moderate to severe disease in 94% at diagnosis. Severe perianal disease was present in 10 patients (9.6%).

Treatment

Induction treatment is standardized and consists of an IFX dose 5 mg/kg at week 0, week 2 and week 6. Median age at IFX induction was 14 y 6 m (range 6 y 6 m-18 y 8 m). Median disease duration at induction was 12 m (5 d-79 m). In 3 patients, the precise date of diagnosis is lacking. IFX was introduced within 3 months of diagnosis in 13 patients (12%), between 3-12 m after diagnosis in 40 patients (38%), between 12-24 m after diagnosis in 28 patients (26%) and more than 24 months after diagnosis in 20 patients (19%). Previously diagnosed patients had a median FU of 4 y 6 m (range 2 y 8 m-9 y 3 m) on January 1th 2011. Their median duration of disease at start IFX was 15 m (range 6 d-6 y 7 m). In the group

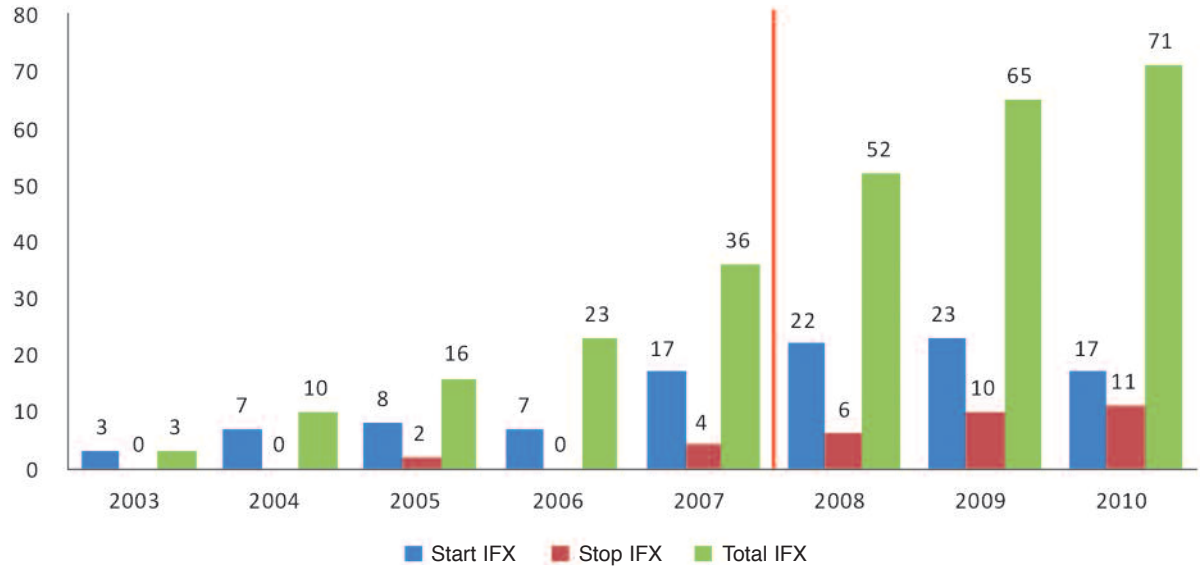

Fig. 1. — Total number of patients in BELCRO cohort on IFX per year including number of patients starting and stopping IFX each year for the period 2003-2010.

newly diagnosed patients, the median follow up was 1 y 7 m (range 9 m-2 y 7 m) and the median time between diagnosis and first IFX in fusion was 5 months (range : 5 d-2 y 3 m).

Maintenance treatment in pediatric patients consists of a 5 mg/kg dose every 8 weeks and is generally applied in all centers. Changes to this schedule depend on the disease behavior and the disease severity. Over the entire observation period, the mean treatment dose was 5 mg/kg and the mean interval 7 weeks. The maximum dose administered was 10 mg/kg and the interval range was 4-8 weeks, except for those who only received induction. In one single patient the interval was temporarily extended to 10 and then 12 weeks. In 8 patients, the interval was not known. In 26/96 (27%) patients, dose and/or interval adaptation was necessary : 17/26 patients had an interval shortening, 5 patients a dose increase and 4 patients a combination of dose increase and interval shortening. After a temporary intensification of therapy, the interval could be reverted to every 8 weeks in 6/21 patients (28.5%). Total follow up of IFX treated patients was 241 yrs.

In 32 patients (30%), IFX was continued for over 3 years. The total number of doses for the 95 patients, for whom the number of doses could be calculated, was 1704. The total exposure time for these patients was 2715.6 months, resulting in an average of 17.9 doses per patients, 7.5 doses a year and average treatment duration of 28.5 months. The median number of total doses per patient was 15 (range 2-50).

On January 1st 2011, 33/104 patients had stopped IFX treatment (32%). Five/33 patients (15%) stopped IFX after induction therapy (3 doses), 9 (27%) other patients stopped within the first year of treatment, 8 (24%) in their second year of treatment, 4 (12%) in the third year of treatment and the remaining patients (22%) stopped after more than three years of treatment.

Table 1. — **Reasons for Stop Infliximab**

Reasons for Stop Ifx	33/104
Loss of response	10
Severe Adverse Event	8
Non Severe Adverse Event	7
Remission	4
Switch to Adalumimab	2
Primary Non Responder	1
Loss to follow up	1

The main reasons for IFX discontinuation are listed in table 1 : 15/33 patients (45%) stopped IFX because of an adverse event (AE), 10 (30%) because of a loss of response. Four patients (12%) went into remission and needed no further treatment. One patient was lost to follow up ; 1 patient was a primary non-responder and 2 patients switched to adalimumab. For the last patients the reasons for change were unclear. Figure 2 shows the percentage of IFX discontinuation over time.

Concomitant therapy

Concomitant IM were administered in 78/104 patients (75%). 71/78 patients (91%) started IM before IFX, 4/78 (5%) simultaneously with IFX and 3 (3.8%) during IFX. In 8 patients, no stop date of IM was available. IM were withdrawn during IFX in 30 patients (38.4%) of whom 24 were young males. The median time to IM withdrawal was 6 m (range 1 m-3 y 1 m). Eighteen patients (23%) continued on IM after discontinuation of IFX. Seven patients were exposed to IM, but not concomitantly to their IFX therapy.

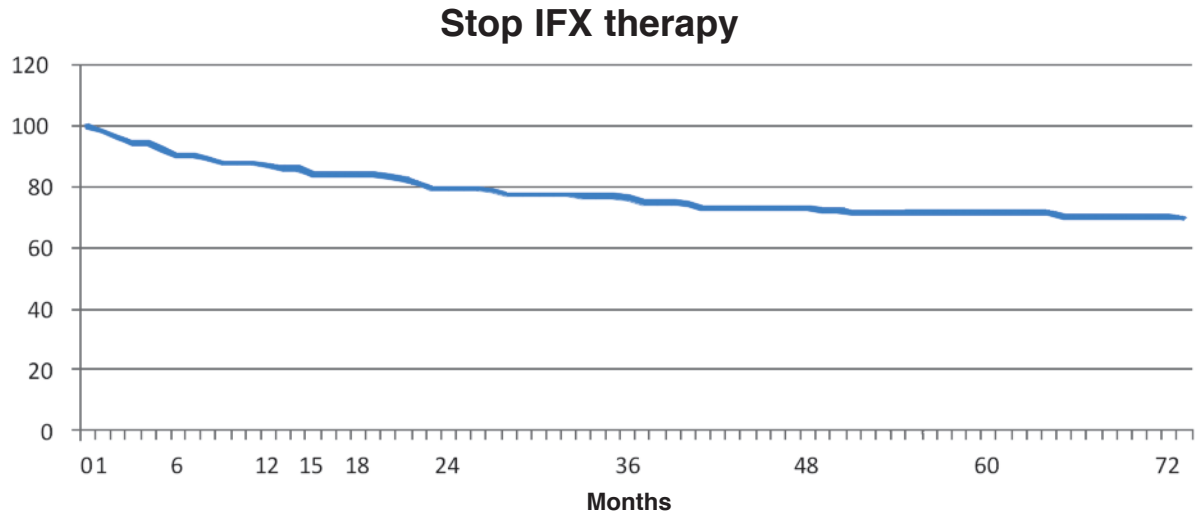

Fig. 2. — Survival curve of Belcro patients on IFX over time

Adverse events

Adverse events are defined as any change of health status or side effect that occurs while a patient is receiving a certain treatment. Severe adverse events (SAE) are defined as AE resulting in hospitalization, long-term disability or death. AE were mentioned in 27/104 patients (26%) (Table 2). SAE's were noted in 8 patients (7%) : 4 anaphylaxis, 1 psoriasis, 1 facial nerve palsy and 1 severe abdominal discomfort. In 1 patient, IFX was temporarily stopped because of an opportunistic infection. Upon IFX reintroduction, the patient developed a severe serum sickness leading to hospitalization and definitive discontinuation of treatment. IFX was withdrawn immediately in all these patients. All were hospitalized and recovered completely with suitable therapy. Twenty-three AE were considered non severe, but they were still reason for treatment withdrawal in an additional 7 patients (6%).

Infusion reactions (hypotension, anaphylaxis, allergic reaction) were mentioned in 11 patients (11% of total, 34% of side effects). Infections were mentioned in 4 patients (4% of total, 14% of side effects). Three of them had a minor viral infection ; one a severe opportunistic infection (pneumonia) necessitating temporary discontinuation of IFX. Twenty-four patients experiencing an AE had been exposed or were concomitantly exposed to IM.

Prophylaxis

All centers administering IFX, performed prior per protocol TB screening. We obtained information on the routine premedication from all participating centers. Twelve centers, treating 66/104 (63.4%) patients, did not use routine premedication. Seven centers, treating 38/104 patients (36.6%), used routine administration of corticosteroids preceding IFX infusion and 2 centers added anti-histaminics when necessary. Seven centers mentioned premedication (corticosteroids and antihistaminics) only when a previous infusion reaction was noted or after a long drug holiday, the other centers did not spontaneously mention their routine for infusion reactions. Out of the 38 patients receiving routine prophylaxis, an infusion reaction (hypotension, anaphylaxis, allergic reaction) was mentioned in 8 patients (21%) compared to 3 out of the 66 patients (4.5%) not receiving routine prophylaxis.

Cost in the Belgian health care system

With a median weight of 52 kg (range 20-90.4 kg) in our population and a mean dose of 5 mg/kg, 3 vials of medication are needed for every infusion at a cost of 1761 euro per infusion. Including the hospital day care cost per infusion, the total cost amounts to 1886,6 euro per infusion. At an average treatment of 7.5 doses a year and an average treatment duration of 28.5 months or based on the average number of doses per patient, the total cost per patient ranges between 33 534 and 28 299 euro and the yearly cost is approximately 14 149,5 euro. Since national health care insurance reimburses treatment in Belgium, the cost for the patient is reduced to 49 euro per infusion with a yearly cost of 367,5 euro or a total cost between 871 and 735 euro, which is 2.6% of the real cost. The calculated cost of IFX infusions is specific for Belgium and limited to the medication and hospital costs for day care. Additional collateral costs such as transport or parental leave are not taken into account. The figures, expressed in euro, are purely informative and not part of a detailed cost-benefit analysis.

Discussion

The increased use of biologicals to treat pediatric CD leads to several recent publications on long term safety

Table 2. — **Adverse Events and Severe Adverse events, reason for stop and presence of concomitant IM therapy**

Severe Adverse Events :	7 patients	AE reason for stop Ifx ?	Concomittant IM ?
Anaphylaxis	4	Yes	Yes
Psoriasis	1	Yes	Yes
Facial Nerve Palsy	1	Yes	Yes
Pneumonia	1	Yes	Yes
Serum Sickness	1	Yes	Yes
Abdominal cramps	1	Yes	Yes
Non Severe Adverse Events :	20 patients		
Eczema +/- Foliculitis	4	No	Yes
Allergic Reaction	3	Yes	2 Yes, 1 No
Hypotension	3	Yes	2 Yes, 1 No
Infection	3	No	Yes
Headache	2	No	Yes
Arthralgia	1	No	Yes
Renal and skin vasculitis	1	No	No
Hepatic Steatosis	1	Yes	Yes
Itching	1	No	Yes
Skin depigmentation	1	No	Yes
Gastro-oesophagal Reflux	1	No	Yes
Abdominal Cramping	1	No	Yes
Bone Marrow Suppression	1	Yes	Yes

and response in registries throughout the world (3,7-10). In Belgium, IFX has been used for childhood CD since 2000 while reimbursement was obtained in August 2008. Analysis of safety data on IFX use in pediatric CD was retrieved from the BELCRO database and was also used for national reimbursement and safety evaluation of this drug in Belgium. Even though virtually all pediatric GI centers participated in the BELCRO registry, it was impossible to evaluate the exact extent of the recruitment of pediatric patients, as it was impossible to quantify the proportion of pediatric patients (< 18 y) treated by adult gastroenterologists throughout the country. There is no national registry of all centers treating IBD patients, but all centers participating in the national scientific societies (Bespghan, Bird) participated. The data were retrieved from a descriptive registry retrieving general information on disease course, disease phenotype and treatment. The registry was not specifically set up for detailed treatment information such as indications for or clinical status at treatment change, specific AE's such as infections or specifics about infusion reactions. Prophylactic measures were asked for independently. On the other hand, it is the best and most extensive national data available on the disease phenotype and disease course in the pediatric age group and it reflects the medical care received by these patients in most of the centers with a specific interest in pediatric IBD in our country.

In BELCRO, 40% of patients (104/256) had received or were receiving IFX for their disease until January 1st 2011, demonstrating the major impact of this drug on CD treatment in childhood and its cost. Reimbursement for children is only accorded for moderate to severe luminal disease or severe perianal disease ; therefore no other indication could be withheld even though the registry did not ask specifically for the indication of any treatment change.

Even though top down treatment is suggested for severe disease in adults or for severe perianal disease at diagnosis, it is unusual for pediatrics because of the reimbursement conditions. Only 2 patients received IFX very shortly after diagnosis, both patients had severe luminal disease and were treated by adult gastroenterologists.

Half of the patients received a biological agent within the first year of treatment, which complies with the American experience (7). The newly diagnosed patients were included after reimbursement had been obtained. Reimbursement made the medication more broadly and easily accessible. The lack of reimbursement implies a more 'experimental' treatment or 'last resort' treatment. The consequence of reimbursement is reflected by the median time of disease before start IFX : 5 months after 2008 compared to 12 m for the total group. Moreover, the increasing knowledge and experience with the drug in pediatric CD certainly lowered the threshold for its use. The notion of mucosal healing is gaining importance in the treatment of adult CD. Patients achieving mucosal healing have longer remissions, superior growth and a better quality of life. Even though mucosal healing was not evaluated in pediatric CD studies, it compels pediatric CD physicians to a more rapid step up therapy. Top down therapy in pediatric CD remains controversial in view of the possible long-term side effects of severe immunosuppression at a young age (14,15).

The median duration of treatment until January 1st 2011 was 22 m. Even though 31.7% of patients had stopped treatment, 30% was receiving the drug for more than 3y with maximum treatment duration of 7 years and

3 months, indicating that efficacy can be maintained long term.

Adaptation of dose or dose interval was mentioned in 26/104 patients (25%). This was less frequent compared to American data where dose adaptation was mentioned in 49% (3,7). Differences in disease behavior, recruited patient population and management style can be a possible explanation. Concomitant IM was given in 75.9% of patients, which is similar to the French data (9). In the majority of patients, the treatment had been initiated before IFX was started. While in 64.5%, both medications were continued together even beyond IFX treatment, in 35.4% IM therapy was stopped during IFX treatment, reducing the number of patients on combination therapy to 46.8% on January 1st 2011. The majority of patients in whom the IM were stopped were male. It is in this gender that hepato-splenic T-cell lymphoma has been described as an uncommon, but lethal AE (16).

In 31.7% of patients, IFX therapy was stopped. The main reasons for stop were AE's (45%) and loss of response (30%). Remission was a reason for discontinuation in a small proportion of patients (12%). It is often challenging to withdraw medication when patients are doing well. No clear guidelines exist (17) and a high percentage of relapse has been noted after IFX withdrawal (18). When IFX needs to be restarted after a long drug holiday, the risk for developing antibodies and for drug reaction is also higher (17).

In 26.9% of patients, AE's were mentioned. This is similar to the French findings (9,10), but much lower than the American experience (8). The difference can be explained by the careful follow-up and monitoring, mandatory in randomized controlled trials, compared to data registration, as well as by the interpretation of the definition of AE's. The number of SAE's was limited in our cohort and no mortality or malignancy is mentioned even though 30% of our patients were treated for more than 3y. The REACH study reported AE's in 94.6% of pediatric patients treated with IFX (3). The main adverse events were infections (54.3%) and infusion reactions (17%). No mortality or malignancy was reported in this cohort with a follow up of 46 weeks. Infectious complications are a major concern for all patients on immunosuppressants. We noted minor infections in only 3 patients. Clearly, the BELCRO is not intended to register minor intercurrent infections. We can assume that patients consulted more often family physicians for this indication and did not always mention it to their specialist. Moreover, most of the patients were previously diagnosed patients with retrospective data collection. The registration of AE's was part of the information retrieved from medical files leaving the registration up to the physician. Adult data recorded in the TREAT database showed a similar rate of infections in IFX and IM treated patients but identified the use of corticosteroids and analgesics as independent risk factors (4). Even though the risk for infections may be similar on IFX or IM monotherapy, it does not account for different combination treatments. The risk for infection remains higher compared to the normal population as does the risk for lymphoproliferative disease (4,5).

Infusion reactions (allergic reaction, hypotension, and anaphylaxis) were mentioned in 11% of patients. This is lower than what is mentioned in the REACH study and in the REACH follow up study (3,8). It may be due to the scheduled administration of the drug that is customary in Belgium. Even though centers administering standard premedication before IFX infusion mentioned more infusion reactions the number of the patients per group is small and caution is needed while interpreting those results. Infusion reactions appear to be more frequent in 10 mg/kg dosing (8) ; this could not be confirmed in our cohort, as the proportion of patients on that dose was too low.

Information on cost effectiveness of IFX treatment in CD patients is limited (19,20) especially in pediatrics (21,22). Data indicate that cost-efficacy is warranted for short induction and maintenance treatments, but is not valid for long-term maintenance. We have estimated the average treatment cost in Belgium with the concise data that were available to date. This estimate is limited to the cost of medication and day care and does not incorporate collateral costs such as transport, parental leave and concomitant medication that need to be taken into account for cost benefit analysis. BELCRO includes a diverse group of patients but is the sole and best reflection of 10 years of national IFX use in pediatric CD.

Conclusion

The available data on safety in BELCRO implies that IFX is relatively safe for pediatric CD patients and can be efficiently used long term. Nevertheless, close follow-up and an increased awareness of short- and long-term adverse reactions remain highly recommended.

Acknowledgment

BELCRO is supported by a grant from Schering-Plough, an MSD company.

References

1. BENCHIMOL E.I., FORTINSKY K.J., GOZDYRA P. *et al.* Epidemiology of pediatric inflammatory bowel disease : a systematic review of international trends. *Inflammatory bowel diseases*, 2010, **17** : 423-439.
2. HANAUER S.B., FEAGAN B.G., LICHTENSTEIN G.R. *et al.* Maintenance infliximab for Crohn's disease : the ACCENT I randomised trial. *Lancet*, 2002, **359** : 1541-1549.
3. HYAMS J., CRANDALL W., KUGATHASAN S. *et al.* Induction and maintenance infliximab therapy for the treatment of moderate-to-severe Crohn's disease in children. *Gastroenterology*, 2007, **132** : 863-873, quiz 1165-1166.
4. LICHTENSTEIN G.R., FEAGAN B.G., COHEN R.D. *et al.* Serious infections and mortality in association with therapies for Crohn's disease : TREAT registry. *Clin. Gastroenterol. Hepatol.*, 2006, **4** : 621-630.
5. BEAUGERIE L., BROUSSE N., BOUVIER A.M. *et al.* Lymphoproliferative disorders in patients receiving thiopurines for inflammatory bowel disease : a prospective observational cohort study. *Lancet*, 2009, **374** : 1617-1625.

6. ROSH J.R., GROSS T., MAMULA P. *et al.* Hepatosplenic T-cell lymphoma in adolescents and young adults with Crohn's disease : a cautionary tale ? *Inflammatory bowel diseases*, 2007, **13** : 1024-1030.
7. HYAMS J.S., LERER T., GRIFFITHS A. *et al.* Long-term outcome of maintenance infliximab therapy in children with Crohn's disease. *Inflammatory bowel diseases*, 2009, **15** : 816-822.
8. HYAMS J., WALTERS T.D., CRANDALL W. *et al.* Safety and efficacy of maintenance infliximab therapy for moderate-to-severe Crohn's disease in children : REACH open-label extension. *Current medical research and opinion*, 2011, **27** : 651-662.
9. 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. *Inflammatory bowel diseases*, 2011.
10. RUEMMELE F.M., LACHAUX A., CEZARD J.P. *et al.* Efficacy of infliximab in pediatric Crohn's disease : a randomized multicenter open-label trial comparing scheduled to on demand maintenance therapy. *Inflammatory bowel diseases*, 2009, **15** : 388-394.
11. Inflammatory bowel disease in children and adolescents : recommendations for diagnosis – the Porto criteria. *J. Pediatr. Gastroenterol. Nutr.*, 2005, **41** : 1-7.
12. SILVERBERG M.S., SATSANGI J., AHMAD T. *et al.* Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease : Report of a Working Party of the, 2005 Montreal World Congress of Gastroenterology. *Canadian journal of gastroenterology = Journal canadien de gastroenterologie*, 2005, **19** Suppl A : 5-36.
13. LEVINE A., GRIFFITHS A., MARKOWITZ J. *et al.* Pediatric modification of the Montreal classification for inflammatory bowel disease : The Paris classification. *Inflammatory bowel diseases*, 2010.
14. BORRELLI O., BASCIETTO C., VIOLA F. *et al.* Infliximab heals intestinal inflammatory lesions and restores growth in children with Crohn's disease. *Dig. Liver Dis.*, 2004, **36** : 342-347.
15. WALTERS T.D., GILMAN A.R., GRIFFITHS A.M. Linear growth improves during infliximab therapy in children with chronically active severe Crohn's disease. *Inflammatory bowel diseases*, 2007, **13** : 424-430.
16. MACKEY A.C., GREEN L., LIANG L.C. *et al.* Hepatosplenic T cell lymphoma associated with infliximab use in young patients treated for inflammatory bowel disease. *J. Pediatr. Gastroenterol. Nutr.*, 2007, **44** : 265-267.
17. D'HAENS G.R., PANACCIONE R., HIGGINS P.D. *et al.* The London Position Statement of the World Congress of Gastroenterology on Biological Therapy for IBD with the European Crohn's and Colitis Organization : when to start, when to stop, which drug to choose, and how to predict response ? *The American journal of gastroenterology*, 2011, **106** : 199-212, quiz 213.
18. WYNANDS J., BELBOUAB R., CANDON S. *et al.* 12-month follow-up after successful infliximab therapy in pediatric crohn disease. *J. Pediatr. Gastroenterol. Nutr.*, 2008, **46** : 293-298.
19. DRETZKE J., EDLIN R., ROUND J., CONNOCK M., HULME C., CZECZOT J., FRY-SMITH A., MC CABE C., MEADS C. A systematic review and economic evaluation of the use of tumour necrosis factor-alpha inhibitors, adalimumab and infliximab, for Crohn's disease. *Health Technology Assessment*, 2011, **15** : 1-244.
20. BODGER K., KIKUCHI T., HUGHES D. Cost-effectiveness of biological therapy for Crohn's disease : Markov cohort analyses incorporating United Kingdom patient-level cost data. *Alimentary pharmacology & therapeutics*, 2009, **30** : 265-274.
21. KAY M., WYLLIE R. The real cost of pediatric Crohn's disease : the role of infliximab in the treatment of pediatric IBD. *The American journal of gastroenterology*, 2003, **98** : 717-720.
22. PUNEKAR YS., SUNDERLAND T., HAWKINS N. *et al.* Cost-effectiveness of scheduled maintenance treatment with infliximab for pediatric Crohn's disease. *Value Health*, 2010, **13** : 188-195.