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Intestinal transplantation for Crohn's Disease: A 5-year nationwide follow-up

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Background: Crohn's disease (CD) is a chronic and progressive inflammatory bowel disease. Despite advances in medical therapy, half of patients still require bowel resection 10 years after diagnosis, and a third will require at least another resection within the next 10 years. A progressive reduction in small bowel length may lead to short gut syndrome and need for long-term total parenteral nutrition (TPN). Intestinal transplantation (ITxp) may benefit these patients who develop TPN-associated liver failure, loss of vascular access, and recurrent catheter-associated sepsis. However, published data on post-transplant outcomes are sparse and limited to small groups of patients. Our primary aim is to characterise long-term risk of rejection, graft failure, and death among CD patients in the largest available ITxp cohort in the United States.
Methods: The study included all adults who underwent ITxp between May 1990 and November 2013, as recorded in the U.S. Scientific Registry of Transplant Recipients. Data were collected on patient demographics, body mass index (BMI), waitlist time, and transplant indications. Outcomes included allograft rejection, graft failure, TPN resumption, and survival. Cox proportional hazards analyses were used to evaluate time to events, comparing CD with non-CD ITxp patients. Multivariable analyses were adjusted for age at transplantation, sex, race, BMI, and time on waitlist.
Results: There were 976 adults who underwent 1069 ITxp from 1990 through 2013; 134 (12.5%) were for CD (Table). Patients were followed for a median of 36 months and a maximum of 60. At transplantation, CD patients had a mean age of 44.7 years, mostly normal or overweight BMI (73.9%), and <6 months on the waitlist (76.8%). Actuarial risk of acute rejection was 22.4% at 1 year, 38.1% at 3 years, and 42.7% at 5 years, while risk of graft failure was lower at 5.6%, 16.8%, and 19.2%, respectively. Patient survival was 69.2%, 62.0%, and 62.0% at 1, 3, and 5 years, respectively. In multivariable analyses, CD patients had a similar risk of acute rejection (hazard ratio [HR] 0.85; 95% confidence interval [CI] 0.59-1.24; P=0.40), graft failure (HR 1.70; 95% CI 0.91-3.17; P=0.09), resumption of TPN (HR 1.48; 95% CI 0.93-2.35; P=0.10), and death (HR 1.07; 95% CI 0.70-1.64; P=0.77) as non-CD patients.
Conclusions: In the largest reported cohort of CD patients undergoing intestinal transplantation, long-term outcomes were similar for CD and non-CD indications. Intestinal transplantation should be considered for CD patients with intestinal failure.

Characteristics of patients undergoing intestinal transplantation for Crohn's disease and other indications.

	Crohn's Disease (N=134)	Other Indications (N=935)	P Value
Age at transplantation (SD)	44.7 (9.8)	40.2 (13.4)	<0.01
Male (%)	63 (47.0)	440 (47.1)	0.99
Race, Caucasian (%)	129 (96.3)	821 (87.8)	<0.01
Body mass index (%)			0.03
- Underweight	17 (12.7)	143 (15.3)	
- Overweight or obese	28 (20.9)	251 (26.9)	
Waitlist time, < 6 months (%)	103 (76.8)	735 (78.7)	0.81
Deceased donor (%)	132 (98.5)	917 (98.1)	0.53

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Impact of induction therapy with 3 doses of infliximab on deep remission in paediatric patients with active Crohn's Disease

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Background: The clinical efficacy of infliximab (IFX) for induction of remission in both adults and children with active Crohn's disease (CD) has been well documented. Recently, so-called "deep remission" defined as mucosal healing has become the ultimate endpoint of the most recent therapeutic advances for CD. However, endoscopic evidence of mucosal healing is not necessarily associated with histological evidence of suppression of inflammation. Since data on that issue are limited, especially in pediatric population, the aim of this study was to assess the impact of induction therapy with IFX on deep microscopic remission in pediatric patients with CD.
Methods: Fifty-six children (32 boys and 24 girls) aged 13.0 ± 9.3 years with moderate to severely active CD diagnosed at the mean age of 5.5 ± 0.83 years were included into the study. Colonoscopy and gastroscopy with sample collection were performed in all patients before and after three injections of IFX. Clinical activity of the disease was assessed using the Pediatric Crohn's Disease Activity Index (PCDAI), and the endoscopic activity was scored using the Simple Endoscopic Score (SES-CD). Histological changes were evaluated by a previously described numerical scoring system.
Results: Thirty-nine patients (69.6%) reached clinical remission (PCDAI below 10). When comparing data at baseline and at week 10, significant decrease was observed in median PCDAI, and in SES-CD score between the initial and control colonoscopies. We also reported a decrease in histological scale. However, the difference was not statistically significant (p=0.63). Three (5.4.%) patients had a score of 0 in the control histological examination. The correlation was found only between histological score and SES-CD score. Clinical remission correlated better with mucosal healing expressed by a decrease in SES-CD score than with microscopic changes.
Conclusions: Biological therapy with infliximab enables mucosal healing in pediatric patients with CD, which is not necessarily associated with histological evidence of suppression of inflammation. Mucosal healing correlates better than microscopic healing with clinical remission

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Association between Inflammatory Bowel Disease activity and therapeutic drug monitoring of azathioprine and infliximab comparing free and total antidrug antibody measurement

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Background: Therapeutic drug monitoring (TDM) of infliximab (IFX) is useful in patients with inflammatory bowel disease (IBD). Therapeutic cut-offs to predict active disease and the influence of thiopurines on drug levels (DL) according to 6-thioguanine nucleotide (TGN) are not defined. There is limited data on the utility of free

"Table 1"

Kit	Outcome	Optimal DL (μ g/mL)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	+LR	AUC	95%CI
LT	FCP>250 μ g/g	5.7	96	51	45	96	1.5	0.73	0.62-0.84
LT	FCP>59 μ g/g	5.7	85	64	75	75	2.3	0.73	0.61-0.85
LT	CRP>5	3.0	70	76	55	85	3.0	0.70	0.56-0.84
LT	HBI>4	1.5	56	89	42	93	4.8	0.75	0.61-0.90

anti-drug antibodies (ADAb) against total ADAb. We assessed the utility of TDM of IFX in IBD using a commercially available ELISA and investigated the influence of TGNs on DL and free/total ADAb.
Methods: Prospective evaluation of trough DL and ADAb using Lisa-Tracker,((LT),Theradiag, France) and Immundiagnostik ELISA, ((IM), Germany) in 79 IBD patients (male=40) between January and May 2014. Only free ADAb is detected with LT assay, whereas IM assay measures total ADAb (semiquantitative). Total ADAb Results were calculated using the cut off control. Results of TDM were assessed with respect to faecal calprotectin,(FC), C-reactive protein (CRP) and clinical activity (Harvey Bradshaw Index,(HBI) <5 remission). The relationship between TGN and DL/ADAb was also assessed. LT kits were provided by Theradiag at no cost.
Results: Higher DL were observed amongst patients in remission (HBI;<5 DL 4.7 vs 1.7µg/mL, p=0.01, CRP<5mg/L DL 5 vs 2.5µg/mL,p=0.007, FC<250µg/g DL 5.6 vs 2.9µg/mL, p=0.001, FC<59µg/g DL 5.8 vs 3.3µg/mL, p< 0.001. ROC curve analysis including thresholds to detect active disease are shown in Table 1. ADAb were detected in 3 (4%) patients using LT vs 19 (24%) using IM assay. All patients with ADAb with LT had undetectable DL and had active disease on FC59. Total ADAb with IM assay did not correlate with outcomes. Concomitant immunomodulation use was associated with absence of ADAb using IM assay (p=0.03), however a therapeutic TGN (>245pmol/8×10^8) was not associated with ADAb (p=0.5). TGN quartile analysis did not identify a value associated with DL, (p>0.5), nor was a therapeutic TGN associated with higher DL(p=0.7).
Conclusions: IFX DL were inversely related to disease activity. A cut-off of 3.0-5.7µg/mL was associated with active disease depending on the definition used. The presence offree ADAb was associated with active inflammation, whereas the presence oftotal ADAbwas not. There was no relationship between TGN and DL or ADAb, although most patients were adequately dosed. This study highlights the limitations and utility of TDM in IBD.

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Immunogenicity of 13-valent pneumococcal conjugated vaccine in pediatric patients with inflammatory bowel disease

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Background: There are only a few studies on immune response to pneumococcal vaccines in patients with inflammatory bowel disease (IBD); all of them assessed polysaccharide vaccines only. The aim of the study was to evaluate the immunogenicity and safety of 13-valent pneumococcal conjugated vaccine (PCV13) in IBD pediatric patients compared with healthy controls.
Methods: This was a multi-center, prospective and controlled study on children and adolescents aged 5-18 years with IBD with no history of pneumococcal immunization or documented pneumococcal infection. The subjects for the study belonged to one of the following groups: patients with IBD on no immunosuppressive therapy (Group A), those on TNF agents or immunomodulators (Group B) and healthy controls (Group C). The study population received one intramuscular injection of PCV13. The primary outcome measure was adequate vaccine response defined as post-vaccination titer greater than or equal to 0.35 µg/mL to all 13 serotypes. Geometric mean titers and geometric mean titer rises (GMTRs) were measured for all serotypes. The evidence of local and systemic adverse effects for five days after the vaccine was registered.
Results: A total of 178 subjects (122 patients and 56 controls) completed the study course. There was no significant difference in the rate of adequate vaccine response between IBD patients and controls measured 4-8 weeks after vaccination (90.4% vs. 96.5%, p=0.5281). Children in group A had higher GMTRs than children in group B (p = 0.0369). There were no serious adverse events related to PCV13 during the study.
Conclusions: PCV13 is both immunogenic and safe in pediatric patients with IBD.

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The sooner, the better: Early treatment of Crohn's Disease precludes a bad outcome

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Background: Early stages of Crohn's disease (CD) are supposed to be predominantly inflammatory, and it is thought that early treatment of the disease could be one of the keys to change the natural history of the disease. We aimed to confirm this concept in our own experience.
Methods: We retrospectively reviewed the clinical records of all CD patients in our database with a stable follow up in our centre. Dates of diagnosis, of starting immunosuppressive therapy (either thiopurines or biologics), and of the first surgery when appropriate were considered. Patients lacking any of those data on our database were excluded from the analysis.
Results: 467 CD patients were included; 71% males, mean age 45yrs (range 18-82 yrs).
We found 422 CD patients with thiopurines. 189 had undergone surgery along the follow up. Those operated patients started thiopurines after a median of 117 months, interquartile range (IQR) 44-196 months since diagnosis, while non-operated CD patients started thiopurines after a median of 30 months IQR 6-128 months; p<0,001. The Odds ratio for undergoing surgery was 1,006 (CI95% 1,004-1,008) for each month of delay in starting thiopurines.
We found 272 CD patients with biologics. 137 had undergone surgery along the follow up. Those operated patients started biologics after a median of 166 months IQR 90-233 months since diagnosis, while non-operated CD patients started thiopurines after a median of 59 months IQR 14-162 months; p<0,001. The Odds ratio for undergoing surgery was 1,008 (CI95% 1,005-1,010) for each month of delay in starting biologics.