Alimentary Pharmacology & Therapeutics

Infliximab dependency in children with Crohn's disease

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SUMMARY

Background
Recently, infliximab dependency has been described.

Aim
To assess frequency of ID in 82 consecutive Crohn's disease children treated with infliximab 2000–2006 and to describe clinical and genetic predictors of long-term infliximab response.

Methods
A phenotype model of infliximab dependency was used to assess treatment response: 'immediate outcome' (30 days after infliximab start) – complete/partial/no response. 'Long-term outcome': (i) prolonged response: maintenance of complete/partial response; (ii) infliximab dependency: relapse ≤90 days after intended infliximab cessation requiring repeated infusions to regain complete/partial response or need of infliximab >12 months to sustain response. Polymorphisms *TNF*-308 A>G, *TNF*-857 C>T, *Casp9* 93 C>T, *FasL*-844 C>T, *LTA* 252 C>T and *CARD15* (R702W, G908R, 1007fs) were analysed.

Results
Ninety-four per cent of children obtained complete/partial response. In long-term outcome, 22% maintained prolonged response, 12% had no response, while 66% became infliximab dependent. Perianal disease and no previous surgery were associated with infliximab dependency (OR 5.34, 95% CI: 1.24–22.55; OR 6.7, 95% CI: 1.67–26.61). No association was found with studied polymorphisms. The cumulative probability of surgery 50 months after starting infliximab was 10% in infliximab dependency, 30% in prolonged responders and 70% in nonresponders ($P = 0.0002$).

Conclusions
Sixty-six per cent of children became infliximab dependent. Perianal disease and no surgery prior to infliximab were associated with infliximab dependency phenotype.

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INTRODUCTION

An increasing incidence of inflammatory bowel disease (IBD) has been described. Six to seven per cent of newly diagnosed patients are children below 15 years of age.[1–6] Medical therapy is symptomatic and with limited efficacy. Biologicals are currently the most potent therapeutic option in severe aggressive IBD in induction as well as in maintenance therapy.[7–11] Infliximab (IFX) has been shown to be efficacious in children with Crohn's disease (CD).[12] Drug dependency is well known in corticosteroid use and has been recently defined and described also in IFX treatment.[13, 14] A retrospective study of 24 children with CD treated with IFX showed that 42% of patients became IFX dependent (ID).[15] ID patients represented a subgroup of patients benefiting from the therapy, but requiring repetitive IFX infusions to sustain their initial response. Although the occurrence of adverse events is relatively low, the risk of severe and potentially fatal adverse events is still present and the long-term side effects due to relatively short clinical use of the drug are still being monitored.[16–21] Therefore, the need for predictors of IFX response defining the subgroup of patients benefiting from the therapy is essential.

The aim of the study was to assess the occurrence of ID phenotype in CD children treated with IFX. The secondary aim was to define clinical and genetic predictors of IFX outcome.

PATIENTS AND METHODS

Study population

A total of 82 consecutive paediatric patients with CD treated with IFX were included and followed up until the end of 2006. Forty-one originated from the Danish Crohn Colitis Database treated at two Departments of Pediatrics in Denmark (Hvidovre and Odense University Hospital) in the period from August 2000 until November 2006. Twenty-four of these children had already been included in a previously published study assessing the occurrence of ID.[15] Forty-one originated from the Czech Republic treated at two Departments of Pediatrics in Prague (Hospitals of the 1st and the 2nd Faculty of Medicine, Charles University) in the period from October 2002 to June 2006. The diagnosis of CD of all patients was assessed according to the international diagnostic criteria.[22] Data regarding age, disease duration, disease behaviour and localization, surgery, date of IFX infusions, infusion dose, treatment indication and concomitant medical therapy (azathioprine/mercaptopurine/methotrexate) were retrospectively retrieved from the files. The indication for IFX treatment was luminal disease (refractory or intolerant to treatment, corticosteroid dependency, with or without growth retardation) in 62 children and perianal disease in 20 children. A total number of 668 infusions (median: 7; range: 1–27) were given in a dose of 5 mg/kg. The treatment strategy and cessation of the therapy were individualized in accordance with the factors such as patient's condition and decision of parents–patient to stop the therapy due to a fear of long-term side effects. Twelve patients received only induction infusions (weeks 0, 2, 6), 38 children were treated with induction infusions followed by maintenance therapy (median: 10 infusions; range: 5–21) and 31 received IFX episodically-nonscheduled (median: 6; range: 1–27). In two patients on maintenance therapy, the dose of IFX was increased to 10 mg/kg later in the treatment course due to loss of efficacy. When IFX was stopped, a majority of children continued on immunomodulators, which were introduced prior to initiation or shortly after the start of IFX therapy. One patient was lost to follow-up. Demographic and clinical characteristics are shown in Table 1.

Healthy individuals, 182 from Denmark and 283 from the Czech Republic, served as controls in the genotype–phenotype association study.

Ethical consideration

This study was approved by The Danish Data Protection Agency and Ethics Committees of the 1st and the 2nd Faculties of Medicine, Charles University in Prague.

Assessment of ID

Clinical outcome of IFX therapy was assessed according to a modified phenotype model of ID developed and described previously.[15] The model aimed to fit more than 90% of all response patterns.

Immediate outcome: 30 days after the first infusion.
Complete response: Luminal disease: ≤2 stools/day (after surgery +2 stools). No blood, pus, mucus, abdominal pain and weight loss. Perianal disease:

Table 1. Demographic and clinical characteristics of 82 Crohn's disease children treated with infliximab (IFX)

	Danish	Czech	*P*
Number of patients	41	41	
Age			
Median (range)	14 (9–18)	15 (8–18)	0.58
Gender			
Male/female	18/23	22/19	0.38
Disease duration (years)			
Median (range)	2 (0–7)	2 (0–6)	0.50
Follow-up after the first IFX infusion (months)			
Median (range)	45 (3–75)	21 (6–50)	<0.001
Disease localization (%)			
Ileum	0	3 (7)	0.23
Colon	15 (37)	10 (24)	
Ileo-colon	17 (41)	20 (49)	
±Upper disease	9 (22)	8 (20)	
Disease behaviour (%)			
Inflammatory	24 (58)	11 (27)	0.01
Stricturing + penetrating	6 (15)	14 (34)	
+Perianal	11 (27)	16 (39)	
Intestinal surgery prior to IFX (%)	8 (20)	3 (7)	0.19
Indication of IFX			
Luminal disease	35 (85)	27 (66)	0.04
Perianal disease	6 (15)	14 (34)	
Concomitant immunosuppressive therapy (%) (azathioprine/ mercaptopurine/methotrexate)	36 (88)	39 (95)	0.49
Treatment regime			
Only induction (0, 2, 6 weeks)	6 (15)	6 (15)	0.04
Induction + maintenance (every 8 or 6 weeks)	14 (34)	24 (60)	
Episodic	21 (51)	10 (25)	
IFX infusions			
Total	314	254	0.18
Median (range)	7 (2–27)	8 (1–21)	

P-values were calculated by Mann–Whitney/chi-squared test.

closure of all fistulas evaluated by thumb pressure or patients announcement of 'no secretion'.

Partial response: Luminal disease: ≤4 stools/day (after surgery +2 stools). Blood, pus, mucus, abdominal pain less than daily, no fever and weight loss. Perianal disease: reduced secretion or discomfort from fistulas or closure of one or some of the fistulas.

No response: Luminal/perianal disease: no regression of symptoms with a need to shift to another immunomodulator and/or surgery within 3 months after initiation of IFX.

Long-term outcome: irrespective of the length of treatment.

Prolonged response: maintenance of complete or partial response.

ID: relapse within 90 days after intended treatment cessation requiring repeated IFX infusions to regain complete/partial response or need of IFX treatment >12 months to sustain complete/partial response.

No response: no regression of symptoms with a need to shift from IFX treatment to another immunomodulator and/or surgery.

Immunomodulator was defined as corticosteroids, azathioprine/mercaptopurine/methotrexate and other biological drugs. Surgery was classified as intestinal (resection, strictureplasty, colectomy) or perianal (incision of abscess, fistulotomy, advancement flap). Incision of perianal abscess as a possible consequence of healing process during IFX treatment was not considered as surgery. If re-infusion of IFX was given more than 1 year after the previous last infusion, the treatment was considered as the second, the third, etc. course. In the present study, the clinical outcome after the first treatment course was analysed.

Furthermore, clinical outcome of IFX therapy was evaluated one year after the last IFX infusion in patients who obtained prolonged response and ID.

Genetic polymorphisms

Association of polymorphisms *TNF*-308 A>G, *TNF*-857 C>T, *Casp9* 93 C>T, *FasL*-844 C>T, *LTA* 252 C>T and *CARD15* (R702W, G908R, 1007fs) was studied with response to IFX treatment.

Genomic DNA was isolated from peripheral blood by routine salting out procedure (Czech Republic) or from buccal swab (Denmark) using Qiagen DNA purification Kit (Qiagen, Hilden, Germany).

All polymorphisms were typed using PCR–restriction fragmented length polymorphism (RFLP). PCR was carried out in a total volume of 15 μL containing 25 ng of genomic DNA, 3 pmol of each primer (Generi Biotech, Hradec Kralove, Czech Republic), 1.5–6 mM $MgCl_2$, 200 μM dNTPs (each), 0.25 units of Taq polymerase and 1× Taq buffer (all from Fermentas, Lithuania). The mixture was incubated for 3 min at 95 °C followed by 30–40 cycles of 10–30 s at 95 °C, 15–20 s at 48–68 °C and 15–30 s at 72 °C. Final extension was 5 min at 72 °C.

About 7–10 μL of PCR product was digested with 1 unit of restriction endonuclease in appropriate buffer

(HpyCHIV was from New England Biolabs, Ipswich, MA, USA, other restriction endonucleases were from Fermentas, Lithuania) for at least 2 h. Digests were separated on 1.5–3.5% agarose gel (low EEO; Applichem, Darmstadt, Germany) in 0.5× TBE buffer and stained with ethidium bromide (Applichem, Germany). For details, see Table S1 (published online). Genotypes of controls were in Hardy–Weinberg equilibrium.

Statistical analysis

Empirical transition probabilities from immediate outcome to long-term outcome were calculated. Univariate logistic analyses were carried out analysing: (i) the probability of being complete or partial responder at immediate outcome and (ii) the probability of being prolonged responder and ID at long-term outcome. Fisher exact test was used, when appropriate. Chi-squared test and Fisher exact test were used to compare allelic and genotype frequencies and to analyse an association of present polymorphisms with response to IFX. Time to surgery was compared by the log-rank test. A significance level of 5% was chosen.

RESULTS

Response to IFX

One month after the first infusion (immediate outcome), 65 (79%) children obtained complete response, 12 (15%) partial response and five (6%) did not respond. In long-term outcome, 18 (22%) patients achieved prolonged response, 53 (66%) developed ID and 10 (12%) patients were nonresponders. The median number of infusions was 3 (range: 1–6) in prolonged responders, 10 (5–27) in ID and 2 (2–3) in nonresponders.

One year after the last IFX infusion, 23 (28%) children were still in remission, while 10 (12%) children lost their response, thus resulting in 20 (25%) nonresponders in total. Thirty-eight (47%) children were still in treatment or their observational time was <1 year after the last infusion (Figure 1).

Transition probabilities from immediate to long-term outcome showed that patients obtaining complete response had a probability of 20% of developing prolonged response, 75% probability of developing ID and 5% probability of becoming nonresponders. Those

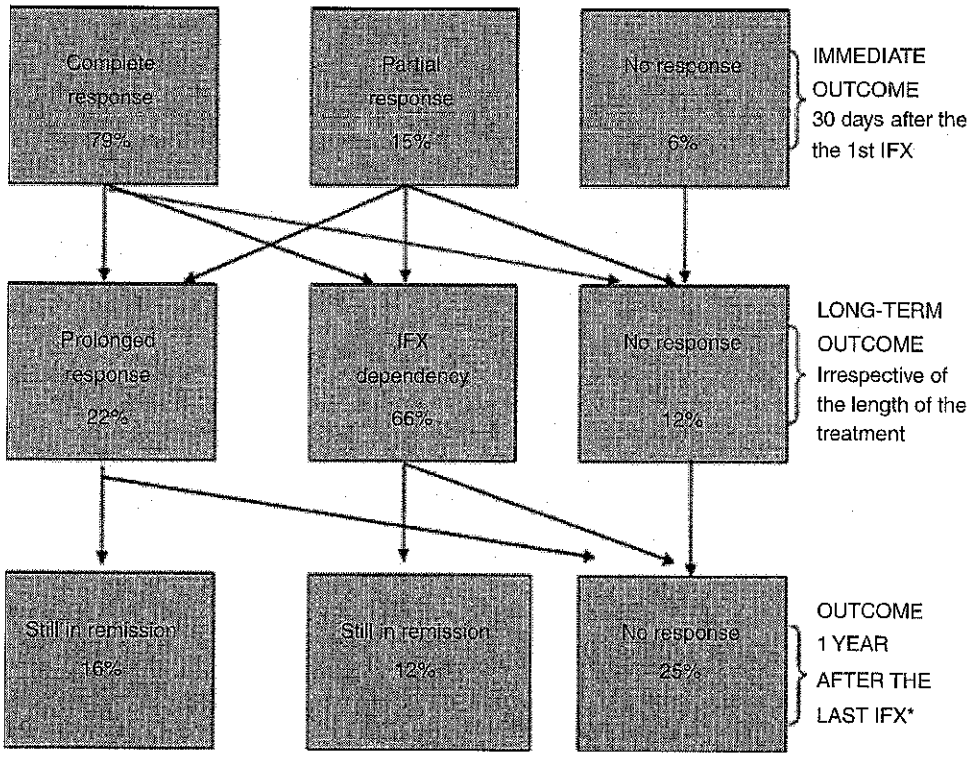


Figure 1. Immediate and long-term outcome of infliximab (IFX) treatment in 82 children with Crohn's disease.
*Thirty-eight (47%) children were still in treatment or their observational time was <1 year after the last IFX infusion.

with partial response had 42% probability of becoming prolonged responders, 42% of becoming ID and 16% of becoming nonresponders (Figure 2).

Clinical predictors

Patients with inflammatory disease behaviour were more likely to become prolonged responders or ID compared with those with stricturing/penetrating disease (OR ∞, 95% CI: 3.23–∞, $P = 0.003$). Intestinal surgery prior to IFX treatment was related to a lower probability to achieve prolonged response or ID (OR 0.05, 95% CI: 0.01–0.32; $P = 0.001$).

Complete responders developed more ID phenotype than partial responders (OR 3.9, 95% CI: 1.13–13.22; $P = 0.036$). Patients with perianal disease compared with luminal disease had higher probability to become ID (OR 5.34, 95% CI: 1.24–22.55; $P = 0.014$). Similarly, children with no intestinal surgery prior to IFX vs. those who underwent surgery were more likely to develop ID response (OR 6.7, 95% CI: 1.67–26.61; $P = 0.007$).

Country, gender, age, disease duration, localization and concomitant immunosuppressive therapy did not influence therapeutic outcome.

Genetic predictors

No association was found between studied polymorphisms and IFX outcome (Table S2, published online).

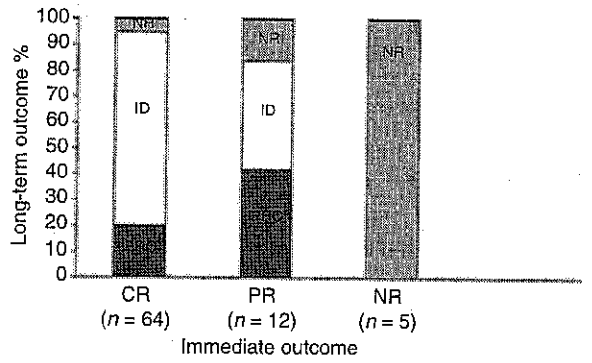


Figure 2. The probability of transition from immediate outcome (30 days after the first infusion) to long-term outcome (irrespective of the length of treatment) in 81 children with Crohn's disease treated with infliximab (one child was lost to follow-up). CR, complete response; PR, partial response; NR, no response; PRO, prolonged response; ID, infliximab dependency.

Significantly higher frequency of C allele of *LTA* 252 C>T polymorphism was observed in Czech patients compared with Czech controls (36% vs. 23%, $P = 0.016$). This association, however, was not confirmed in the Danish cohort. No significant differences in allele frequencies of *FasL*-844 C>T; *Casp9* 93 C>T; *TNF*-308 A>G and *TNF*-857 C>T polymorphisms were found.

Surgery

Complete and partial responders had significantly lower cumulative probability of undergoing intestinal surgery than nonresponders ($P = 0.0012$). The median time to the first surgery was 62 months in complete and partial responders compared to 25 months in nonresponders. The cumulative probability of surgery 50 months after the start of IFX was 10% in ID, 30% in prolonged responders and 70% in nonresponders ($P = 0.0002$). ID patients had significantly less surgeries compared with patients with prolonged response ($P = 0.036$) (Figure 3).

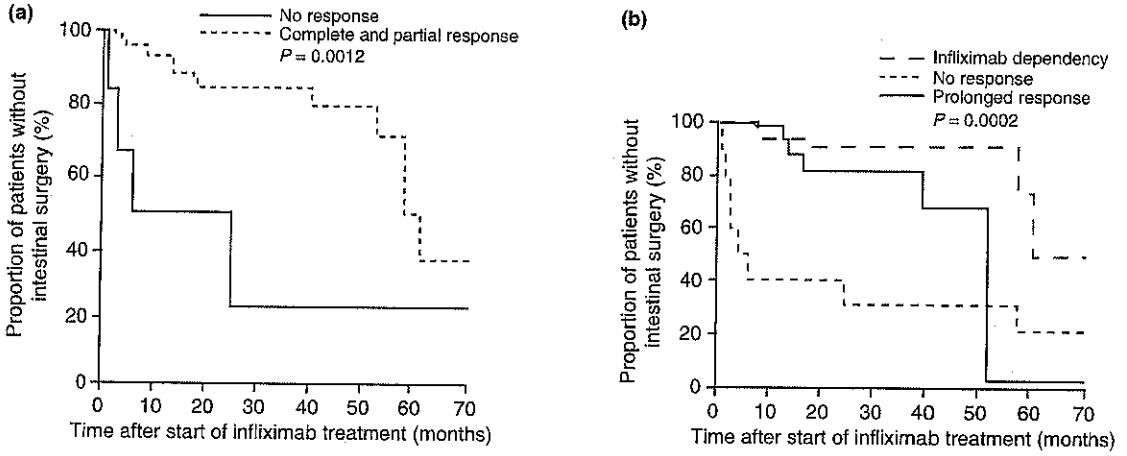
Safety

No cancer, death or severe adverse events, such as infections, occurred during the treatment with IFX or follow-up.

DISCUSSION

One type of ID patients was characterized by early relapse after the treatment cessation with a need for repetitive infusions to regain and sustain initial response. The other type was defined by inability to stop maintenance or episodic therapy within 1 year after the treatment start. In this study, we demonstrated the occurrence of ID in 66% of CD children treated with IFX. Children having perianal disease or no history of surgery prior to IFX were indicative of developing ID response. No association was revealed between selected polymorphisms and IFX response.

Thirty days after the first infusion, 94% of CD children obtained complete or partial response. These results are in agreement with previous studies showing a tendency of higher response rate in children compared with adult patients.[7, 12, 23] This high positive response was maintained also in the long-term as 22% of children were in remission without further need for IFX; however, 66% became ID. In the previously published studies, the frequency of ID with a magnitude



Number of patients at risk

Complete and partial response	75	64	42	28	18	11	4	0
No response	5	2	2	1	1	1	0	0

Number of patients at risk

Prolonged response	17	15	11	8	6	2	0	0
Infliximab dependency	53	47	29	18	10	7	3	0
No response	10	4	4	3	3	3	1	0

Figure 3. Proportion of Crohn's disease patients without intestinal surgery (resection, strictureplasty, colectomy) after the start of infliximab therapy (log-rank test). (a) Comparison with respect to immediate outcome (30 days after the first infusion); (b) Comparison with respect to long-term outcome (irrespective of the length of treatment). Significant difference found also between prolonged response and infliximab dependency ($P = 0.036$).

of 42–56% has been reported.[15, 24] A study evaluating long-term outcome of CD children after only three induction infusions or after induction + maintenance 1-year therapy revealed that 75% and 72% of children respectively relapsed within 1-year after the treatment cessation (median time to relapse 4 and 3 months). In the majority, IFX reintroduction was required to maintain clinical response.[25] These results are very indicative of the new response pattern of ID.

Corticosteroids are not effective in maintaining remission and their long-term use is often accompanied by serious adverse events.[26] Thus, corticosteroid dependency is an undesirable condition and the prompt withdrawal of the drug is required, especially in children where corticosteroids cause growth failure. Contrary to this, IFX is efficacious in maintenance therapy[7] and has rather a good safety profile as outlined in national and local cohorts.[19, 21, 27] From these perspectives, it seems that ID, in contrast to corticosteroid dependency, may be considered beneficial. However, severe adverse events are still matter of concern, especially in ID patients in whom the number of infusions is high and the drug is often combined with azathioprine.[16, 17, 20] Although neither cancer nor death occurred in our cohort, the median follow-up (45 and 21 months respectively) was too short and possible long-term adverse effects could not be excluded.

The transition probabilities from immediate to long-term outcome showed that 95% of children with immediate complete response and 84% with partial response had a benefit in long-term outcome. These results suggest that patients with partial as well as complete response may profit from the therapy not only in short term but also in long-term perspective.

Children with inflammatory behaviour had significantly better long-term outcome compared with those with stricturing/penetrating disease. This is in agreement with the finding that patients with no intestinal surgery prior to IFX (assumed non-stricturing/non-penetrating disease) had higher probability to become prolonged responders or ID. The explanation could be the anti-inflammatory activity of IFX. Occurrence of perianal fistula was predicative of ID phenotype. Perianal disease is characterized by varied complexity and severity, which influence the therapeutic success. Deep and permanent healing of all tracks is an important assumption of sustained response.[28] We speculate that superficial healing or premature closure with

remaining deep tracks could lead to early and recurrent relapses and thus contribute to ID. The limitation concerning validity of the results is relatively small number of patients involved in analysis. New studies are needed to confirm our findings.

As the frequencies of studied polymorphisms in background populations of Denmark and Czech Republic were different (results not shown), analyses were carried out separately.

No association between the polymorphisms and IFX outcome was found in our study. In a previous study, genes involved in apoptosis such as *FasL/Fas* system and *Casp9* have been shown to have an influence on therapeutic outcome.[29] A certain haplotype of lymphotoxin alpha has been reported to be responsible for a decreased response to IFX in CD.[30] Although no association was found with TNF-α promoter polymorphisms and *CARD15* variants,[31–33] studies showing their role in a disease course and disease behaviour[34–36] have suggested these polymorphisms as conceivable predictors of ID response. The small number of individuals involved could be a reason that possible association was not detected in our study. Further studies with large sample sizes are needed.

Biologicals were believed to change the natural course of the disease and thus decrease the need for surgery. A retrospective study evaluating risk factors for initial surgery in CD children showed that the treatment with IFX was associated with a decreased risk for the 1st surgery (HR 0.36, 95% CI: 0.20–0.64).[37] In contrast, another study proposed that IFX may only delay the need for surgery. Up to 60% of treated children required surgery within 12 months, 47% of those with initial complete response.[38] Our results showed lower cumulative probability of surgery in patients with prolonged response and ID compared with nonresponders. This observation confirms the validity of the definitions and indicates a long-term benefit of IFX. The follow-up is too short to conclude if IFX may change the disease course, but at least we can see that the need for surgery was postponed.

In conclusion, IFX had high efficacy in children with CD. Up to 66% developed ID and needed repetitive infusions to regain and sustain initial response. ID, contrary to corticosteroid dependency, was associated with a good overall clinical outcome, but one has to be aware of potential long-term adverse events. Perianal disease and status without previous surgery were found to be possible predictors of ID response. No genetic predictor was revealed. IFX seems to delay the necessity for surgery in those responding to therapy. Prospective trials with further assessment of the occurrence of ID are needed.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1. Details of polymorphisms' typing using PCR–RFLP

Table S2. Minor allele frequency (%) vs. infliximab outcome in children with Crohn's disease

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Infliximab dependency is related to decreased surgical rates in adult Crohn's disease patients

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Background Infliximab dependency in children with Crohn's disease (CD) has recently been described and found to be associated with a decreased surgery rate.

Aim To assess infliximab dependency of adult CD patients, evaluate the impact on surgery, and search for possible clinical and genetic predictors.

Methods Two hundred and forty-five CD patients treated with infliximab were included from Danish and Czech Crohn Colitis Database (1999–2006). Infliximab response was assessed as immediate outcome, 1 month after infliximab start: complete, partial, and no response. Three months outcome, after last intended infusion: prolonged response (maintenance of complete/partial response), infliximab dependency (relapse requiring repeated infusions to regain complete/partial response or need of infliximab >12 months to sustain response).

Results Forty-seven percent obtained prolonged response, 29% were infliximab dependent and 24% nonresponders. The cumulative probability of surgery 40 months after infliximab start was 20% in prolonged responders, 23% in infliximab-dependent patients and 76% in nonresponders ($P<0.001$). The cumulative probability of surgery at 40 months in patients on maintenance versus on demand regime was 33 and 31%, respectively ($P=0.63$). No relevant clinical or genetic predictors were identified.

Conclusion The infliximab dependency response seems to be equivalent to the prolonged response in adult CD patients when comparing surgery rates. *Eur J Gastroenterol Hepatol* 22:1196–1203 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Keywords: Crohn's disease, genotype, infliximab dependency, phenotype, surgery

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Introduction

Infliximab (IFX), an anti-TNF-α antibody, has been shown to be effective in Crohn's disease (CD) [1] and its steroid sparing effect has been demonstrated [2,3]. A dependent behavior pattern, similar to steroid dependency [4,5], has been described in therapy with IFX. Three pediatric studies have assessed the occurrence of infliximab dependency (ID) in CD children to be 42–66% [6–8]. ID patients were defined as having relapse early after IFX cessation together with regaining a prompt remission after IFX reintroduction or being unable to discontinue IFX treatment for more than a year. Interestingly, contrary to corticosteroid dependency, ID has been suggested to be a rather beneficial phenotype decreasing the long-term surgery rate [7].

Although IFX has been proven to be a relatively safe drug [2,9–11], serious side-effects, such as hepatosplenic lymphoma, tuberculosis, or opportunistic infections with lethal outcome are still potential complications [12–17]. Treatment with IFX is relatively expensive and the cost-effectiveness is essential.

From these two perspectives, early identification of prolonged responders and ID patients might be helpful in clinical practice, when selecting the right patient for the treatment. This IFX trial is observational and provides a reflection of everyday life impact on clinical decisions and long-term disease course.

The aim of this study was to assess the occurrence of ID outcome in adult patients with CD using the IFX dependency model developed earlier by our group, evaluate the impact of ID on the surgical rate, and search for possible clinical and genetic predictors of prolonged and ID response.

Patients and methods

In this retrospective cohort study, 245 patients with CD were consecutively included: 132 from the Danish Crohn Colitis Database treated with IFX at Herlev and Slagelse University Hospitals between June 1999 and July 2006 and 113 patients from the Czech Crohn Colitis Database treated at Charles University Hospital in Prague between

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January 1999 and December 2005 (Table 1). The diagnosis of CD was assessed according to the International Diagnostic Criteria [18]. Medical records were scrutinized to abstract information on demographic and clinical data at the entry of the study (sex, age, disease localization and behavior, disease duration, history of surgery), details on IFX treatment (infusion dose, date of infusions), and C-reactive protein level before IFX treatment.

Surgery was classified as intestinal (resection, strictureplasty, colectomy) and/or perianal (fistulotomy, advancement flap). Incision of an abscess, which occurred as a possible consequence of the healing process during IFX therapy was not considered as surgery. IFX treatment was given to patients with moderate-to-severe CD, refractory or intolerant to conventional treatment.

The treatment strategy and cessation of the therapy were individualized and influenced by patients' clinical condition and treating physician's decision. Retrospectively, treatment strategy was divided into three groups according to how IFX was administrated: (i) induction therapy only (0, 2, and 6 weeks), (ii) induction therapy followed by scheduled maintenance therapy every 6 or 8 weeks, and (iii) on demand therapy – all nonscheduled. In the 'on demand' approach, after initial 1–3 infusions, the following infusions were given as nonscheduled in accordance to the activity of the disease.

Table 1 Clinical and demographic characteristics of Danish and Czech Crohn's disease patients treated with infliximab

	Danish	Czech	*P* value
Number of patients	132	113	
Age at the start of IFX treatment			0.08*
Median (range)	34 (15–66)	31 (16–67)	
Male (%)	56 (42)	53 (47)	0.48
Disease duration at the start of IFX treatment (year)			0.50*
Median (range)	6 (0–33)	5 (0–39)	
Time of follow-up after the start of IFX treatment (month)			0.44*
Median (range)	37.5 (6–92)	38 (13–89)	
Disease localization at the start of IFX treatment (%)			0.01
Ileum	18 (14)	12 (11)	
Colon	47 (35)	35 (31)	
Ileo–colon	63 (48)	49 (43)	
+Upper disease	4 (3)	17 (15)	
Disease behavior at the start of IFX treatment (%)			0.07
Inflammatory	48 (36)	26 (23)	
Stricturing/penetrating	18 (14)	20 (18)	
+Perianal disease	66 (50)	67 (59)	
Intestinal surgery before IFX treatment (%)	56 (42)	64 (57)	0.03
Intestinal surgery after IFX treatment (%)	39 (30)	21 (19)	0.047**
Indication of IFX (%)			0.10
Luminal disease	77 (58)	54 (48)	
Perianal disease	55 (42)	59 (52)	
Concomitant immunosuppressive therapy (%) (azathioprine/mercaptopurine/methotrexate)	114 (86)	79 (70)	0.002
Treatment regime (%)			<0.001
Only induction (0, 2, 6 week)	31 (23)	84 (74)	
Induction plus maintenance (every 8 or 6 weeks)	26 (20)	8 (7)	
On demand (nonscheduled)	75 (57)	21 (19)	
IFX infusions			0.02*
Total	772	459	
Median (range)	4 (1–28)	3 (1–17)	

IFX, infliximab.
*P value was calculated by χ^2 and Mann–Whitney test.
**P value was calculated by Pearson χ^2 test.

One hundred and eighty-two healthy individuals from Denmark and 283 from the Czech Republic were used as controls in genotype–phenotype analyses.

Assessment of infliximab outcome

The clinical outcome of IFX therapy was assessed according to a phenotype model of ID developed and described earlier [7].

Immediate outcome: 1 month after the first IFX infusion [5]:

(1) Complete response–absence or almost absence of all clinical symptoms;
(2) Partial response–improvement of symptoms;
(3) No response–no improvement or worsening of symptoms.

Three months outcome: 3 months after the last intended infusion as:

(1) Prolonged response–maintenance of the complete or partial response;
(2) ID relapse requiring repeated infusions to regain the complete or partial response. Patients who needed IFX therapy for more than 12 months to sustain response were also considered ID;
(3) No response meaning no improvement or worsening of symptoms.

The last intended infusion meant that the treating clinicians had primarily decided to stop IFX therapy. The number of infusions given to patients before planned IFX stop differed among the patients (from 1 up to several IFX infusions); thus the long-term outcome was evaluated irrespective of the prior treatment length.

The definitions of the phenotype model of ID are illustrated in Fig. 1.

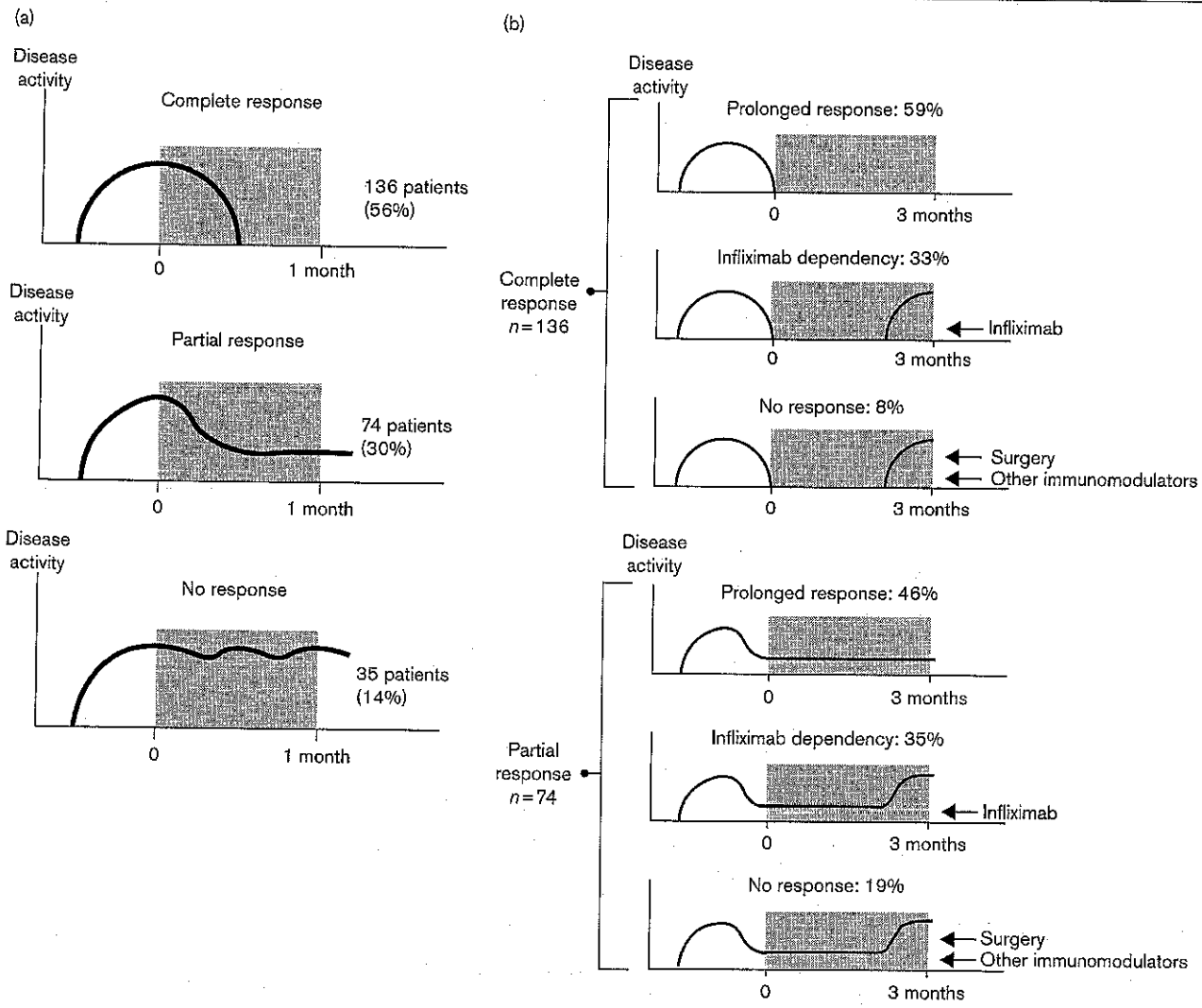
If the interval between the infusions was longer than 1 year the treatment was considered as the second, the third course, etc. Only the first course of treatment was analyzed in this study.

In addition, the outcome of IFX treatment was also assessed 1 year after the cessation of IFX therapy.

Genetic analyses

Genomic DNA was isolated from peripheral blood by routine salting out procedure (Czech Republic) or from a buccal swab (Denmark) using Qiagen DNA purification Kit (Qiagen, Hilden, Germany). Following candidate genetic predictors of ID, and prolonged response was

Fig. 1



(a) Outcome of infliximab treatment: 1 month after the first infliximab infusion. (b) Outcome of infliximab treatment: 3 months after the last intended IFX infusion in patients initially obtaining complete and partial response.

selected: *TNF* c.−1037 C>T, *TNF* c. −488 A>G, *CASP9* c.93 C>T, *LTA* c.207 A>G, *FASLG* c. −844 C>T. All variants were typed using PCR–restriction fragment length polymorphism as described earlier [7]. To ensure consistency between runs, samples of known genotypes were repeated in every analysis. DNA samples were analyzed under numeric codes, and genotype–phenotype matching was done at the end of the study. Genotypes of controls were in Hardy–Weinberg equilibrium.

Czech and Danish cohorts were analyzed separately because of significant differences of *FASLG* c: −844 C>T, *LTA* c: −207 A>G, *TNF* c. −488 A>G, *TNF* c. −1037 C>T variants in general populations (data not shown).

Statistical analysis

Empirical transition probabilities of response from immediate to 3-month outcome were calculated. Univariate logistic analyses were carried out analyzing: (i) the probability of being a complete or partial responder 1 month after the start of IFX therapy, (ii) the probability of being a prolonged responder or ID. Fisher's exact test was used when appropriate. Chi-square test and Fisher's exact test were used to compare allelic and genotypic frequencies, and to analyze an association of present variants with response to IFX. Comparisons of different treatment regimes, and Hardy–Weinberg equilibrium were done by χ^2 test. Surgery rate before and after the start of IFX therapy was compared by Wilcoxon signed-rank test. Mean surgery rate before and after IFX was then compared in view of 3 months outcome. Kaplan–Meier

analyses with accompanying log-rank tests were used for assessment of time until surgical treatment was needed. A significance level of 5% was chosen.

Ethical considerations

The study was approved by The Danish Data Protection Agency and Ethics Committees in Prague and in Copenhagen.

Results

IFX was used in 131 patients with luminal disease refractory or intolerant to conventional treatment and 114 patients with perianal disease. A total of 1231 infusions (median three infusions, range 1–28) were given in a dose of 5 mg/kg. Two patients needed an increased dosage (10 mg/kg) during the course of treatment. Only induction therapy was given to 47% of patients, induction followed by maintenance therapy to 14% (median eight infusions, range: 4–17) and on demand treatment to 39% of patients (median four infusions, range: 1–28). The interval between infusions given on demand was 6–50 weeks. Concomitant immunosuppressive therapy (azathioprine, mercaptopurine, or methotrexate) was given to 86% Danish and 79% Czech patients during and after IFX cessation. The demographic and clinical data of included patients are presented in Table 1.

Outcome of infliximab treatment

Immediate outcome

One hundred and thirty-six (56%) patients achieved complete, 74 (30%) partial, and 35 (14%) had no response.

Three months outcome

One hundred and fourteen (47%) patients obtained prolonged response, 71 (29%) developed ID, and 60 (24%) had no response. The median number of infusions was three (range: 1–7) in prolonged responders, nine (3–28) in ID, and three (1–7) in nonresponders. The analysis of transition probabilities disclosed that complete responders had a 59% probability to become prolonged responders, 33% ID, and 8% nonresponders. Partial responders had 46% probability to become prolonged responders, 35% ID and 19% nonresponders (Fig. 1).

One hundred and nineteen (49%) patients sustained the initial positive response after a year of cessation of IFX. Twenty-two patients (9%) were not classified as they were still in treatment with IFX or the observational time after the last infusion was less than a year.

Surgery

Three hundred and twenty-seven surgeries (58% intestinal, 42% perianal) were before and 96 (57% intestinal, 43% perianal) after IFX therapy. A 70% decrease in the mean annual surgery rate in prolonged responders ($P < 0.001$), 57% decrease in ID ($P = 0.017$), and a nonsignificant increase in nonresponders (9%, $P = 0.48$) was observed after IFX therapy.

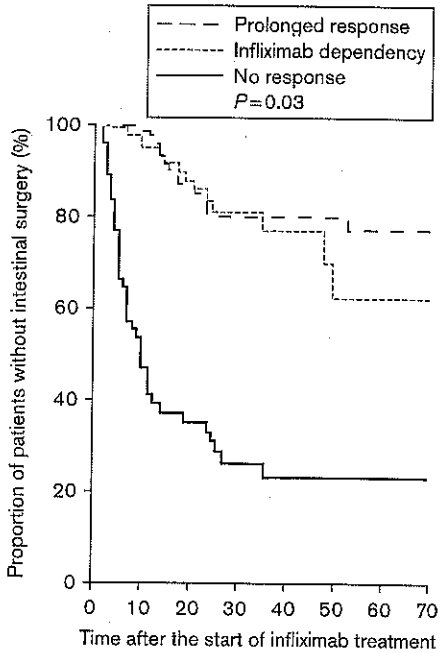
Regarding the type of surgery, prolonged responders had a significant decrease in intestinal and perianal surgeries ($P < 0.001$). In ID patients reduction of both intestinal and perianal surgeries was observed with only perianal surgeries being statistically significant ($P = 0.01$). Intestinal surgery before IFX was shown to be negatively associated with ID phenotype [odds ratio (OR) 0.45, 95% confidence interval (CI): 0.24–0.82, $P = 0.007$]. The cumulative probability of intestinal surgery 40 months after the start of IFX was 20% in prolonged responders, 23% in ID, and 76% in nonresponders (log-rank test: $P < 0.001$) (Fig. 2).

There was a significant difference in post-IFX surgical rate between the two countries with 39 (30%) Danish and 21 (19%) Czech patients undergoing surgery after the start of IFX therapy.

Treatment regimes

No difference in cumulative probability of surgery 40 months after the start of IFX therapy was observed comparing maintenance therapy versus on demand regime in patients responding at 1 month (33 vs. 31%, log-rank test: $P = 0.63$) (Fig. 3).

Fig. 2



Number of patients at risk

Prolonged response	113	110	86	61	41	36	25	9
Infliximab dependency	69	62	46	26	18	10	7	4
No response	58	31	18	12	9	7	5	0

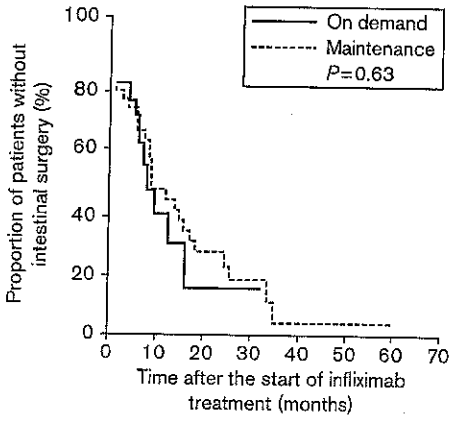
The cumulative probability of intestinal surgery after the start of infliximab therapy with respect to outcomes (log-rank test).

Clinical predictors

Patients with an immediate complete response were more likely to sustain prolonged response or ID than those with partial response (OR 2.65, 95% CI: 1.54–6.09, $P = 0.024$). Czech patients developed significantly less ID than Danish patients (OR 0.37, 95% CI: 0.20–0.69, $P = 0.001$).

Sex, disease duration, age, localization of disease, disease behavior, previous surgery, indication for IFX (luminal vs. perianal disease), concomitant immunosuppressive therapy, and CRP level at baseline were not significantly associated with IFX outcome (data not shown).

Fig. 3



Number of patients at risk

On demand	78	71	56	37	25	19	13	7
Maintenance	33	26	13	6	6	0	0	0

The cumulative probability of intestinal surgery after infliximab start (log-rank test) with respect to treatment regime. Induction = 0, 2, 6 week; on demand = nonscheduled; maintenance = induction + every 8 or 6 weeks.

Genetic predictors

Danish patients carrying at least one G allele of *LTA* c-207 A > G variant were more likely to become prolonged responders or ID compared with those homozygous for A allele (93 vs. 69%, respectively; OR 6.04, 95% CI: 1.48–25.26, $P = 0.027$). In Czech patients, ID phenotype was associated with the presence of at least one T allele of CASP9 *c.93 C > T* variant (CT/TT vs. *CC*: 37 vs. 14%, OR 3.55, 95% CI: 1.21–10.37, $P = 0.033$). No association was found between *FASLG* c.−844 C > T, *TNF* c. −488 A > G or *TNF* c. −1037 C > T variants and IFX response (Table 2). Similarly, no significant differences were found in allele frequencies of *TNF* c. −1037 C > T, *TNF* c. −488 A > G, *CASP9* c. 93 C > T, *LTA* c. −207 A > G or *FASLG* c. −844 C > T between CD patients and controls.

Discussion

This study assessed the occurrence of ID in adult CD patients and found that 29% of patients developed ID, requiring repetitive infusions to sustain initial remission, whereas 47% became prolonged responders maintaining initial response without the need of further infusions. This is the first study estimating the frequency of ID in adult CD patients. To date, three studies of children cohorts evaluating ID have been published and reported that 42–66% of children developed ID [6–8]. Our results indicate a lower frequency of ID in adults compared with children. This difference could be explained by children having a more extensive and aggressive disease [19,20]. Moreover, higher remission rates of IFX treatment have been observed in children compared with adult patients [1,21].

Significantly more Danish than Czech patients developed ID. The significant difference in IFX treatment regimes between the countries suggests itself as a probable cause of this finding. However, the treatment policy

Table 2 Genotype frequencies versus infliximab outcome in patients with Crohn's disease

		Denmark					Czech Republic				
		Immediate outcome (*n*=100)		Three months outcome (*n*=86)			Immediate outcome (*n*=90)		Three months outcome (*n*=77)		
Variant	Genotype	CR+PR (*n*=86)	NR (*n*=14)	PRO+ID (*n*=77)	NR (*n*=9)	ID (*n*=39)	CR+PR (*n*=77)	NR (*n*=13)	PRO+ID (*n*=58)	NR (*n*=10)	ID (*n*=19)
FASL c.−844 C>T	CC	29	7	26	3	9	35	8	28	7	6
	CT	39	4	34	5	20	35	5	32	3	10
	TT	18	3	17	1	10	7	0	7	0	3
CASP9 c.−93 C>T	CC	53	6	45	8	20	42	7	36	6	6[a]
	CT	27	7	26	1	15	28	6	24	4	11
	TT	6	1	6	0	4	7	0	7	0	2
LTA c.207 A>G	AA	13	3	9[a]	4	7	5	2	4	1	1
	AG	36	5	33	3	16	33	6	30	3	6
	GG	37	6	35	2	16	39	5	33	6	12
TNF c. −488 A>G	AA	3	0	2	1	1	2	0	2	0	0
	AG	26	5	23	3	14	15	2	13	2	3
	GG	57	9	52	5	24	60	11	52	8	16
TNF c. −1037 C>T	CC	72	10	63	9	32	57	13	50	7	14
	CT	14	4	14	0	7	19	0	16	3	5
	TT	0	0	0	0	0	1	0	1	0	0

CR, complete response; ID, infliximab dependency; NR, no response; PR, partial response; PRO, prolonged response.
[a]Statistically significant result ($P<0.05$).

was discussed before the start of the study and assumed to be very similar in both the countries. Moreover, if the potentional nonavailability of IFX (and thus more induction regimes only) was the cause of low frequency of ID phenotype in Czech patients, the individuals with a good initial response and early relapse after IFX stop, but not obtaining repetitive IFX would have been considered as nonresponders as per the definition. However, no significant difference in nonresponders was observed. In contrast, Czech patients maintained significantly more prolonged response than Danish patients (data not shown). Moreover, no increase in surgery rate after IFX start was observed in Czech patients. In contrast, Czech patients underwent significantly less intestinal surgery compared with Danish population. We speculate that different environmental factors and potential referral center bias could contribute to this observation. Both the countries had the same policy regarding concomitant immunosuppressive therapy. The observed significant difference was influenced mainly by higher intolerance of immunosuppressive preparations (mainly azathioprine) in the Czech population together with higher patients' reluctance to take combination therapy.

Approximately half of our patients were still in remission 1 year after the last IFX infusion. This reflects a high proportion of sustained response in our cohorts. The relatively high number of patients on concomitant immunosuppressive therapy with the majority continuing this therapy after IFX cessation could have an impact on the result. Similar favorable findings were also reported in other studies [22,23].

Danish patients carrying G allele of *LTA* c.−207 A > G variant were found to have a better outcome. Taking in account the results by Taylor *et al.* [24] this could suggest a possible role of *LTA* variants in prediction of IFX outcome. However, this could not be replicated in our Czech cohort. Hlavaty *et al.* [25] reported an association of TT genotype of *CASP9* c.93 C > T variant with positive IFX response. Similarly, in Czech patients we revealed an association of T allele of this variant with ID phenotype. No such association was found among Danish patients, despite the same frequency of this variant in both background populations. Larger independent cohort is needed to decide whether the observed associations exist or whether it was a random observation. The *TNF*–308 A > G variant has been shown to influence the production of TNF-α [26,27] and to be associated with disease activity of CD [26,28]. However, neither association of variants within genes encoding TNF-α or its receptor with IFX outcome has been proven in studies published earlier [27,29] nor has our study proven it. No adjustment for other confounders (such as smoking, disease localisation and behaviour) was performed in our study because of relatively small numbers of participants. Therefore our results should be interpreted with caution.

Early introduction of IFX in newly diagnosed patients has been shown to prolong the remission and revealed a higher proportion of mucosal healing [30]. Mucosal healing has been reported to be associated with a lower risk of surgery [31]. Our study showed that patients with prolonged response, and ID had a significant decrease in the surgery rate compared with nonresponders. Similar results have been observed in a recent pediatric study assessing ID [7]. Interestingly, the decrease was observed in only perianal surgeries, but not intestinal. This is in agreement with a study published earlier showing that IFX reduced surgeries in fistula patients, but not in patients with luminal disease [32]. This might be explained by the fact that newly diagnosed patients are mostly present with pure inflammatory disease and the occurrence of complications, such as strictures or internal fistulas, increases during the course of the disease.

Maintenance therapy has been proposed to be superior to the 'on demand' treatment with a higher number of patients with a sustained clinical response, better endoscopic outcome, and lower surgical rate [33]. Although this study was not designed to compare different treatment regimes, our data propose no difference between maintenance and 'on demand' regimes with regard to probability of surgery. The majority of patients were treated on demand meaning that after the induction phase IFX was given, when patients started to experience the clinical symptoms and/or had laboratory markers of relapse. Thus, timing of infusions was regulated by the patients' need and phenotype. This could partially explain our favorable results. A study comparing early introduction of IFX with conventional treatment reported that although patients received IFX intermittently, no reduction of response rate or development of hypersensitivity was observed [30]. In contrast, a recent open-label study of 31 CD children [34], comparing maintenance therapy and on demand revealed that significantly more children on maintenance regime were in clinical remission and achieved better growth improvement than those in the on demand group. This contradicts our observation, although study design and end-points were different.

IFX seems to have a good safety profile, both in a short and long term, as outlined by several cohort studies, national registries and also in a recent meta-analysis [2,9,35,36]. In contrast, corticosteroid use is accompanied by a wide range of severe adverse events [37], moreover an association with a high-surgery rate was reported in earlier studies [4,5,38]. Whereas, corticosteroid dependency is a 'harmful' condition, so far ID seems to be a positive response phenotype with a low surgery rate and favorable safety.

In conclusion, ID in adult patients with CD was assessed for the first time. ID was identified in 29% of adult CD patients and was associated with a significant decrease of surgery rate. This suggests ID, in contrast

to corticosteroid dependency, to be a beneficial response phenotype. Prospective studies are warranted to assess the impact of ID on long-term disease prognosis. On demand therapy might be considered as a possible therapeutic option. The role of *LTA* c.207 A > G and *CASP9* c.93 C > T variants as predictors of IFX outcome remains to be elucidated.

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Conflicts of interest: none declared.

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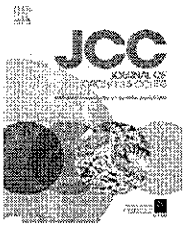

5-Aminosalicylic acid dependency in Crohn's disease: A Danish Crohn Colitis Database study

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Abstract

Background and aims: The role of 5-aminosalicylic acid (5-ASA) in Crohn's disease is unclear. The outcome of the first course of 5-ASA monotherapy with emphasis on 5-ASA dependency was retrospectively assessed in consecutive cohort of 537 Crohn's disease patients diagnosed 1953–2007.
Methods: Following outcome definitions were used: *Immediate outcome* (30 days after 5-ASA start) defined as *complete/partial response* (total regression/improvement of symptoms) and *no response* (no regression of symptoms with a need of corticosteroids, immunomodulator or surgery). *Long-term outcome* defined as *prolonged response* (still in complete/partial response 1 year after induction of response); *5-ASA dependency* (relapse on stable/reduced dose of 5-ASA requiring dose escalation to regain response or relapse ≤1 year after 5-ASA cessation regaining response after 5-ASA re-introduction).
Results: One hundred sixty-five (31%) patients had monotherapy with 5-ASA. In 50% 5-ASA monotherapy was initiated ≤1 year after diagnosis (range 0–49 years). Complete/partial response was obtained in 75% and no response in 25% of patients. Thirty-six percent had prolonged response, 23% developed 5-ASA dependency and 38% were non-responders in long-term outcome. Female gender had higher probability to develop prolonged response or 5-ASA dependency (OR 2.89, 95%CI: 1.08–7.75, $p=0.04$). The median duration (range) of 5-ASA monotherapy was 34 months (1–304) in prolonged responders, 63 (6–336) in 5-ASA dependent and 2 (0–10) in non-responders.
Conclusions: A selected phenotype of Crohn's disease patients may profit from 5-ASA. Fifty-nine percent of patients obtained long-term benefit with 23% becoming 5-ASA dependent. Prospective studies are warranted to assess the role of 5-ASA in Crohn's disease.

Abbreviations 5-ASA, 5-Aminosalicylic acid; CD, Crohn's disease; DCCD, Danish Crohn Colitis Database.

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1. Introduction

5-Aminosalicylic acid (5-ASA) is an efficacious drug in mild to moderate ulcerative colitis in induction as well as in maintenance of remission.[1,2] Contrary to this, the role of 5-ASA in Crohn's disease (CD) is conflicting. Several trials comparing effect of 5-ASA to placebo have been done with divergent results.[3–8] A meta-analysis investigating efficacy of 5-ASA in treatment of active CD and 2 meta-analyses focused on maintenance therapy failed to prove its efficacy.[9–11] Consequently, the use of 5-ASA in CD was not further recommended.[12] However, the studies included were differently designed, the study population was quite heterogeneous and different drug formulations and dosages were used.

The newer 5-ASA preparations have a very good safety profile with the occurrence of the adverse events comparable to placebo.[13,14] Moreover, there is evidence from population based studies that a significant proportion of CD patients has a mild disease course.[15,16] Drug dependency has already been described in corticosteroid treatment and more recently also in infliximab therapy.[17–19] A similar dependent pattern, however, can be observed also in CD patients on 5-ASA treatment. Thus, the role of 5-ASA in CD is still unclear and several factors indicate that there might be a subgroup of CD patients who could benefit from 5-ASA therapy.

The primary aim of the study was to assess the outcome of the first course of 5-ASA monotherapy with emphasis on 5-ASA dependency in a retrospective cohort of CD patients from the Danish Crohn Colitis Database (*DCCD*) treated at Herlev University Hospital. The secondary aim was to define conceivable clinical predictors of positive response to 5-ASA and mainly of 5-ASA dependency.

2. Material and methods

2.1. Study population

During the period from May 2007 until April 2008 medical records of CD patients from *DCCD* diagnosed from 1953 to

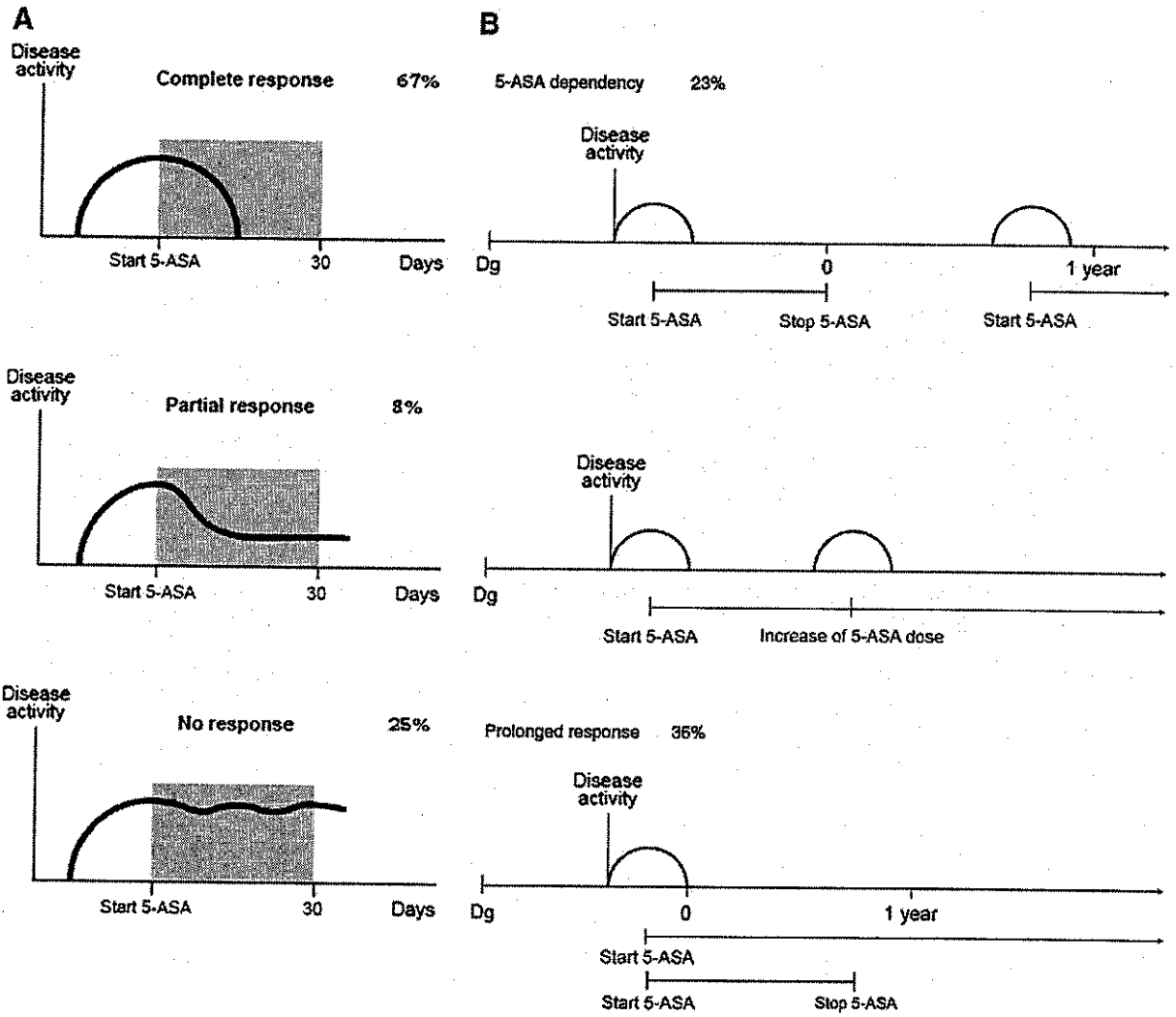

Figure 1 Clarification of the definitions. A) Immediate outcome; B) Long-term outcome. Abbreviations: Dg, diagnosis; 5-ASA, 5-Aminosalicylic acid.

2007 and treated at Herlev University Hospital were scrutinized to abstract information on treatment with per oral and topical 5-ASA preparations. Inclusion criterion was defined as "Relapse of the disease with the intention to treat only with 5-ASA preparations during the disease course".

Information on disease duration, behaviour and localization, patient's age and data on previous surgery at the start of 5-ASA treatment course were recorded from patients' files.

2.2. Assessment of 5-ASA response

Response to 5-ASA treatment was evaluated by two investigators according to a developed phenotype model of 5-ASA dependency (Fig. 1, Table 1). The model was created with the aim that more than 90% of all response patterns would fit into the model. Response to 5-ASA was assessed using the medical records where the description of patient's clinical symptoms and/or overall estimation of the treatment efficacy from the treating physician were provided.

The outcome of 5-ASA therapy was defined as:

1) Immediate outcome: 30 days after the start of 5-ASA therapy
   - *Complete response*: total regression of clinical symptoms
   - *Partial response*: improvement of clinical symptoms
   - *No response*: no regression of symptoms with a need to shift from 5-ASA to immunomodulator and/or surgery
2) Long-term outcome: irrespective of the length of the treatment
   - *Prolonged response*: still in complete/partial response one year after induction of response, either on the initial/reduced dose of 5-ASA or after 5-ASA discontinuance
   - *5-ASA dependency*: relapse within one year after 5-ASA treatment cessation and regain of complete/partial response after 5-ASA re-introduction or relapse on a dose reduction or stable dose requiring dose escalation to regain complete/partial response
   - *No response*: no regression of symptoms with a need to shift from 5-ASA treatment to immunomodulator therapy and/or surgery

Table 1 Phenotype model of 5-Aminosalicylic acid (5-ASA) dependency.

	Phenotype	Definition
Immediate outcome	Complete response	Total regression of clinical symptoms 30 days after 5-ASA initiation
	Partial response	Improvement of clinical symptoms 30 days after 5-ASA initiation
	No response	No regression of symptoms with a need to shift from 5-ASA to an immunomodulator or surgery
Long-term outcome	Prolonged response	Still in complete/partial response 1 year after induction of response (maintained on 5-ASA or after cessation of 5-ASA)
	5-ASA dependency	Relapse within 1 year after 5-ASA cessation regaining complete/partial response after 5-ASA re-introduction or relapse on stable/reduced dose of 5-ASA requiring dose escalation to regain response

Immunomodulator therapy was defined as corticosteroids (intravenous, per oral, enemas/foams), azathioprine/mercaptopurine/methotrexate and biological drugs. Surgery was classified as intestinal (resection, strictureplasty, colectomy) or perianal (incision of abscess, seton, fistulotomy). A new relapse with the intention to treat only with 5-ASA >1 year after the previous 5-ASA course or after the immunomodulator treatment or surgery was considered as the 2nd, 3rd etc. course. Only the 1st treatment course was analyzed.

Additionally, the treatment outcome one year after the cessation of 5-ASA therapy was studied.

2.3. Statistical analysis

Logistic regression analyses were performed in order to investigate which disease characteristics were predictable for a certain treatment response.

Kaplan–Meier curve with accompanying log-rank test was done for cumulative probability of surgery.

3. Results

Five hundred thirty-seven patients with CD from *DCCD* treated at Herlev University Hospital were identified (Fig. 2). In 7 patients medical records were not available and 185 were either never treated with 5-ASA or the information about previous 5-ASA treatment was missing due to incomplete medical records. Of the rest 345 patients treated with 5-ASA, 165 fulfilled the inclusion criterion and were assessed according to above described phenotype model of 5-ASA dependency. Clinical and demographic characteristics of included patients are outlined in Table 2.

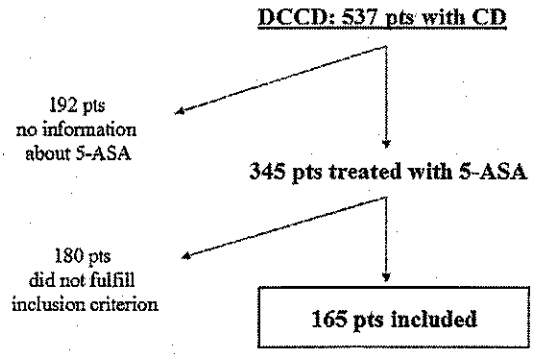

Figure 2 Recruitment of patients (pts) with Crohn's disease (CD) from the Danish Crohn Colitis Database (*DCCD*) treated at Herlev University Hospital. Abbreviation: 5-ASA, 5-Aminosalicylic acid.

Table 2 Demographic and clinical characteristics of Crohn's disease patients treated with 5-Aminosalicylic acid (5-ASA) monotherapy at the start of 5-ASA treatment course.

	$n=165$
Decade of diagnosis (%)	
1953–1969	4 (2)
1970–1979	12 (7)
1980–1989	34 (21)
1990–1999	69 (42)
2000–2007	46 (28)
Male (%)	71 (43)
Age (year): median (range)	33 (13–83)
Disease duration (year): median (range)	0 (0–49)
Disease localization (%)[a]	
Terminal ileum	45 (27)
Colon	79 (48)
Ileo-colon	29 (18)
Upper disease +/− ileum and/or colon	8 (5)
Unknown	4 (2)
Disease behaviour (%)[a]	
Inflammatory	146 (88)
Stricturing	6 (4)
Penetrating	12 (7)
Unknown	1 (1)
Perianal disease at any time prior to 5-ASA monotherapy (%)	21 (13)
Intestinal surgery prior to 5-ASA course (%)	30 (18)

[a] Montreal classification.

3.1. 5-ASA treatment outcome

Thirty days after the start of 5-ASA treatment, 124 (75%) patients responded either completely or partially and 41 (25%) did not respond. In long-term outcome, 59 (36%) patients obtained prolonged response, 38 (23%) developed 5-ASA dependency and 63 (38%) patients were non-responders and had to shift to immunomodulator therapy (47 patients) or surgery (16 patients) (Fig. 3). The median duration of the 5-ASA course was 34 months (range: 1–304 months) in those with prolonged response, 63 (6–336) in 5-ASA dependent patients and 2 (0–10) in non-responders. Five (3%) patients were not assessed in long-term outcome due to a short treatment course.

One year after cessation of 5-ASA, 17 (11%) patients still kept remission, while 124 (75%) patients in total were non-responders (either primary or secondary due to loss of initial response). Twenty-four (14%) patients were still on 5-ASA treatment or their observational time after the last 5-ASA was less than 1 year.

Kaplan–Meier analysis illustrates the cumulative probability of the first intestinal surgery since the diagnosis comparing prolonged responders, 5-ASA dependent patients and non-responders (Fig. 4).

3.2. Predictors of 5-ASA response

Logistic regression analyses identified female gender to be positively associated with the favourable long-term outcome. Sixty-eight percent (63/93) of women achieved prolonged response or developed 5-ASA dependency compared to 51% (34/67) of men (OR 2.89, 95%CI: 1.08–7.75, $p=0.04$). Focusing on 5-ASA dependent response, patients with longer disease duration were more likely to become 5-ASA dependent than those with shorter disease duration (38% (11/29) vs. 18% (23/127); OR 4.06, 95%CI: 1.09–15.1, $p=0.04$). No association was revealed between the disease localization, behaviour, patients' age, history of surgery and 5-ASA outcome.

4. Discussion

This is a retrospective study evaluating the efficacy of 5-ASA therapy in patients with CD focusing on the newly defined phenotype of 5-ASA dependency. Thirty one percent of all patients treated at our hospital had a monotherapy with 5-ASA preparations and their response to 5-ASA could be assessed. Short-term response was obtained in 75% of them, whereas 59% of patients maintained long-term benefit as prolonged responders or 5-ASA dependent with 23% becoming 5-ASA dependent. Female gender was found to be associated with better long-term outcome whereas patients with longer disease duration were more likely to become 5-ASA dependent.

The efficacy of 5-ASA in treatment of mild to moderate CD was assessed in 6 randomized placebo controlled trials (RCT) with different results.[11,20–22] In the first two studies mesalazine 1.5 g/day given for 16 and 6 weeks respectively failed to show any benefit over placebo in induction of remission.[20,21] Tremaine et al.[22] later investigated 3.2 g/day mesalazine given for 16 weeks. A significantly greater proportion of mesalazine-treated patients obtained partial remission vs. placebo, but no benefit in terms of complete remission was found. Pentasa 1, 2 and 4 g daily was evaluated in three subsequent RCTs.[7,11] The study by Singleton et al.[7] demonstrated the superiority of Pentasa 4 g over placebo with 43% and 18% of patients achieving remission at week 16 ($p=0.0017$). However, the subsequent two studies failed to confirm this result.[11] Finally, the meta-analysis of these trials showed a significant, but clinically irrelevant 18-point reduction in Crohn's disease activity index in favour of 4 g mesalazine.[11]

Similarly, several trials studying 5-ASA preparations in maintenance of medically or surgically induced remission in CD have been published with conflicting results.[9,10] In the meta-analysis by Camma et al.[10] 15 RCTs comparing the efficacy of mesalazine (1–4 g/day) to either placebo or no treatment were included. In 13 out of 15 studies mesalazine was found to be superior, however only in 2 studies a significant difference was achieved.[10] The pooled estimates revealed a significant risk reduction in patients with postsurgical remission, but not in the group of medically-induced remission. However, a significant heterogeneity between the studies was observed. Another meta-analysis included 7 RCTs comparing 5-ASA agents (1–3 g/day) with placebo.[9] The authors found no evidence of 5-ASA preparations to be superior to placebo for maintenance of medically-induced remission.

Corticosteroids are very potent anti-inflammatory agents and corticosteroid dependency would be a "nice phenotype"-due to a prompt response to repeated or increased dose of corticosteroids resulting in induction and maintenance of remission.[18] However, the frequent occurrence of serious side

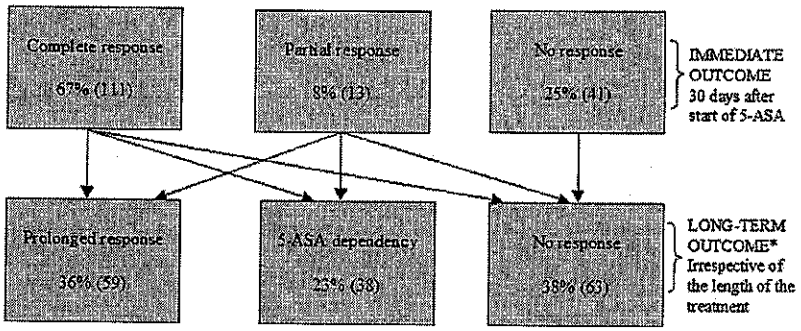

Figure 3 The outcome of the 1st course of 5-Aminosalicylic (5-ASA) monotherapy in 165 patients with Crohn's disease. *Five (3%) patients were not assessed in long-term outcome because of short treatment course ≤1 year.

effects makes the corticosteroid dependency an unpleasant condition demanding the quick withdrawal of the drug.[12] Infliximab in contrast to corticosteroids is relatively safe although the long-term side effects are still being monitored.[23,24] Thus, recently described infliximab dependency,[17,19,25] contrary to corticosteroid dependency, seems to be a rather beneficial phenotype. Whereas corticosteroids and infliximab are potent anti-inflammatory agents[18,26] 5-ASA is only a mild anti-inflammatory drug with number needed to treat of 10 for induction and 13 for maintenance of remission.[27] However, results of our study propose that there is a group of CD patients with a good response to 5-ASA. Fifty-nine percent of patients benefited from the therapy in long-term period (prolonged responders and 5-ASA dependent) with 23% becoming 5-ASA dependent. Patients classified as 5-ASA dependent were characterized by relapse of the disease repetitively responding to 5-ASA and thus confirming its efficacy. It has to be emphasized, that nearly 1/3 of patients were diagnosed in the era of sulphasalazine, pure 5-ASA preparations were introduced only in the 2nd half of 1980s.

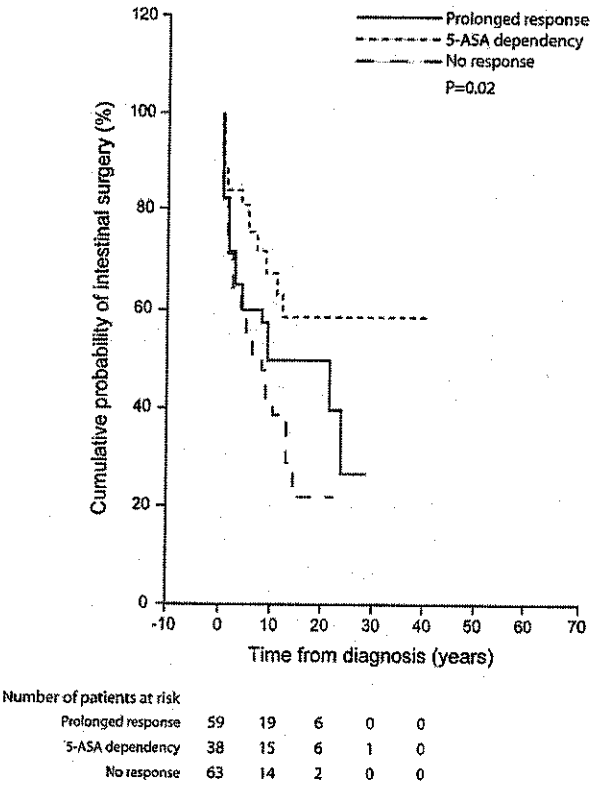

Figure 4 The cumulative probability of the 1st intestinal surgery from diagnosis in Crohn's disease patients with respect to long-term outcome of 5-Aminosalicylic acid (5-ASA) monotherapy (log-rank test). Significant difference was revealed between 5-ASA dependent patients and non-responders ($p=0.007$). No difference between prolonged responders vs. non-responders ($p=0.1$) and 5-ASA dependent vs. prolonged responders ($p=0.12$) was found.

Remarkably, 5-ASA dependent patients had a lower cumulative probability of the 1st intestinal surgery compared to non-responders ($p=0.007$), whereas no such difference was observed between prolonged responders and non-responders ($p=0.1$). This may suggest 5-ASA dependent patients to be a specific disease phenotype, probably associated with a milder course of CD.

Although the results seem too favourable one has to be aware that highly selected group was analyzed and the total number of patients profiting from 5-ASA was not high, as expected. However, 5-ASA is a very safe drug and in case that 5-ASA was not used in CD any longer, these patients would have been offered corticosteroids or other anti-inflammatory agents and thus exposed to a higher risk of side effects. In addition, self-management of the disease has been suggested as one of the strategies optimizing patient adherence to therapy, reducing the healthcare costs and accelerating treatment provision for patients.[28–30] 5-ASA preparations with their good safety profile would be a suitable drug which could offer the opportunity of disease self-managing to a certain group of CD patients.

Interestingly, in a recent retrospective study from Germany a disease course of 103 newly diagnosed CD patients was assessed.[31] Twenty seven percent of all patients were found to have a mild long-term disease course requiring only mesalazine therapy and almost 50% of those starting on 5-ASA monotherapy were maintained only on 5-ASA up to 48 months without need of more potent anti-inflammatory agents. This mild disease group was characterized by older age at diagnosis and lower inflammatory activity expressed by lower C-reactive protein and lack of severe endoscopic findings.[31]

In our study, women were found to have a better long-term response to 5-ASA than men. A lower adherence with

maintenance 5-ASA medication reported in male gender could explain this finding.[32] Patients with longer disease duration were more likely to become 5-ASA dependent. Sachar et al.[33] have reported that long preoperative disease duration correlated with a low post surgical recurrence rate. Authors of that article speculated that late operation and subsequent late recurrence were rather a reflection of an indolent disease course. Hypothetically, our observation that longer disease duration is associated with 5-ASA dependent response might also be an expression of mild disease phenotype.

The limitation of the study is the retrospective character; this may result in potential risk of misinterpretation of the treatment response based on medical records only. Moreover, the adherence to the therapy could not be assessed and was assumed only by the record that the patient was taking the drug, which to some extent may be unreliable data. Furthermore, other factors with a significant impact on disease course, such as smoking or stressful events were not available due to the study design and were not analyzed. Different 5-ASA preparations and doses were used with a possible impact on the results. Low doses or unsuitable drug forms could be a reason of worse outcome in some patients. As mentioned above the efficacy of 5-ASA in CD patients compared to other anti-inflammatory drugs is relatively low. Therefore the inclusion criterion was chosen aiming to minimize the overestimate in evaluation of 5-ASA.

In conclusion, patients with CD may benefit from 5-ASA treatment. Fifty-nine percent of patients profited from the therapy in long-term perspectives with 23% of them becoming 5-ASA dependent. Female gender was found to be associated with a better long-term outcome. An ongoing international prospective controlled study is warranted to assess the role of 5-ASA in CD and to recognize the "right patient" for this drug.

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Writing assistance: none

Statement of authorship:

"DD" collected the data, carried out data analyses, conceived and drafted the manuscript

"NP" collected the data, helped to draft the manuscript and provided a significant advice

"ME" helped to draft the manuscript, provided a significant advice

"CJ" performed the statistical analyses, helped to draft the manuscript and provided a significant advice

"PM" conceived the study, helped to draft the manuscript, provided a significant advice

All authors read and approved the final manuscript.

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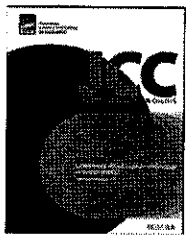

REVIEW ARTICLE

The clinical implication of drug dependency in children and adults with inflammatory bowel disease: A review

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Abstract

Drug dependency in adult and paediatric patients with inflammatory bowel disease (IBD) is described and the significance of this response pattern in clinical practice discussed in this review. Dependent patients maintain remission while on the treatment, but they relapse shortly after drug cessation or dose decrease. However, a quick restoration of remission and sustained response is achieved when the therapy is re-introduced or dose increased.

Population-based studies have demonstrated that 22–36% of adults and 14–50% of children become corticosteroid dependent. Approximately 1/4–1/3 of treated patients undergo surgery ≤1 year after treatment start, although newer paediatric studies reported lower risk of surgery (5–11%), including dependent patients. The frequent use of immunosuppressants (68–80% of children) might explain this favourable outcome and thus reduce importance of the term corticosteroid dependency.

Infliximab dependency was described in 42–66% of children and 29% of adults with Crohn's disease. The risk of surgery 50 and 40 months after treatment start was 10% and 23% in infliximab dependent children and adults, respectively. Maintenance of infliximab in dependent patients was suggested to postpone if not avoid the need of surgery.

Lastly, mesalazine dependency was identified in 23% of adults with Crohn's disease. These patients were characterized by mild disease course and lower surgical risk compared to non-responders to mesalazine (32 vs. 61%).

Identification of drug dependency is useful for prediction of a certain disease course and surgery. An adjustment of medical therapy may alter the prognosis and disease course.

Abbreviations: IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis.

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Contents

1. Background

Inflammatory bowel disease (IBD) is a chronic disorder of unknown aetiology and various manifestations regarding disease localization, occurrence of complications and frequency of relapses.[1] According to this, different behaviour patterns and disease courses have been identified classifying patients into several subtypes.[2–4] Patients, however, differ also in response patterns – response/no response – a phenotype "drug dependency" has been described in children and adults with IBD.[5–7] The dependent patients represent a specific population of individuals who maintain remission while on the treatment, but relapse promptly after drug cessation or dose decrease. However, a quick restoration of remission, repeating the way of former response, is achieved and sustained when the therapy is re-introduced or dose increased.

Drug dependency was first described in corticosteroid therapy,[5] later in infliximab treatment [7–9] and most recently in the use of mesalazine preparations.[10]

The aim of this review is to describe drug dependencies in paediatric and adult patients with IBD and to elucidate the significance of this response pattern in clinical practice.

2. Corticosteroid dependency

2.1. The development of the term corticosteroid dependency

Corticosteroid dependency was first introduced in an inception cohort of adult Crohn's disease (CD) patients from Copenhagen County in 1994.[5] In this study, the first steroid treatment course was evaluated in 109/196 CD patients diagnosed between 1979 and 1987. Later, Faubion et al. [11] published a population-based study assessing the course of the initial corticosteroid treatment in 74/173 CD patients and 63/185 patients with ulcerative colitis (UC) diagnosed in Olmsted county from 1970 to 1993. Furthermore, the outcome of corticosteroid treatment has been studied in several non-population based cohorts.[12–16]

Four paediatric studies of unselected cohorts have also addressed the term corticosteroid dependency.[6,17-19] In addition, two paediatric studies based on prospective multicentre database from US and Canada [20,21] assessed the outcome of the first steroid course in newly diagnosed children with IBD.

The term corticosteroid dependency was recognized as an important clinical response pattern and the definition has been implemented to the European Crohn's and Colitis Organization (ECCO) guidelines for CD and UC in 2006 and 2008 and has also been accepted by the Food and Drug Administration (FDA) agency as one of the end points for randomized controlled trials. [22,23]

The different definitions of corticosteroid dependency are summarized in Table 1.

2.2. How many become corticosteroid dependent?

From the population-based studies it is known that 28–36% of CD adult patients and 22% of UC patients became corticosteroid dependent.[5,11] Among paediatric patients, 24–39% of children with CD and 14–50% of those with UC developed

Table 1 Definitions of corticosteroid dependency.

Author	Definition
Munkholm et al. [5] (1994)	Relapse within 30 days after treatment had finished or relapse at dose reduction impeding discontinuation of prednisolone treatment for more than one year.
Faubion et al. [11] (2001)	Continued corticosteroid (CS) therapy at year-end caused by relapse after CSs were discontinued or caused by relapse at dose reduction impeding discontinuation of CS therapy.
Tung et al. [6] (2006)	Relapse within 30 days of treatment cessation or relapse when dose reduction was attempted.
ECCO guidelines on Crohn's disease [22] (2006)	Relapse when the steroid dose is reduced below 20 mg/day, or within 6 weeks of stopping steroids.
ECCO guidelines on ulcerative colitis [23] (2008)	Inability to reduce steroid below the equivalent of prednisolone 10 mg/day within 3 months of starting steroids, without recurrent active disease or relapse within 3 months of stopping steroids.
Jakobsen et al. [17] (2010)	Relapse within 30 days after steroid was stopped or the need for azathioprine or 6-mercaptopurine, methotrexate or anti-TNF to end steroid treatment due to relapse during tapering of steroids.

corticosteroid dependency [6,17-19] (Table 2). Similar results were observed in two multicentre studies with 31% of CD and 43% of UC children becoming steroid dependent.[20,21]

The frequency of steroid dependency in adult studies of selected cohorts ranges from 7.5 to 58% of patients with CD and from 17 to 47% of those with UC.[12–16]

2.3. What does corticosteroid dependency imply in terms of surgery?

In the study by Munkholm et al. [5] one month after cessation of corticosteroid therapy, 59% of non-responders and 26% of corticosteroid dependent patients, respectively, underwent surgical intervention. None of those with prolonged response had surgery within this time period. However, no significant difference in surgery rate among the response groups has been observed during the following two years.

Faubion et al. [11] described that cumulative probability of surgery 12 months after the start of corticosteroid treatment was 38% in CD and 29% in UC patients. No specification regarding response to corticosteroids was given.

The risk of resection one year after the initial course of corticosteroids was 27% in CD and 29% in UC children as reported by Tung et al. [6], again without specification as to corticosteroid outcome.

Finally, in the most recent paediatric study[17] the cumulative probability of surgery one year after start of corticosteroid treatment was 11.5% and 7.8% for CD and UC. Interestingly, when stratifying for outcome 30 days after stopping corticosteroids, the risk of surgery was equal for steroid dependent patients and patients with prolonged response in both CD and UC. Similar low risk of surgery was observed in two multicentre studies [20,21] where 8% and 5% of children with CD and UC respectively underwent surgery for IBD within one year after start of corticosteroids.

2.4. Are there any predictors for corticosteroid dependency?

No predictor of treatment response has been identified in any of the studies of unselected cohorts assessing adult patient populations,[5,11] whereas the paper by Jakobsen et al. identified that CD children with disease localization

Table 2 Frequency of corticosteroid dependency in population-based studies.

Author	Crohn's disease			Ulcerative colitis		
	n	Prolonged response (%)	Corticosteroid dependency (%)	n	Prolonged response (%)	Corticosteroid dependency (%)
Adult study						
Munkholm et al. [5]	109	48 (44)	39 (36)	–	–	–
Faubion et al. [11]	74	24 (32)	21 (28)	63	31 (49)	14 (22)
Paediatric study						
Tung et al. [6]	26	11 (42)	8 (31)	14	8 (57)	2 (14)
Vernier-Massouille et al. [18]	343	243 (71)	83 (24)	–	–	–
Gower-Rousseau et al. [19]	–	–	–	77	47 (61)	20 (26)
Jakobsen et al. [17]	82	50 (61)	32 (39)	77	38 (50)	38 (50)

n = number of patients treated with corticosteroids.

involving terminal ileum at diagnosis were at increased risk of steroid dependency.[17]

3. Infliximab dependency

3.1. The development of the term infliximab dependency

Dependent response pattern was recognized in infliximab treatment first in 2006.[7] Some patients maintained the remission after induction therapy alone or induction and one year maintenance therapy, while others relapsed and required further infusions to sustain the initial response.[24,25] This phenotype model was first developed and evaluated in a cohort of 24 children with CD treated in Denmark from 1999 to 2003.[7] Infliximab dependency was assessed 90 days after the intended treatment cessation and patients relapsing within this time period but regaining the initial response after re-introduction of infliximab were considered as infliximab dependent.

The model was later adjusted (Fig. 1) and used in a subsequent study of 82 paediatric CD patients treated with infliximab.[9] The study was an extension of the previous one [7] and included patients from Denmark and the Czech Republic, treated with infliximab from 2000 to 2006.

Furthermore, a national cohort of CD children from the Netherlands has been assessed for infliximab dependency.[8] Sixty-six children, treated from 2002 to 2007, were included and considered as infliximab dependent in case of relapse of symptoms requiring repeated infusions to regain good clinical response.

Lastly, infliximab dependency has been studied in a cohort of adult CD patients.[26] In 132 patients from Denmark and 115 patients from the Czech Republic, treated 1999–2006, infliximab outcome was evaluated according to a phenotype model developed and used in a previous paediatric study.[9]

3.2. How many patients developed infliximab dependency?

In paediatric studies 42–66% of children became infliximab dependent, whereas 15–29% maintained initial response as prolonged responders.[7–9] In contrast, a study of adult patients found that 49% of the patients were prolonged responders and only 29% became infliximab dependent.[26] The results are summarized in Table 3.

3.3. What does infliximab dependency imply in term of surgery?

Three articles reported risk of surgery.[8,9,26] In the Danish-Czech study,[9] the cumulative probability of surgery 50 months after the start of infliximab was 10% in infliximab dependent children, 30% in prolonged responders and 70% in non-responders ($p=0.0002$). Similarly, in a study by Pedersen et al. [26] 23% of infliximab dependent adult patients, 20% of prolonged responders and 76% of non-responders had surgery 40 months after the start of therapy ($p<0.001$) (Fig. 2). Thirty-nine per cent of infliximab treated children required surgery in a study by de Ridder et al., [8] no specification regarding treatment outcome has been described.

3.4. Are there any predictors of infliximab dependency?

An association of dependent phenotype with perianal disease and absence of intestinal surgery prior to infliximab therapy has been found in one paediatric study.[9] Contrary to this, the paper from the Netherlands [8] reported that infliximab

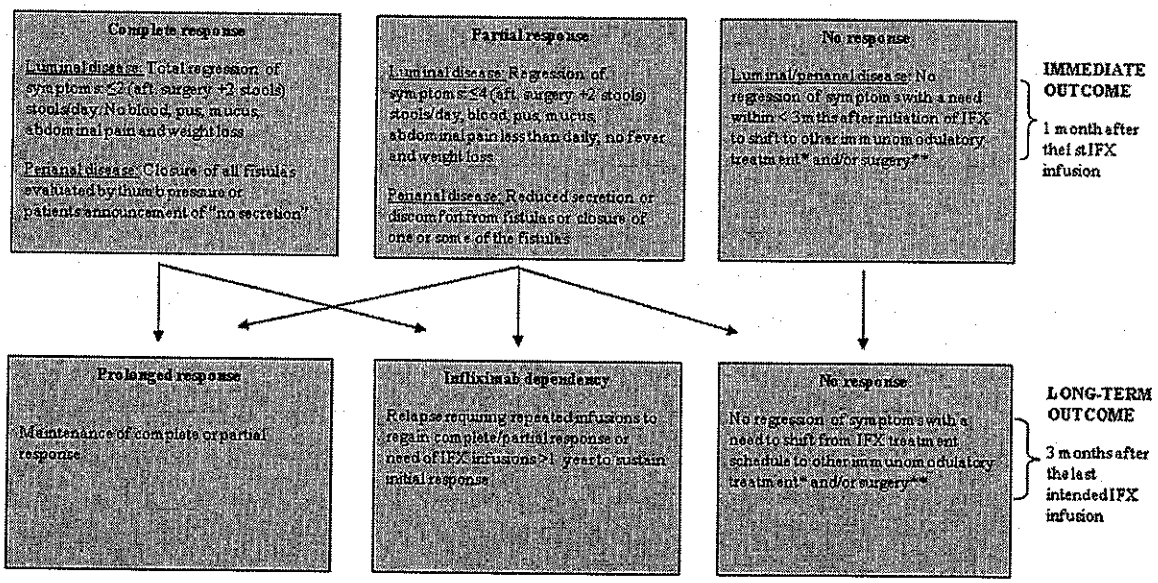


Figure 1 The phenotype model of infliximab (IFX) dependency. Footnote: *corticosteroids, azathioprine or mercaptopurine or methotrexate, other biologicals. **intestinal (resection, strictureplasty, and colectomy) and/or perianal (fistulotomy, incision of abscess, and advancement flap).

Table 3 Frequency of infliximab dependency in patients with Crohn's disease.

Author	n	Prolonged response (%)	Infliximab dependency (%)
Wewer et al. [7]	24	7 (29)	10 (42)
Duricova et al. [9]	82	18 (22)	53 (66)
de Ridder et al. [8]	66	15 (15)	37 (56)
Pedersen et al. *[26]	245	114 (47)	71 (29)

n = number of patients treated with infliximab.
*study including adult patients.

dependent response occurred significantly more in children without fistulas than in those with fistulizing disease.

Two genetic variants (*LTA* c.207 A>G and *CASP9* c.93 C>T) have been suggested as conceivable predictors of long-term and infliximab dependent outcome in a study of adult patients,[26] but needs to be confirmed.

4. 5-ASA dependency

4.1. The development of the term 5-ASA dependency

The most recently described dependent pattern has been in therapy with 5-ASA preparations.[17] Five hundred thirty-seven CD patients treated at one centre in Denmark from 1953 to 2007 were retrospectively assessed for the use of 5-ASA preparations. One hundred sixty-five (31%) of them had monotherapy with 5-ASA and were evaluated according to the phenotype model of 5-ASA dependency outlined in Table 4.

4.2. How many patients became 5-ASA dependent?

Out of 165 CD patients included, 36% obtained prolonged response and 23% developed 5-ASA dependency.[10]

4.3. What does 5-ASA dependency imply in term of surgery?

Patients responding to 5-ASA in a dependent way had a lower cumulative probability of surgery during the disease course compared with non-responders (32% vs. 61% at ten years after diagnosis, $p=0.02$).[10]

4.4. Are there any predictors of 5-ASA dependency?

Female gender was identified as a predictor of prolonged response and 5-ASA dependency. Sixty-eight percent of women achieved prolonged response or developed 5-ASA dependency compared to 51% of men (OR 2.89, 95%CI: 1.08–7.75). Interestingly, patients with longer disease duration (>3 years) were more likely to become 5-ASA dependent than those with shorter disease course (38% and 18%; OR 4.06, 95% CI: 1.09–15.1).[10]

Fig. 3 summarizes the occurrence of drug dependencies in therapy of corticosteroids, infliximab and 5-ASA preparations.

5. Discussion

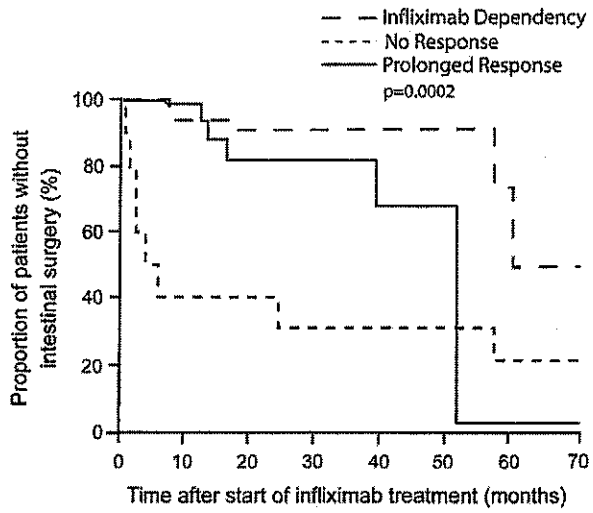
Up to now, clinical, genetic and serological markers have been of a little help when trying to predict patient's disease course and deciding for long-term treatment management [27-29] and a good clinical predictor in daily clinical practice is still lacking.

Drug dependency is dealing with a specific disease phenotype, which to some extent determines patients' prognosis. Hence it should not be understood as a simple description of drug response only, but also as a clinical tool, which can be used for identification of patients' phenotype with a certain disease course and a need for maintenance treatment.

To assess an impact of drug dependency on disease prognosis, one has to consider the efficacy and safety profile of the drug. Corticosteroids are highly efficacious anti-inflammatory agents as the number needed to treat for the induction of remission is three.[30] Nevertheless, corticosteroid dependency is a condition connected with many side effects, mainly growth retardation in children and furthermore associated with a high risk of surgery as obvious from above mentioned studies.[5,11] Therefore, early identification of dependent patients, carrying a poor prognosis, is important to introduce early immunomodulator therapy. This has been suggested by results of a recent paediatric population-based study from Denmark17. Despite the high frequency of corticosteroid dependency in this cohort, the cumulative probability of surgery was low for both CD and UC. The frequent use of immunosuppressive preparations among the children (68% of CD and 64% of UC children) could probably explain this favourable outcome. Similar results were found in two multicenter studies; only 8% of children with CD and 5% with UC had a surgery one year after starting steroids; nevertheless 81% and 61% of CD and UC patients received immunomodulators and 28% and 12%, respectively, infliximab within the observed year.[20,21]

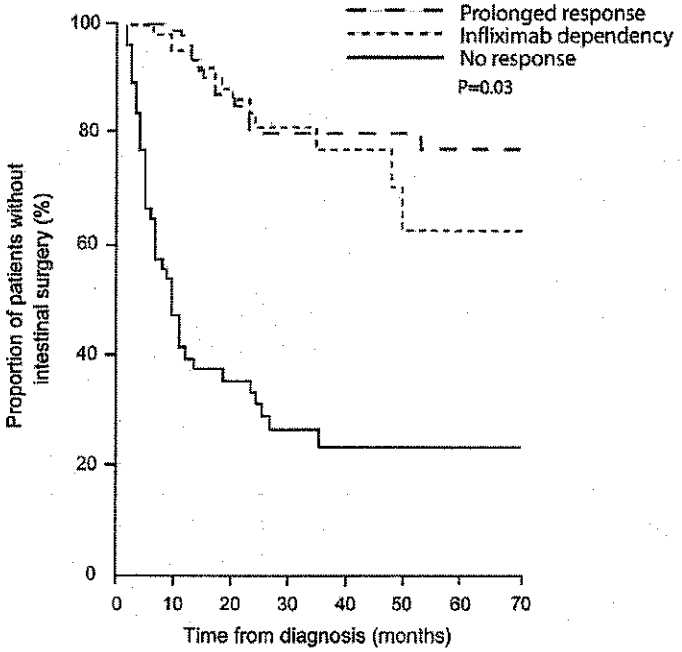
Drug dependency, however, does not need to be only a "negative" response phenotype as apparent from infliximab dependency papers.[9,26] The strong supportive evidence has been provided mainly by the findings regarding surgical intervention. One paediatric [9] and one adult [26] study have shown a significantly lower cumulative probability of surgery up to 50 months after treatment start in prolonged responders as well as infliximab dependent patients compared to non-responders. Of note is that infliximab dependent children had a lower risk of undergoing surgery than children with prolonged response. This suggests that in patients responding in a dependent way the need for surgical intervention could be at least postponed, if not avoided. Thus, development of infliximab and corticosteroid dependency might be considered as a useful prognostic marker, which may indicate whether patient will benefit from maintenance therapy (infliximab dependency) or should be shifted to another immunosuppressive or biological treatment (corticosteroid dependency).

a



Number of patients at risk								
Prolonged Response	17	15	11	8	6	2	0	0
Infliximab Dependency	53	47	29	18	10	7	3	0
No Response	10	4	4	3	3	3	1	0

b



Number of patients at risk								
Prolonged response	113	110	86	61	41	36	25	9
Infliximab dependency	69	62	46	26	18	10	7	4
No response	58	31	18	12	9	7	5	0

Figure 2 The cumulative probability of intestinal surgery in Crohn's disease patients after the start of infliximab therapy (log-rank test). Comparison with respect to long-term outcome: a) paediatric patients [9]; and b) adult patients [26].

So far, the safety profile of infliximab seems to be favourable as outlined by national cohorts [31,32] and recently also confirmed by meta-analysis [33]. However, potential adverse events can be very serious and life-threatening [34-37] and in recent period, there is an increasing evidence of probably immunopathological adverse events induced by anti-

Table 4 Phenotype model of 5-Aminosalicylic acid (5-ASA) dependency.

Immediate outcome	Long-term outcome
Complete response Total regression of symptoms 30 days after 5-ASA initiation.	*Prolonged response* Still in complete/partial response 1 year after induction of response (maintained on 5-ASA or after cessation of 5-ASA).
Partial response Improvement of symptoms 30 days after 5-ASA initiation.	*5-ASA dependency* Relapse ≤ 1 year after 5-ASA cessation regaining complete/partial response after 5-ASA re-introduction or relapse on stable or reduced dose of 5-ASA requiring dose escalation to regain response.
No response No regression of symptoms ≤ 30 days with a need to shift from 5-ASA to an immunomodulator or surgery.	*No response* No regression of symptoms with a need to shift from 5-ASA to an immunomodulator or surgery.

TNF alpha therapy such as various skin eruptions and joint problems.[38,39] Therefore, the safety profile is always the matter of concern. Identification of dependent and non-dependent individuals might prevent "unnecessary" use of the drug in non-dependent patients and so limit potential toxicity in this group. Moreover, directing the therapy mainly to dependent individuals could increase overall treatment efficacy and lead to more effective allocation of resources.

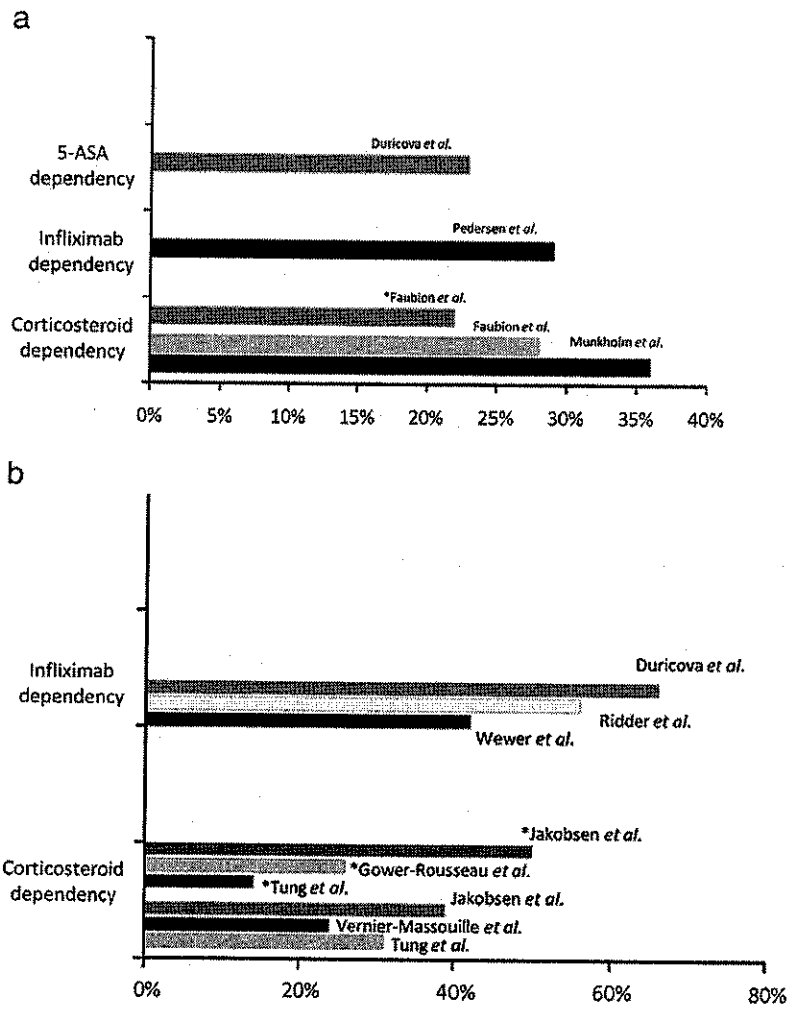


Figure 3 Drug dependency in adults (a) and children (b) with inflammatory bowel disease — summary of the studies. 5-ASA = 5-Aminosalicylic acid, *ulcerative colitis.

This speculation might be supported by a recent prospective withdrawal study with infliximab.[40] Infliximab has been discontinued in 115 patients with luminal CD who had been treated with combined infliximab and immunosuppressive therapy for at least one year and obtained a stable corticosteroid-free remission. During the following 12 months 45 patients relapsed while more than half of the patients maintained long-standing remission on immunosuppressors without further need of infliximab treatment. Of note is that re-introduction of infliximab in those relapsing induced a quick remission in all but one patient and was well tolerated.[40]

Higher occurrence of infliximab dependency has been observed in children compared to adults,[7–9,26] whereas no such difference has been seen in case of corticosteroids. Based on previously published data, childhood-onset IBD seems to be a different entity than adult-onset disease, characterized by a more extensive disease and severe phenotype.[18,41,42] Moreover, higher remission rates have been obtained in studies evaluating efficacy of infliximab in children compared with adults.[24,43] Biologicals are nowadays considered the most potent therapy, reserved mainly for patients refractory to conventional treatment including corticosteroids.[44] It can be only speculated whether the observed differences between paediatrics and adults are a consequence of the probably different natural courses of the diseases in these two groups. New studies should confirm or disprove these findings.

The most recent description of dependent response has been in 5-ASA treatment of CD patients.[10] Although the efficacy of 5-ASA in CD is low as compared to above mentioned drugs,[30] the findings have demonstrated that there is a certain, although small population of CD patients – 5-ASA dependent – which benefit from 5-ASA. Advantage of 5-ASA therapy is a high safety profile which is comparable to placebo.[45,46] Thus, in case the prescription of 5-ASA was stopped in CD patients; this group would have to be exposed to "stronger" but also more toxic preparations. Therefore, the ongoing use of 5-ASA in CD would be of great benefit.

The future development of dependency definitions should aim at more than 90% of patients would fit into the model, thus leading to the coefficient of variations of <10%. In practice, a pilot study including small group of patients (about 20 individuals) is performed to evaluate if definitions are generally applicable to patients' disease pattern. The model is then adjusted until the desired goal is reached.

There are several factors having an impact on the rate of drug dependencies, causing the difficulties when trying to compare the outcomes of individual studies. Firstly, there is heterogeneity of the definitions used. An attempt to overcome this problem was made by implementing the unified definition for corticosteroid dependency in the ECCO guidelines. [22,23] Nevertheless, the use of the definitions in daily clinical practice is still problematic. Secondly, the recommended treatment policy has been changing over the time. Immunosuppressives are nowadays introduced earlier, mainly in paediatric population, to avoid corticosteroid dependency.[47,48] Infliximab is recommended as a long-term maintenance treatment in all patients responding to induction infusions;[47,48] hence the frequency of infliximab dependency may be biased. Further, the doctor preference and economical possibilities have to be also considered. Therefore, it is important that as the daily clinical practice is altered over the time; the definitions are also adjusted according to the actual requirements. This might be already observed in the definition of corticosteroid dependency proposed by Jakobsen et al.[17] which has taken in account the use of immunosuppressive or biological drugs in dependent patients.

In the future, there is a need to assess the occurrence of infliximab and 5-ASA dependency also in UC. Furthermore, in addition to already described dependent phenotypes, possible dependencies on other drugs used in IBD, like azathioprine and adalimumab, should be studied and mainly their prognostic value should be assessed.

6. Conclusion

Drug dependency is a specific disease phenotype which may determine patients' disease course and therefore can be used as a prognostic marker when deciding for treatment management. Whereas corticosteroid dependency is considered to be harmful condition, infliximab and 5-ASA dependency seem to be beneficial. In daily clinic, early identification of dependent patients might prevent serious consequences of corticosteroid therapy as well as probably improve patients' disease course by maintaining infliximab treatment.

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Dr. Munkholm serves as an advisory board member for Ferring, Tillotts and Shire.

Dr. Elkjaer serves as an advisory board member for Orphan.

Dr. Lukas serves as a consultant for MSD-Schering Plough, Abbott Laboratories and Takeda.

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Dr. Wewer serves as an advisory board member for MSD.

Statement of authorship

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