Surgery and medical therapy in Crohn’s disease

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Thesis summary, general discussion and future perspectives
THESIS SUMMARY, GENERAL DISCUSSION AND FUTURE PERSPECTIVES

Part I - Epidemiology

In chapter 1, we reported the current population-based epidemiology in a cohort of 1,461 patients. An increase in prevalence of inflammatory bowel disease (IBD) within the 6-year study period was observed while the incidence rates remained stable. This could not be explained by decreasing mortality in the IBD cohort during the study period or shifts in the age distribution of the population due to moving of individuals. Hence, the most likely explanation is a steady incidence and negligible mortality from the disease itself and in general in IBD patients because of the age distribution. Compared to previous epidemiological data from The Netherlands, current incidence rates of ulcerative colitis (UC) and Crohn’s disease (CD) are considerably higher than the observed incidence rates in the past decades. It is generally assumed that tertiary referral patients will have a more severe phenotype and burden of disease as compared to patients in teaching hospitals. CD patients treated in the tertiary referral centre were significantly more often treated with thiopurines and anti-TNF and underwent perianal surgery more frequently when compared to patients treated in a teaching hospital. This also applied to proctocolectomies in UC patients.

Part II – Ileocecal Crohn’s disease

Chapter 2 consists of the The LIR!C trial comparing laparoscopic ileocecal resection with infliximab treatment for terminal ileitis in CD. This study showed that at 12 months laparoscopic ileocecal resection was at least as effective as infliximab in improving QoL. Although superiority of the surgical strategy in terms of IBDQ could not be demonstrated (MD 6.1, 95% confidence interval -4.2 to 16.4, p=0.245), resection is not inferior to infliximab treatment with regard to regaining QoL, given the lower bound of the confidence interval of -4.2 for the difference in IBDQ at 12 months. Additionally, the physical subscale of the more generic SF-36 was significantly better in the resection compared to the infliximab group at 6 and 9 months. Although disease specific quality of life is generally considered to be the best instrument to document specific changes in disease associated symptoms, the majority of patients was in remission at the end of this study. Hence, in patients with ileocecal CD failing conventional therapy resection should be offered as a good alternative to starting infliximab.

Chapter 3 reviewed treatment options for perforating complications as intra abdominal abscesses or fistulas in CD patients. Percutaneous drainage and antibiotics should be
the treatment of choice in patients with a (‘drainable’) intra abdominal abscess in CD. If sepsis is controlled medication should be started with monitoring of the effect. Today, there is a role for surgery in these patients in case of failure of percutaneous drainage and antibiotics. In addition, surgery is indicated if there is a stenosis, fistula or refractory active disease. Nevertheless, if possible, surgery should rather be delayed until local sepsis is resolved.

During the last decades treatment protocols have changed for patients with ileocolic Crohn’s disease. Anti-TNF has become part of standard medical treatment, usually in a step-up approach. In chapter 4 we demonstrated that over time patients were treated more intensively with different types of drug combinations since the introduction of anti-TNF. As a result, the time interval from initial diagnosis to surgery increased. The optimization of medical treatment protocols did not result in more limited resections throughout the years as is sometimes argued as one of the benefits of extensive treatment.

The feasibility of single port ileocecal resection in CD has previously been reported. However, large studies comparing SP and multi port laparoscopic surgery are not available. In chapter 5 we showed in an international multicentre study that visual analog scale scores were significantly lower after single port ileocecal resection on postoperative day 1 and 2. Additionally, analgesia requirement was significantly reduced on postoperative day 2 in the single port group compared to the multi port group. Duration of surgery, conversion to open surgery and stoma rates were comparable between the two groups and no significant differences were observed in postoperative complication rates, postoperative food intake, length of stay and readmissions.

Operative techniques have evolved rapidly over the past decades. There is still limited literature on single port laparoscopic surgery in IBD. However several (matched) case series demonstrated that single port laparoscopic surgery is a feasible and safe approach in IBD. These studies are reviewed in chapter 6. There are several beneficial aspects with single port laparoscopy with respect to postoperative pain, morphine use, length of hospital stay and (functional) long term outcomes, when compared to conventional multi-port laparoscopic surgery. Promising indications are ileocolic resections, (subtotal or procto) colectomy if the specimen is not too bulky. The transanal minimally invasive surgery (TAMIS) completion proctectomy in Crohn’s or completion proctectomy with an ileoanal pouch are likewise promising developments that need to be studied further.

In chapter 7 we described lessons learned from the LIRIC study. During the last decades, treatment protocols have changed for patients with ileocecal CD. New medical thera-
pies were introduced and surgical techniques improved. Discussing the most optimal treatment approach for terminal ileitis, the LIRIC trial was designed almost a decade ago. After 7.5 years, the results will be published soon. Although this RCT will probably change current guidelines, there are also several drawbacks in terms of external validity to any trial taking this long to complete accrual. An interesting alternative to the conventional RCT could be the patient’s preference RCT design, where both randomised and non-randomised patients participate, which benefits the external validity of the study results.

**Part III – Perianal Crohn’s disease**

**Chapter 8** reviews advanced soft tissue techniques for complex fistulas. Treatment of complex fistulas is challenging and carries a high risk of poor wound healing and continence impairment due to iatrogenic injury of the sphincter complex. Proper management requires a detailed understanding of perianal anatomy, knowledge of the extent of the disease and its relation to the various structures.

In all sphincter-sparing advanced soft tissue flap techniques, controlling local sepsis before any attempt at definitive repair is essential. Therefore, seton drainage prior to advancement flap repair is of significant importance. Furthermore, the creation of a broad based, well vascularised, tension free flap, de-epithelialization of the fistula tract and excision of the internal opening of the tract are essential steps in these type of procedures.

Sphincteroplasty can be an appropriate approach in some cases, especially when preoperative incontinence is present. However patient selection should be prudent, and careful description and detailed informed consent in these advanced techniques is critical.

**Chapter 9** consists of a systematic review and meta-analysis on the effect of seton drainage and/or anti-TNF on perianal fistula partial and complete closure and recurrence. Based on the results of this systematic literature review it can be concluded that closure and recurrence rates after treatment with seton drainage as well as with anti-TNF vary widely. Despite a large number of studies analysing the results of both treatment options, no conclusion can be drawn regarding the preferred strategy. However, combination therapy with (temporary) seton drainage, an immunomodulator and anti-TNF may be beneficial in achieving perianal fistula closure.

Treatment of perianal fistula has evolved with the introduction of new techniques and biologicals in CD. Worldwide several guidelines are available, but many recommenda-
Tions are controversial or lack high quality evidence. In chapter 10 we provided an overview of the current available national and international guidelines for perianal fistula and analysed areas of consensus and areas of conflicting recommendations, thereby identifying topics and questions for future research. The included topics were classified as having consensus (unanimous recommendations in at least two thirds of the guidelines) or controversy (less than three guidelines commenting on topic or no consensus) between guidelines. The highest level of evidence was scored as sufficient (Oxford level of Evidence 2009 3a or higher) or insufficient. Twelve guidelines were included and topics with recommendations were compared. Overall, consensus was present in 15 topics, whereas six topics were rated as controversy. Evidence levels varied from strong to lack of evidence. Therefore, evidence on the diagnosis and treatment of perianal fistulas (cryptoglandular or related to CD) ranged from nonexistent to strong, regardless of consensus.

Currently there is no guideline for the treatment of Crohn’s patients with high perianal fistulas. Most patients receive anti-TNF medication, but no long-term results of this expensive medication have been described, nor has its efficiency been compared to surgical strategies. With this study we hope to provide treatment consensus for daily clinical practice with reduction in costs. The PISA-trial described in chapter 11 is a multicentre randomised controlled trial in patients with high perianal fistulas in CD. Patients will then be randomised to (I) chronic seton drainage (with 6MP) for one year, to (II) anti-TNF medication (with 6MP) for one year (seton removal after 6 weeks) or to (III) surgical closure via e.g. an advancement plasty after 8 weeks seton drainage (under 4 months anti-TNF and 6MP for one year). The primary outcome parameter is the number of patients needing fistula-related re-intervention(s). Secondary outcomes are the number of patients with closed fistulas (based on an evaluated MRI-score) after 18 months, disease activity, QoL and costs. With the comparison of three generally accepted treatment strategies we will be able to comment on the efficiency of the various treatment strategies with respect to several long-term outcome parameters.

Although, it could be hypothesised that close rectal dissection would reduce complications in IBD patients by leaving the rectal mesentery in situ, we showed the contrary in chapter 12. Perineal complications and impaired perineal wound healing occurred significantly more frequent in CD patients when compared to UC patients, especially after close rectal dissection. Perineal complications in CD patients were almost three fold after close rectal dissection when compared to total mesorectal excision. No dif-
ferences between the two surgical techniques were observed in UC regarding perineal complication and healing rates.

More infectious complications after preserving the mesorectum in CD may be explained by the increased pro-inflammatory myeloid cell population with decreased wound healing macrophages, irrespective of the presence of a defunctioning stoma. Therefore, the pro-inflammatory phenotype seems not to be a mere reflection of the inflammatory status of the intestine. These findings suggest that excision of the mesorectum at time of proctectomy is of crucial importance in CD.

Salvage surgery for pelvic septic complications following colorectal surgery most often dictates radical removal of pelvic bowel structures with a definitive ostomy. Patients undergoing redo surgery are prone for developing recurrent pelvic infectious complications. Contaminated pelvic dead space after salvage surgery may progress into a sinus with persistent abscesses and the risk of secondary complications. Previous research suggests that obliterating the pelvic space with an omental plasty after abdominoperineal resection for rectal cancer results in enhanced perineal wound healing and a decrease in sinus formation due to angiogenesis and enhancement of inflammatory response. In chapter 13 a novel technique is described. In the absence of omentum, and considering the morbidity related to autologous tissue flaps, obliteration of pelvic dead space with viable mesentery of a bowel segment that has to be removed as part of salvage procedures seems to be a valuable alternative. Although one patient had a persistent pelvic abscess, complete pelvic sinus healing was accomplished in all four patients.

More research is necessary to understand the physiologic immune responses of mesentery, which may be of additional value to control infectious complications besides anatomical filling itself. Availability of mesenteric tissue of adequate length and volume has to be assessed in every single patient, but might be preferred over myocutaneous flap reconstructions.

FUTURE PERSPECTIVES

In this thesis we have focused on medical and surgical treatment strategies for Crohn’s disease (CD). We have demonstrated that the currently worldwide used step up medical protocol, with surgical resection considered as a last resort option, is not an universal truth. In contrast, the results of the LIRIC study showed that laparoscopic ileocecal
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Resection was a cost-effective non-inferior alternative treatment option to infliximab, with respect to specific quality of life (QoL), and improved generic QoL in patients following resection several months after start of treatment. Since the primary endpoint of this study was set at one year, it is expected that long-term results will be even more promising, with more pronounced differences in QoL when comparing surgical results to chronic medical treatment.

These results will establish a new place for surgical resection in current guidelines of terminal ileitis treatment and it is time to extend this research to the newly diagnosed patients. Currently, the LIRIC II study is being set up for these patients, where we hypothesize that early surgery followed by tight follow up and early treatment of recurrent inflammation is the preferred strategy for limited newly diagnosed CD of the terminal ileum with respect to QoL. The design of this subsequent study will be optimized taking into account the largest drawback of LIRIC I, which was the slow accrual rate. As it took 7.5 years to complete inclusions, it can be concluded that many patients were not randomized in this randomized controlled trial (RCT), resulting in reduced external validity. To ensure that all eligible patients will be included in LIRIC II, a multicentre, comprehensive cohort design (patient-preference or ‘Brewin-Bradley design’) has been chosen. The patient-preference design is suggested to be a more suitable approach for studies comparing significantly different strategies, with QoL as the primary outcome parameter. With this design, all Crohn’s patients with newly diagnosed terminal ileitis can be included, resulting in a dynamic study with generally applicable results. Since the patient is allowed to make its own choice after extensive counselling, it can be expected that the willingness to participate will be high. The primary outcome parameter will again be QoL as measured with the Inflammatory Bowel Disease Questionnaire (IBDQ), as patient reported outcome parameters remain the most important indicator in chronic diseases.

To optimize data collection and ensure patient empowering, we will use the MyIBDcoach app. This is expected to have a positive effect on patient satisfaction and compliance as well. Patients will feel more engaged in the research project, and can be kept up-to-date by providing updates in the MyIBDcoach about the number of inclusions and participating centers, changes in the protocol, and the final results. Furthermore, strict monitoring of the disease warrants patient safety and makes it possible for the Crohn en Colitis Ulcerosa Vereniging Nederland (CCUVN) to collect data from the system, which can be used for future studies.
Optimizing the surgical technique for CD patients, will also be part of future research plans to improve clinical outcome. It has been known for a long time that pathological changes within the enhanced mesenteric tissue (creeping fat) are associated with disease activity. So far this has been largely ignored and the general concept is to perform close bowel resections in this benign disease. However, we have demonstrated that in Crohn’s mesentery the balance between CD3+ T-cells and CD14+ myeloid cells is skewed significantly towards the myeloid population, with an altered pro-inflammatory phenotype of macrophages irrespective of a defunctioning stoma. This suggests a mesentery specific rather than a reactive inflammation induced phenotype. As the affected mesentery is correlated to ongoing disease activity and disturbed perineal healing after proctectomy, it could also be hypothesized that leaving diseased mesentery in situ after ileocelecal resection could result in increased recurrences. We are currently completing a proof of principle clinical study by performing surgical excision of the mesorectum in ten CD patients suffering from a persistent presacral abscess after proctectomy, thus providing the evidence required to drastically change the current surgical management. In another follow-up study, we will use the macrophage phenotype to determine the extend of mesenteric alterations. If a gradient does occur, with increasing proportions of regulatory macrophages towards the non-affected resection margin and central vasculature, the next step will be to analyse if endoscopic and surgical recurrences of Crohn’s disease can be reduced by mesenteric-based surgical strategies. Further research should assess if there is indeed a cut-off point where more extensive mesenteric excision no longer outweighs the disadvantages of tissue damage.

Finally, treatment options for perianal fistulas should be optimized as well. There should be a surgical algorithm of the treatment options for the various types of fistulas. A current RCT compares existing treatment strategies, which will gives us insight in the role of setons, anti-TNF and surgical closure, but with all currently available options, closure rates are disappointing, and QoL is still severely affected. Guidelines for treatment are preferably based on the highest level of evidence; level 1 evidence which is derived from a systematic review RCTs. For some clinical questions however, other sources of data and study designs can be (more) informative. Population based studies derived from national audits or other forms of registration can provide us with valuable information. Several years ago the Snapshot principle was introduced in the research field of colorectal surgery. With these successful cross-sectional multicentre studies we are able to gather large sample sizes in a short period of time from physicians (mainly residents) from many (inter)national hospitals giving insight in routine daily practice.
Data can be used to explore differences in patients, techniques and management across the cohort in order to identify areas of practice variability that may result in apparent differences in outcome. In order to address research questions e.g. timing of seton removal in CD patients with perianal fistulas, closure rates after combining medical therapy with surgical strategies or when to stop anti-TNF, we are planning to set up a Snapshot study for fistula treatment.

Recently an innovative treatment option, the Super Seton, was designed by Medishield BV. The conventional knotted seton is relatively difficult to clean, and the knot has a tendency to rotate towards the external opening of the fistula tract and sometimes even migrates into the fistula tract. This can cause complaints of pain and discomfort. The Super Seton is a knotless smooth seton that aims at improving comfort and QoL for patients with perianal fistulising disease. We are currently assessing the feasibility of the Super Seton. The Snapshot study design could also be a suitable design for a follow-up study with this promising new treatment option.