Treatment of inflammatory bowel disease: medical and surgical aspects
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SUMMARY

The aim of this thesis was to investigate aspects of medical and surgical treatment options for patients with Crohn’s disease (CD) and ulcerative colitis (UC). In part I, biological therapy was evaluated in terms of efficacy and safety. Part II concerned the aspects of the surgical management of IBD. Finally, in part III the question whether biologic agents or surgery should be applied in case of recurrent ileocecal CD was addressed in more detail.

Biological therapy for inflammatory bowel disease: efficacy and safety (part I)

In Chapter 1, a cohort study was performed to assess the long-term effectiveness of infliximab (IFX) therapy for CD patients treated in cohorts from two third-line referral centers. Included were 469 patients (median length of follow-up: 4.5 year (IQR: 2.7 – 6.8)). Seventy patients (15%) had an unsuccessful remission induction course. Of the 316 patients who received maintenance therapy, a successful scheduled maintenance regimen was documented in 169/276 (61%) with an estimated 5-year sustained benefit of 55.7% (95% CI: 48.8 – 62.6). Episodic maintenance therapy was successful in 19/40 patients (48%). Concomitant immunosuppression and younger age at diagnosis were associated with improved sustained benefit of IFX. A second course of IFX after previous discontinuation was started in 131 patients, with similar effectiveness rates. Of these, 27 of 59 patients (46%) with a second IFX-episode despite failure of previous IFX-treatment showed therapeutic success. Number of abdominal surgical interventions was significantly reduced after start with IFX as compared to before IFX in the 276 patients with a scheduled maintenance regime (p = 0.018). Mortality and malignancy rates were comparable to previous publications on safety. This study showed that long-term use of IFX was effective and safe and reduced need for surgery in patients with scheduled maintenance therapy.

The aim of Chapter 2 was to assess efficacy of adalimumab (ADA) therapy for CD patients in a daily practice setting. For this purpose, all CD patients treated with ADA in the 18 hospitals from one province were included. A total of 438 patients (median follow-up 1.95 year (IQR: 1.08-2.72) were identified. Primary non-response occurred in 7.5% of patients. Presence of strictures was associated with remission induction failure (OR 2.2; 95% CI 1.1-4.1; p = 0.02). Four hundred five patients (92.5%) started maintenance treatment after successful remission induction. After one year, 82% of patients had sustained benefit of ADA, with 10-15% reduction per following year. In 40% of patients, dose escalation from 40 mg every other week to 40 mg every week was deemed necessary. Response to ADA was equal in patients with prior IFX therapy (n=270) and IFX naïve patients (n=168), both for remission induction as well as for maintenance therapy. Furthermore, outcome of ADA therapy in IFX failure and IFX benefit patients was equal. Concomitant immunosuppressive medication did not influence ADA benefit, although a trend was noted for a beneficial effect of thiopurines. It was concluded that induction therapy with ADA was successful in more than 90 % of patients, with 60% of patients having sustained benefit after 3 years of treatment. Furthermore, prior infliximab failure should not withhold treatment with ADA.

Although the occurrence of intestinal perforation in CD is rare, clinical observation has led to the question whether anti-TNF treatment is a risk factor for free perforation. Aim of the study presented in Chapter 3 was to investigate the possible relation between anti-TNF treatment and occurrence of “free” perforation, defined
as intestinal perforations leading to emergency surgery. In a case control study, previous or current exposure to anti-TNF treatment in all CD patients with a free perforation in the period 1998-2009 (n=13) was compared with a 6-fold larger control group derived from our CD patient database. Cases and controls were matched for age, gender, Montreal classification and surgical stage to ensure equal disease severity. Eight case patients (62%) had been treated with anti-TNF within 5 months before the perforation. In the 78 matched controls, 29 (37%) had been or were still treated with anti-TNF. The odds for a free perforation adjusted for known confounders in two separate regression analyses were significantly higher in anti-TNF treated CD patients, albeit with a large confidence interval (OR 4.1, 95% CI: 1.1 – 16.0 and OR 23.0, 95% CI 2.2 – 238.5). Therefore, this study showed a higher occurrence of free perforations in CD patients with anti-TNF therapy compared to those without anti-TNF therapy.

It is not clear from the literature whether previous IFX treatment increases the risk of postoperative complications after ileum pouch anal anastomosis (IPAA) in refractory ulcerative colitis (UC) patients. The aim of Chapter 4 was to compare complication rates in patients with vs. without preoperative IFX therapy. For this purpose, all patients who underwent a pouch procedure for medical refractory UC between January 2006 and January 2010 were selected. Postoperative complications, IFX use and time interval between last IFX administration and restorative surgery were assessed. One-stage procedures (proctocolectomy with IPAA) and 2-stage procedures (emergency colectomy and subsequent completion proctectomy with IPAA) were analysed separately. In the 1-stage group, 21 patients (64%) had preoperative IFX therapy; median time between last infusion and surgery was 7.1 months (IQR 2.6-8.3). IFX-treated patients had a higher incidence of anastomotic leakage (4/21 vs. 0/12; risk difference (RD) 19%; 95% CI: 2 to 36) and non-infectious complications (8/21 vs. 1/12; RD 30%; 95% CI: 4 to 56). Total and infectious complications were not different between IFX and non-IFX patients. In the 2-stage group, 17 patients (44%) had preoperative IFX therapy; median time between last infusion and pouch surgery was 11.8 (IQR 7.3-15.5) months. Total, infectious and non-infectious complication rates as well as the number of anastomotic leakages were similar for IFX and non-IFX patients in the 2-stage group. This small study therefore suggests that IFX use prior to a 1-stage restorative proctocolectomy in patients with UC is associated with an increased incidence of anastomotic leakage. A 2-stage procedure in these patients should be considered.

Surgical therapy for inflammatory bowel disease: efficacy, safety and new techniques (part II)

Patients with isolated ileocecal CD refractory to medical therapy are best treated by means of an ileocolic resection. Literature suggests that this is a safe and effective therapy. Aim of Chapter 5 was to assess short- and long-term outcomes of a large consecutive unselected cohort of CD patients in modern times. All patients (n=184) who underwent primary ileocolic resection in the AMC within the period 1998-2009 were included. Median length of follow-up was 5.8 (iqr 3.0 – 8.5) years. Laparoscopy was performed in 109 patients (59%), of whom 4 were converted to a laparotomy (3.7%). Complications occurred in 33 patients (18%), resulting in 9 patients requiring reoperation (4.9%). Factors associated with complications were an open approach (OR 2.377 (95%CI: 1.034-5.461; p=0.041)) and an ASA classification > 3 (OR 4.955 (95%CI: 1.288-19.063; p=0.020)). On the long-term, 109 patients (61%) remained relapse free after resection. Of the 70 (39%) patients with recurrent disease, 48 could be treated
in an outpatient setting. The remaining 22 patients (22/179: 12%) were readmitted and of those, 18 underwent a re-resection (18/179: 10.1%). Median time to re-resection was 48.11 (IQR: 12.7 – 70.5) months. In multivariate analysis, smoking at time of surgery was associated with re-resection (OR 3.050 (1.063 – 8.753), p=0.038). These results showed that an ileocolic resection is an effective treatment option for isolated CD of the terminal ileum. Important topics for further research are an evidence-based postoperative therapy schedule and timing of surgery in the treatment algorithm of ileocecal CD.

In Chapter 6, the long-term results of a randomized trial comparing laparoscopically assisted with open ileocolic resection for CD were evaluated. Sixty patients who underwent ileocolic resection between 1999 and 2003 were followed prospectively. Five patients were lost to follow-up. Median follow-up was 6.7 (IQR 5.7–7.9) years. Sixteen of 29 and 16 of 26 patients remained relapse free after ileocolic resection in the laparoscopic and open groups respectively (risk difference 6 (95% confidence interval −20 to 32)%). Resection of recurrent CD occurred in 2/29 versus 3/26 patients (risk difference 5 (−11 to 20)%). Overall reoperation rates for recurrent Crohn’s disease, incisional hernia and adhesion-related problems were 2/29 versus 6/26 (risk difference 16 (−3 to 35)%). QOL was similar, whereas body image and cosmesis scores were significantly higher after laparoscopy (P = 0.029 and P < 0.001 respectively). Chapter 7 also focussed on the long-term outcomes after laparoscopic-assisted versus open ileocolic resection. In this retrospective comparative cohort study, 71 patients who underwent ileocolic resection during the period 1995 to 1998, with a median follow-up of 8.5 years, were analysed. The two groups of 48 (open approach) and 30 patients (laparoscopic-assisted approach) were comparable for characteristics of sex, age, and immunosuppressive therapy. Resection for recurrent Crohn’s disease was performed in 6 of 27 (22%) and 10 of 44 (23%) patients in the laparoscopic and the open groups, respectively. Reoperations for incisional hernia were only performed after conventional open ileocolic resection (3/44=6.8%). Quality of life and body image were comparable, but cosmesis scores were significantly higher in the laparoscopic group. Chapter 6 and 7 therefore showed that laparoscopically assisted ileocolic resection resulted in better body image and cosmesis, whereas open surgery was more likely to produce incisional hernia and obstruction.

Currently, ileocolic resections for Crohn’s disease can be performed entirely laparoscopically. Only for specimen extraction an incision is needed. The prospective observational study presented in Chapter 8 assessed the feasibility of endoscopic transcolonic specimen removal. This was attempted in a consecutive series of ten patients scheduled for laparoscopic ileocolic resection. Primary outcomes were feasibility, operating time, reoperation rate, pain scores, morphine requirement and hospital stay. To assess applicability, outcomes were compared with previous data from patients who had laparoscopically assisted operations. Transcolonic removal was successful in 8/10 patients; it was considered not feasible in two patients because the inflammatory mass was too large (7–8 cm). Median operating time was 208 minutes and median postoperative hospital stay was 5 days. After surgery two patients developed an intra-abdominal abscess, drained laparoscopically or percutaneously, and one patient had another site-specific infection. The operation took longer than conventional laparoscopy, with no benefits perceived by patients in terms of cosmesis or body image. Therefore, this observational study showed
that transcolonic removal of the specimen was feasible in the absence of a large inflammatory mass, but infection may be a problem. It is unclear whether the technique offers benefit compared with conventional laparoscopic surgery.

Previous studies showed significantly lower appendectomy rates in ulcerative colitis (UC) patients compared to healthy controls. Since then, evidence indicating that the appendix has an immunomodulatory role in UC has been accumulating. The aim of Chapter 9 was to examine the latest evidence on the effect of appendectomy on the disease course in patients with UC. After a systematic search, 6 observational studies totalling 2532 patients were included, 5 case control studies and one cohort study. Due to clinical heterogeneity, no meta-analysis could be conducted. One study found lower relapse rates in patients appendectomised before onset of UC (absolute risk reduction (ARR) 21.5%; 95% CI -1.71% - 45.92%). Another 2 studies found a reduced requirement for immunosuppression in appendectomised patients (ARR 20.2%; 95% CI 9.67% - 30.46% and ARR 21.4%; 95% CI 10.32% - 32.97%). In addition, one study found lower colectomy rates in non-appendectomised patients (ARR 8.7%; 95% CI -1.29% - 18.66%) and 2 studies found lower colectomy rates in appendectomised patients (ARR 21.4%; 95% CI 13.17% - 28.79% and ARR 18.7%; 95% CI 7.50% - 29.97%). Based on the presently available evidence, there is limited and conflicting data available regarding the effect of appendectomy on the disease course of UC. Most studies suggest a beneficial effect, the minority find no or a negative effect. A prospective randomized trial evaluating the disease modifying effect of appendectomy on the disease course of UC is therefore justified.

Medical or surgical therapy for Crohn’s disease (part III)

As shown in part I and II of the present thesis, ileocecal CD can be treated medically as well as surgically. Both treatment modalities have been improved markedly in the last two decades, making CD more manageable. However, multidisciplinary research, addressing issues such as timing of surgery or medical treatment versus surgery, is scarce. Particularly in limited ileocecal CD, ileocolic resection might be a good alternative for long-term medical therapy. The review presented in Chapter 10 discusses the current evidence on medical and surgical treatment options for ileocecal CD. Up to now, however, consensus statements offer either treatment with infliximab or surgical resection in limited disease, because no comparative studies on the two alternatives exist. To address this scientific question, the LIRIC-trial (Laparoscopic ileocolic resection versus infliximab treatment of distal ileitis in Crohn’s disease) was designed. This multicenter randomized clinical trial started in December 2007, to compare infliximab treatment with laparoscopic ileocolic resection in patients with recurrent Crohn’s disease of the distal ileum. Patients with recurrent terminal ileitis despite immunomodulatory therapy are being included for analysis of QOL and costs. Secondary outcomes are hospital stay, early and late morbidity, sick leave and surgical recurrence. In total, 130 patients will be included and will be followed up for 1 year. The design and rationale of the LIRIC-trial were presented in detail in Chapter 11.