Health-related quality of life and disability in patients with ulcerative colitis and proctocolectomy with ileoanal pouch versus treatment with anti-TNF agents

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KEYWORDS
Anti-TNF agents; Disability; Health-related quality of life; Restorative proctocolectomy; Ulcerative colitis; Work productivity

Abstract

Background and aims: We compared health-related quality of life (HRQL) and disability in ulcerative colitis (UC) patients in remission with anti-tumor necrosis factor agents (TNF) or after restorative proctocolectomy (RPC) with ileal pouch-anal anastomosis (IPAA).

Methods: Two patient cohorts were studied. The first group consisted of patients in remission after RPC with IPAA (surgery group). The second group consisted of patients in remission with infliximab or adalimumab (medical group). For inclusion in the surgery group the pouch had to be functional for ≥ 1 year and patients were excluded in case of postoperative complications. In the medical group, patients had to be on maintenance therapy with anti-TNF agents for ≥ 1 year and in clinical remission. HRQL and disability outcomes were assessed using SF-36, COREFO, WPAI:UC and EORTC questionnaires.

Results: 60 patients were included, 30 patients in both groups. 58 out of 60 patients (97%) returned the completed questionnaires: 29 patients in the surgery group (median age 42 years [22–67]; 48% female) and 29 patients in the medical group (median age 45 years [19–68]; 65% female). Patient characteristics were comparable between the two groups. There were no significant differences in SF-36, WPAI:UC and EORTC questionnaires between both groups, except for the medication and stool frequency scale (COREFO questionnaire) that was significantly higher in the surgery vs. the medical group (p = 0.004 and p < 0.001, respectively).
1. Introduction

Ulcerative colitis (UC) is a chronic inflammatory disorder of the colon that is characterized by mucosal ulceration, rectal bleeding, diarrhea and abdominal pain [1,2]. Patients with UC experience substantial impairment in health-related quality of life (HRQL) compared to the general population [3]. Restorative proctocolectomy (RPC) with ileal pouch-anal anastomosis (IPAA) provides satisfactory outcomes in a vast majority of patients with therapy-refractory UC and is associated with an increased HRQL [4]. On the other hand, RPC with IPAA is associated with a wide range of complications, such as direct postoperative complications and acute and chronic pouchitis. The incidence of pouchitis varies throughout the literature, ranging from 16% to 48% [5]. The medical management of UC has changed significantly since the introduction of anti-tumor necrosis factor (TNF) agents. Infliximab and adalimumab represent two monoclonal antibodies that are directed against TNF. They are effective for remission induction and maintenance treatment in UC [6-9]. However, approximately one-fourth of patients are primary non-responders to induction therapy with anti-TNF agents, and about 50% have a durable response to these drugs [10].

In certain jurisdictions reimbursement of maintenance treatment with anti-TNF agents is not provided because the local regulators consider RPC a cheaper and at least equally effective treatment option. Given this situation, evaluation of the incremental cost-effectiveness of anti-TNF therapies compared to surgical management is required. One of the essential pieces of information that is needed is quality of life and disability assessments associated with medical or surgical treatment in these patients. Cohen et al compared quality-of-life in patients treated with intravenously administered cyclosporine versus those undergoing colectomy. They showed patients with severe steroid-refractory UC in the cyclosporine arm scored as well as or better as compared to patients who underwent surgery [11]. To our knowledge, there are no studies available that compare HRQL and disability outcomes in UC patients who underwent RPC with IPAA versus patients who receive treatment with anti-TNF agents. The aim of this exploratory study was to explore HRQL in a selected group of patients who had an optimal response to anti-TNF agents or after surgery. Thus, we target patients with UC who are in clinical remission with anti-TNF agents or after surgery and excluded patients with a poor response or complications. We reasoned that if these groups with optimal clinical outcome would differ in HRQL, the results would be meaningful and have clinical implications. Of note, HRQL and disability outcomes in the medical and surgery group were compared with the general population using the SF-36 questionnaire and so-called norm-based scores.

2. Patients and methods

2.1. Study design

The present study was performed at a single tertiary referral center in the Netherlands (Academic Medical Center, Amsterdam). The institutional review board granted a waiver for this study based on Dutch legislation. All patients with severe UC that needed to be hospitalized and treated between January 2008 and December 2011 were included in the analysis. The practical definition that we used for severe colitis was the need for hospitalization. Patients in the surgery group underwent RPC with IPAA and were in remission at least one year after the pouch was functional. Indications for RPC with IPAA were therapy refractory disease or fulminant/toxic colitis. Patients were excluded in case of postoperative complications after IPAA creation. Remission with a pouch was defined as a functional pouch without chronic pouchitis, fewer than 3 episodes of acute pouchitis in the past year and absence of pouchitis in the 3 months prior to the present study. Patients were classified as having pouchitis if the gastroenterologist or surgeon started antibiotic therapy in the presence of clinical findings and/or endoscopic findings compatible with the diagnosis of pouchitis. Acute pouchitis was defined as symptom duration < 4 weeks and chronic pouchitis was defined as symptom duration > 4 weeks. The second group consisted of UC patients with medically induced remission with infliximab (Remicade®, Jansen Biologics, Malvern PA and MSD, New Jersey, USA) or adalimumab (Humira®, Abbvie, Chicago IL, USA) (medical group). All patients on maintenance therapy with anti-TNF agents for at least one year prior to the start of the study were analyzed. Patients in remission (defined by the partial Mayo score) were selected for inclusion in the present study. Remission was defined as a total partial Mayo score ≤ 2 with no subscore > 1 and with a rectal bleeding score of 0 [12].

2.2. Outcome measures

Generic quality of life was measured with the validated Medical Outcomes Study 36-Item Short Form (SF-36). This questionnaire is particularly useful for comparing HRQL of a diseased population with the general population [13]. Thirty-six items are combined to form 8 scales (physical functioning (PF), role-physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role-emotional (RE), and mental health (MH)). Scale scores were transformed to a scale ranging from 0 (worst health status) to 100 (best health status). Two summary components (Physical Component Summary (PCS) and Mental Component Summary (MCS)) were derived by aggregating and weighting the individual scale scores. Norm-based scores were constructed such that the mean (±SD) for the general Dutch population was 50 (±10) [14].

Conclusion: HRQL and disability were not different among the medical and surgical group, except for stool frequency and anti-diarrhea medication use that was significantly higher in surgically treated patients.

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Disease-specific quality of life was assessed with the Colorectal Functional Outcome Questionnaire (COREFO) [15]. This questionnaire contains 27 questions that are combined in 5 multi-item scales (i.e. fecal incontinence (for example pad use), social impact, stool frequency, stool related aspects and need for anti-diarrhea medication use). The scores were linearly transformed into a score ranging from 0 to 100, with higher scores indicating more bowel-function problems.

Furthermore, questions were selected from three EORTC questionnaires (i.e. QLQ-LMC21 (Colorectal Liver Metastases), QLQ-OV28 (Ovarian) and QLQ-CR38 (Colorectal)). The selected questions focus on possible side effects of anti-TNF agents, such as muscle and joint pain. Since sexual functioning may be affected by pouch surgery [16,17] questions with specific focus on sexual functioning were selected from these EORTC questionnaires (including sexual enjoyment, male sexual problems (erection problems and ejaculation problems) and female sexual problems (dry vagina and pain during sexual intercourse)). The scores of the 6 individual items (i.e. muscle and joint, skin, female sexual problems, male sexual problems, sexual enjoyment and sexual functioning) were transformed into scores ranging from 0 to 100. A higher score indicates a better quality of life for sexual enjoyment. With regard to the other items, a higher score indicates a higher level of symptomatology.

Work productivity was assessed using the Work Productivity and Activity Impairment in UC (WPAI:UC) that consists of six questions that focus on the previous five workdays. These six questions were combined into four items: hours missed of work due to the disease (absenteeism), degree of reduced productivity while working (presenteeism), patients’ regular daily activities (activity impairment) and the overall impairment. A higher score indicates more activity impairment.

### 2.3. Procedure

The combined questionnaires and the cover letter were first pilot-tested among healthy volunteers (n = 5) in order to check for relevance, grammar and clarity. This led to minimal changes in the cover letter.

Eligible patients were contacted by telephone and invited to participate. In order to measure quality of life and disability scores, we undertook a postal survey in February 2013. In the
accompanying cover letter, the aim of the study was explained and patients were requested to complete and return the questionnaires using the supplied return envelope. If the questionnaires were not returned within 2 weeks, patients were contacted by telephone in order to encourage them to complete the questionnaires. Again after 2 weeks the patients were contacted, if necessary.

2.4. Statistical analysis

Data are presented as mean ± standard deviation in case of parametric data and as median with inter quartile range (IQR) in case of non parametric data. Associations between baseline characteristics of both groups were analyzed using the Chi-Square Test or Fisher exact tests for categorical variables and the Independent-Sample t-test for continuous variables. Data with a non-parametric distribution were analyzed using the Mann–Whitney test. Differences in HRQL and disability between both groups were compared for each questionnaire using the Mann–Whitney–Wilcoxon test or Independent-Sample t-test in case of non-parametric distribution or parametric distribution, respectively (p value < 0.05 was considered significant). Data was analyzed using IBM SPSS Statistics for Windows®, Version 19.0. (IBM Corp., Armonk, NY, United States).

3. Results

3.1. Baseline characteristics of study population

Seventy patients were eligible for inclusion in this study (Fig. 1). Nine patients could not be reached by phone and 1 patient declined participation. In total 60 patients were included: 30 patients in each group. Fifty-eight out of 60 patients (97%) returned the completed questionnaires: 29 patients in the surgery group (median age 42 years [22 – 67]; 48% female) and 29 patients in the medical group (median age 45 years [19 – 68]; 65% female). Fifteen patients (51.7%) undergoing IPAA had received anti-TNF treatment prior to surgery. Baseline characteristics of both study groups were comparable (Table 1).

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Baseline demographics. Surgery group; UC patients in clinical remission after proctocolectomy and ileoanal pouch reconstruction. Medical group; UC patients in clinical remission with infliximab or adalimumab. Data are presented as n (%), mean ± SD or median [IQR].</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameter</td>
<td>Surgery group (n = 29)</td>
</tr>
<tr>
<td>Age</td>
<td>42 [22–67]</td>
</tr>
<tr>
<td>Sex, female</td>
<td>14 (48.3%)</td>
</tr>
<tr>
<td>Race, Caucasian</td>
<td>27 (93.1%)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>4/29 (14%)</td>
</tr>
<tr>
<td>Disease characteristics</td>
<td></td>
</tr>
<tr>
<td>Age at onset</td>
<td>33.4 ± 9.5</td>
</tr>
<tr>
<td>Age at restorative procedure</td>
<td>38.9 ± 12.1</td>
</tr>
<tr>
<td>Age at start anti-TNF</td>
<td>40.2 ± 9.7 *</td>
</tr>
<tr>
<td>Extent of disease</td>
<td></td>
</tr>
<tr>
<td>Left-sided colitis</td>
<td>12/29 (41.4%)</td>
</tr>
<tr>
<td>Pancolitis</td>
<td>17/29 (58.6%)</td>
</tr>
<tr>
<td>Previous medication †</td>
<td></td>
</tr>
<tr>
<td>Aminosalicylates</td>
<td>29/29 (100%)</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>28/29 (96.5%)</td>
</tr>
<tr>
<td>Thiopurines ‡</td>
<td>25/29 (86.2%)</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>5/29 (17.2%)</td>
</tr>
<tr>
<td>Anti-TNF</td>
<td>15/29 (51.7%)</td>
</tr>
<tr>
<td>- Infliximab</td>
<td>14/29 (48.3%)</td>
</tr>
<tr>
<td>- Adalimumab</td>
<td>1/29 (3.4%)</td>
</tr>
<tr>
<td>Co-medication ‡</td>
<td></td>
</tr>
<tr>
<td>Aminosalicylates</td>
<td>0/29 (0%)</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>0/29 (0%)</td>
</tr>
<tr>
<td>Thiopurines ¥</td>
<td>0/29 (0%)</td>
</tr>
<tr>
<td>Previous surgery</td>
<td>7/29 (24.1%)</td>
</tr>
<tr>
<td>- Bowel surgery</td>
<td>5/29 (17.2%)</td>
</tr>
<tr>
<td>- Other surgery</td>
<td>2/29 (6.9%)</td>
</tr>
</tbody>
</table>

† medication use before index date (31-12-2011) ‡ thiopurines included azathioprine (Surgery group n = 23, Medical group n = 21), 6-Mercaptopurine (Surgery group n = 7, Medical group n = 10), 6-Thioguanine (Surgery group n = 0, Medical group n = 5). ¥ Medication use at the time of survey. ¥ Thiopurines included Azathioprine (n = 8) and 6-Mercaptopurine (n = 1).
3.2. Generic quality of life

There were no significant differences in SF-36 scores between the two study groups for each item (Fig. 2). Outcomes of the entire study population were compared with the reference scores of the general Dutch population. Significantly lower scores were found in the surgery group compared to the general Dutch population with regard to the following items: role physical \( (p = 0.021) \), general health \( (p = 0.001) \) and vitality \( (p = 0.038) \) (Fig. 2). Furthermore, significantly lower scores were found in the medical group compared to the general Dutch population regarding the following items: role physical \( (p = 0.035) \), general health \( (p < 0.001) \) social functioning \( (p = 0.026) \), mental health \( (p = 0.021) \), vitality \( (p < 0.001) \) and the mental summary score \( (p = 0.006) \).

3.3. Disease-specific quality of life

The COREFO total score was significantly higher in the surgery group compared to the medical group \( (p = 0.006) \). Both the medication and stool frequency subscales were significantly higher in the surgery group compared to the medical group \( (p = 0.004 \text{ and } p < 0.001, \text{ respectively}) \). The median stool frequency was 5–7 during daytime and 1–2 during nighttime in the surgery group versus 2–4 during daytime and 0 during nighttime in the medical group. The other items (i.e., fecal incontinence, stool-related aspects and social impact) were not significantly different between the two study groups (Fig. 3).

With regard to the selected EORTC questions on sexual items, skin problems and muscle or joint pain, no significant differences were found between the surgery and medical group (Fig. 4).

3.4. Work productivity

No significant differences were found between the two groups with regard to the WPAI:UC questionnaire on all items (i.e., absenteeism, presenteeism, overall impairment and activity impairment) (Table 2).

4. Discussion

This study shows that HRQL and disability outcomes do not differ in UC patients who are in clinical remission with anti-TNF agents or after RPC with IPAA, except for stool frequency and anti-diarrhea medication use that were significantly higher in the surgery group. The higher stool frequency and anti-diarrhea medication use is an expected outcome in patients who underwent pouch surgery due to the anatomical changes and given the fact that inclusion criteria for the medical group were based on the partial mayo score using the absolute number of bowel movements. Of note, patients who do well with anti-TNF agents report a significantly lower level of HRQL in more SF-36 subscales compared to patients with a favorable response following pouch surgery compared to the general population using norm-based scores.

UC impairs patients’ perception of health and has a negative impact on HRQL [18]. Quality of life is an important outcome parameter in UC and HRQL questionnaires have been developed and validated over the past two decades. HRQL assessments are used for multiple purposes, such as in cost-effective studies to assess the relative value of competing treatment options [9, 19].

Anti-TNF agents are powerful drugs to treat moderate to severe UC. However, a large proportion of patients loses their response to these agents or become intolerant [10].

Figure 2  Mean (SD) SF-36 score for each item. Both study groups were compared to the general Dutch population. P1 is the statistical difference between restorative proctocolectomy (surgery group) and anti-TNF agents (medical group), P2 is the statistical difference between the general Dutch population and the surgery group and P3 is the statistical difference between the general Dutch population and the medical group. RP; P1 = 0.784, P2 = 0.021*, P3 = 0.035*. PF; P1 = 0.931, P2 = 0.236, P3 = 0.472. GH; P1 = 0.242, P2 = 0.001*, P3 < 0.001*. BP; P1 = 0.750, P2 = 0.748, P3 = 0.858. SF; P1 = 0.213, P2 = 0.330, P3 = 0.026*. MH; P1 = 0.175, P2 = 0.386, P3 = 0.021*. VT; P1 = 0.409, P2 = 0.038*, P3 < 0.001*. RE; P1 = 0.148, P2 = 0.130, P3 = 0.834. MCS; P1 = 0.423, P2 = 0.095 = P3 = 0.006*. PCS; P1 = 0.529 P2 = 0.155 P3 = 0.059. *p < 0.05 in either P1, P3 or P3.
Quality of life in UC after surgery or with anti-TNF agents

Although RPC provides satisfactory outcomes in a vast majority of patients with therapy-refractory UC [4], surgery is associated with complications, such as acute and chronic pouchitis. The present exploratory study examined for the first time HRQL and disability outcomes in UC patients in clinical remission with anti-TNF agents or following RPC with IPAA. To this aim, a selected group of patients was analyzed who had an optimal ‘response’ to their treatment. Hence, in this pilot study we excluded patients with significant pouch problems (surgery group) and patients with a poor response to anti-TNF agents (medical group). A limitation of this exploratory study is the small sample size in both study groups. The results should therefore be viewed with caution in light of the limited power. Larger prospective trials are needed that should also focus on patients who are not in clinical remission. Secondly, most patients in the surgery group failed on medical treatment (including biologics), and this could have biased the results. Moreover, it is highly likely that these patients are benchmarking their current health state to the experience they had prior to surgery. It is well established that patients with therapy-refractory UC have a poor HRQL [9]. Therefore, a patient who has what would be considered by others as an important impairment of HRQL following colectomy may rate their current HRQL relatively high compared to the poor HRQL they previously experienced, also referred to as ‘response shift’ [20]. Thirdly, laboratory tests or endoscopy were not used to objectively confirm remission in patients in clinical remission with anti-TNF agents or following pouch surgery. However, clinical remission (defined by the partial Mayo score) usually corresponds very well with the endoscopic appearance of the colonic mucosa.

Although we did not find significant differences in quality of life and disability outcomes between the two study groups, except for stool frequency and anti-diarrhea medication use that were significantly higher in the surgery group, differences in treatment costs have been reported. It has been shown that immediate colectomy with IPAA after diagnosing severe UC is more cost-effective compared to treatment with medical therapy. In the study by Park et al, it was calculated that standard medical therapy strategy accrued a total discounted lifetime cost of $236,370 (95% CI: 219,057–255,328) [21]. The early colectomy with IPAA strategy accrued a total discounted lifetime cost of $147,763 (95% CI: 137,013–158,904). This represents a cost saving of $88,607 (95% CI: 73,726–105,865) per person over a lifetime [21]. In this particular study a Markov model was created to simulate a cohort of adult UC patients with newly diagnosed severe pancolitis from diagnosis at age 21 until death or 100 years of age using 3-month time steps. In this model the cost of an ‘average’ patient with severe UC undergoing either of these two different care models was calculated, including the most common complications in both treatment groups. In addition, it has been shown that healthcare costs in UC are mainly driven by medication costs, most importantly by anti-TNF therapy, whereas hospitalisation and surgery accounted only for a minor part of the healthcare costs [22].

In conclusion, this exploratory study did not find significant differences in HRQL and disability outcomes in a selected group of UC patients who were in clinical remission following surgery or with anti-TNF agents, except for stool frequency and anti-diarrhea medication use that were significantly higher in the surgery group. As a next step, we are designing a study that will analyse all patients on anti-TNF agents or following pouch surgery, including patients with pouch problems and with a poor response or side effects to anti-TNF agents.

Table 2 Outcome work productivity and activity impairment.

<table>
<thead>
<tr>
<th></th>
<th>Surgery group</th>
<th>Medical group B</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absenteeism, mean (SD)</td>
<td>4.81 (16.77)</td>
<td>1.98 (5.48)</td>
<td>0.66</td>
</tr>
<tr>
<td>Presenteeism, mean (SD)</td>
<td>12.11 (22.99)</td>
<td>11.11 (20.26)</td>
<td>0.96</td>
</tr>
<tr>
<td>Overall impairment, mean (SD)</td>
<td>145.27 (98.25)</td>
<td>121.78 (50.21)</td>
<td>0.67</td>
</tr>
<tr>
<td>Activity impairment, mean (SD)</td>
<td>24.44 (32.50)</td>
<td>24.29 (25.74)</td>
<td>0.58</td>
</tr>
</tbody>
</table>

Figure 4 Mean (SD) outcomes of a selection of EORTC questions (LCC21, OV28 and CR38 questionnaires) in both study groups. A higher score indicates a better quality of life for sexual enjoyment. With regard to the other items, a higher score indicates a higher level of symptomatology.

Figure 3 Mean (SD) COREFO outcomes for each dimension in the two study groups (surgery group and medical group), * p < 0.05. Higher scores indicate more bowel-function problems.
Acknowledgments

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No conflicts of interest.

Statement of authorship

SM carried out the study, performed statistical analysis and drafted the manuscript. TG participated in the statistical analysis and data interpretation. MS provided significant advice. GD participated in the design of the study and writing the manuscript. CB provided advice in data interpretation. ML drafted the manuscript, was involved in data interpretation, participated in the design and coordination of the project and writing the manuscript. All authors read and approved the final manuscript.

References


