The impact of biologics on health-related quality of life in patients with inflammatory bowel disease

Lauran Vogelaar1
Adriaan van’t Spijker2
C Janneke van der Woude1
1Department of Gastroenterology and Hepatology, 2Department of Psychology and Psychotherapy, Erasmus medical centre, Rotterdam

Background: Inflammatory bowel disease (IBD) is characterized by a chronic relapsing inflammation of the gastrointestinal tract. Adult IBD patients suffer from a disabling disease which greatly affects health-related quality of life (HRQoL). A worse HRQoL in these patients may result in a defensive and ineffective use of medical attention and thus higher medical costs. Because of its chronic nature, IBD may also cause psychological problems in many patients which may also influence HRQoL and care-seeking behavior. An important factor reducing HRQoL is disease activity. Induction of remission and long-term remission are important goals for improving HRQoL. Furthermore, remission is associated with a decreased need for hospitalization and surgery and increased employment, which in turn improve HRQoL. Treatment strategies available for many years are corticosteroids, 5-aminosalicylates and immunosuppressants, but these treatments did not show significant long-term improvement on HRQoL. The biologics, which induce rapid and sustained remission, may improve HRQoL.

Objective: To review and evaluate the current literature on the effect of biologics on HRQoL of IBD patients.

Methods: We performed a MEDLINE search and reviewed the effect of different biologics on HRQoL. The following subjects and synonyms of these terms were used: inflammatory bowel disease, Crohn’s disease, ulcerative colitis, quality of life, health-related quality of life, fatigue, different anti-TNF medication, and biologicals/biologics (MESH). Studies included were limited to English-language, adult population, full-text, randomized, double-blind, placebo-controlled in which HRQoL was measured.

Results: Out of 202 identified articles, 8 randomized controlled trials (RCT) met the inclusion criteria. Two RCTs on infliximab showed significant improvement of HRQoL compared to placebo which was sustained over the long term. One RCT on adalimumab showed a significant and sustained improvement of HRQoL compared to placebo. This study showed also significant decrease of fatigue in the adalimumab-treated patients. Three RCTs on certolizumab showed a significant improvement of HRQoL in the intervention group compared to placebo. Two RCTs of natalizumab treatment were found. One study showed significant and sustained improvement compared to placebo, and also scores of HRQoL comparable to that in the general population, but in the other no significant results were found.

Conclusion: The biologics infliximab, adalimumab, certolizumab, and natalizumab demonstrated significant improvement of HRQoL of IBD patients compared with placebo. However, we found differences in improvement of HRQoL between the different biologics.

Keywords: inflammatory bowel disease, health-related quality of life, health care costs, biologics

Introduction
Inflammatory bowel disease (IBD) is characterized by a chronic relapsing inflammation of the gastrointestinal tract.
Although IBD is a chronic disease with a normal life expectancy, the disease decreases health-related quality of life (HRQoL). Adult IBD patients have a lower HRQoL than the general population. A reduction of HRQoL can be predicted by symptom severity, disease severity, rheumatic symptoms, female gender and higher need for hospitalization. The chronic nature of the disease also affects HRQoL. The long period of time needed to adapt to the disease may cause psychological symptoms which negatively influence HRQoL and care-seeking behavior.  

IBD patients frequently complain of fatigue. Approximately 41% patients with quiescent IBD are known to suffer from fatigue, which is frequently associated with a decreased HRQoL.  

In a substantial group of IBD patients HRQoL may impaired because of prolonged treatment and the adverse effects associated with such treatment, the need for surgery and hospitalization. Another important factor influencing HRQoL is disease activity. Improvement of HRQoL can therefore be achieved by inducing remission. Furthermore, remission is associated with less medical care, increased employment, and thus improved HRQoL.  

For decades, 5-aminosalicylates (5-ASA), corticosteroids and immunosuppressants comprised the cornerstone of treatment for IBD patients. Despite their effectiveness in active disease, these drugs cannot prevent progression to a more complicated disease. Although IBD patients showed significant improvement of HRQoL on the short term, during prolonged treatment no significant improvement of HRQoL has been shown with these drugs, partly because of side effects that also negatively affect HRQoL. 

Because current treatments fail to prevent progression to more complicated disease stages, and because of the negative influence of the disease and its treatment on HRQoL, a more effective treatment is needed.  

Biologics, which induce rapid and sustained disease remission, may provide effective treatment.

However, biologics are more expensive than 5-ASA, corticosteroids and immunosuppressants used for treating IBD. IBID has high direct and indirect costs for patients and society. The direct costs (±50%) comprise inpatient care, outpatient care, self-care, medications and tests/procedures. The indirect costs comprise work absenteeism, decreased incomes, decreased HRQoL and fatigue. The direct costs vary between €6,000 and €40,000 per patient year. In the near future, the costs for IBD will increase, largely because of the increased incidence rates of IBD over recent decades in developed countries together with the early onset of the disease. 

Treatment with expensive biologics will increase the up front health care costs for IBD, however they can be cost-effective due to rapid induction and long-term remission. In order to reduce indirect costs, biologics must improve HRQoL. We therefore focus our review on the effect of these drugs on HRQoL.

Methods

Search

In MEDLINE we searched (from 1980 up to January 2009) for the following subjects and synonyms: inflammatory bowel disease (MESH), Crohn’s disease (MESH), ulcerative colitis (MESH), quality of life (MESH), health related quality of life, fatigue (MESH), infliximab, adalimumab, certolizumab and natalizumab, and biologicals/biologics (MESH). We also hand-searched the reference lists of the relevant articles for titles which included a biologic and quality of life.

The search was limited to English-language, adult population and full-text publications. Studies were included for review if they were randomized, double blind, placebo-controlled trials (RCTs) of biologics (ie: infliximab, adalimumab, certolizumab or natalizumab) maintenance treatment in IBD and if HRQoL was measured by the Inflammatory Bowel Disease Questionnaire (IBDQ) and/or the Short Form Health Survey (SF-36) as a primary or secondary outcome measurement. Only studies using these questionnaires were included, because in current research these are the most commonly used validated questionnaires, enabling reliable comparison of the study outcomes. We included only randomized, double blind, placebo-controlled trials, to rule out confounding of the results by placebo effects or physician preference for biologics.

Questionnaires

The IBDQ is a disease-specific HRQoL questionnaire containing 4 subscales: bowel symptoms, systemic symptoms, emotional functioning, and social functioning. The total IBDQ score is the sum of the responses to each of the IBDQ questions. Total IBDQ score can range from 32 (very poor HRQoL) to 224 (perfect HRQoL). Patients in symptomatic remission usually have a score of 170 or greater. An absolute change of 16 points in the total IBDQ score has been used to define a minimum clinically relevant improvement. The SF-36 is a generic HRQoL assessment and is also much used in IBD studies. The SF-36 consists of 8 scales (physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental function).
health). The SF-36 comprises two summary components, the physical component summary (PCS) and the mental component summary (MCS) which are derived from individual scale scores.\textsuperscript{44–46} The 8 scales are scored on a scale of 0 to 100, higher scores indicating better health.\textsuperscript{49} For the PCS and the MCS the mean score is 50 and the SD 10 for the general population in the US.\textsuperscript{50}

An absolute increase of 3 to 5 points in the PCS or MCS scale is generally accepted as a meaningful change.\textsuperscript{51,52}

Results
The literature search identified 202 potentially eligible articles. Of these, 143 were not focused on HRQoL. Fifty studies were excluded because they were not RCTs. Of the 9 remaining studies, we excluded 1 RCT which reported results from only a single infusion of infliximab.\textsuperscript{53} The first author determined which studies were excluded and an inter-rater agreement check of 10% of the articles was done by the last author. A perfect agreement was reached in this random sample.

Table 1 summarizes the studies, which are discussed below.

Infliximab and HRQoL
Two studies, the Active Ulcerative Colitis Trials 1 and 2 (ACT 1 and 2) and the ACCENT 1 study (Crohn’s disease), investigated the effect of infliximab on the HRQoL.\textsuperscript{54,55}

The ACT 1 and 2 compared infliximab 5 mg/kg with 10 mg/kg and a placebo-controlled group. Both the ACT 1 and ACT 2 studies showed a significant improvement of total IBDQ and SF-36 scores at week 8 compared with baseline in both the infliximab 5 mg/kg and 10 mg/kg groups. There were no differences in HRQoL between the 2 treatment groups. The improvement in HRQoL was significantly greater in the treatment groups than in the placebo-control group for the IBDQ (\(P < 0.05\)) and the SF-36 (\(P < 0.01\)). Also, the percentage of patients achieving clinically relevant improvement on the IBDQ and SF-36 was significantly greater in the treatment groups than in the placebo-controlled group (\(P < 0.05\)). The bowel and social domain scores seemed to be responsible for the improvement of the IBDQ, whereas both PCS and MCS of the SF-36 scores were responsible for the improvement. At 30 and 54 weeks the improvement in the treatment groups was still significantly greater than in the placebo-controlled group (\(P < 0.001\)).

The ACCENT I study compared 3 treatment modalities (single infusion of 5 mg/kg with placebo maintenance; 5 mg/kg single infusion with 10 mg/kg maintenance). In all 3 treatment groups, all 4 IBDQ dimensional scores (emotional functioning, social functioning, systemic symptoms and bowel symptoms dimensions) improved from baseline throughout the study. However, the improvement in total IBDQ score at week 10, 30, and 54 was consistently larger (\(P < 0.05\)) in both infliximab maintenance groups compared with the placebo maintenance group. The IBDQ subscales for bowel and systemic symptoms showed the largest improvement. The SF-36 scores improved from baseline to week 54 in all treatment groups. The summary scale PCS improved significantly in both infliximab groups (\(P < 0.05\)). The summary scale MCS improved significantly in the 10 mg/kg infliximab group (\(P < 0.05\)). The PCS scale improved more than the MCS scale.

Adalimumab and HRQoL
The CHARM study investigated the effect of adalimumab on HRQoL and fatigue.\textsuperscript{56} This study compared 3 arms. Every treatment arm started with 80 mg induction of adalimumab followed by 40 mg at week 2. At week 4, patients followed the treatment arm for which they were randomized: 40 mg adalimumab every other week (eow) for 1 year, 40 mg adalimumab every week for 1 year, or placebo injections. The analyses included only the 499 patients responding to treatment at week 4. Induction therapy of adalimumab significantly improved HRQoL (\(P < 0.0001\)).

The IBDQ significantly improved in the adalimumab groups up to 1 year later (\(P < 0.001\) for adalimumab eow and \(P < 0.05\) for adalimumab weekly).

No differences were found between both maintenance groups. The systemic and social domains were particularly responsible for the improvement of the IBDQ. On the SF-36, patients in the 40 mg every other week group showed significantly more improvement on PCS and MCS at 1 year than the induction-only group (\(P < 0.05\)). The 40-mg-every-week group did not show a significantly greater improvement than the induction-only group. The 2 maintenance groups did not differ significantly. Finally, both maintenance groups reported fewer fatigue symptoms than the placebo group (0.05 > \(P < 0.001\)).

Certolizumab and HRQoL
Three studies investigated the effect of certolizumab pegol on HRQoL (Table 1).\textsuperscript{57–59} In the first study patients received either 100 mg, 200 mg, 400 mg, or placebo at weeks 0, 4, and 8. HRQoL was measured with the IBDQ for 3 months.\textsuperscript{57} Analyses focused on the
400 mg group, because this dose was identified in another study as the most effective dose. HRQoL improved significantly from baseline to 12 weeks follow-up (P < 0.05), and significantly more than in the placebo group at all time points (P < 0.05). On the subscales of the IBDQ, at 12 weeks patients receiving 400 mg certolizumab reported significantly more improvement on emotional functioning and systemic functioning compared with the placebo group. No significant differences were found at 12 weeks for bowel functioning and social functioning.

Table 1 Demographic and baseline characteristics

| Study          | n  | Crohn’s disease/ulcerative colitis | Age, years (mean ± SD) | Sex male, number (%) |
|----------------|----|------------------------------------|------------------------|----------------------|
| Feagan 200714  | 728| Ulcerative colitis                 | Placebo: 40.3 ± 13.6   | 291 (40)             |
|                |    |                                    | Infliximab (5 mg/kg): 41.5 ± 13.7 |
| Feagan 200741  | 339| Crohn’s disease                    | Natalizumab: 37 ± 13   | Natalizumab: 77 (46) |
| (ENACT-2)      |    |                                    | Placebo: 37 ± 12        | Placebo: 59 (35)     |
| Feagan 200355  | 573| Crohn’s disease                    | 37 ± 12 (all patients)  | 239 (41.7)           |
| Loftus 200866  | 499| Crohn’s disease                    | Group 1: 36.9 ± 11.9    | Group 1: 65 (38)     |
|                |    |                                    | Group 2: 36.4 ± 11.1    | Group 2: 61 (36)     |
|                |    |                                    | Group 3: 36.9 ± 11.8    | Group 3: 62 (39)     |
| Rutgeerts 200877| 292| Crohn’s disease                    | Placebo: 35.8 (range 19–64) | Placebo: 24 (32.9) certolizumab 100 mg; 35 (47.3)/200 mg: 22 (30.6)/400 mg: 32 (44.4) |
|                |    |                                    | certolizumab 100 mg: 33.5 (range 18–56)/200 mg: 40.1 (range 19–71)/400 mg: 35.9 (18–67) |
| Sands 200752   | 79 | Crohn’s disease                    | Natalizumab + infliximab: 39.9 ± 12.6 | Natalizumab + infliximab: 24 (46) |
|                |    |                                    | Placebo + infliximab: 38.9 ± 13.2 | Placebo + infliximab: 17 (63) |
| Sanborn 200758 (PRECISE) | 662 | Crohn’s disease | Certolizumab: 37 ± 12 | Certolizumab: 157 (47) |
|                |    |                                    | Placebo: 38 ± 12        | Placebo: 131 (40)    |
| Sanborn 200758 (PRECISE 2) | 668 | Crohn’s disease | Certolizumab: 38 ± 11 | Certolizumab: 92 (43) |
|                |    |                                    | Placebo: 38 ± 12        | Placebo: 109 (52)    |
### Table 1

| Intervention | Control group |
|--------------|---------------|
| **CDAI (mean ± SD) baseline** | **Total IBDQ score (mean ± SD) baseline** | **Total SF-36 score (mean ± SD) baseline** |
| Placebo: 302 ± 58 | 126 ± 31.7 | PCS: 38.4 ± 8.5 |
| Placebo: 302 ± 54 | 123.6 ± 29.7 | PCS: 33.7 ± 8.0 |
| Natalizumab: 296 ± 56 | 124.6 ± 28.7 | PCS: 36.9 ± 7.6 |
| Placebo: 302 ± 58 | 126.1 ± 27.4 | MCS: 40.3 ± 11.5 |
| Placebo: 302 ± 54 | 128 ± 27 | MCS: 39 ± 11 |
| Natalizumab: 296 ± 56 | 126.6 ± 29.7 | MCS: 39 ± 11 |
| Placebo: 302 ± 58 | 124.6 ± 28.7 | MCS: 37.6 ± 10.8 |
| Placebo: 291.5 (206–448)/certolizumab 100 mg: 299.2 (194–520)/200 mg: 310.7 (184–446)/400 mg: 304.5 (204–461) | 126.1 ± 27.4 | MCS: 38 ± 11.5 |
| Natalizumab + infliximab: 263.8 ± 89.3 | Not mentioned | Natalizumab induction (300 mg) or placebo wk 0, 4, 8 |
| Placebo + infliximab: 243.6 ± 57.1 | Not mentioned | Responders: Natalizumab (300 mg/4 wk) |
|Certolizumab: 301 ± 62 | Not mentioned | Natalizumab induction (80 mg) wk 0, 2 |
|Placebo: 306 ± 61 | Not mentioned | Responders: Group 1: Adalimumab (40 mg/every other week) |
|Certolizumab: 300 ± 64 | Not mentioned | Group 1: certolizumab (100 mg) wk 0, 4, 8 |
|Placebo: 297 ± 62 | Not mentioned | Group 2: certolizumab (200 mg) wk 0, 4, 8 |
|Certolizumab: 300 ± 64 | Not mentioned | Group 3: certolizumab (400 mg) wk 0, 4, 8 |

**Abbreviations:** CDAI, Crohn’s Disease Activity Index; IBDQ, Inflammatory Bowel Disease Questionnaire; MCS, mental component summary; PCS, physical component summary; SF-36, Short-Form Health Survey; N, number of patients.

The PRECISE 1 and 2 studies investigated the efficacy of certolizumab pegol treatment and the efficacy of the maintenance of this treatment, respectively. The studies included also measurements of the HRQoL with the IBDQ.58,59

The PRECISE 1 study patients received either 400 mg certolizumab pegol or placebo at weeks –0, –2, and 4 followed by every 4 weeks through week 26.58 The HRQoL increased from baseline to week 26, and in the certolizumab group significantly more than in the placebo group (P = 0.03).58
The PRECISE 2 study patients received induction therapy of certolizumab pegol 400 mg at weeks −0, −2, and 4. Patients with a clinical response at week 6 were included in the intervention group (certolizumab 400 mg every 4 weeks) or the placebo group (placebo every 4 weeks) and received injections through week 24. The IBDQ was measured at weeks 0, −6, −16, and 26. The scores of the IBDQ were significantly higher in the intervention group (certolizumab 400 mg) than the control group (P = 0.007) at week 26.59

Natalizumab and HRQoL

For the effect of natalizumab on HRQoL, which is registered for the treatment of Crohn’s disease in the US only, 2 studies were included (Table 1).61,62

The first study investigated the combination therapy of infliximab (5 mg/kg) at weeks −10, −2, and 6 and natalizumab (300 mg) at weeks 0, 4 and 8 compared with infliximab (5 mg/kg) and placebo. The combination therapy of natalizumab and infliximab showed a similar increase of the IBDQ compared with the combination of infliximab and placebo in CD patients (P = 0.811).62

Another study (ENACT-2) followed up on patients responding to natalizumab with continued treatment (300 mg infusions every 4 weeks up to 48 weeks) or placebo. HRQoL was not reported in the ENACT-1 study. In the follow-up study, it was reported that the scores of patients had already improved from baseline to inclusion in the ENACT-2 study. From inclusion in the follow-up study to 60 weeks, patients in the intervention group showed significantly greater increase in IBDQ total score and subscale scores at all time points than the placebo group (0.05 > P < 0.001). The highest percentages of patients who exceeded the minimally important difference on the 4 subscales of the IBDQ were seen in the bowel and social domains.

The SF-36, PCS and MCS scores improved significantly more in the intervention group than the placebo group at weeks 48 and 60 (P < 0.01).

Of particular note in this study is that the SF-36 profile of the natalizumab group was similar to the profile of the general population.61

Disease activity and HRQoL

HRQoL appears to be related to disease activity in the articles that studied this relationship. ACT 1 and 2 (infliximab) showed that response or remission (Mayo subscore) was correlated with improvement of IBDQ and SF-36.54,63 ACCEPt 1 (infliximab) showed significant correlations between the IBDQ scores and Crohn’s disease activity index (CDAI) scores at week 54.54,63

For certolizumab, CDAI score was correlated positively with IBDQ score.57 This study showed that the clinical efficacy of certolizumab pegol in patients with moderate-to-severe Crohn’s disease is paralleled by improvement in HRQoL.

Discussion

Adult IBD patients suffer from a chronic disease with an impaired HRQoL. Impairment of HRQoL and in particular fatigue in patients may result in a defensive and ineffective use of medical resources. Therefore impaired HRQoL may lead to more frequent visits, more tests and often variable treatment, and thus higher medical costs.8,64–66 It is expected that improvement of HRQoL will redirect medical attention-seeking behavior of patients, resulting in a more cost-effective way of treating these patients. Therapeutic strategies that have been available for many years include corticosteroids, 5-aminosalicylates and immunosuppressants. However, no significant long-term improvement has been seen on HRQoL with these therapies. More recently, biologics have been introduced in the treatment of IBD. Individual studies report favorable results of biologics on HRQoL.

This present review showed that 7 studies report a significant improvement of HRQoL (IBDQ and/or SF-36) in patients treated with a variety of biologics compared to placebo. One study reported on the use of 2 biologics. This study found no incremental effect on HRQoL of natalizumab over infliximab.

Although all biologics improve HRQoL, we found differences in the effect on HRQL between different biologics. On the IBDQ, adalimumab, natalizumab and certolizumab all improved HRQoL to a level of patients in remission (>170 points). Infliximab showed improvement on total IBDQ score (improvement with ≥16 points), but not to a total score above 170 points. Further differences were shown in the SF-36 profiles. Patients using natalizumab had a profile comparable with that of the general population. Patients using infliximab, adalimumab or certolizumab did not have such a profile.

The reason for the differences in effect on HRQoL between the biologics is unclear. One hypothesis is that the differences found may be due to the route of administration of these drugs. Infliximab is given in the outpatient setting or in the hospital intravenously, while certolizumab and adalimumab is administered subcutaneously at home. However, natalizumab, which is also administered intravenously, demonstrated the greatest improvement on HRQoL.
Another explanation for the differences found could be that the patients included in the different studies are not comparable. For instance, CDAI scores at baseline were lower in the intervention group of the natalizumab study (ENACT 2) than in the intervention groups of the infliximab, adalimumab and certolizumab studies. Baseline IBDQ and SF-36 scores were also lower in the natalizumab study (ENACT 2) than in the infliximab, adalimumab and certolizumab studies (except MCS score of the SF-36 in the adalimumab study) (Table 1). These differences are in contrast of what is expected, because natalizumab increased IBDQ scores up to a level of patients in remission.

Although fatigue is one of the factors that alter HRQoL in IBD patients, leading to increased costs and occurring in a high percentage of IBD patients, only one study reported the effects of treatment on fatigue. In the CHARM study adalimumab significantly decreased fatigue. Further research is needed to investigate the long-term effects of other biologics on fatigue.

Although all drugs appeared to have beneficial effects on HRQoL, a limitation of our review is that the number of studies included in this review is low. Therefore no definitive conclusions on the influence of biologics on the different dimensions of the IBDQ can be made yet.

With that caveat in mind, it appears that treatment with biologics particularly improves the bowel, systemic and social domains of the IBDQ. Emotional functioning seems to be less responsive to biologics.

Another limit is that the studies included in this review included only patients with active disease and most studies included only patients with moderate-to-severe disease. This could bias the outcome, since more improvement is feasible in patients with a low HRQoL than in patients with a high HRQoL. Whether biologics have comparable favorable results in patients with limited disease needs to be studied separately.

**Expert opinion**

In recent years awareness of the importance of HRQoL has increased, not only for the benefit of the patients but also for reducing health care costs in IBD. However, research on the magnitude of fatigue, which is an important factor in altering HRQoL and the health care costs, is limited in IBD patients.

Biologics increase health care costs and in the near future newer expensive biologics will be introduced. Because biologics can induce and sustain remission and therefore improve HRQoL, these strategies are expected to be cost-effective despite the high costs of treatment with biologics.

For future therapeutic strategies more research is needed on HRQoL and fatigue and the influence of newer therapeutic agents on different domains of HRQoL. Furthermore, studies must increase the duration of follow-up to investigate whether the new biologics are capable of sustaining the short-term benefits on HRQoL in IBD patients.

**Acknowledgment**

This review was supported by the Broad Medical Research Program of the Broad Foundation.

**Disclosures**

The authors report no conflicts of interest.

**References**

1. Helzer JE, Chammas S, Norland CC, Stillings WA, Alpers DH. A study of the association between Crohn’s disease and psychiatric illness. *Gastroenterology*. 1984;86:324-330.
2. Fullwood A, Drossman DA. The relationship of psychiatric illness with gastrointestinal disease. *Annu Rev Med*. 1995;46:483-496.
3. Levenstein S, Li Z, Almer S, et al. Cross-cultural variation in disease-related concerns among patients with inflammatory bowel disease. *Am J Gastroenterol*. 2001;96:1822-1830.
4. Janke KH, Klump B, Gregor M, Meisner C, Haeuser W. Determinants of life satisfaction in inflammatory bowel disease. *Inflamm Bowel Dis*. 2005;11:272-286.
5. Bernklev T, Jahnson J, Aadland E, et al; Group IS. Health-related quality of life in patients with inflammatory bowel disease five years after the initial diagnosis. *Scand J Gastroenterol*. 2004;39:365-373.
6. Mussell M, Bocker U, Nagel N, Singer MV. Predictors of disease-related concerns and other aspects of health-related quality of life in outpatients with inflammatory bowel disease. *Eur J Gastroenterol Hepatol*. 2004;16:1273-1280.
7. van der Zaag-Loonen HJ, Grootenhuis MA, Last BF, Derkx HH. Coping strategies and quality of life of adolescents with inflammatory bowel disease. *Qual Life Res*. 2004;13:1011-1019.
8. Minderhoud IM, Oldenburg B, van Dam PS, van Berge Henegouwen GP. High prevalence of fatigue in quiescent inflammatory bowel disease is not related to adrenocortical insufficiency. *Am J Gastroenterol*. 2003;98:1088-1093.
9. Casellas F, Lopez-Vivancos J, Vergara M, Malagelada J. Impact of inflammatory bowel disease on health-related quality of life. *Dig Dis*. 1999;17:208-218.
10. Irvine EJ. Quality of life issues in patients with inflammatory bowel disease. *Am J Gastroenterol*. 1997;92:18S-24S.
11. Singleton JW, Law DH, Kelley ML Jr, Mekhjian HS, Sturdevant RA. National Cooperative Crohn’s Disease Study: adverse reactions to study drugs. *Gastroenterology*. 1979;77:870-882.
12. Present DH, Meltzer SJ, Krumholz MP, Wolke A, Koralitz BI. 6-Mercaptopurine in the management of inflammatory bowel disease: short- and long-term toxicity. *Ann Intern Med*. 1989;111:641-649.
13. Egan LJ, Sandborn WJ. Methotrexate for inflammatory bowel disease: pharmacology and preliminary results. *Mayo Clin Proc*. 1996;71:69-80.
14. Drossman DA, Leserman J, Li ZM, Mitchell CM, Zagami EA, Patrick DL. The rating form of IBD patient concerns: a new measure of health status. *Psychosom Med*. 1991;53:701-712.
15. Casellas F, Lopez-Vivancos J, Casado A, Malagelada JR. Factors affecting health related quality of life of patients with inflammatory bowel disease. *Qual Life Res*. 2002;11:775–781.

16. Pizzi LT, Weston CM, Goldfarb NI, et al. Impact of chronic conditions on quality of life in patients with inflammatory bowel disease. *Inflamm Bowel Dis*. 2006;12:47–52.

17. Salbini S, Cortinovis I, Borelta L, et al. Gender and disease activity influence health-related quality of life in inflammatory bowel diseases. *Hepatogastroenterology*. 2005;52:509–515.

18. Casellas F, Lopez-Vivancos J, Badia X, Vilaseca J, Malagelada JR. Influence of inflammatory bowel disease on different dimensions of quality of life. *Eur J Gastroenterol Hepatol*. 2001;13:567–572.

19. Casellas F, Arenas JI, Baudet JS, et al. Impairment of health-related quality of life in patients with inflammatory bowel disease: a Spanish multicenter study. *Inflamm Bowel Dis*. 2005;11:488–496.

20. Reinisch W, Sandborn WJ, Bala M, et al. Response and remission are associated with improved quality of life, employment and disability status, hours worked, and productivity of patients with ulcerative colitis. *Inflamm Bowel Dis*. 2007;13:1135–1140.

21. Casellas F, Lopez-Vivancos J, Badia X, Vilaseca J, Malagelada JR. Impact of surgery for Crohn's disease on health-related quality of life. *Am J Gastroenterol*. 2000;95:177–182.

22. Lichtenstein GR, Yan S, Bala M, Hanauer S. Remission in patients with Crohn's disease is associated with improvement in employment and quality of life and a decrease in hospitalizations and surgeries. *Am J Gastroenterol*. 2004;99:91–96.

23. Cosnes J, Cattan S, Blain A, et al. Long-term evolution of disease behavior of Crohn's disease. *Inflamm Bowel Dis*. 2002;8:244–250.

24. Robinson M, Hanauer S, Hoop R, Zbrozek A, Wilkinson C. Mesalamine capsules enhance the quality of life for patients with ulcerative colitis. *Aliment Pharmacol Ther*. 1994;8:27–34.

25. Singleton JW, Hanauer SB, Gitnick GL, et al; Mesalamine capsules for the treatment of active Crohn's disease: results of a 16-week trial. *Pentasa Crohn's Disease Study Group*. *Gastroenterology*. 1993;104:1293–1301.

26. Sutherland LR, Martin F, Bailey RJ, et al; A randomized, placebo-controlled, double-blind trial of mesalamine in the maintenance of Crohn's disease. The North American Crohn's Study Group. *Canadian Inflammatory Bowel Disease Study Group*. *Gastroenterology*. 1994;106:287–296.

27. Singleton JW, Hanauer S, Robinson M. Quality-of-life results of double-blind placebo-controlled trial of mesalamine in patients with Crohn's disease. *Inflamm Bowel Dis*. 2000;6:410–415.

28. Feagan BG, McDonald JW, Rochon J, et al; History and quality of life and a decrease in hospitalizations and surgeries. *Am J Gastroenterol*. 1993;88:1379–1385.

29. Singleton JW, Hanauer S, Robinson M. Impact of surgery for Crohn's disease on health-related quality of life. *Inflamm Bowel Dis*. 2000;6:410–415.

30. Bonen A, Dagnelie PC, Feuleu A, et al. The impact of inflammatory bowel disease on labor force participation: results of a population sampled case-control study. *Inflamm Bowel Dis*. 2002;8:382–389.
56. Loftus EV, Feagan BG, Colombel JF, et al. Effects of adalimumab maintenance therapy on health-related quality of life of patients with Crohn’s disease: patient-reported outcomes of the CHARM trial. *Am J Gastroenterol*. 2008;103:3132–3141.

57. Rutgeerts P, Schreiber S, Feagan B, Keininger DL, O’Neil L, Fedorak RN, Group CDPCsDS. Certolizumab pegol, a monthly subcutaneously administered Fc-free anti-TNFalpha, improves health-related quality of life in patients with moderate to severe Crohn’s disease. *Int J Colorectal Dis*. 2008;23:289–296.

58. Sandborn WJ, Feagan BG, Stoinov S, et al. Certolizumab pegol for the treatment of Crohn’s disease. *N Engl J Med*. 2007;357:228–238.

59. Schreiber S, Khaliq-Kareemi M, Lawrance IC, et al. Maintenance therapy with certolizumab pegol for Crohn’s disease. *N Engl J Med*. 2007;357:239–250.

60. Schreiber S, Rutgeerts P, Fedorak RN, et al. A randomized, placebo-controlled trial of certolizumab pegol (CDP870) for treatment of Crohn’s disease. *Gastroenterology*. 2005;129:807–818.

61. Feagan BG, Sandborn WJ, Hass S, Niecko T, White J. Health-related quality of life during natalizumab maintenance therapy for Crohn’s disease. *Am J Gastroenterol*. 2007;102:2737–2746.

62. Sands BE, Kozarek R, Spainhour J, et al. Safety and tolerability of concurrent natalizumab treatment for patients with Crohn’s disease not in remission while receiving infliximab. *Inflamm Bowel Dis*. 2007;13:2–11.

63. Feagan BG. Maintenance therapy for inflammatory bowel disease. *Am J Gastroenterol*. 2003;98:S6–S17.

64. Creed F, Fernandes L, Guthrie E, et al; North of England IBSRG. The cost-effectiveness of psychotherapy and paroxetine for severe irritable bowel syndrome. *Gastroenterology*. 2003;124:303–317.

65. Deter HC, Keller W, von Wietersheim J, Jantschek G, Duchmann R, Zeitz M, German Study Group on Psychosocial Intervention in Crohn’s D. Psychological treatment may reduce the need for healthcare in patients with Crohn’s disease. *Inflamm Bowel Dis*. 2007;13:745–752.

66. Feagan BG, Bala M, Yan S, Olson A, Hanauer S. Unemployment and disability in patients with moderately to severely active Crohn’s disease. *J Clin Gastroenterol*. 2005;39:390–395.