Costs of inflammatory bowel disease in the Netherlands: The COIN study

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Costs of inflammatory bowel disease in the Netherlands: the COIN study

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Proefschrift

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Chapter 1

General introduction and outline of the thesis

GENERAL INTRODUCTION

Inflammatory bowel disease (IBD), which includes Crohn's disease (CD) and ulcerative colitis (UC), is a chronic condition of the gastrointestinal tract. The diseases are thought to be the result of a deregulated mucosal immune response to commensal gut flora in genetically susceptible individuals.[1] The prevalence of IBD in the Netherlands was recently estimated to be 432 per 100,000 patients.[2] Extrapolating this number to the Dutch population, there would be approximately 72,910 IBD patients in the Netherlands. The peak age of onset in IBD is in the third and fourth decade of life.[3]

Treatment of CD

Although there is proof that early combined immunosuppressive therapy (or top-down treatment) with anti-TNF therapy and immunomodulators is more effective,[4-5] the current therapeutic management of CD typically follows a step-up strategy.[6] The early use of immunomodulators in combination with steroids is a commonly used option for moderately-active localized ileocecal CD.

Anti-TNF therapy should be considered as an alternative for patients with active disease who have previously been steroid-refractory, steroid-dependent, or steroid-intolerant. [6] In patients with clinical features suggesting a poor prognosis such as deep and/or extensive ulcerations at endoscopy, post-surgical recurrence, extensive small bowel involvement or symptomatic fistulas, an 'accelerated-step-up' approach is advocated with early introduction of immunosuppressants and/or anti-TNF.[6]

For patients with severe, active ileocecal Crohn's disease who relapse, anti-TNF therapy or surgery is an appropriate alternative. Active colonic disease can be treated with sulphasalazine if only mildly active, or with systemic corticosteroids. For those who have relapsed, restarting corticosteroids with immunomodulators or anti-TNF therapy might be appropriate.[6] All currently available anti-TNF therapies in the Netherlands, infliximab and adalimumab, appear to have similar efficacy and adverse-event profiles.

[7] Before initiating immunomodulator or anti-TNF therapy, surgical options should also be considered and discussed.[6]

Treatment of UC

In UC, the current treatment algorithm also involves a step-up strategy.[8] Overall, mesalazine and corticosteroids are effective and fast acting agents, but, with time, a considerable proportion of patients fail to respond or become steroid-dependent. In these patients the introduction of immunomodulators is advocated in order to minimize steroid exposure. In more severe cases, further escalation to a combination with anti-TNF antibodies should be considered.[8] In the Netherlands, infliximab, adalimumab and golimumab are approved for the treatment of UC with comparable clinical response rates.[9–11] In a subgroup of patients with severe extensive disease, an early top-down strategy can also be followed.[8]

While most UC patients benefit from long-term medical treatment, previous studies (mostly conducted before 1990) have reported colectomy rates up to 45% due to treatment failure, development of colonic cancer or dysplasia, or to intolerable drug side effects.[12] The current colectomy rates seem significantly lower, i.e. approximately 15%.[12] Restorative proctocolectomy with construction of an ileo-anal pouch-anal anastomosis (IPAA) is the procedure of choice, as it preserves body image and restores the "conservative" route of defecation.[13] In an emergency setting or in case of contra-indications for IPAA, such as an impaired sphincter function, significant comorbidities, or an unclear diagnosis (IBD-unclassified), the surgical procedure of choice is a colectomy with an end-ileostomy and a closed rectal stump.[13]

Cost-of-illness and economic evaluations

In the current age of escalating healthcare costs and growing constraints on nation healthcare budgets, economic evaluations of newly available treatment strategies, and (re)evaluation of implemented treatment strategies are of great importance to healthcare providers and decision makers. In some countries is, apart from proven effectiveness, the reimbursement decisions for new pharmaceutical agents also dependent on how the incremental cost-effectiveness ratio relates to national cost-effectiveness thresholds.[14] The perspective taken for this depends on the stakeholder for whom the analysis is conducted (e.g. the healthcare provider), and/or on national health economic guidelines.[14–18]

The most complete perspective is the societal perspective, including 1) direct healthcare costs - also referred to as direct medical costs - consisting of costs such as surgery, hospitalization, visits to outpatient clinic, medication use, diagnostic procedures; 2) direct

non-healthcare costs, including any out-of-pocket expenses and therefore also referred to as patient costs; and 3) indirect non-healthcare costs, which in the case of IBD consist of productivity losses due to sick leave or work disability. Although several guidelines recommend adopting a societal perspective, direct healthcare costs are often the only cost categories incorporated in economic evaluations of new treatment strategies in IBD.

Anti-TNF therapy

The widespread and increasing use of anti-TNF therapy has resulted in a growing interest in economic evaluations to determine whether the high medication costs will be offset by better quality-of-life at acceptable additional costs.

To date, there are no cost-effectiveness studies based on real-life data comparing anti-TNF versus conventional treatment in patients with active Crohn's disease. All cost-effectiveness studies available are based on Markov models or decision trees, thereby representing a simplification of reality.[19] In addition, the available cost-of-illness studies were mainly performed before the introduction and widespread use of anti-TNF therapy.[20–27]

Prior to the introduction of anti-TNF, mean annual healthcare costs for IBD in the Netherlands were €2,548 per patient (inflated to 2011).[22] Hospitalization and surgery accounted for more than half of the healthcare costs in this study. Medication costs due to mesalazine accounted for 25% of the healthcare costs.[22] This cost profile was in line with other cost-of-illness studies conducted in the era before the introduction of anti-TNF therapy.[20–25]

As IBD is often diagnosed in the second or third decade of life, and therefore within the working age (between 20-40 years), it is associated with a reduced ability to work.[26,28–32] This is obviously a decisive period for future achievements in life and the societal impact due to reduced ability to work could therefore be enormous. However, only a limited number of cost-of-illness studies had considered, apart from healthcare costs, productivity losses. In these studies productivity losses, resulting from sick leave and work disability, accounted for almost 50% of the total costs.[24–26,33]

Aim of the thesis

Over the last decade, treatment goals of IBD have evolved from the induction and maintenance of clinical remission to the prevention of structural damage and long-term (work) disability with expanding use and early introduction of anti-TNF therapy and immunomodulators. These strategies are associated with a substantially improved

quality-of-life,[30,34,35] a reduction of hospitalization and surgery,[34,36,37] and might benefit work productivity.[30,34,35,38,39]

The aim of the COIN-study was to quantify the costs and quality-of-life of IBD in the Netherlands in the anti-TNF era from both a healthcare and a societal perspective, and to evaluate the differences in cost-effectiveness of conventional versus anti-TNF therapy.

Study design COIN-study

In order to be able to address the above issues, we initiated the **C**ost **O**f **I**nflammatory bowel disease in the **N**etherlands (COIN) study (Figure 1) to collect data on outcomes, quality-of-life and resources used by Dutch IBD patients.

Within the COIN-study we identified all IBD patients using the Diagnosis Treatment Combinations (DTCs) for respectively CD and UC in the participating hospitals. DTCs are based on the International Classification of Disease (9th Revision). All patients from seven university medical centres and seven general hospitals aged ≥18 years were eligible for participation (Figure 1).

We developed a secure web-based questionnaire and participants were provided with a unique username and password combination. Patients were invited to enter the username and password-secured and firewall-protected website and to fill out the questionnaires. After completing the baseline questionnaire, patients received an invitation to fill out the three-month follow-up questionnaire.

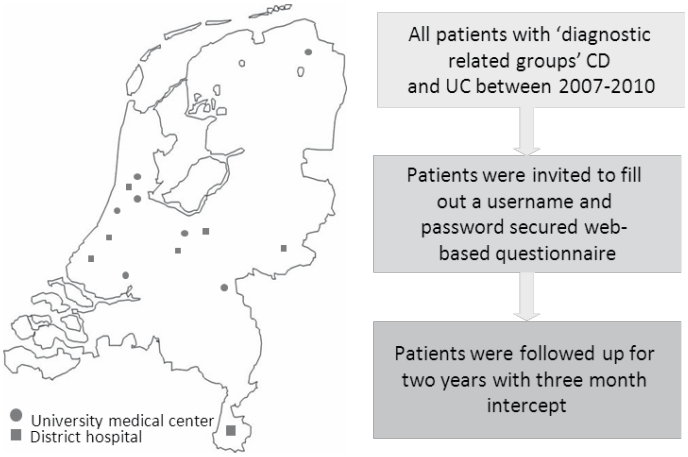

Figure 1. Study design COIN study

Baseline questionnaire included demographic-, clinical- and treatment-related questions, but also health-related quality-of-life data was collected. Follow-up questionnaires included questions regarding resource utilization of healthcare and other resources, patient costs, sick leave from paid and unpaid work, disease activity and health-related quality-of-life.

Thesis outline

In **Chapter 2** we describe the prevalence of work disability in IBD patients. In this study, we compared the work disability rates of IBD patients with the general Dutch population. Furthermore, we assessed the predictive factors for work disability. **Chapter 3** focuses on IBD-related costs and identification of major cost drivers in IBD patients in the anti-TNF era. **Chapter 4** describes the evolution of IBD-related costs over two years of follow-up and identifies predictors of future IBD-related costs. **Chapter 5** reports on the effect of different treatment modalities in UC patients on UC-related costs and quality-of-life. **Chapter 6** describes the analysis of cost-effectiveness of remission-induction with anti-TNF compounds versus corticosteroid-based therapy in CD using two-year follow-up data. In **Chapter 7** the benefit of immunomodulators in anti-TNF therapy is assessed, which is based on a large, nationwide registry database from "Apotheekzorg", including all CD patients receiving adalimumab between 2004-2010. In **Chapter 8** the results are summarized and discussed and suggestions for further research is given. A Dutch summary is presented in **Chapter 9**.

REFERENCES

1 Podolsky DK. Inflammatory bowel disease. *N Engl J Med* 2002;347:417–29.
2 De Groof EJ, Rossen NGM, van Rhijn BD, et al. *Abstr NVGE* 2015.
3 Cosnes J, Gower-Rousseau C, Seksik P, *et al.* Epidemiology and natural history of inflammatory bowel diseases. *Gastroenterology* 2011;140:1785–94.
4 Colombel JF, Sandborn WJ, Reinisch W, *et al.* Infliximab, azathioprine, or combination therapy for Crohn's disease. *N Engl J Med* 2010;362:1383–95.
5 D'Haens G, Baert F, van Assche G, *et al.* Early combined immunosuppression or conventional management in patients with newly diagnosed Crohn's disease: an open randomised trial. *Lancet* 2008;371:660–7.
6 Dignass A, Van Assche G, Lindsay JO, *et al.* The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: Current management. *J Crohns Colitis* 2010;4: 28–62.
7 Stidham RW, Lee TCH, Higgins PDR, *et al.* Systematic review with network meta-analysis: the efficacy of anti-TNF agents for the treatment of Crohn's disease. *Aliment Pharmacol Ther* 2014;39: 1349–62.
8 Dignass A, Lindsay JO, Sturm A, *et al.* Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 2: current management. *J Crohns Colitis* 2012;6: 991–1030.
9 Sandborn WJ, Feagan BG, Marano C, *et al.* Subcutaneous golimumab maintains clinical response in patients with moderate-to-severe ulcerative colitis. *Gastroenterology* 2014;146:96–109.
10 Rutgeerts P, Sandborn WJ, Feagan BG, *et al.* Infliximab for induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2005;353:2462–76.
11 Reinisch W, Sandborn WJ, Hommes DW, *et al.* Adalimumab for induction of clinical remission in moderately to severely active ulcerative colitis: results of a randomised controlled trial. *Gut* 2011; 60:780–7.
12 Bernstein CN, Ng SC, Lakatos PL, *et al.* A review of mortality and surgery in ulcerative colitis: milestones of the seriousness of the disease. *Inflamm Bowel Dis* 2013;19:2001–10.
13 Oresland T, Bemelman WA, Sampietro GM, *et al.* European evidence based consensus on surgery for ulcerative colitis. *J Crohns Colitis* 2015;9:4–25. doi:10.1016/j.crohns.2014.08.012
14 Hakkaart- van Roijen L., Tan S.S., Bouwmans C.A.M. Handleiding voor kostenonderzoek. 2010.
15 Siegel JE, Weinstein MC, Russell LB, *et al.* Recommendations for reporting cost-effectiveness analyses. Panel on Cost-Effectiveness in Health and Medicine. *JAMA* 1996;276:1339–41.
16 Drummond M, Manca A, Sculpher M. Increasing the generalizability of economic evaluations: recommendations for the design, analysis, and reporting of studies. *Int J Technol Assess Health Care* 2005;21:165–71.
17 Tan-Torres Edejer T, Baltussen R, Adam T, *et al. WHO guide to cost-effectiveness analysis*. 2003.
18 McCabe C, Claxton K, Culyer AJ. The NICE cost-effectiveness threshold: What it is and what that means. Pharmacoeconomics 2008;26:733–44.
19 Tang DH, Harrington AR, Lee JK, *et al.* A Systematic Review of Economic Studies on Biological Agents Used to Treat Crohn's Disease. *Inflamm Bowel Dis* 2013:19;2673-94
20 Bassi A, Dodd S, Williamson P, *et al.* Cost of illness of inflammatory bowel disease in the UK: a single centre retrospective study. *Gut* 2004;53:1471–8.
21 Bodger K. Cost of illness of Crohn's disease. *Pharmacoeconomics* 2002;20:639–52.

22 Odes S, Vardi H, Friger M, *et al.* Cost analysis and cost determinants in a European inflammatory bowel disease inception cohort with 10 years of follow-up evaluation. *Gastroenterology* 2006;131: 719–28.

23 Stark R, Konig H-H, Leidl R. Costs of inflammatory bowel disease in Germany. *Pharmacoeconomics* 2006;24:797–814.

24 Juan J, Estiarte R, Colome E, *et al.* Burden of illness of Crohn's disease in Spain. *Dig Liver Dis* 2003; 35:853–61.

25 Blomqvist P, Ekbom A. Inflammatory bowel diseases: health care and costs in Sweden in 1994. *Scand J Gastroenterol* 1997;32:1134–9.

26 Mesterton J, Jonsson L, Almer SHC, *et al.* Resource use and societal costs for Crohn's disease in Sweden. *Inflamm Bowel Dis* 2009;15:1882–90.

27 Gibson TB, Ng E, Ozminkowski RJ, *et al.* The direct and indirect cost burden of Crohn's disease and ulcerative colitis. *J Occup Environ Med* 2008;50:1261–72.

28 Bernklev T, Jahnsen J, Henriksen M, *et al.* Relationship between sick leave, unemployment, disability, and health-related quality of life in patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2006;12:402–12.

29 Boonen A, Dagnelie PC, Feleus 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: 382–9.

30 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;13:1135–40.

31 Longobardi T, Jacobs P, Wu L, *et al.* Work losses related to inflammatory bowel disease in Canada: results from a National Population Health Survey. *Am J Gastroenterol* 2003;98:844–9.

32 Longobardi T, Jacobs P, Bernstein CN. Work losses related to inflammatory bowel disease in the United States: results from the National Health Interview Survey. *Am J Gastroenterol* 2003;98: 1064–72.

33 Gibson TB, Ng E, Ozminkowski RJ, *et al.* The direct and indirect cost burden of Crohn's disease and ulcerative colitis. *J Occup Environ Med* 2008;50:1261–72.

34 Lichtenstein GR, Yan S, Bala M, *et al.* 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;99:91–6.

35 Lichtiger S, Binion DG, Wolf DC, *et al.* The CHOICE trial: Adalimumab demonstrates safety, fistula healing, improved quality of life and increased work productivity in patients with Crohns disease who failed prior infliximab therapy. *Aliment Pharmacol Ther* 2010;32:1228–39.

36 Feagan BG, Panaccione R, Sandborn WJ, *et al.* Effects of Adalimumab Therapy on Incidence of Hospitalization and Surgery in Crohn's Disease: Results From the CHARM Study. *Gastroenterology* 2008;135:1493–9.

37 Peyrin-Biroulet L, Oussalah A, Williet N, *et al.* Impact of azathioprine and tumour necrosis factor antagonists on the need for surgery in newly diagnosed Crohn's disease. *Gut* 2011;60:930–6.

38 Feagan BG, Sandborn WJ, Wolf DC, *et al.* Randomised clinical trial: Improvement in health outcomes with certolizumab pegol in patients with active Crohn's disease with prior loss of response to infliximab. *Aliment Pharmacol Ther* 2011;33:541–50.

39 Feagan BG, Reilly MC, Gerlier L, *et al.* Clinical trial: The effects of certolizumab pegol therapy on work productivity in patients with moderate-to-severe Crohn's disease in the precise 2 study. *Aliment Pharmacol Ther* 2010;31:1276–85.

Chapter 2

Risk factors of work disability in patients with inflammatory bowel disease – a Dutch nationwide web-based survey

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ABSTRACT

Introduction:

Inflammatory bowel disease (IBD) is associated with high costs to society. Few data on the impact of IBD on work disability and potential predictive factors are available. To assess the prevalence of and predictive factors for work disability in Crohn's disease (CD) and ulcerative colitis (UC).

Methods:

A web-based questionnaire was sent out in seven university hospitals and seven general hospitals in the Netherlands. Initially, 3,050 adult IBD patients were included in this prospective, nationwide cohort study, whereof 2,629 patients within the working-age (18-64 years). We used the baseline questionnaire to assess the prevalence rates of work disability in CD and UC patients within working-age. Prevalence rates were compared with the Dutch background population using age- and sex-matched data obtained from Statistics Netherlands. Multivariable logistic regression analyses were performed to identify independent demographic- and disease-specific risk factors for work disability.

Results:

In CD, 18.3% of patients was fully disabled and 8.8% partially disabled, compared to 9.5% and 5.4% in UC patients ($p<0.01$), respectively. Compared to Dutch controls, the prevalence was significantly higher, especially in CD patients. Higher age, low education, depression, chronic back pain, joint manifestations and typical disease-related risk factors such as penetrating disease course and surgery in the past were all found to be associated with work disability.

Conclusion:

We report high work disability rates in a large sample of IBD patients in the Netherlands. CD patients suffer more frequently from work disability than UC patients. A combination of demographic and disease-related factors is predictive of work disability.

INTRODUCTION

Inflammatory bowel diseases (IBD) are chronic intestinal disorders, comprising Crohn's disease (CD) and ulcerative colitis (UC). IBD affects 2.5–3 million people in Europe, many of whom develop disease as working-age adults.[1] An important consequence is therefore a reduced ability to work, which can be decisive for future life expectations for patients themselves.(2-10) Work disability is associated with high costs to society.[7,9,11-13] The prevention or postponement of work disability should therefore be an important goal in the treatment of IBD patients.

The disability rates in previous reported studies vary considerably and range between 15-25% in CD and 5-13% in UC.[2-9,12] This is undoubtedly related to different patient populations, geographical differences and employed tools for the measurement of disability. Over the last decade, treatment goals of IBD have evolved from the induction and maintenance of clinical remission to the prevention of structural damage and long-term (work) disability with expanding use and early introduction of anti-tumour necrosis (anti-TNF) therapy and immunomodulators. Aggressive strategies seem to result in a substantially improved quality-of-life,[14] a reduction of hospitalisation and surgery,[15,16] and might benefit work productivity.[17,18] Knowledge on predictive factors for work disability could improve prevention strategies, increase quality-of-life and reduce future productivity losses.

To date, few studies have attempted to explore the predictive factors for work disability in IBD. Most of these were underpowered,[2,6] or were conducted in highly selected populations,[5,8]. In the present study we aimed to 1) assess the prevalence of work disability rate in a large nationwide cohort of IBD patients, 2) compare the disability rates with the general Dutch population and 3) determine predictive factors for work disability.

METHODS

Study design

Between October 2010 and October 2011 we invited by letter all identified IBD patients aged 18 years or older from seven university hospitals and seven general hospitals (n=9,550) to participate in the COIN study. Identification was based on the Diagnosis Treatment Combinations (DTCs). We designed a secure web-based questionnaire and participants were invited to enter a username and password-secured and firewall-protected website to fill-out questionnaires. All patients were followed-up for 2 years at

3 month intervals. In total, 3,050 patients were initially included in this cohort. Here, we report on the results from the baseline questionnaire. For the current analysis, we only included patients within working-age, i.e. adults between 18 and 64 years. The cohort organisation, patient diagnostic criteria, the representativeness and validity (including a non-responder study) of the study cohort have been described in detail elsewhere.[13]

Outcome measure: work disability and predictive factors

We used the same definition for work disability as employed by the Dutch social security system.[19] The self-reported work disability is from 'all causes' and not exclusively attributable to IBD. There are two types of disability benefits; the first is for patients who are declared to be fully (>80%) disabled after assessment. These patients are entitled to an income-replacing disability benefit. The second type of benefit is for patients who are declared to be more than 35% disabled, but not fully and permanently after assessment. These partially disabled patients are entitled an income supplement benefit if their disability force them to switch to a less-well paid job. To compare the work disability rates of

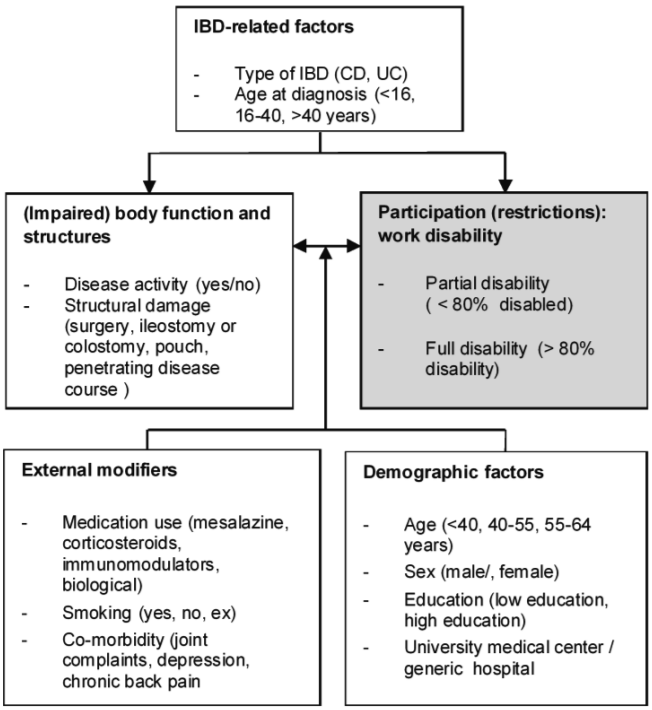

Figure 1. Work disability according to the International Classification of Functioning, Disability and Health (ICF)[17]

the IBD patients with the Dutch background population, we retrieved data on age- and sex-matched work disability rates of the Dutch population from Statistics Netherlands. [20] Reference data from the Dutch population were from 2011. We compared disability by sex, by age groups, and separately for university hospitals and general hospitals. We used the International Classification of Functioning Disability and Health (ICF) to explain work disability and to classify possible predictive factors for work disability.[21] Figure 1 clarifies the classification and classified all variables from the baseline questionnaire into demographic factors, disease related factors, impaired body function and structures, and external modifiers.

Statistical considerations

We analysed our data using SPSS version 18.0. We used descriptive statistics to characterize patients with CD and UC. Differences among groups were assessed by Student t-test for continuous variables and χ^2 for dichotomous variables, Fisher's exact test was used where appropriate. To compare the prevalence of work disability in our study cohort with the Dutch background population, we used the Student t-test. In order to determine factors associated with work disability, we performed univariable logistic regression analysis with demographic and disease characteristics. Demographic and disease specific characteristics that were associated ($p<0.10$) with chronic disability following univariable analysis were included in the multivariable logistic regression analyses to identify independent risk factors for work disability.

Ethical statement

The study was centrally approved by the medical ethics committee of the University Medical Center Utrecht.

RESULTS

Patient population

Figure 2. shows the study flowchart. In total, 2,282 patients were within working-age, of whom 1,373 with CD and 909 with UC. Table 1 presents the demographics and disease characteristics of the CD and UC population between 18 and 64 years old.

There were more females in the CD group than in the UC group (65.7% and 56.2%, respectively). The mean age of CD and UC patients was 44.1 (SD 11.8) and 46.1 (SD 11.4) years. Of all CD patients, 906 (66.0%) were cared for in university hospitals versus 510 (56.1%) of all UC patients. The remaining patients were treated in general hospitals. In total, 724 (52.7%) CD patients reported a penetrating disease course. Of all CD patients,

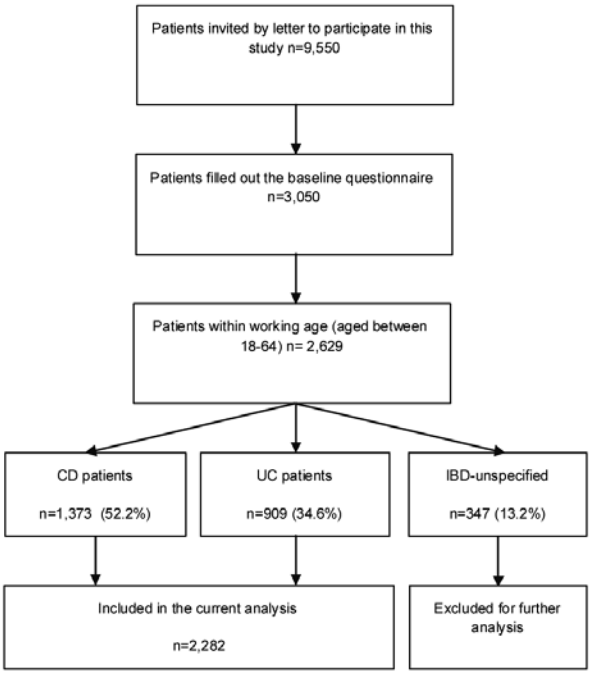

Figure 2. Study flowchart

Table 1. Demographic and disease characteristics of study population within the labor force (18-65 years)

	CD n=1,373	UC n=909
Male sex (%)	471 (34.3)	416 (45.8)
Age - years (± SD)	44.1 (11.8)	46.1 (11.4)
Smoking (%)		
Current	307 (22.4)	86 (9.5)
Never	691 (50.3)	533 (58.6)
Ex smoker	375 (27.3)	290 (31.9)
Education (%)		
Low education	868 (65.2)	519 (57.1)
Age at diagnosis - years (±SD)	27.8 (10.7)	32.0 (11.6)
Disease duration - median (IQR)	16.4 (10.8)	14.1 (9.9)
Disease localization (%)		
Large bowel	379 (27.6)	909 (100)
Small bowel	261 (19.0)	n.a.
Both small and large bowel	691 (50.3)	n.a.
Unknown	42 (3.1)	n.a.
Penetrating disease (%)	724 (52.7)	n.a.

Table 1. Demographic and disease characteristics of study population within the labor force (18-65 years) (continued)

	CD n=1,373	UC n=909
Disease in remission (%)	1166 (85.0)	759 (83.5)
Stoma (%)	161 (11.7)	51 (5.6)
Pouch (%)	22 (1.6)	86 (9.5)
Abdominal surgery (%)	734 (53.5)	164 (18.0)
Medication use - ever (%)		
5-ASA	986 (71.8)	745 (82.0)
Corticosteroids	1,063 (77.4)	551 (60.6)
Immunomodulators	865 (63)	327 (36.0)
Biological therapy	457 (33.3)	87 (9.6)
Joint complaints (%)	301 (21.9)	158 (17.4)
Chronic back pain (%)	143 (10.4)	86 (9.5)
Depression (%)	141 (10.3)	90 (9.9)
Ùniversity medical center - now (%)	906 (66)	510 (56.1)

734 (53.5%) underwent abdominal surgery previously, as compared to 164 (18.0%) in UC patients. Of the CD patients, 457 (33.3%) received biological therapy in the past as compared to 87 (9.6%) of the UC patients.

Prevalence of work disability

In total, 728 (53.0%) CD and 605 (66.6%) UC patients were currently employed ($p<0.01$). In the CD group, 251 (18.3%) patients were fully disabled as compared to 86 (9.5%) of the UC patients ($p<0.01$). Partial disability was encountered in 121 (8.8%) of CD patients and 49 (5.4%) of UC patients ($p<0.01$). Among partially disabled patients, the mean work hours per week were 20 (SD 10) in CD patients and 22 (SD 9) in UC patients. This was significantly lower as compared to fully employed CD and UC patients, 32 (SD 10) and 33 (SD 9) hours per week respectively ($p<0.01$), which is in line with to the average work hours/week (32 hours/week) for the Dutch background population aged 15 to 64 years. (16)

Comparison with the Dutch background population

Figure 3.A and figure 3.B show work disability in CD, UC and the Dutch general population, stratified by age and sex. Overall work disability rates were significantly higher in both female and male CD patients than in the Dutch general population ($p<0.01$). The highest prevalence rates were found among female CD patients. Unlike CD patients, UC patients treated in general hospitals did not have higher work disability rates than age- and sex-matched controls, whereas UC patients treated in university hospitals did have higher work disability rates than age- and sex-matched controls.

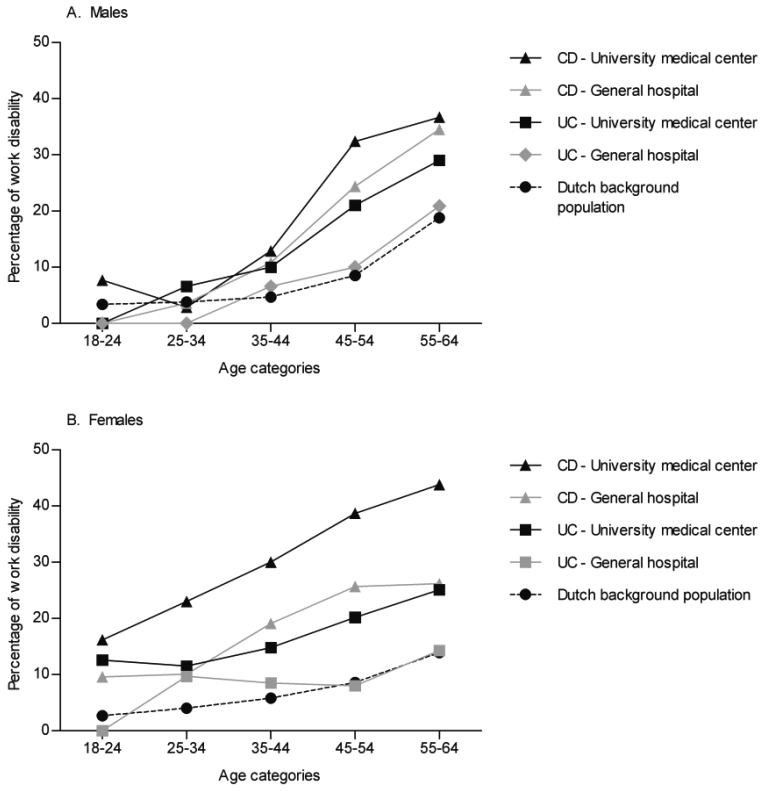

Figure 3. Work disability in patients aged between 18-65 years with Crohn's Disease (CD) and ulcerative colitis (UC) compared to the general population in the Netherlands

Predictive factors of work disability

Non-adjusted and adjusted odds ratios for work disability in CD and UC are presented in Table 2 and Table 3, respectively. In both UC and CD higher age and lower education were associated with work disability. Females with CD, but not UC were prone to disability as well. Impaired body function (i.e. self-reported disease activity) and structural body functions (i.e. penetrating disease course and surgery in the past) were associated with work disability in CD. In UC patients, only abdominal surgery in the past was an independent predictor for work disability. Additional external modifiers such as co-morbidities (joint manifestations, chronic back pain and depression) were strong risk factors in both groups. Previous use of corticosteroids was an independent predictor for work disability in UC, while medication use in CD patients was not a significant predictive factor.

Table 2. Univariate and multivariate analysis of factors associated with work disability in employed or disabled Crohn's disease (CD) patients aged 18 to 65 years

	CD patients			
	Disabled n= 372	**Employed n= 728**	**Unadj. OR (95% CI)**	**Adj. OR (95% CI)**
Demographic factors				
Female sex (%)	258 (69.4)	285 (39.1)	1.46 (1.12-1.89)	1.55 (1.13-2.13)
Age - years (%)				
< 40	84 (22.6)	326 (44.8)	1.00	1.00
40-55	171 (46.0)	304 (41.8)	2.18 (1.61-2.96)	1.48 (1.01-2.19)
> 55	117 (31.5)	98 (13.5)	4.87 (3.42-6.94)	3.44 (2.15-5.51)
Low education (%)	301 (78.6)	381 (52.0)	3.38 (2.55-4.49)	2.63 (1.90-3.65)
Disease related factors				
Age at diagnosis - years (%)				
< 16	35 (9.1)	64 (8.7)	1.00	-
16-40	279 (72.8)	568 (77.6)	0.90 (0.58-1.39)	
> 40	69 (18.0)	100 (13.7)	1.26 (0.76-2.11)	
Disease duration - years (%)				
<10	71 (18.8)	290 (39.8)	1.00	1.00
10-20	130 (34.9)	235 (32.2)	2.32 (1.66-3.24)	1.37 (0.92-2.04)
> 20	172 (46.2)	203 (27.9)	3.61 (2.60-5.01)	1.52 (0.97-2.37)
Body function and structures				
Self reported flare (%)	80 (21.5)	89 (12.2)	1.94 (1.39-2.70)	1.60 (1.07-2.39)
Penetrating disease (%)	242 (65.1)	347 (47.7)	2.11 (1.63-2.73)	1.47 (0.94-2.30)
Stoma (%)	71 (19.1)	60 (8.2)	2.77 (1.93-3.99)	1.55 (1.13-2.13)
Pouch (%)	7 (1.9)	12 (1.6)	1.18 (0.49-2.87)	-
Abdominal surgery (%)	262 (70.4)	344 (47.3)	2.65 (2.04-3.44)	1.57 (1.12-2.19)
External modifiers				
Medication use – ever (%)				
5-ASA	283 (76.1)	513 (70.5)	1.30 (0.98-1.72)	-
Corticosteroids	318 (85.5)	541 (74.3)	1.95 (1.41-2.70)	1.37 (0.90-2.09)
Immunomodulators	259 (69.6)	445 (61.1)	1.46 (1.12-1.90)	1.09 (0.75-1.58)
Biological therapy	156 (41.9)	215 (29.5)	1.69 (1.30-2.19)	1.40 (0.99-1.97)
Joint complaints (%)	147 (39.5)	94 (12.9)	4.41 (3.28-5.94)	2.60 (1.84-3.69)
Chronic back pain (%)	76 (20.4)	728 (6.5)	3.85 (2.62-5.65)	2.47 (1.55-3.94)
Depression (%)	62 (16.7)	47 (6.5)	2.82 (1.88-4.21)	1.92 (1.19-3.10)
University medical center (%)	279 (75.0)	447 (61.4)	1.87 (1.42-2.47)	1.68 (1.21-2.35)
Smoking (%)				
Never	141 (37.9)	401 (55.1)	1.00	1.00
Current	104 (28.0)	141 (19.4)	2.08 (1.51-2.85)	1.34 (0.91-1.96)
Ex-smoker	127 (34.1)	186 (25.5)	1.98 (1.48-2.65)	1.36 (0.96-1.93)

Table 3. Univariate and multivariate analysis of factors associated with work disability in ulcerative colitis (UC)

	UC patients			
	Disabled n= 135	**Employed n=605**	**Unadj. OR (95% CI)**	**Adj. OR (95% CI)**
Demographic factors				
Female sex (%)	69 (51.1)	306 (50.6)	0.97 (0.67-1.39)	1.08 (0.70-1.66)
Age - years (%)				
< 40	23 (17.0)	203 (33.6)	1.00	1.00
40-55	59 (43.7)	281 (46.4)	1.85 (1.11-3.10)	1.41 (0.78-2.53)
> 55	53 (39.3)	121 (20.0)	4.41 (2.60-7.50)	4.31 (2.24-8.30)
Low education (%)	99 (69.2)	304 (50.2)	2.24 (1.52-3.30)	1.77 (1.14-2.76)
Disease related factors				
Age at diagnosis - years (%)				
< 16	10 (7.0)	36 (6.0)	1.00	-
16-40	84 (58.7)	436 (72.1)	0.69 (0.33-1.45)	
> 40	49 (34.3)	133 (22.0)	1.33 (0.61-2.87)	
Disease duration - years (%)				
<10	34 (25.2)	269 (44.5)	1.00	1.00
10-20	55 (40.7)	183 (30.2)	2.35 (1.50-3.70)	1.85 (1.11-3.06)
> 20	46 (34.1)	153 (25.3)	2.24 (1.40-3.60)	1.02 (0.58-1.80)
Body function and structures				
Self reported flare (%)	21 (15.6)	103 (17.0)	0.89 (0.54-1.47)	-
Stoma (%)	14 (10.4)	26 (4.3)	2.81 (1.47-5.39)	1.03 (0.45-2.33)
Pouch (%)	24 (17.8)	49 (8.1)	2.53 (1.51-4.23)	0.92 (0.45-1.88)
Abdominal surgery (%)	262 (70.4)	344 (47.3)	3.71 (2.46-5.60)	3.62 (2.01-6.52)
External modifiers				
Medication use – ever (%)				
5-ASA	109 (80.7)	501 (82.8)	0.89 (0.56-1.42)	-
Corticosteroids	100 (74.1)	349 (57.7)	2.26 (1.49-3.41)	2.43 (1.49-3.96)
Immunomodulators	51 (37.8)	210 (34.7)	1.17 (0.80-1.70)	-
Biological therapy	15 (11.1)	53 (8.8)	1.22 (0.67-2.24)	-
Joint complaints	45 (33.3)	71 (11.7)	4.05 (2.65-6.19)	2.27 (1.36-3.78)
Chronic back pain	23 (17.0)	42 (6.9)	2.71 (1.58-4.64)	2.51 (1.31-4.83)
Depression	27 (20.0)	45 (7.4)	3.04 (1.82-5.07)	2.25 (1.23-4.11)
University medical center (%)	97 (71.9)	326 (53.9)	2.00 (1.35-2.30)	1.37 (0.86-2.16)
Smoking (%)				
Never	72 (53.3)	359 (59.3)	1.00	1.00
Current	20 (14.8)	57 (9.4)	1.77 (1.01-3.09)	1.32 (0.68-2.55)
Ex-smoker	43 (31.9)	189 (31.2)	1.19 (0.80-1.79)	0.81 (0.51-1.30)

DISCUSSION

In this large, nationwide study, we report high work disability rates in patients with IBD. The overall proportion of individuals with CD or UC with full work disability was 18.3% and 9.5%, respectively. Compared to the general Dutch population, the work disability rates were the highest among CD patients, especially those treated in university medical centers. UC patients cared for in general hospitals did not differ from the general Dutch population with respect to reported work disability.

Rates of IBD-related work disability in literature range widely between 5% and 25% percent.[2-9] The two largest studies to date reported high disability rates in line with our data,[4,5] although the former included IBD patients of younger age with a relative short disease duration of 7 years (SD 3), and the latter studied a highly selected group with CD patients with moderate to severe disease activity enrolled in a clinical trial. Lower disability rates of 15% in CD patients and 5% in UC patients have been reported by Bernklev et al.[3] These results were based on data, generated from 5 year follow-up visits of newly diagnosed patients. Comparison of work disability rates between different countries is hampered by differences in socioeconomic and political factors.

We found higher disability rates in our IBD cohort as compared to the Dutch general population, in line with a previously published Dutch population-based study.[4] A Norwegian inception cohort study, however, found higher disability rates for patients with CD, but not for patients with UC.[3] An explanation for this discrepancy could be the high prevalence of work disability among the general Norwegian population, being 8.8% (as compared to 6.6% in Dutch controls).

The large size of our cohort of IBD patients enabled us to study a large panel of possible predictive factors for work disability. In order to explain work disability as a multifactorial problem, we classified predictive variables according to the International Classification of Functioning Disability and Health into demographic factors, IBD-related factors, impaired body function or structural damage, and external modifiers. We found that in patients with CD, demographic factors such as female gender, increasing age and low education are associated with work disability. The analysis of patients with UC offered a similar picture, except that female gender was not found to be a predictive factor. We did not find consistent evidence that disease duration predicted work disability. It is possible that disease activity hampers work disability most profoundly in early disease, whereas structural damage and IBD-related complications may become more important in long-term disease.

Most of the factors related to impaired body functions or body structures were associated with increased risk of work disability. We found abdominal surgery in the past to be an independent predictor for work disability in both CD and UC. This has been reported in previous studies as well, with a 1.6 to 7.1 time higher risk for work disability [2,4,5]. Furthermore, we found an association between penetrating disease course and work disability. Previous studies showed a comparable cumulative risk of perianal involvement in CD of 50%, which is in line with our findings.[22,23]. One potential explanation for the increased risk of work disability is the poor prognosis of CD patients with fistulas. Perianal fistulas are associated with high morbidity, local pain and discomfort, frequent surgical drainage with associated risks of complications, and therefore have a negative impact on quality of life and subsequently work productivity.[22,23] These findings underscore the importance of preventing structural damage. Whether this can be achieved by adopting an accelerated step-up or early top-down approach remains to be proven. [24,25]

In multivariate analysis, CD patients with joint complaints have a 2.6-fold increased risk of work disability as compared to a 2.3-fold increased risk in UC patients. These musculoskeletal disorders are known to be a primary cause of disability in the general working population. Joint manifestations are reported in 16 to 33% of all IBD patients, which is in line with the rates found in our study.[26] Furthermore, axial arthropathies are common in IBD and can result in chronic back pain.[27] Almost 10% of our study population reported chronic back pain (IBD related or non-IBD related) which was associated with a 2.5-fold increased risk of work disability in CD patients and 2.7-fold increased risk in UC patients.

To our knowledge, this is the largest study to date, examining the prevalence and risk factors for work disability in IBD patients. The inclusion of patient from both university and general hospitals throughout the Netherlands ascertained a good case mix. In order to enrol a large number of patients, we opted for the present web-based design. An inherent limitation of such a strategy is sampling bias. We assessed the representativeness of our study by performing a non-responder study. Significant differences in demographic and disease characteristics between responders and non-responders were not identified.[13] In addition, data on disease characteristics and employment status were self-reported, possibly introducing bias as well. Yet, previous studies showed that the accuracy of responses to health-related questionnaires from patients with IBD is as high as 95%.[28]

In an era of increasing financial pressure on every stakeholder in the society, it is imperative to maximize the value of healthcare costs by also demonstrating a return on invest-

ment through improvement in work productivity. Collaboration of medical specialists and occupation physicians might prevent future work disability or job loss and decrease prevalent work disability. This study shows that disease activity, and structural damage due to surgery and penetrating disease is associated with loss of productivity. We need long-term prospective studies to determine whether or not improving the management of IBD will result in preventing structural damage, improvements in work productivity and a reduction in the economic burden of the disease.

REFERENCES

1. Burisch J, Jess T, Martinato M, *et al.* The burden of inflammatory bowel disease in Europe. *J.Crohns. Colitis.* 2013; 7: 322-337.
2. Ananthakrishnan AN, Weber LR, Knox JF, *et al. Am.J.Gastroenterol.* 2008; 103: 154-161.
3. Bernklev T, Jahnsen J, Henriksen M, *et al.* Relationship between sick leave, unemployment, disability, and health-related quality of life in patients with inflammatory bowel disease. *Inflamm. Bowel.Dis.* 2006; 12: 402-412.
4. Boonen A, Dagnelie PC, Feleus 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.
5. Feagan BG, Bala M, Yan S, *et al.* Unemployment and disability in patients with moderately to severely active Crohn's disease. *J.Clin.Gastroenterol.* 2005; 39: 390-395.
6. Hoivik ML, Moum B, Solberg IC, *et al.* Work disability in inflammatory bowel disease patients 10 years after disease onset: results from the IBSEN Study. *Gut.* 2013;62:368-75.
7. Juan J, Estiarte R, Colome E, *et al.* Burden of illness of Crohn's disease in Spain. *Dig.Liver Dis.* 2003; 35: 853-861.
8. 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.
9. Stark R, Konig HH, Leidl R. Costs of inflammatory bowel disease in Germany. *Pharmacoeconomics.* 2006; 24: 797-814.
10. Sulz MC, Siebert U, Arvandi M, *et al.* Predictors for hospitalization and outpatient visits in patients with inflammatory bowel disease: results from the Swiss Inflammatory Bowel Disease Cohort Study. *Eur.J.Gastroenterol.Hepatol.* 2013; 25: 790-797.
11. Gibson TB, Ng E, Ozminkowski RJ, *et al.* The direct and indirect cost burden of Crohn's disease and ulcerative colitis. *J.Occup.Environ.Med.* 2008; 50: 1261-1272.
12. Mesterton J, Jonsson L, Almer SH, *et al.* Resource use and societal costs for Crohn's disease in Sweden. *Inflamm.Bowel.Dis.* 2009; 15: 1882-1890.
13. van der Valk ME, Mangen MJ, Leenders M, *et al.* Healthcare costs of inflammatory bowel disease have shifted from hospitalisation and surgery towards anti-TNFalpha therapy: results from the COIN study. *Gut* 2012.
14. Colombel JF, Sandborn WJ, Reinisch W, *et al.* Infliximab, azathioprine, or combination therapy for Crohn's disease. *N.Engl.J.Med.* 2010; 362: 1383-1395.
15. Feagan BG, Panaccione R, Sandborn WJ, *et al.* Effects of adalimumab therapy on incidence of hospitalization and surgery in Crohn's disease: results from the CHARM study. *Gastroenterology.* 2008; 135: 1493-1499.
16. Lichtenstein GR, Yan S, Bala M, *et al.* 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.
17. Feagan BG, Reilly MC, Gerlier L, *et al. Aliment.Pharmacol.Ther.* 2010; 31: 1276-1285.
18. Lichtiger S, Binion DG, Wolf DC, *et al.* The CHOICE trial: adalimumab demonstrates safety, fistula healing, improved quality of life and increased work productivity in patients with Crohn's disease who failed prior infliximab therapy. *Aliment.Pharmacol.Ther.* 2010; 32: 1228-1239.
19. www.government.nl**.** 2013.
20. Statistics Netherland. Available at www.cbs.nl. 2011 . 2011.

21. World Health Organization (WHO). International Classification of Functioning, Disability and Health (ICF). Available at http://www.who.int/classifications/icf/wha-en.pdf 2001. 2012.
22. Schwartz DA, Pemberton JH, Sandborn WJ. Diagnosis and treatment of perianal fistulas in Crohn disease. *Ann.Intern.Med.* 2001;135:906-18.
23. Schwartz DA, Loftus EV, Jr., Tremaine WJ, *et al.* The natural history of fistulizing Crohn's disease in Olmsted County, Minnesota. *Gastroenterology.* 2002; 122: 875-880.
24. D'Haens GR. Top-down therapy for IBD: rationale and requisite evidence. *Nat.Rev.Gastroenterol. Hepatol.* 2010; 7: 86-92.
25. Oldenburg B, Hommes D. Biological therapies in inflammatory bowel disease: top-down or bottom-up? *Curr.Opin.Gastroenterol.* 2007; 23: 395-399.
26. Orchard TR, Wordsworth BP, Jewell DP. Peripheral arthropathies in inflammatory bowel disease: their articular distribution and natural history. *Gut.* 1998; 42: 387-391.
27. Brakenhoff LK, van der Heijde DM, Hommes DW. IBD and arthropathies: a practical approach to its diagnosis and management. *Gut* 2011; 60: 1426-1435.
28. Bernstein CN, Blanchard JF, Rawsthorne P, *et al.* Epidemiology of Crohn's disease and ulcerative colitis in a central Canadian province: a population-based study. *Am.J.Epidemiol.* 1999; 149: 916-924.

Chapter 3

Healthcare costs of inflammatory bowel disease have shifted from hospitalisation and surgery towards anti-TNF therapy – results from the COIN study

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ABSTRACT

Objective:

The introduction of anti-tumour necrosis factor-α (anti-TNF) therapy might impact healthcare expenditures, but there are limited data regarding the costs of IBD following the introduction of these drugs. We aimed to assess the healthcare costs and productivity losses in a large cohort of IBD patients.

Design:

Crohn's disease (CD) and ulcerative colitis (UC) patients from seven university hospitals and seven general hospitals were invited to fill-out a web-based questionnaire. Cost items were derived from a three month follow-up questionnaire and categorised in outpatient clinic, diagnostics, medication, surgery and hospitalisation. Productivity losses included sick leave of paid and unpaid work. Costs were expressed as mean three-month costs per patients with a 95% confidence interval (CI) obtained using non-parametric bootstrapping.

Results:

A total of 1,315 CD patients and 937 UC patients were included. Healthcare costs were almost three times higher in CD as compared to UC, €1,625 (95% CI €1,476-€1,775) versus €595 (95% CI €505-€685), respectively ($p<0.01$). Anti-TNF use was the main costs driver, accounting for 64% and 31% of the total cost in CD and UC. Hospitalisation and surgery together accounted for 19% and <1% of the healthcare costs in CD and 23% and 1% in UC, respectively. Productivity losses accounted for 16% and 39% of the total costs in CD and UC.

Conclusion:

We showed that healthcare costs are mainly driven by medication costs, most importantly by anti-TNF therapy. Hospitalisation and surgery accounted only for a minor part of the healthcare costs.

INTRODUCTION

Inflammatory bowel diseases (IBD), comprising Crohn's disease (CD) and ulcerative colitis (UC), are characterised by a chronic relapsing intestinal inflammation that may lead to severe complications and disability. As there is no curative treatment, most patients need life-long drug treatment and many will face surgery.[1] Consequently, IBD is associated with a high economic burden to society, in which hospitalisation and surgery account for more than half of the healthcare costs.[2-4] Moreover, due to its early onset and chronic character, IBD profoundly affects work productivity with productivity losses resulting from sick leave and work disability amounting to almost 50% of the total costs.[2,3,5-7]

In the current era of escalating healthcare costs and growing constraints on healthcare budgets, there is a need for more accurate information regarding costs of chronic diseases. Most cost-of-illness studies in IBD have been performed before the introduction of the highly effective, but expensive biological therapies and can therefore be considered outdated.[2-4,7] It has been suggested that costs of anti-TNF therapy are being offset by a reduction in surgery and hospitalisation rates on the one hand,[8-11] and increased work productivity on the other,[12-14] but accurate data on total costs in Europe are presently lacking.

To address these issues, we recently initiated the 'Costs Of Inflammatory bowel disease in the Netherlands' or 'COIN' study in order to 1) estimate the total healthcare and productivity losses in a large cohort of IBD patient attending both university medical centres and general hospitals; and 2) identify the main costs drivers.

METHODS

Patient population

In the Netherlands, most patients with an established diagnosis of IBD and need for medical or surgical therapy are treated in university hospitals or general hospitals. We identified Crohn's disease (CD) patients and ulcerative colitis (UC) patients using the Diagnosis Treatment Combinations (DTCs) for respectively CD and UC. DTCs are based on the International Classification of Disease, Ninth Revision.[15,16] DTCs were introduced in 2005 and can be considered the Dutch version of the Diagnosis Related Groups (DRGs) as used in other countries, e.g. United States. DTCs form the basis to pay inpatient services provided by hospitals and physicians. DTCs have been used to identify IBD patients in the Netherlands previously and have been found to be useful and reliable in this respect.

[17,18] All patients from seven university medical centres and seven general hospitals aged 18 years or older were eligible for participation. The study was centrally approved by the ethics committee of the University Medical Centre Utrecht.

Web-based questionnaire

We developed a secure web-based questionnaire and participants were provided with a unique username and password combination. Patients were invited to enter the username and password-secured and firewall-protected website and were asked to fill out the questionnaires. After completing the baseline questionnaire, patients received an invitation to fill out the three-month follow-up questionnaire and an e-mail reminder two weeks after the initial invitation.

Demographic and disease characteristics

The baseline questionnaire included questions on demographics (gender, age, smoking habits and education) and disease characteristics. Education was categorised as low education (no education, primary education, secondary education and technical or professional school) or high education (higher vocational education and university). Disease characteristics included type of IBD, year of diagnosis, disease localisation, penetrating disease course, abdominal surgery in the past, and self-reported disease activity. Patients in whom medical treatment was initiated or changed or who received IBD related surgery were considered to have active disease.

Healthcare utilisation

We obtained information on resource utilisation from the three-month follow-up questionnaire. IBD-related resource utilisation within healthcare was categorised under the following subgroups: 1) outpatient clinic, including the number of outpatient physician consultations (e.g. gastroenterologist, internist, surgeon, and rheumatologist), visits to IBD or stoma nurses and dieticians, visits at the emergency department and visits to the general practitioner; 2) diagnostic procedures including number and type of endoscopies, radiological procedures and blood tests; 3) medication use, which included all IBD specific drug use such as mesalazine, corticosteroids, immunomodulators and anti-TNF therapies. The mean number of daily doses over the three-month time frame was estimated. We assumed that all maintenance therapies were used without interruption over the study period; 4) hospitalisation, defined as the number of days hospitalised, including number of days at the intensive care unit; 5) type of IBD related surgery.

Productivity losses

Productivity losses (also referred to as 'indirect (non-healthcare) costs') refer to the costs associated with lost or impaired ability to work of paid and unpaid (voluntary) work. To

assess productivity losses we used sick leave (absenteeism) of patients and their caregivers as outcome measurement. Patients were asked which of the following situations applied best to their situation: being employed, fully or partially disabled, retired or early retired, homemaker, student or unemployed. Employed patients or partially disabled patients with a paid job indicated the number of work hours and number of workdays per week. Patients were asked to report the number of sick leave days from both paid and unpaid (voluntary work) work within the previous three months. Additionally patients were asked to report whether caregivers were absent from paid work in order to take care of them, and for how many days. For caregivers we assumed an average work day of 6.28 hours, based on data from the Statistics Netherlands.[19]

Out-of-pocket costs

Patients were asked to report IBD-related out-of-pocket costs within the previous three months. These expenditures included patient's deductibles for healthcare insurance, travel costs and over the counter drug use (e.g. antidiarrhoeals, analgesics and vitamins).

Calculation of costs

We performed a cost-of-illness study from a societal perspective. For each patient, costs were calculated by multiplying units of resource utilisation as reported by the patients by their unit costs. Reference prices are listed in appendix 1. Costs are expressed per three months in 2011 Euros, using Dutch consumer price indices where appropriate. Discounting was not applied as all costs were made within the same year. As practice patterns and the patient case mix may vary between university medical centres and general hospitals, we compared healthcare costs between university and general hospitals. The number of days patients and caregivers were absent from paid or unpaid work due to sick leave over three months could not exceed 65 days (weekends days were excluded) and were valued using age- and sex-specific productivity losses.[20] Out-of-pocket costs were calculated according to patient specifications, and where necessary update to 2011 euros. In order to provide decision makers with explicit information, and allowing health-economic analyses from different perspectives (i.e. societal versus healthcare-payer perspective), costs are presented according to the classification of Drummond et al. i.e. healthcare costs, productivity losses and patient costs.[21]

Non responders

To control equality between the study population (responders) and the patients who did not respond (non-responders), we performed a non-responder study. All non-responders from one participating centre (n=685) were sampled to assess the demographic (age, gender) and disease characteristics (disease duration, penetrating disease course and abdominal surgery in the past) of a subset of the non-responders. The demographic

and disease characteristics between the responders and the non-responders were compared.

Statistical analysis

Data analysis was performed using SPSS version 18.0. Descriptive statistics were used to characterise patients with CD and UC. We reported means with a standard deviation (SD) and medians with an interquartile range (IQR). Comparisons between CD and UC patients were analysed with Student t-test for continuous variables and χ^2 for dichotomous variables. To compare disease duration between CD and UC patients, the Mann-Whitney U test was used. To increase transparency, all unit costs are stated in appendix 1 and frequency tables of resource utilisation are displayed. Despite the skewed nature of cost data, we reported mean patient costs, as overall total costs - which matters most - then can be calculated. Costs were expressed as mean costs with 95% confidence intervals (CI) estimated using non parametric bootstrap sampling. To compare costs between the general hospitals and university medical centres, the Mann-Whitney U test was used. To identify independent predictors of high healthcare costs we included demographic and disease-specific characteristics associated with top 10% high healthcare in a multivariable logistic regression analysis.

RESULTS

Study population

Figure 1 shows the study flowchart. In total 2,252 patients were included in the cost analysis. Table 1 present the demographic and disease characteristics of the CD (n=1,315) and UC (n=937) study population. Distinction was made based on self-reported type of IBD. Patients who did not know their type of IBD, reported UC with disease localisation in the ileum or reported UC with fistulas were excluded from the cost analysis and categorised as IBD-unspecified (n=324, 13%). Appendix 2. shows data on gender, age, disease duration, penetrating disease course and previous abdominal surgery in both the responders (CD: n=1315 and UC: n=937) and a subset of non-responders (CD: n=405 and UC: n=247). There were no relevant statistical significant differences between these groups.

Healthcare costs

The mean healthcare costs per CD patients per three-months were €1,652 (95% CI €1,476-€1,775). With a mean of €1,145 (95% CI €1,042-€1,249), medication costs were the major cost driver of healthcare costs (71% of healthcare costs). Of the CD patients, 297 (23%) were on anti-TNF therapy, accounting for 64% of the healthcare costs in this three-month

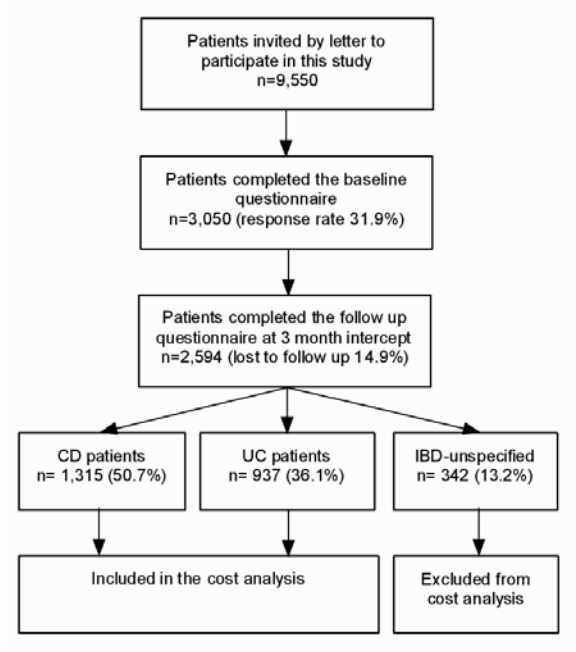

Figure 1. Study flowchart

Table 1. Demographic and disease characteristics of the study participants

	CD n=1,315	UC n=937	P-value
Male gender (%)	490 (37.3)	482 (51.4)	<0.01
Age - years (± SD)	47.8 (13.6)	49.8 (13.3)	<0.01
Smoking (%)			<0.01
Current	265 (20.2)	77 (8.2)	
Never	672 (51.1)	542 (57.8)	
Ex smoker	378 (28.7)	318 (33.9)	
Disease duration - median (IQR)	16.2 (8.3-26.3)	13.3 (6.6-21.5)	<0.01
Disease localisation (%)			N/A
Large bowel	369 (28.1)	937 (100)	
Small bowel	260 (19.7)	N/A	
Both small and large bowel	647 (49.2)	N/A	
Unknown	39 (3.0)	N/A	
Penetrating disease course (%)	693 (52.7)	N/A	N/A
Disease in remission (%)	1,035 (78.7)	699 (74.6)	0.03
Abdominal surgery in the past (%)	717 (54.4)	171 (18.2)	<0.01
Stoma (%)	159 (12.1)	53 (5.7)	<0.01
Low education (%)	821 (62.4)	543 (58.0)	<0.03

Table 1. Demographic and disease characteristics of the study participants (continued)

	CD n=1,315	UC n=937	P-value
Employment status (18-65 years) (%)	1,177 (89.5)	816 (87.1)	<0.01
Employed	705 (53.6)	573 (61.2)	
Fully work disabled	206 (17.5)	80 (9.8)	
Partial work disabled	98 (8.3)	40 (4.9)	
Retired	52 (4.4)	37 (4.5)	
Homemaker	111 (9.4)	62 (7.6)	
Student	44 (3.7)	12 (1.5)	

SD, Standard deviation; IQR, Interquartile range

Table 2. Healthcare resource utilisation and costs of CD patients during three months in 2011 euros

	Number of patients n= 1,315 (%)	Mean resource utilisation per patient (95% CI)	Mean healthcare costs per 3 months per patient € (95% CI)	Proportion (%) of healthcare costs
Outpatient clinic				
Gastroenterologist	588 (44.7)	0.56 (0.03-0.07)	60.65 (54.70-66.59)	3.7
Specialized nurse	255 (19.4)	0.19 (0.15-0.22)	5.67 (4.86-6.47)	0.3
Internist	64 (4.9)	0.06 (0.04-0.08)	5.61 (3.66-6.66)	0.3
Dietician	47 (3.6)	0.07 (0.05-0.09)	3.52 (2.33-4.70)	0.2
Surgeon	36 (2.7)	0.06 (0.03-0.08)	6.24 (3.71-8.78)	0.4
Rheumatologist	36 (2.7)	0.04 (0.02-0.05)	4.06 (2.62-5.50)	0.2
Dermatologist	25 (1.9)	0.03 (0.02-0.04)	3.50 (1.90-5.11)	0.2
Occupational physician	19 (1.4)	0.02 (0.01-0.03)	1.88 (0.87-2.88)	0.1
Psychiatrist	9 (0.7)	0.06 (-0.4-0.15)	7.68 (-5.12-20.47)	0.5
Emergency room	39 (3.0)	0.04 (0.03-0.05)	5.83 (3.73-7.94)	0.4
General practitioner during day-time				
Visit Home visit	111 (8.4) 8 (0.6)	0.16 (0.12-0.19) 0.01 (0.00-0.02)	4.95 (3.82-6.09)	0.3
General practitioner (during night/weekend-time)				
Visit Home visit	68 (5.2) 8 (0.6)	0.09 (0.06-0.06) 0.01 (0.00-0.01)	4.99 (3.85-6.13)	0.3
Subtotal			**114.12 (97.35-130.89)**	**7.0**
Diagnostics procedures				
Laboratory	155 (11.8)	0.23 (0.17-0.29)	4.18 (3.08-5.27)	0.3
Colonoscopy	90 (6.8)	0.07 (0.06-0.09)	24.31 (19.71-29.46)	1.5
MRI scan	40 (3.1)	0.03 (0.05-0.17)	5.86 (3.96-7.76)	0.4
CT scan	27 (2.1)	0.02 (0.01-0.04)	3.61 (1.72-5.49)	0.2
Abdominal X-ray	13 (1.0)	0.01 (0.00-0.01)	0.36 (0.15-0.58)	0.0

Table 2. Healthcare resource utilisation and costs of CD patients during three months in 2011 euros (continued)

	Number of patients n= 1,315 (%)	Mean resource utilisation per patient (95% CI)	Mean healthcare costs per 3 months per patient € (95% CI)	Proportion (%) of healthcare costs
Ultrasonography	36 (2.7)	0.03 (0.02-0.04)	1.03 (0.62-1.44)	0.1
DXA scan	22 (1.7)	0.01 (0.01-0.02)	1.22 (0.68-1.77)	0.1
Subtotal			**40.60 (33.58-47.56**	**2.5**
Medication use				
Mesalazine	292 (22.2)	N/A	54.82 (49.27-60.38)	3.4
Budesonide	75 (5.7)	N/A	10.83 (8.44-13.21)	0.7
Prednison	35 (2.7)	N/A	0.40 (0.27-0.53)	0.0
Azathioprine	338 (25.7)	N/A	23.30 (21.15-25.44)	1.4
6-mercaptopurine	89 (6.8)	N/A	6.13 (4.90-7.37)	0.4
Methotrexate	43 (3.3)	N/A	8.12 (5.73-10.52)	0.5
Infliximab	137 (10.4)	N/A	490.84 (411.65-570.03)	30.2
Adalimumab	166 (12.3)	N/A	550.89 (427.46-629.33)	33.9
Subtotal			**1,145.33 (1041.80-1248.86)**	**70.5**
Hospitalisation	60 (4.6)	10 (2-19)*	**315.25 (231.18-399.33)**	**19.4**
Surgery	12 (0.9)	N/A	**9.90 (2.71-17.10)**	**0.6**
Total healthcare costs			**1,625.18 (1,475.87-1,774.50)**	**100.0**

CI, Confidence Interval; CT, Computer tomography; MRI, Magnetic Resonance Imaging; DXA, Dual-emission X-ray absorptiometry

* mean number of days hospitalised (range)

intercept. Hospitalisation and surgery accounted for 19% and <1% of the healthcare costs, respectively. The relative contribution of each cost item or service category as a proportion of the total healthcare costs is summarised in Table 2.

The components of resource utilisation and healthcare costs of UC patients are presented in table 3. The mean healthcare costs over three months for UC were significantly lower as compared to CD, namely €595 (95% CI €505-€685), p<0.01. Again, with 59% of the healthcare costs, the main cost driver was medication use. In UC, mesalazine (€136; 95% CI €130-€143) and anti-TNF therapy (€187; 95% CI €128-€246) together accounted for over half of the healthcare costs (54%), with 602 (64%) patients treated with mesalazine and 37 (4%) with anti-TNF therapy. There were no statistically significant differences in healthcare costs of CD and UC patients between university medical centres and general hospitals, as shown in figure 2. The top 10% high-cost patients accounted for 40% of the healthcare costs in CD and 59% in UC. In CD, factors associated with high healthcare costs were current flares (adjusted (adj.) odds ratio (OR) 4.00; 95% CI 2.74-5.82) and pen-

Table 3. Healthcare resource utilisation and costs of UC patients during three months in 2011 euros

	Number of patients n= 937 (%)	Mean resource utilisation per patient (95% CI)	Mean healthcare costs per 3 months per patient - € (95% CI)	Proportion (%) of healthcare costs
Outpatient clinic				
Gastroenterologist	347 (37.0)	0.41 (0.36-0.46)	41.06 (36.22-45.90)	6.9
Specialized nurse	133 (14.2)	0.13 (0.09-0.16)	3.76 (2.97-4.56)	1.0
Internist	40 (4.3)	0.05 (0.03-0.07)	4.26 (2.57-5.95)	0.7
Dietician	30 (3.2)	0.05 (0.03-0.07)	2.34 (1.39-3.28)	0.4
Surgeon	16 (1.7)	0.03 (0.01-0.04)	3.06 (1.40-4.72)	0.5
Rheumatologist	8 (0.9)	0.04 (0.02-0.05)	1.28 (0.30-2.27)	0.2
Dermatologist	8 (0.9)	0.01 (0.00-0.03)	1.71 (-0.13-3.43)	0.3
Occupational physician	5 (0.5)	0.01 (0.00-0.02)	1.07 (-0.09-2.23)	0.2
Psychiatrist	2 (0.2)	0.00 (0.00-0.01)	0.36 (-0.15-0.86)	0.1
Emergency room	15 (1.6)	0.02 (0.01-0.03)	2.67 (1.14-4.20)	0.4
General practitioner (during day-time)				
Visit	52 (5.5)	0.08 (0.06-0.11)	2.48 (1.71-3.25)	0.4
Home visit	2 (0.2)	0.01 (0.00-0.02)		
General practitioner (during night/weekend-time)				
Visit	42 (4.5)	0.07 (0.04-0.09)	4.33 (3.11-5.55)	0.7
Home visit	5 (0.5)	0.01 (0.00-0.01)		
Subtotal			**68.38 (60.48-76-29)**	**11.5**
Diagnostics procedures				
Laboratory	57 (6.1)	0.11 (0.05-0.17)	1.95 (0.89-3.00)	0.3
Colonoscopy	66 (7.0)	0.07 (0.05-0.09)	24.31(18.22-30.22)	4.1
MRI scan	7 (0.7)	0.01 (0.00-0.02)	1.60 (0.36-2.85)	0.3
CT scan	5 (0.5)	0.01 (0.00-0.01)	0.82 (0.10-1.53)	0.1
Abdominal X-ray	5 (0.5)	0.01 (-0.00-0.03)	0.42 (-0.15-0.98)	0.1
Ultrasonography	12 (1.3)	0.01 (0.00-0.02)	0.40 (0.15-0.65)	0.1
DXA scan	7 (0.7)	0.01 (0.00-0.01)	0.45 (0.06-0.85)	0.1
Subtotal			**29.85 (22.97-36.73)**	**5.0**
Medication use				
Mesalazine	602 (64.2)	N/A	136.47 (129.9-143.01)	22.9
Budesonide	24 (2.6)	N/A	4.86 (2.93-6.79)	0.8
Prednison	24 (2.6)	N/A	0.39 (0.23-0.54)	0.1
Azathioprine	143 (15.3)	N/A	13.83 (11.74-15.92)	2.3
6-mercaptopurine	57 (6.1)	N/A	5.51 (4.12-6.90)	0.9
Methotrexate	7 (0.7)	N/A	1.86 (0.48-3.23)	0.3
Infliximab	28 (3.0)	N/A	145.02 (92.02-198.02)	24.4
Adalimumab	9 (1.0)	N/A	41.92 (14.61-69.22)	7.0
Subtotal			**349.86 (290.86-409.58)**	**58.8**
Hospitalisation	25 (2.7)	11 (2-19)*	**138.64 (83.85-193.42)**	**23.3**
Surgery	5 (0.5)	N/A	**8.16 (0.78-15.54)**	**1.4**
Total health care costs			**594.89 (504.90-684.89)**	**100.0**

CI, Confidence Interval; CT, Computer tomography; MRI, Magnetic Resonance Imaging; DXA, Dual-emission X-ray absorptiometry

* mean number of days hospitalised (range)

etrating disease course (adj. OR 2.30; 95% CI 1.54-3.44). In UC patients, self-reported flares (adj. OR 2.35; 95% CI 2.50-3.68) and current ileostomy (adj. OR 2.35; 95% CI 1.06-5.23) were associated with top 10% high-cost patients.

Productivity losses

A total of 705 (54%) CD and 573 (61%) UC patients were currently employed. Of all CD patients currently employed, 18% reported sick leave with a mean loss of employment days of 2.5 (95% CI: 1.8-3.4), translating in a mean loss of earnings of €289 (95% CI: €198-€379) over three months (table 4). In UC patients, 13% were absent from work due to sick leave with a mean loss of work days of 2.5 (95% CI: 1.6-3.4), with associated loss-of-productivity of €362 (95% CI €231-€493); $p < 0.01$. Total productivity losses were €326 (95% CI €234-€418) in CD and €395 (95% CI €261-€529) in UC (table 4).

Out-of-pocket costs

Out-of-pocket costs were €75 (95% CI €65-€84) in CD and €57 (95% CI €49-€66) in UC. According to patient specifications, most expenditures were on deductibles of health-care insurance, vitamins and other over-the-counter expenditures, and memberships of patient associations.

Total costs

The total costs (healthcare costs + productivity costs + out-of-pocket costs) were €2,026 (95% CI €1,808-€2,194) for CD patients and €1,047 (95% CI €838-€1,208) for UC patients. Productivity costs accounted for 16% of the total costs in CD patients and 38% in UC patients. Out of pocket costs accounted for 4% of the total costs in CD and 5% in UC, respectively.

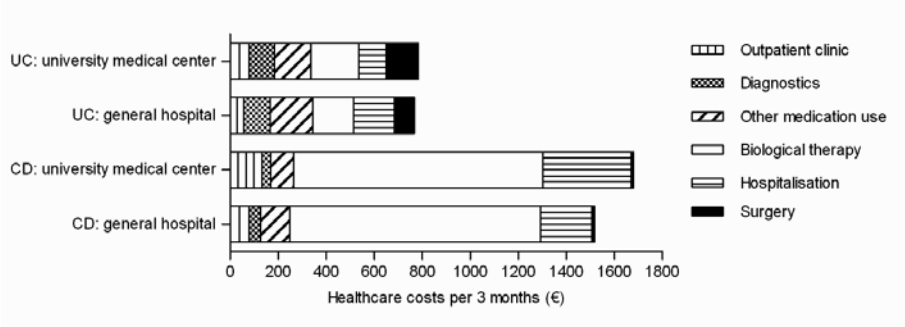

Figure 2. Comparison of distribution of healthcare costs between university medical centres and general hospitals

Table 4. Productivity losses in CD and UC patients in 2011 euros

	Number of patients (%)		Mean number of days (95% CI)		Mean costs per 3 months per patient - € (95% CI)	
	CD n=1,315	**UC n=937**	**CD n=1,315**	**UC n=937**	**CD n=1,315**	**UC n=937**
Sick leave of paid work (patients)	129/705 (18.3)	77/573 (13.4)	2.5 (1.8-3.3)	2.5 (1.6-3.4)	288.57 (198.21-378.92)	361.79 (230.79-492.80)
Sick leave of paid work (caregivers)	45 (3.4)	16 (1.7)	2.4 (1.2-3.5)	7.5 (-6.2-21.2)	17.76 (9.80-25.72)	15.08 (3.45-26.72)
Sick leave of unpaid work (patients)	62 (4.7)	28 (3.0)	5.4 (2.9-7.9)	7.8 (2.8-12.7)	19.40 (9.37-29.43)	18.33 (5.46-31.19)
Total productivity losses					**325.73 (233.96-417.52)**	**395.21 (261.00-529.41)**

CI, Confidence Interval

DISCUSSION

This study provides the most comprehensive update on the cost profile of IBD since the introduction and expanding use of anti-TNF therapy in Europe. Up to the 2000s, hospitalisation and surgery were the major cost-drivers in IBD. We report that nowadays medication use, anti-TNF in particular, represents the main source of healthcare costs while costs related to hospitalisation and surgery are substantially reduced as compared to previous studies.[2-4]

Interestingly, total healthcare costs in IBD patients over time do not seem to increase. Extrapolating the three-month healthcare costs from our study towards annual costs yielded mean costs of €6,501 and €2,380 per year in CD and UC patients. A cross sectional, single centre study conducted in the United Kingdom (UK), with an almost similar study population reported six-month healthcare costs of £1,652 and £1,256 in CD and UC patients for the year 2004.[2] Extrapolating these costs to a 1-year period, and using UK consumer price index to inflate (1.23) and convert (1£=€1.56 on December 1, 2011) these costs to 2011 euros, this would equal €6,338 for CD and €4,819 for UC. In this study, medical and surgical hospitalisation contributed to over half of total costs, but only 18% of healthcare costs in CD and 24% in UC was due to direct medication expenditure. This contrasts with data from our study, in which medication costs accounted for up to 71% and 59% of the healthcare costs for CD and UC respectively. Results from a large European cohort study by Odes et al.[4] were in line with the UK study. They reported that over half of the healthcare costs were due to hospitalisation and surgery, while only 30% of total costs were due to medication use, with mesalazine being the most expensive drug.[4] The same cost profile was reported in a hospital-based nationwide Spanish study conducted in 1997 in which medical and surgical hospitalisation accounted for 53% of the healthcare costs.[3]

Even though healthcare costs between the United States and Europe differ to a large extend, comparable trends in treatment paradigms should have induced the same alterations in cost profiles as observed in our study. Kappelman et al. studied healthcare costs using medical and pharmacy claims from an administrative database between 2003 and 2004, in which 10% of all CD patients had at least two claims of infliximab infusions.[22] In this study, pharmaceutical claims accounted for the largest proportion of healthcare costs (35%), in which infliximab was the most costly medication. But none of the cost studies in the past have taken the economic impact of adalimumab into account, as this agent was registered only in 2007 for CD. Thus it seems that there is a shift in cost profile from surgery and hospitalisation towards anti-TNF treatment. Apparently, the high costs of these drugs are partly compensated for by a significant reduction of

surgery and hospitalisation rates. Obviously, a longer follow-up period of 2-5 years is needed to confirm this trend. Recent published reviews and cohort studies, however, showed decrease in surgery and hospitalisation rates as well, underscoring our findings.[11,23] A similar development has been reported in the treatment of rheumatoid arthritis, with a decline in surgery rates since the introduction of anti-TNF therapy for this indication.[9,24-26]

We also examined productivity losses due to IBD related sick leave, accounting for 16% of total costs in CD and 39% in UC. Comparisons between this study and older studies are limited due to varying methodologies in measurement and valuation of productivity losses, as well as differences in social security policies. We therefore focused on sick leave in days to illustrate changes in productivity losses. We found that 18% of employed CD patients and 13% of employed UC patients reported sick leave in the previous three months. Previous studies found that 14%-50% of CD patients and 15%-32% of UC patients reported sick leave.[2,3,7,27] Higher age was found to be an independent predictor of sick leave.[27] Although patients from our study cohort were older with longer disease duration as previous reported, we found similar or even lower rates of sick leave. We did not incorporate productivity losses due to work disability, as we did not know the cause of work disability. Inclusion of these costs would have therefore overestimated the total productivity costs. From literature, however, we know that the impact of work disability is considerable. A German study employing a four week diary reported that 49% of the total costs were due to work disability in CD and 32% in UC, respectively.[7] Similarly, a Swedish study reported that 36% of the total costs of IBD were due to work disability.[5] Finally, we did not include productivity losses while at work due to the disease (presenteeism). At this point, there are no validated questionnaires to assess presenteeism with a longer recall time than seven days. Therefore we might have underestimated the productivity losses.

The strengths of this study included both the size and the diversity of the case mix by including patients from both university and general hospitals throughout the Netherlands. In order to enrol a large number of patients, we opted for the present web-based design. An inherent limitation of such a strategy is sampling bias. Although internet access among IBD patients has been reported to be high and the Netherlands has a very high internet penetration of 89%,[28] our sample is not necessarily representative of the IBD population as a whole. It was expected that relatively few elderly would participate, but we did recruit a total of 302 (10%) patients over the age of 65.

In general, participation rates for single questionnaires can be expected to be higher. However, we asked patients to participate in a longitudinal cohort study, possible ex-

plaining the lower participation rate. We assessed the representativeness of our study by performing a non-responder study and could not detect major differences in demographic and disease characteristics between responders and non-responders. Reassuringly, we were able to confirm previously reported outcome data, supporting the internal validity of our cohort. For example, prior studies found slightly more frequently UC in men, whereas CD occurs 20%-30% more frequently in women,[29-31] as we found in our study. Furthermore, we found comparable rates of abdominal surgery of 54% in CD patients and 18% in UC patients as previously reported.[23,32] Additionally, over 10% of the CD patients will eventually require permanent faecal diversion,[32] similar to the 12% reported in our population. Finally, during disease course, the cumulative risk for perianal involvement was 50%,[32;33] comparable with the 53% of reported penetrating disease course in our CD population. As such, in spite of potential limitations, we believe that our study provides reliable and generalizable data on total costs in IBD.

It could well be possible that due to the relatively short observation period healthcare costs have skewed in favour of the medical costs. However, we have chosen to set a strict time limit for the observation period, as it is known from previous studies that the reliability of productivity and healthcare data is decreasing if the recall times exceed more than three months. Our larges study size, however, provides a substantial cumulative observation time of nearly 600 patient years.

Our study provides valuable information, which, if interpreted with caution can be used for theoretical modelling and cost-effectiveness studies, and aids to put the high costs of anti-TNF drugs into perspective. Its selective use could lead to a reduction of hospitalisation and surgery rates and in an increase in work productivity thereby rendering these drugs cost-effective. In conclusion, this is the first cost-of-illness study since the introduction of anti-TNF therapy in Europe. Total costs do not seem to increase, but cost profiles have changed markedly. Healthcare costs are now mainly driven by medication costs. Hospitalisation and surgery did only account for small percentages of healthcare costs.

REFERENCES

1. Cosnes J, Cattan S, Blain A *et al*. Long-term evolution of disease behavior of Crohn's disease. *Inflamm Bowel Dis* 2002;8(4):244-50.
2. Bassi A, Dodd S, Williamson P *et al*. Cost of illness of inflammatory bowel disease in the UK: a single centre retrospective study. *Gut* 2004;53:1471-8.
3. Juan J, Estiarte R, Colome E *et al*. Burden of illness of Crohn's disease in Spain. *Dig Liver Dis* 2003; 35:853-61.
4. Odes S, Vardi H, Friger M *et al*. Cost analysis and cost determinants in a European inflammatory bowel disease inception cohort with 10 years of follow-up evaluation. *Gastroenterology* 2006;131: 719-28.
5. Blomqvist P, Ekbom A. Inflammatory bowel diseases: health care and costs in Sweden in 1994. *Scand J Gastroenterol* 1997;32:1134-9.
6. Gibson TB, Ng E, Ozminkowski RJ *et al*. The direct and indirect cost burden of Crohn's disease and ulcerative colitis. *J Occup Environ Med* 2008;50:1261-72.
7. Stark R, Konig HH, Leidl R. Costs of inflammatory bowel disease in Germany. *Pharmacoeconomics* 2006;24:797-814.
8. Feagan BG, Panaccione R, Sandborn WJ *et al*. Effects of adalimumab therapy on incidence of hospitalization and surgery in Crohn's disease: results from the CHARM study. *Gastroenterology* 2008;135:1493-9.
9. Lichtenstein GR, Yan S, Bala M *et al*. 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;99:91-6.
10. Peyrin-Biroulet L, Oussalah A, Williet N *et al*. Impact of azathioprine and tumour necrosis factor antagonists on the need for surgery in newly diagnosed Crohn's disease. *Gut* 2011;60:930-6.
11. Targownik LE, Singh H, Nugent Z *et al*. The Epidemiology of Colectomy in Ulcerative Colitis: Results From a Population-Based Cohort. *Am J Gastroenterol* 2012;10.
12. Feagan BG, Bala M, Yan S *et al*. Unemployment and disability in patients with moderately to severely active Crohn's disease. *J Clin Gastroenterol* 2005;39:390-5.
13. Feagan BG, Reilly MC, Gerlier L *et al*. Clinical trial: the effects of certolizumab pegol therapy on work productivity in patients with moderate-to-severe Crohn's disease in the PRECiSE 2 study. *Aliment Pharmacol Ther* 2010;31:1276-85.
14. Lichtiger S, Binion DG, Wolf DC *et al*. The CHOICE trial: adalimumab demonstrates safety, fistula healing, improved quality of life and increased work productivity in patients with Crohn's disease who failed prior infliximab therapy. *Aliment Pharmacol Ther* 2010;32:1228-39.
15. Enthoven AC, van d, V. Going Dutch--managed-competition health insurance in the Netherlands. *N Engl J Med* 2007;357:2421-3.
16. Tsiachristas A, Hipple-Walters B, Lemmens KM *et al*. Towards integrated care for chronic conditions: Dutch policy developments to overcome the (financial) barriers. *Health Policy* 2011;101: 122-32.
17. van Schaik FD, van Oijen MG, Smeets HM *et al*. Thiopurines prevent advanced colorectal neoplasia in patients with inflammatory bowel disease. *Gut* 2012;61:235-40.
18. Baars JE, Looman CW, Steyerberg EW *et al*. The risk of inflammatory bowel disease-related colorectal carcinoma is limited: results from a nationwide nested case-control study. *Am J Gastroenterol* 2011;106:319-28.
19. Statistics Netherland. Available at www.cbs.nl**.** 2011

20. Hakkaart-van Roijen L, Tan SS, and Bouwmans CAM. Handleiding voor kostenonderzoek, methoden en standaard kostprijzen voor economische evaluaties in de gezondheidszorg. 2010.
21. Drummond M, Manca A, Sculpher M. Increasing the generalizability of economic evaluations: recommendations for the design, analysis, and reporting of studies. *Int J Technol Assess Health Care* 2005;21:165-71.
22. Kappelman MD, Rifas-Shiman SL, Porter CQ *et al*. Direct health care costs of Crohn's disease and ulcerative colitis in US children and adults. *Gastroenterology* 2008;135:1907-13.
23. Bernstein CN, Loftus EV, Jr., Ng SC *et al*. Hospitalisations and surgery in Crohn's disease. *Gut* 2012; 61:622-9.
24. Weiss RJ, Stark A, Wick MC *et al*. Orthopaedic surgery of the lower limbs in 49,802 rheumatoid arthritis patients: results from the Swedish National Inpatient Registry during 1987 to 2001. *Ann Rheum Dis* 2006;65:335-41.
25. Da SE, Doran MF, Crowson CS *et al*. Declining use of orthopedic surgery in patients with rheumatoid arthritis? Results of a long-term, population-based assessment. *Arthritis Rheum* 2003;49: 216-20.
26. Boonen A, Matricali GA, Verduyckt J *et al*. Orthopaedic surgery in patients with rheumatoid arthritis: a shift towards more frequent and earlier non-joint-sacrificing surgery. *Ann Rheum Dis* 2006;65:694-5.
27. Boonen A, Dagnelie PC, Feleus 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;8:382-9.
28. Internet world statistics. Available at www.internetworldstats.com. December 2011.
29. Molinie F, Gower-Rousseau C, Yzet T *et al*. Opposite evolution in incidence of Crohn's disease and ulcerative colitis in Northern France (1988-1999). *Gut* 2004;53:843-8.
30. Bernstein CN, Wajda A, Svenson LW *et al*. The epidemiology of inflammatory bowel disease in Canada: a population-based study. *Am J Gastroenterol* 2006;101:1559-68.
31. Gearry RB, Richardson A, Frampton CM *et al*. High incidence of Crohn's disease in Canterbury, New Zealand: results of an epidemiologic study. *Inflamm Bowel Dis* 2006;12:936-43.
32. Cosnes J. Crohn's disease phenotype, prognosis, and long-term complications: what to expect? *Acta Gastroenterol Belg* 2008;71:303-7.
33. Schwartz DA, Pemberton JH, Sandborn WJ. Diagnosis and treatment of perianal fistulas in Crohn disease. *Ann Intern Med* 2001;2001;135(10):906-18.

Supplementary Table 1. Unit costs of resource use, updated to 2011 Euros

	Cost price (€)	References
	Cost price per visit	
Outpatient clinic consultations		
District hospital	64.64	(20)
University medical centre	130.29	(20)
Emergency room	152.51	(20)
General practitioner		(20)
Visit (day-time)	28.28	(20)
Home visit (day-time)	43.43	(20)
Visit (weekend/ night-time)	82.00[a]	(w1)
Home visit (weekend/ night-time)	123.00[a]	(w1)
	Cost price per hour	
IBD or stoma nurse – per hour	44.50	(20)
Dietician – per hour	48.70	(20)
Hospitalisation	Cost price per day	
Medical ward		
General hospital	439.35	(20)
University medical centre	580.75	(20)
Intensive care unit	2204.83	(20)
Medication use	Costs price per 3 months	
Mesalazine	UC: 212.42[b] CD: 246,90[c]	(w2)
Prednisone	15.09[d]	(w2)
Budesonide	189.81[e]	(w2)
Azathioprine - 150 g/day	90.62[f]	(w2)
Mercaptopurine - 50 mg/day	90.62[g]	(w2)
Methotrexate - 15 mg/ week	248,44[h]	(w2)
Infliximab	4,853[i]	(w2)
Adalimumab	4,364[j]	(w2)
Surgery	Cost price per type of surgery[k]	
Ileocecal resection/ resection neoterminal ileum	1,184.00	(w1)
Partial colectomy	1,726.00	(w1)
Subtotal colectomy	1,726.00	(w1)
Abcess surgery	168.00	(w1)
Complex fistula surgery	2,302.00	(w1)
Rectum amputation	3,149.00	(w1)
Ileostomy	743.00	(w1)
Diagnostic procedures	Cost price per type of diagnostic procedure	
Colonoscopy	343.79	(w1)
CT scan	152.96	(w1)
MRI scan	187.96	(w1)
Abdominal X-ray	43.38	(w1)

Supplementary Table 1. Unit costs of resource use, updated to 2011 Euros (continued)

	Cost price (€)		References
	Cost price per visit		
Ultrasonography	37.67		(w1)
DXA scan	84.47		(w1)
Laboratory	18.06[l]		(w1)
Sick leave from paid work	Productivity losses per working hour		
	Females	Males	
15-19 years	8.94	9.84	(20)
20-24 years	17.52	18.11	(20)
25-29 years	24.09	24.67	(20)
30-34 years	28.09	30.24	(20)
35-39 years	29.84	34.71	(20)
40-44 years	29.64	37.40	(20)
45-49 years	29.49	39.09	(20)
50-54 years	29.84	39.84	(20)
55-59 years	30.09	40.17	(20)
60-64 years	29.24	39.91	(20)
Sick leave from paid work (caregiver)	Productivity losses per working hour		
	31.11		(20)
Sick leave from unpaid work	Productivity losses per working hour		
	12.96		(20)

[a] Price based on average cost price of 55 general practitioners (weekend/evening/night).

[b] Price based on average dose of 2000 mg/day during 91 days.

[c] Price based on average dose of 2400 mg/day during 91 days.

[d] Price based on average dose of 10 mg/day during 91 days.

[e] Price based on average dose of 6 g/day during 91 days.

[f] Price based on average dose of 150 mg/day during 91 days.

[g] Price based on average dose of 50 mg/day during 91 days.

[h] Price based on average dose of 15 mg/ week during 13 weeks.

[i] Price based on average weight of 75 kg and 1.8 infusions per 3 months.

[j] Price based on 6,5 injections per 3 months (81% administered adalimumab 40 mgs per 2 weeks) or 13 injections per 3 months (19% of patients administered adalimumab 80 mgs per 2 weeks).

[k] Days admitted at the surgical or medical were not included in the cost price of surgery, but assessed separately.

[l] Price based on full blood count and differential, C-reactive protein, alanine aminotransferase, aspartate aminotransferase, y-glutamyl transferase, sodium, potassium, creatinine, albumin.

[m] For patients with an ileostomy costs for caring for the stoma were based on a standard care package. This is based on the assumption of an exhange of base disk 4 times per week and of the ileostomy bag twice/day.

w1. Dutch healthcare authority. Available at www.nza.nl, 2011.

w2. Healthcare Insurance Board. Available at www.medicijnkosten.nl. 2011.

Supplementary Table 2. Comparison of responders and a subgroup of non – responders

	CD			UC		
	Responders n=1,315	**Non responders n= 405**	**P-value**	**Responders N=937**	**Non responders n= 247**	**P-value**
Male gender (%)	490 (37.3)	171 (42.2)	0.13	482 (51.4)	119 (48.2)	0.36
Age – years (± SD)	47.8 (13.6)	47.9 (15.4)	0.18	49.8 (13.3)	50.6 (14.8)	0.50
Disease duration - median (IQR)	16.2 (8.3-26.3)	15.3 (10.3-24.5)	0.06	13.3 (6.6-21.5)	13.4 (10.5-21.1)	0.14
Penetrating disease course (%)	693 (52.7)	193 (47.7)	0.08	n/a	n/a	n/a
Abdominal surgery in the past (%)	717 (54.4)	224 (55.3)	0.78	171 (18.2)	41 (16.6)	0.55
Medication use						
Mesalazine	292 (22.2)	85 (21.0)	0.60	602 (64.2)	167 (67.6)	0.32
Budesonide	75 (5.7)	18 (4.4)	0.45	24 (2.6)	2 (0.8)	0.09
Prednison	35 (2.7)	17 (4.2)	0.11	24 (2.6)	6 (2.4)	0.91
Azathioprine	338 (25.7)	111 (27.4)	0.49	143 (15.3)	32 (13.0)	0.36
6-mercaptopurine	89 (6.8)	46 (11.4)	<0.01	57 (6.1)	20 (8.1)	0.25
Methotrexate	43 (3.3)	8 (2.0)	0.18	7 (0.7)	1 (0.4)	0.40
Infliximab	137 (10.4)	50 (12.3)	0.28	28 (3.0)	7 (2.8)	0.90
Adalimumab	166 (12.3)	35 (8.6)	0.03	9 (1.0)	1 (0.4)	0.40

CD, Crohn's disease; UC, Ulcerative colitis; SD, Standard deviation; IQR, Interquartile range;

Chapter 4

Evolution of costs of inflammatory bowel disease over two years of follow-up

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on Crohn and Colitis

Revisions – PLOS one

ABSTRACT

Background:

With the increasing use of anti-TNF therapy in inflammatory bowel disease (IBD), a shift of costs has been observed with medication costs replacing hospitalization and surgery as major cost driver. We aimed to explore the evolution of IBD-related costs over two years of follow-up.

Methods and Findings

In total 1,307 Crohn's disease (CD) patients and 915 ulcerative colitis (UC) patients were prospectively followed for two years by three-monthly web-based questionnaires. Changes of healthcare costs, productivity costs and out-of-pocket costs over time were assessed using mixed model analysis. Multivariable logistic regression analysis was used to identify costs drivers.

In total 737 CD patients and 566 UC were included. Total costs were stable over two years of follow-up, with annual total costs of €7,835 in CD and €3,600 in UC. However, within healthcare costs, the proportion of anti-TNF therapy-related costs increased from 64% to 72% in CD ($p<0.01$) and from 31% to 39% in UC ($p < 0.01$). In contrast, the proportion of hospitalization costs decreased from 19% to 13% in CD ($p<0.01$), and 22% to 15% in UC ($p < 0.01$). Penetrating disease course predicted an increase of healthcare costs (adjusted odds ratio (adj. OR) 1.95 (95% CI 1.02-3.37) in CD and age <40 years in UC (adj. OR 4.72 (95% CI 1.61-13.86)).

Conclusions:

IBD-related costs remained stable over two years. However, the proportion of anti-TNF-related healthcare costs increased, while hospitalization costs decreased. Factors associated with increased costs were penetrating disease course in CD and age <40 in UC.

Key words:

Crohn's disease, ulcerative colitis, anti-TNF therapy, healthcare costs, productivity costs

INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC), collectively known as inflammatory bowel diseases (IBD), are characterized by chronic relapsing intestinal inflammation that may lead to severe complications and disability. Therefore, IBD represent a high economic burden to society.[1-8] The early onset and chronicity of IBD profoundly affects work productivity with accompanying economic losses mainly resulting from sick leave and work disability accounting for up to 50% of the total costs.[1;2;5-8]

With the introduction and increasing use of anti-TNF therapy in IBD, a major shift of costs has been observed with medication costs replacing in-patient care, such as hospitalization and surgery, as the greatest source of healthcare expenditure.[1] Most previous cost studies in IBD, however, relied on a single measurement of costs and were performed before the introduction of anti-TNF therapy in IBD.[2;3;7-10] Furthermore, only a limited number of studies have aimed to identify factors predicting IBD-related costs.[1;4;10;11]

The 'Costs Of Inflammatory bowel disease in the Netherlands' or COIN-study has been initiated to generate longitudinal cost data in order to assess the impact of anti-TNF therapy on IBD-related costs. In the present study we aimed 1) to assess the evolution of costs of IBD over a period of two years, 2) to explore the contribution of healthcare, productivity and out-of-pocket costs on IBD-related costs; and 3) to identify predictors for high costs over two years of follow-up.

MATERIAL AND METHODS

Study design and patient population

From October 2010 to October 2011 we invited all IBD patients aged 18 years or older from seven university hospitals and seven district hospitals to participate in the COIN-study by letter (Fig. 1).

A secure web-based questionnaire was developed to obtain baseline characteristics and collect cost data on a three-month basis during two years of follow-up. The cohort organisation and study follow-up protocol have been described in detail elsewhere.[1] The study was centrally approved by the Ethics Committee of the University Medical Centre Utrecht.

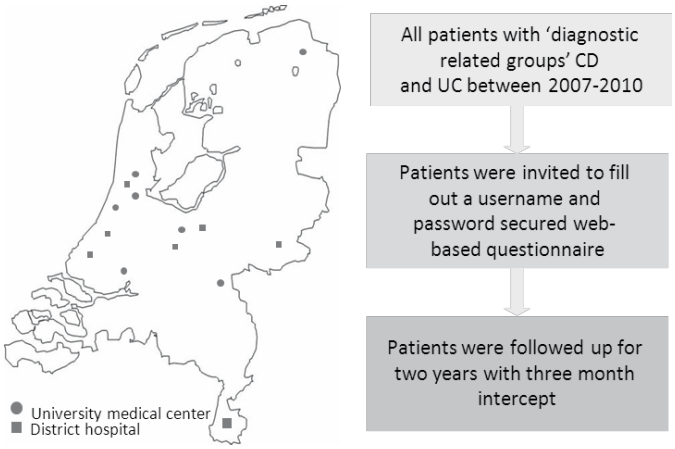

Figure 1. Design of the COIN study

Data collection

Demographic characteristics included gender, age, age at diagnosis, education level, work status, family history, and smoking status. Clinical characteristics included subtype of IBD, disease duration and localization, disease behaviour, stoma or pouch surgery, and clinical disease activity.

In accordance with Drummond et al.[12], we distinguished three main IBD-related cost categories including healthcare costs, productivity losses and patient costs. Applying the human capital approach, productivity losses were estimated by multiplying the self-reported number of sick leave days from both paid and unpaid (i.e. voluntary work) work of patients and the caregivers taking care of the sick persons by age- and sex-specific productivity losses. A work-week was assumed to have at maximum of five working days. Patient costs were calculated according to patient specifications. Reference prices used in the COIN-study are described in Table S1. All costs are expressed in 2011 euros, using Dutch consumer price index when appropriate. No discounting was applied, given the limited follow-up period of two years. Potential predictive variables were identified from earlier studies on predictors for poor clinical outcome or high healthcare-or productivity losses (Table S2).

Statistical analysis

Data analysis was performed using SPSS version 18.0. Descriptive statistics were used to characterize patients with CD and UC. We report means with a standard deviation (SD) and medians with an interquartile range (IQR). Comparisons between CD and UC

patients were analysed with Student's t-test for continuous variables and $\chi 2$ for dichotomous variables. To compare medians, the Mann-Whitney U test was used. Costs were reported as mean cost/patient with a 95% confidence interval.

To control equality between the study population (i.e. responders) and the patients who were lost to follow-up over time (i.e. non-responders) we performed a non-responder study. To account for missing data and repeated measurements, we used a generalized mixed model to compare costs between different subgroups.

We performed a multivariate logistic regression analysis to identify factors predicting increase of healthcare costs over two-years of follow-up. As a dependent variable we used the 10 percent of patients who displayed the highest increase in healthcare costs over two years of follow-up. Variables that reached borderline significance ($p<0.1$) in the univariate analysis were considered for inclusion into the multivariate models. We fitted separate models for UC and CD. P-values <0.05 were considered statistically significant.

RESULTS

Study population

At baseline, 1,307 CD patients and 915 UC patients were included. The two-year follow-up questionnaire was filled-out by 736 CD patients and 566 UC patients (response rates of 47% and 54%, respectively). Additional response rates per time point are provided in Table S3. From the patients who were lost to follow-up, 10 subjects died during the follow-up period, 54 were unreachable due to automatic email response bouncing our request (possibly due to a change of email address), 153 withdrew consent and 1,049 were lost for unknown reasons. Responders were older ($p<0.01$) and had longer disease duration ($p<0.01$) as compared to non-responders (Table S4).

The baseline characteristics of the study population completing the two-year follow-up are described in Table 1. CD patients were more often females (60% versus 46%, $p<0.01$), smokers (19% versus 8%, $p<0.01$), and had a higher probability of previous abdominal surgery (56% versus 19%) compared to UC patients. CD patients were more frequently treated with immunomodulators (36% versus 23%, $p<0.01$) and/or anti-TNF (21% versus 4%, $p<0.01$) as compared to UC patients.

Table 1. Demographic and disease characteristics of study population

	CD n= 737	UC n= 566	P-value
Male gender (%)	295 (40.0)	300 (53.0)	<0.01
Age - years (± SD)	50.5 (13.5)	52.4 (12.9)	0.01
Smoking (%)			<0.01
Current	137 (18.6)	45 (8.0)	
Never	382 (51.8)	336 (59.4)	
Ex-smoker	218 (29.6)	185 (32.7)	
Low education (%)	445 (60.4)	314 (55.5)	0.08
Disease duration - median (IQR)	18.2 (10.1-18.2)	16.0 (9.0-16.0)	<0.01
Disease localisation (%)			
Large bowel	204 (27.7)	566 (100)	n/a
Small bowel	152 (20.6)	n/a	
Both small and large bowel	361 (49.0)	n/a	
Unknown	20 (2.7)	n/a	
Penetrating disease course (%)	400 (54.3)	n/a	n/a
Clinical remission (%)	618 (83.9)	452 (79.9)	0.06
Abdominal surgery (%)	416 (56.4)	106 (18.7)	<0.01
Medication use (%)			
Mesalazine	175 (23.7)	373 (65.9)	<0.01
Azathioprine	189 (25.6)	91 (16.1)	<0.01
Mercaptopurine	51 (6.9)	36 (6.4)	NS
Methotrexate	25 (3.4)	1 (0.2)	NS
Prednisone	37 (4.9)	31 (5.5)	NS
Budesonide	44 (6.0)	19 (3.4)	NS
Infliximab	72 (9.8)	14 (2.5)	<0.01
Adalimumab	85 (11.5)	5 (0.9)	<0.01

SD: Standard deviation; IQR: Interquartile range; n/a: not applicable; NS: not significant.

IBD-related costs

Over the two-year follow-up period, IBD-related costs did not change (Figs. 2A-B). The mean annual IBD-related costs were €7,835 (95% CI €7,235- €9,563) for CD patients and €3,600 (95% CI €2,865- €4,669) for UC patients. Healthcare costs accounted for the major part of the IBD-related costs, 81% (€6,326 (95% CI €5,241- €7,102)) in CD and 65% (€2,340 (95% CI €1,540- €3,105)) in UC. In addition, productivity losses accounted for 17% (€1,335 (95% CI €860- €2,130)) of the total costs in CD patients and 31% (€1,120 (95% CI €571- €1,891)) in UC patients, whereas out-of-pocket costs accounted for 2% (€174 (95% CI €95- €220) in CD and 4% (€140 (95%CI €110-€195) in UC. Associated healthcare costs per 3 months are displayed in Tables S5A-B.

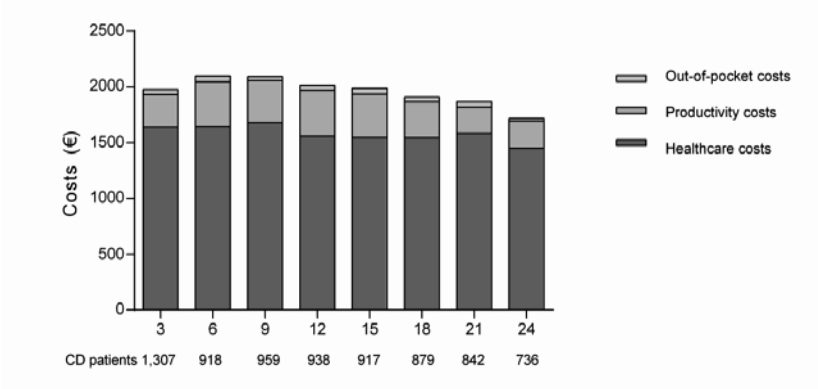

Figure 2A. Three-monthly total costs per average CD-patient over two year of follow up

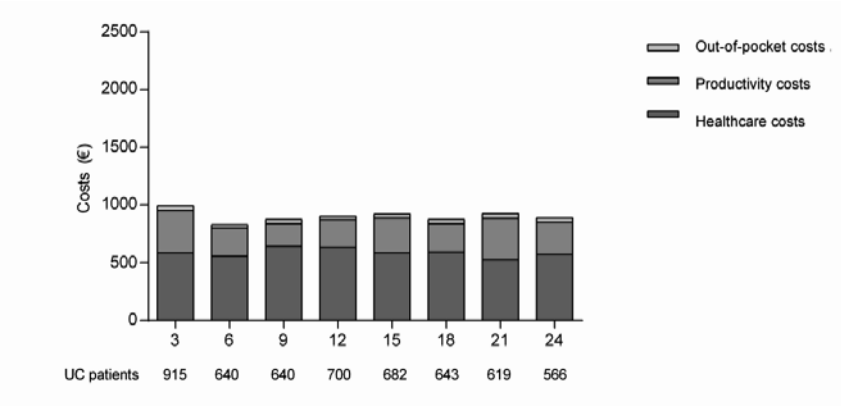

Figure 2B. Three-monthly total costs per average UC-patient over two year of follow up

In Figs. 3A-B, the breakdown of healthcare costs over time in the CD and UC cohorts is depicted. Although the absolute healthcare costs did not change significantly over the two years of follow-up, the proportion of anti-TNF therapy-related costs increased from 64% to 72% in CD ($p<0.01$), and from 31% to 39% in UC ($p<0.01$). This was mainly due to an increased use of anti-TNF over two years of follow up. This increase was accompanied by a reduction of the proportion of hospitalization costs, which decreased from 19% to 13% in CD ($p<0.01$), and from 22% to 15% in UC ($p<0.01$). The proportion of healthcare costs due to surgery, outpatient clinic, other mediation use and diagnostic procedures remained stable over time (Tables S5C-D).

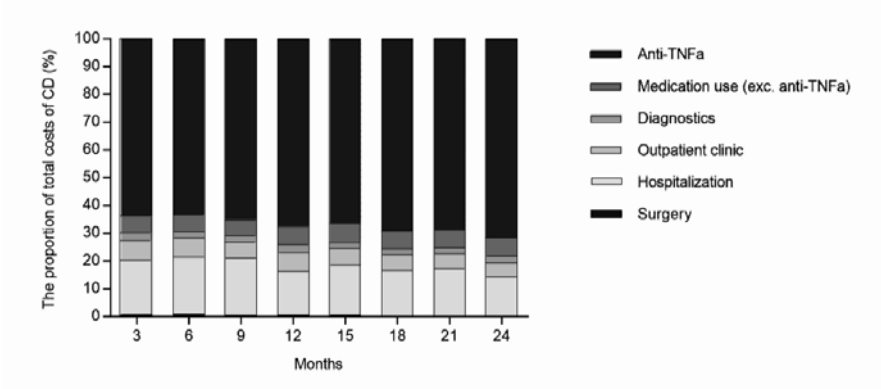

Figure 3A. The proportion of healthcare costs for an average CD-patient over two years follow up

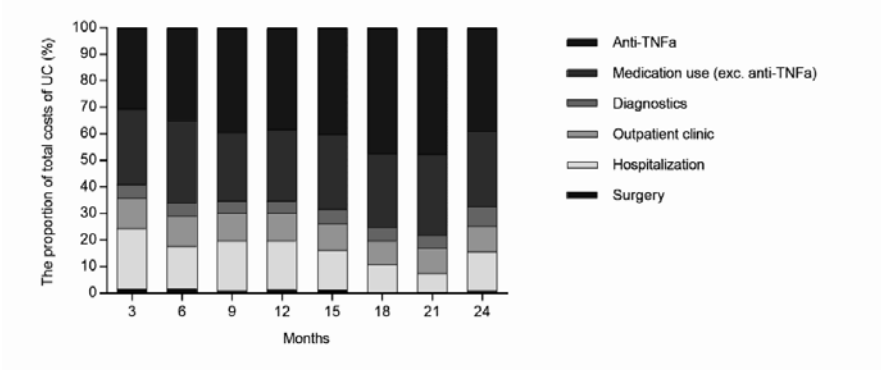

Figure 3B. The proportion of healthcare costs for an average UC-patient over two years follow up

Predictors of healthcare costs

In Table 2 the results of the multivariate analysis on predictors of healthcare costs are shown. In CD, penetrating disease course was associated with an increase of healthcare costs (adjusted odds ratio (Adj. OR) 1.95 (95% CI 1.02-3.37)). Furthermore, anti-TNF therapy (Adj. OR 0.09 (95% CI 0.02-0.12)) and disease activity (0.47 (95% CI 0.24-0.93)) at three months of follow-up were found to be associated with a decrease of healthcare costs over two years of follow-up. This was mainly due to discontinuation of anti-TNF therapy in 20% of CD patients with disease activity. In case of UC, only age <40 years (n=225, 39.8% of the UC population) was found to independently predict an increase of healthcare costs (adj. OR 4.72 (95% CI 1.61-13.86)). The percentage UC patients <40 years receiving Anti-TNF therapy increased from 4.9% at baseline to 9.9% over two years of follow up.

Table 2. Multivariate logistic regression analyses of CD and UC patients with increase of healthcare costs as dependent variable

Variable	CD		UC	
	Adj. OR (95% CI)	p-value	Adj. OR (95% CI)	p-value
Age (at 3 months follow up)				
<40 years	1.03 (0.54-1.98)	0.93	4.72 (1.61-13.86)	<0.01
>40 years (ref)	1		1	
Disease duration (at 3 months follow up)				
< 3 years	0.54 (0.17-1.68)	0.29	2.03 (0.55-7.54)	0.29
>3 years (ref)	1		1	
Abdominal surgery in the past				
Yes	0.68 (0.35-1.35)	0.27	3.36 (0.13-1.070)	0.07
No (ref)	1		1	
Anti-TNF therapy (at 3 months follow up)				
Yes	0.09 (0.02-0.12)	<0.01	0.14 (0.02-1.40)	0.10
No (ref)	1		1	
Disease activity (at 3 months follow up)				
Yes	0.47 (0.24-0.93)	0.03	-	
No (ref)	1			
Penetrating disease course				
Yes	1.95 (1.02-3.73)	0.04		
No (ref)	1			

DISCUSSION

The widespread use of anti-TNF in the treatment of patients with IBD has changed the healthcare landscape radically and has led to a major shift in cost profiles.[1] For the first time, we prospectively show in a large longitudinal study that IBD-related costs remain stable over a period of two years. In this period, we observed an ongoing shift of cost profiles with an increasing proportion of anti-TNF-related healthcare costs and a reduction of hospitalization costs.

Most of the IBD-related costs were incurred by anti-TNF therapy, both in CD and UC patients. The present data underscore our previous observations that healthcare expenditures in IBD shift from costs related to hospitalization and surgery to costs driven by medication use.[1] Due to the differences in study design and study populations, it is difficult to compare our results with other studies. For example, the recently published EPICOM cost data from a population-based inception cohort of patients in the first year after the diagnosis reported that the main cost drivers were investigative procedures (21%), surgical procedures (26%) and anti-TNF therapy (15%).[13] Interestingly, 20% and 4% of their CD and UC patients were already on anti-TNF therapy in the first year after

diagnosis, which is almost identical to the rates observed in our cohort (21% in CD and 3% in UC).

An important observation is the ongoing rise of anti-TNF therapy-related costs, with a concurrent reduction of hospitalization costs. A similar trend in increase of anti-TNF therapy-related costs has been found in rheumatoid arthritis.[14;15] In two national registry cost-of-illness studies covering 20-years of follow-up, a downward trend for all costs, apart from the costs for anti-TNF, therapy has been reported. The decline of costs related to hospitalization in IBD is consistent with the observed decrease in surgery and hospitalisation rates in population-based studies.[16;17]

Even though that healthcare cost differ to a large extend between Western countries, comparable trends in treatment paradigms should have induced the same alterations in cost profiles as observed in our study. For example, Kappelman et al. studied healthcare costs using medical and pharmacy claims from an administrative database between 2003 and 2004, in which 10% of all CD patients had at least two claims of infliximab infusions.[18] In this study, pharmaceutical claims accounted for the largest proportion of healthcare costs (35%), from which infliximab was the most costly medication.

The large sample size and longitudinal data enabled us to study predictors of healthcare costs over time. In CD, penetrating disease was found to be associated with an increase of costs over two years of follow-up. This can be attributed to the fact that a penetrating disease is a predictor of poor outcome in CD, resulting in frequent surgery and hospitalizations[19-21]. Furthermore, this complication of CD is often treated with anti-TNF compounds (26.9% in our cohort, data not shown).

In UC patients younger than 40 years of age, an increase of healthcare costs was encountered as well. We found a 100% increase of anti-TNF use among young UC patients during two years of follow-up. This finding is in line with previous studies in which younger age in UC was found to be associated with a more severe disease course and an increased risk of relapses.[22-24] Furthermore, young age is associated with more extended colitis in which escalating therapy towards anti-TNF medication or surgery is frequently required.[25] In contrast, anti-TNF therapy and disease activity were associated with a decrease of healthcare costs. This was mainly due to the fact that in these patients, anti-TNF therapy was eventually discontinued. Whether this was due to treatment failure, side effects or cessation of this drug because of treatment success could not be discerned from our data.

Our study has several limitations. First, an inherent limitation of a longitudinal study using a web-based questionnaire design is the high rate of loss to follow-up. We tried to

reduce the impact of this problem by using mixed models to correct for missing values. Furthermore, we performed a non-responder study, which showed that responders (i.e. the individuals completing all questionnaires) were older and had a longer disease duration. Since costs in elderly IBD patients are lower than in younger patients,[26] we may have underestimated total healthcare costs. Interestingly, even in this relatively old population, the prescription of anti-TNF therapy increased over a follow-up period of two years. Furthermore, we did not have clinical data such as endoscopic or laboratory markers of disease activity at our disposal. Potentially, these might prove to be important determinants of future healthcare costs as well. For example, deep ulcers or high faecal calprotectin levels may predict a severe disease course with associated high costs.

In conclusion, there is an apparent shift in cost profiles from surgery and hospitalization towards anti-TNF therapy. However, total IBD costs remain remarkably stable over time, suggesting that the anti-TNF-related costs are compensated by a reduction of hospitalization costs. This may corroborate the notion that investment in expensive medical therapy might be cost-effective from a pharmaco-economical point of view,presuming that a reduction in hospital admission is equal with an improvement in quality-of-life. Whether long-term anti-TNF therapy is truly cost-effective in IBD has yet to be determined. Further careful monitoring of changes in the costs of care for IBD patients will aid timely, sensible economic decision-making.

REFERENCES

1. van der Valk ME, Mangen MJ, Leenders M, et al. Healthcare costs of inflammatory bowel disease have shifted from hospitalisation and surgery towards anti-TNF alpha therapy: results from the COIN study. Gut 2014;63:72-9.
2. Stark R, Konig HH, Leidl R. Costs of inflammatory bowel disease in Germany. Pharmacoeconomics 2006;24:797-814.
3. Odes S, Vardi H, Friger M, et al. Cost analysis and cost determinants in a European inflammatory bowel disease inception cohort with 10 years of follow-up evaluation. Gastroenterology 2006;131:719-728.
4. Kappelman MD, Rifas-Shiman SL, Porter CQ, et al. Direct health care costs of Crohn's disease and ulcerative colitis in US children and adults. Gastroenterology 2008;135:1907-1913.
5. Juan J, Estiarte R, Colome E, et al. Burden of illness of Crohn's disease in Spain. Dig Liver Dis 2003;35:853-861.
6. Gibson TB, Ng E, Ozminkowski RJ, et al. The direct and indirect cost burden of Crohn's disease and ulcerative colitis. J Occup Environ Med 2008;50:1261-1272.
7. Blomqvist P, Ekbom A. Inflammatory bowel diseases: health care and costs in Sweden in 1994. Scand J Gastroenterol 1997;32:1134-1139.
8. Bassi A, Dodd S, Williamson P, et al. Cost of illness of inflammatory bowel disease in the UK: a single centre retrospective study. Gut 2004;53:1471-1478.
9. Bodger K. Cost of illness of Crohn's disease. Pharmacoeconomics 2002;20:639-652.
10. Mesterton J, Jonsson L, Almer SH, et al. Resource use and societal costs for Crohn's disease in Sweden. Inflamm Bowel Dis 2009;15:1882-1890.
11. Prenzler A, Bokemeyer B, von der Schulenburg JM, et al. Health care costs and their predictors of inflammatory bowel diseases in Germany. Eur J Health Econ 2011;12:273-283.
12. Drummond M, Manca A, Sculpher M. Increasing the generalizability of economic evaluations: recommendations for the design, analysis, and reporting of studies. Int J Technol Assess Health Care 2005;21:165-171.
13. Burisch J, Vardi H, Pedersen N, et al. Costs and resource utilization for diagnosis and treatment during the initial year in a European inflammatory bowel disease inception cohort: an ECCO-EpiCom Study. Inflamm Bowel Dis 2015;21:121-131.
14. Kalkan A, Hallert E, Bernfort L, et al. Costs of rheumatoid arthritis during the period 1990-2010: a register-based cost-of-illness study in Sweden. Rheumatology 2014;53:153-160.
15. Huscher D, Mittendorf T, von HU, et al. Evolution of cost structures in rheumatoid arthritis over the past decade. Ann Rheum Dis 2015;74:738-745.
16. Bernstein CN, Loftus EV, Jr., Ng SC, et al. Hospitalisations and surgery in Crohn's disease. Gut 2012;61:622-629.
17. Targownik LE, Singh H, Nugent Z, et al. The Epidemiology of Colectomy in Ulcerative Colitis: Results From a Population-Based Cohort. Am J Gastroenterol 2012;107:1228-1235.
18. Loly C, Belaiche J, Louis E. Predictors of severe Crohn's disease. Scand J Gastroenterol 2008;43:948-954.
18. Kappelman MD, Rifas-Shiman SL, Porter CQ et al. Direct health care costs of Crohn's disease and ulcerative colitis in US children and adults. Gastroenterology 2008;135:1907-13.
20. Solberg IC, Vatn MH, Hoie O, et al. Clinical course in Crohn's disease: results of a Norwegian population-based ten-year follow-up study. Clin Gastroenterol Hepatol 2007;5:1430-1438.

21. Beaugerie L, Seksik P, Nion-Larmurier I, et al. Predictors of Crohn's disease. Gastroenterology 2006;130:650-656.
22. Hoie O, Wolters F, Riis L, et al. Ulcerative colitis: patient characteristics may predict 10-yr disease recurrence in a European-wide population-based cohort Am J Gastroenterol. 2007;102:1692-1701.
23. Moum B, Ekbom A, Vatn MH, et al. Clinical course during the 1st year after diagnosis in ulcerative colitis and Crohn's disease. Results of a large, prospective population-based study in southeastern Norway, 1990-93. Scand J Gastroenterol 1997;32:1005-1012.
24. Bitton A, Peppercorn MA, Antonioli DA, et al. Clinical, biological, and histologic parameters as predictors of relapse in ulcerative colitis. Gastroenterology 2001;120:13-20.
25. Etchevers MJ, Aceituno M, Garcia-Bosch O, et al. Risk factors and characteristics of extent progression in ulcerative colitis. Inflamm Bowel Dis 2009;15:1320-1325.
26. van der Have M, Mangen MJ, van der Valk ME, et al. Effect of aging on healthcare costs of inflammatory bowel disease: a glimpse into the future. Inflamm Bowel Dis 2014;20:637-645.

Supplementary Table 1 (see Chapter 3 - supplementary Table 1)

Supplementary Table 2. Possible predictive factors for future high costs

	Study references		
Variable	**Predictors of healthcare costs**	**Predictors of productivity losses or costs**	**Predictors of poor prognosis**
Female gender	(1)	(4)	(6;7)
Age	(2;3)	(2;4;5)	(6-10)
Smoking			(7)
Education level		(4)	
Short disease duration	(1)		
Penetrating disease course	(2;11)		(8;10;12)
Disease localisation			(6;9;10;12)
Disease activity/ flare	(1;2;11)	(2;4;5;11)	(7;13)
Hospitalization	(1)		
Surgery		(4;5)	
Ileostomy	(11)		
Anti TNFa therapy	(1)	(4)	
Steroids		(4;5)	(8;12)
Joint complaints		(4)	
Chronic back pain		(4)	
Depression		(4)	

References

1. Prenzler A, Bokemeyer B, von der Schulenburg JM, et al. Health care costs and their predictors of inflammatory bowel diseases in Germany. Eur J Health Econ. 2011;12:273-283.
2. Mesterton J, Jonsson L, Almer SH, et al. Resource use and societal costs for Crohn's disease in Sweden. Inflamm Bowel Dis. 2009;15:1882-1890.
3. Kappelman MD, Rifas-Shiman SL, Porter CQ, et al. Direct health care costs of Crohn's disease and ulcerative colitis in US children and adults. Gastroenterology. 2008;135:1907-1913.
4. van der Valk ME, Mangen MJ, Leenders M, et al. Risk factors of work disability in patients with inflammatory bowel disease - A Dutch nationwide web-based survey: Work disability in inflammatory bowel disease. J Crohns Colitis. 2013.
5. Hoivik ML, Moum B, Solberg IC, et al. Work disability in inflammatory bowel disease patients 10 years after disease onset: results from the IBSEN Study. Gut.
6. Henriksen M, Jahnsen J, Lygren I, et al. Ulcerative colitis and clinical course: results of a 5-year population-based follow-up study (the IBSEN study). Inflamm Bowel Dis. 2006;12:543-550.
7. Hoie O, Schouten LJ, Wolters FL, et al. Ulcerative colitis: no rise in mortality in a European-wide population based cohort 10 years after diagnosis. Gut. 2007;56:497-503.
8. Beaugerie L, Seksik P, Nion-Larmurier I, et al. Predictors of Crohn's disease. Gastroenterology. 2006;130:650-656.
9. Wolters FL, Russel MG, Sijbrandij J, et al. Phenotype at diagnosis predicts recurrence rates in Crohn's disease. Gut. 2006;55:1124-1130.
10. Solberg IC, Vatn MH, Hoie O, et al. Clinical course in Crohn's disease: results of a Norwegian population-based ten-year follow-up study. Clin Gastroenterol Hepatol. 2007;5:1430-1438.
11. van der Valk ME, Mangen MJ, Leenders M, et al. Healthcare costs of inflammatory bowel disease have shifted from hospitalisation and surgery towards anti-TNFalpha therapy: results from the COIN study. Gut. 2012.
12. Loly C, Belaiche J, Louis E. Predictors of severe Crohn's disease. Scand J Gastroenterol. 2008;43:948-954.
13. Solberg IC, Lygren I, Jahnsen J, et al. Clinical course during the first 10 years of ulcerative colitis: results from a population-based inception cohort (IBSEN Study). Scand J Gastroenterol. 2009;44:431-440.

Supplementary Table 3. Number of responders per time point

Time point	Number of CD patients	Number of UC patients
Baseline	1,558	1,056
3 months	1,307	915
6 months	918	640
9 months	859	640
12 months	938	700
15 months	917	682
18 months	879	643
21 months	842	619
24 months	736*	566*

**Response rate CD: 47%, UC: 54%*

Supplementary Table 4. Comparison between patients who completed the two year follow up (responders) and patients who were lost to follow up (non-responders)

	CD		UC	
	Responders n=737	Non-responders n=821	Responders n= 566	Non-responders n=490
Male gender (%)	295 (40.0)	279 (34.0)	300 (53.0)	228 (46.5)
Age – years (± SD)	50.5 (13.5)	45.6 (13.8)	52.4 (12.9)	48.0 (13.7)
Disease duration – median (IQR)	18.2 (10.1-18.2)	16.8 (11.4)	16.0 (9.0-16.0)	13.9 (10.0)
Disease localisation (%)				
Large bowel	204 (27.7)	227 (27.6)	566 (100)	490 (100)
Small bowel	152 (20.6)	154 (18.8)	n/a	n/a
Both small and large bowel	361 (49.0)	407 (49.6)	n/a	n/a
Unknown	20 (2.7)	33 (4.0)	n/a	n/a
Penetrating disease course (%)	348 (47.2)	396 (48.2)	n/a	n/a
Disease activity (%)	618 (16.1)	117 (14.3)	452 (20.1)	98 (20.0)
Abdominal surgery (%)	416 (56.4)	427 (52.0)	106 (21.3)	89 (18.2)

SD: Standard deviation; IQR: Interquartile range; n/a: not applicable.

Supplementary Table 5A. Average healthcare costs/patients per 3 months in CD patients (€)

Months	Surgery	Hospitalization	Outpatient clinic	Diagnostic procedures	Medication use (exc. Anti-TNFa)	Anti-TNFa
3	996	319.23	119.93	40.81	103.84	1,048.1
6	13.33	334.31	111.47	38.14	106.12	1,042.55
9	3.34	340.89	102.75	35.9	103.09	1,093.27
12	7.63	244	107.52	41.36	103.97	1,053.93
15	7.41	275.51	96.78	35.06	103.62	1,027.32
18	1.53	251.89	86.66	32.65	100.53	1,070.62
21	2.24	268.91	85.61	33.66	102.28	1,090.59
24	1.83	195.61	74.1	36.34	99.24	1,044.54

Supplementary Table 5B. Average healthcare costs/patients per 3 months in UC patients (€)

Months	Surgery	Hospitalization	Outpatient clinic	Diagnostic procedures	Medication use (exc. Anti-TNFa)	Anti-TNFa
3	8,36	130,58	68,46	29,95	163,87	181.35
6	8,09	87,89	63,67	26,81	172,27	194.09
9	2,7	122,25	64,56	30,7	164,98	253.22
12	5,17	118,17	63,97	30,37	169,29	243.99
15	5,06	87,24	58,05	30,68	163,78	237.63
18	0	60,47	55,21	29,33	163,73	280.71
21	0	37,19	50,37	24,51	159,47	251.6
24	3,05	82,87	55,23	40,84	161,56	223.72

Supplementary Table 5C. Proportion of healthcare costs in CD (%)

Months	Surgery	Hospitalization	Outpatient clinic	Diagnostic procedures	Medication use (exc. Anti-TNFa)	Anti-TNFa
3	0.61	19.44	7.30	2.49	6.32	63.84
6	0.81	20.31	6.77	2.32	6.45	63.34
9	0.20	20.30	6.12	2.14	6.14	65.11
12	0.49	15.66	6.90	2.65	6.67	67.63
15	0.48	17.82	6.26	2.27	6.70	66.46
18	0.10	16.32	5.61	2.11	6.51	69.35
21	0.14	16.98	5.41	2.13	6.46	68.88
24	0.13	13.47	5.10	2.50	6.84	71.95

Supplementary Table 5D.. Proportion of healthcare costs in UC (%)

Monthts	Surgery	Hospitalization	Outpatient clinic	Diagnostic procedures	Medication use (exc. Anti-TNFa)	Anti-TNFa
3	1.44	22.41	11.75	5.14	28.13	31.13
6	1.46	15.90	11.52	4.85	31.16	35.11
9	0.42	19.15	10.11	4.81	25.84	39.66
12	0.82	18.73	10.14	4.81	26.83	38.67
15	0.87	14.98	9.97	5.27	28.12	40.80
18	0.00	10.26	9.37	4.98	27.78	47.62
21	0.00	7.11	9.63	4.69	30.48	48.09
24	0.54	14.61	9.74	7.20	28.48	39.44

Chapter 5

Comparison of costs and quality of life in ulcerative colitis patients with an ileal pouch-anal anastomosis, ileostomy and anti-TNF therapy

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J Crohns and Colitis (in press)

ABSTRACT

Background and aims:

More data is warranted on the economic impact of different treatment strategies in ulcerative colitis (UC) patients. We compared the costs and quality-of-life of UC patients with a pouch reconstruction, an ileostomy or anti-TNF therapy.

Methods:

UC patients filled out 3-monthly questionnaires for 2 years. Differences in 3-monthly healthcare costs, productivity costs and patient costs were tested using mixed model analysis. Quality-of-life was assed employing the EQ-5D-3L and the inflammatory bowel disease questionnaire (IBDQ).

Results:

Out of 915 UC patients, 81 (9%) had a pouch, 48 (5%) an ileostomy, and 34 (4%) were on anti-TNF therapy. Anti-TNF-treated patients reported high UC related-healthcare costs per 3 months (€5,350). Medication use accounted for 92% of the healthcare costs. UC-attributable healthcare costs were 3 times higher in ileostomy patients compared to pouch patients, €1,581 versus €407 [p<0.01]. Main cost drivers in ileostomy patients were healthcare costs and ileostomy supplies (2% and 23% of healthcare costs, respectively). In pouch patients, the main cost driver was hospitalisation, accounting for 50% of the healthcare costs. Productivity losses did not differ between pouch and ileostomy patients (€483 versus €377 [p<0.23]), but was significantly higher in anti-TNF (€1,085). No difference was found in IBDQ-scores, but pouch patient were found to have higher QALYs than ileostomy patients and anti-TNF-treated patients (0.90 (IQR 0.78-1.00) versus 0.84 (IQR 0.78-1.00) and 0.84 (IQR 0.69-1.00) respectively [p<0.01]).

Conclusion:

Patients receiving anti-TNF therapy reported the highest healthcare cost, in which medication use was the major cost driver. Ileostomy patients were three times more expensive than pouch patients due to frequent hospitalisation and ileostomy supplies.

INTRODUCTION

The management of ulcerative colitis (UC) has changed dramatically over the past 10 years with an increasing role of anti-TNF drugs in patients failing conservative therapy.[1] However, anti-TNF therapy is expensive and accounts for one third of the UC-related healthcare costs.[2]

A restorative proctocolectomy with construction of an ileoanal pouch-anal anastomosis (pouch) is an alternative treatment option. Pouch surgery preserves body image and restores the conservative route of defecation.[3] Yet, the construction of a pouch is a difficult surgical procedure and complications are common, such as the occurrence of pouchitis,[4-7] and a decreased fecundity in young women.[8] Recently, a significant reduction of complications after pouch surgery has been reported and overall success rates of 96.3% after five year, 92.4% after ten year and 92.1% after twenty years have been described.[9]

In the emergency setting or in case of contraindications for pouch surgery, such as an impaired sphincter function, significant comorbidities, or an unclear diagnosis (IBD-unclassified), the surgical procedure of choice is a colectomy with an end-ileostomy and a closed rectal stump.[3] A number of studies have shown that this procedure is safe in the emergency setting with a post-operative complication rate varying from 23% to 33%.[10,11] In the absence of contraindications, pouch reconstruction may be considered over time in these cases as well.

To date, no studies comparing long-term outcomes of medically versus surgically-treated patients have been published. In light of the escalating healthcare costs, more data on the economic impact of different treatment strategies are warranted in UC patients failing conservative treatment. We aimed to study the costs and quality of life of UC patients with a pouch, an ileostomy or anti-TNF using a cross-sectional prospectively followed cohort.

MATERIAL AND METHODS

Study design

In 2010 we initiated the 'Costs Of Inflammatory bowel disease in the Netherlands or COIN study' in order to evaluate the total costs of IBD. We have published the cohort organization and results on internal validity of our cohort in detail elsewhere.[2,12]. In summary, between October 2010 and October 2011 we invited by letter all identified

IBD patients aged 18 years or older from seven university hospitals and seven general hospitals to participate in the COIN study. Identification was based on the Diagnosis Treatment Combinations (DTCs). We developed a secure web-based questionnaire to obtain longitudinal data on costs and quality of life. All patients were followed-up for two years at three-month intervals. The web-based questionnaires contained question on demographic and clinical characteristics, as well as questions on costs and quality of life. Demographic characteristics included sex, age, age at diagnosis, education level, work status, and smoking status. Clinical characteristics included subtype of IBD, disease duration and localization, penetrating disease course, and self-reported disease activity.

Patient population

For the current analysis, we compared three groups of UC patients. The first group consisted of UC patients who have had pouch surgery before start of the study. The second group were patients who reported to have had a colectomy with formation of an ileostomy before the start of the study. Finally, the third group consisted of UC patients on infliximab or adalimumab therapy (anti-TNF-therapy) group.

UC-related costs

We analyse UC-related costs from a societal perspective, including three main cost categories, as suggested by Drummond et al., outlined in Table 1.[13] Healthcare costs were calculated by multiplying self-reported units of UC-related resource utilization by their unit prices (see Supplementary Table S1). To assess productivity losses, we used self-reported sick leave of employed patients from paid work. The number of sick leave days per week was limited to maximum 5 days per week. Hours of sick leave were valued using age- and sex-specific unit prices as presented in Supplementary Table S1. Patient costs, including deductibles for healthcare insurances, over the counter drugs and travel costs, were calculated according to patient specifications. All costs are expressed in Euros for the year 2011. Discounting was not applied due to the short time period considered (i.e. 2 years).

Table 1. UC-related cost categories and used quality-of-life questionnaires.

Healthcare	Productivity	Patient	Quality-of-life
Surgery Hospitalisation Outpatient clinic Medication use Diagnostics Procedures Ileostomy supplies	Absenteeism (the number of sick leave days from paid work)	Out of pocket costs (e.g. travel costs, deductibles for healthcare insurance, over the counter drug use)	Disease specific: Inflammatory bowel disease questionnaire Generic: Euroqol Group EQ-5D-3L questionnaire

Quality-of-life

To assess disease specific quality-of-life, we used the Dutch version of the Inflammatory Bowel Disease Questionnaire (IBDQ).[14] In addition, the EuroQol group EQ-5D-3L questionnaire (EQ-5D-3L) was employed as a generic tool for quality-of-life measurement.[15] The IBDQ consists of 32-items, grouped into four dimensions: bowel symptoms, systemic symptoms, emotional function and social function. The answers are rated on a graded response range from "worst" (1) to "best" (7) and a possible total score of minimum 32 (i.e. "worst") to maximum 224 (i.e. "best" score). The EQ-5D-3L consists of a descriptive system and comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 3 levels: 1) no problems, 2) some problems and 3) extreme problems. EQ-5D health states, defined by the EQ-5D descriptive system, are converted into a weighted health state index (utility), the so-called quality-adjusted life year (QALY) using the Dutch EQ-5D tariff elicited from a Dutch general population samples.[16] The so-obtained QALY lie on a scale on which full health has a value of 1 and dead a value of 0.

Ethical considerations

The study was centrally approved by the Ethics Committee of the University Medical Centre Utrecht.

Statistical analysis

Data analysis was performed using SPSS version 18.0 (Chicago, Il, USA). Descriptive statistics were used to characterize the three study groups. Means and medians were reported with a standard deviation (SD) and an inter quartile range (IQR), respectively. Differences amongst baseline characteristics were assessed by one-way ANOVA for continuous variables and χ^2 for dichotomous variables. To account for missing data, we used a generalized mixed model to calculate the three-month costs and quality-of-life. Despite the skewed nature of cost data, we reported mean costs (95% CI), as overall total costs then can be calculated. Quality-of-life scores were presented as median scores with an IQR.

RESULTS

Figure 1 shows the study flowchart. Of the 915 included UC patients in the COIN-study, 163 UC patients met the inclusion criteria, including 81 (9%) with a pouch, 48 (5%) with an ileostomy, and 34 (4%) on anti-TNF therapy. In total 51/81 (63%) pouch patients, 27/48 (56%) ileostomy patients and 25/34 (74%) patients receiving TNF-therapy filled out the

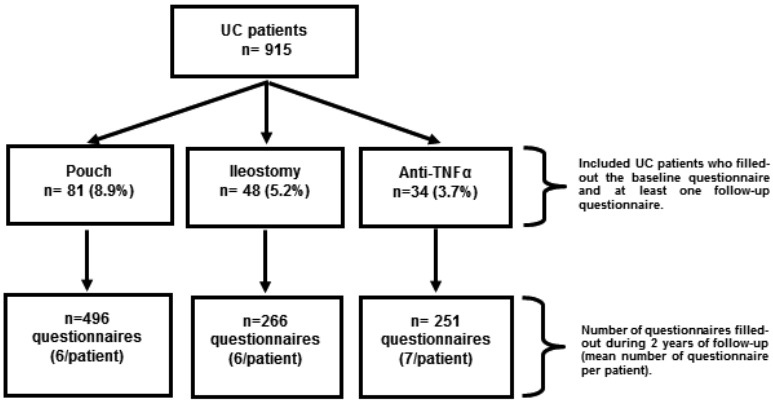


Figure 1. Study flowchart

two-year follow up questionnaire. The number of responders per 3-month intercept is provided in Supplementary Table S2.

Table 2 shows the baseline characteristics of the three study-groups. Patients with an ileostomy were older than patients with a pouch or patients on anti-TNF [p<0.07]. Patients on anti-TNF therapy were more likely to be female compared to stoma and pouch patients, although this did not reach significance [p=0.48]. The median time since surgery was not different between pouch and ileostomy patients [p=0.77]. Clinical disease activity was reported by 35% of the patients on anti-TNF therapy. The mean treatment duration of anti-TNF therapy was 2 years in infliximab and 1 year in adalimumab [p=0.77].

Table 2. Baseline characteristics of UC-patients with a pouch, ileostomy versus anti-TNF patients

	Pouch n=81	Ileostomy n=48	Anti-TNF n= 34	P-value
Demographic characterises				
Female gender (%)	36 (44.4)	21 (43.8)	19 (55.9)	0.48
Age - years (± SD)	46.7 (12.1)	53.4 (11.6)	45.4 (10.8)	0.07
Smoking (%)				0.61
Current	7 (8.6)	1 (2.1)	2 (5.9)	
Never	49 (60.5)	30 (62.5)	17 (50.0)	
Ex-smoker	25 (30.9)	17 (35.4)	15 (44.1)	
Weight – kg (± SD)	74 (8)	75 (10)	74 (10)	0.58
Employed (% - 18-64 year	44 (71.0)	17 (56.7)	19 (67.9)	0.39
Disabled (%) – 18-64 year				

Clinical characteristics				
Disease duration (years) – median (IQR)	15 (8.9)	18 (11.3)	12.6 (7.8)	0.10
Self-reported disease activity (%)	n/a	n/a	12 (35.3)	n/a
Bowel complaints	14 (17.3)	6 (12.5)	n/a	0.47*
Time since surgery (years) – median (IQR)	12 (3 -20)	11 (2 -22)	n/a	0.63*
IBDQ total – mean (SD)	187 (172-198)	181 (147-200)	177 (148-194)	0.17
QALY - mean (SD)	0.90 (0.78-1.00)	0.84 (0.65-1.00)	0.84 (0.69-1.00)	0.38
Treatment-related characteristics				
Abdominal surgery in the past	n/a	n/a	2 (5.9)	n/a
Medication use in the past (%)				
Corticosteroids	69 (85.2)	41 (85.4)	29 (85.3)	
Immunomodulators	40 (49.4)	19 (39.6)	27 (79.4)	<0.01
Treatment duration				
Infliximab	n/a	n/a	2.0 (0.7-2.9)	0.77**
Adalimumab	n/a	n/a	1.1.(0.3-1.9)	

Used abbreviations: SD: standard deviation; IQR: interquartile range; IBDQ: inflammatory bowel disease questionnaire; QALY: quality-adjusted life years.

*Pouch versus ileostomy, **Infliximab versus adalimumab

UC-related healthcare use and associated costs

Table 3 presents the mean 3-month resource use within healthcare. Anti-TNF patients were more likely to visit the gastroenterologist [p<0.01], a specialized nurse [p<0.01], an internist [p<0.01] and rheumatologist [p<0.01] as compared to pouch and ileostomy patients. Ileostomy patients visited a specialized nurse and surgeon more often compared to pouch patients [p=0.01]. Colonoscopies and ileoscopies were more often performed in anti-TNF-treated patients compared with pouch and ileostomy patients. 'No medication use' was significantly more encountered in ileostomy patients as compared to pouch patients [p<0.01]. Ileostomy patients were more often hospitalized as compared to patients from the pouch group [p<0.01]. In the anti-TNF group, 80% received infliximab and 20% received adalimumab [p<0.01]. Of all anti-TNF-treated patients, 42% received combination therapy with immunomodulators. Additional data on healthcare use is presented as supplementary tables S3-S5.

Figure 2. depicts the mean 3-monthly healthcare costs per patient. The mean 3-monthly healthcare costs of anti-TNF patients were €5,350, which was significant higher compared to pouch and ileostomy patients [p<0.01]. Medication use was the main cost driver, accounting for 92% of the healthcare costs. Healthcare costs of ileostomy patients were at least 3-times higher compared with pouch patients, €1,581 versus €407 [p<0.01]. Hospitalisation was the main cost driver in pouch patients (50% of the total healthcare costs), followed by medication use, accounting for 23% of the healthcare costs. The main

Table 3. Mean healthcare use per 3-months (based on all questionnaires filled-out during 2-years of follow up) in UC patients with a pouch, ileostomy and anti-TNF therapy.

	Pouch n= 496 (%)	Ileostomy n= 266 (%)	Anti-TNF n= 251 (%)	P-value
Outpatient clinic				
Gastroenterologist	134 (27.0)	81 (30.5)	116 (46.2)	<0.01
Specialized nurse	53 (10.7)	77 (28.9)	92 (36.7)	<0.01
Internist	3 (0.6)	13 (4.9)	17 (6.8)	<0.01
Dietician	13 (2.6)	16 (6.0)	11 (4.4)	0.06
Surgeon	20 (4.0)	27 (10.2)	2 (0.8)	<0.01
Rheumatologist	3 (0.6)	10 (3.8)	12 (4.8)	<0.01
Dermatologist	4 (0.8)	2 (0.8)	7 (2.8)	0.05
Psychiatrist	2 (0.4)	3 (1.1)	-	0.17
Occupational physician	3 (0.6)	4 (1.5)	6 (2.4)	0.12
Emergency room	14 (2.8)	14 (5.3)	4 (1.6)	0.05
General practitioner during day-time	26 (5.2)	16 (6.0)	17 (6.8)	0.69
General practitioner (during night/ weekend-time)	15 (3.0)	15 (5.6)	12 (4.8)	0.19
Diagnostics procedures				
Laboratory	31 (6.2)	20 (7.5)	38 (15.1)	<0.01
Colonoscopy	11 (2.2)	7 (2.6)	28 (11.2)	<0.01
MRI scan	2 (0.4)	2 (0.8)	2 (0.8)	0.74
CT scan	3 (0.6)	3 (1.1)	-	0.25
Abdominal X-ray	4 (0.8)	2 (0.8)	2 (0.8)	0.99
Ultrasonography	4 (0.8)	2 (0.8)	4 1.6)	0.53
DXA scan	7 (1.4)	3 (1.1)	4 (1.6)	0.900
Medication use				
None	302 (61.0)	148 (70.2)	n/a	n/a
Adalimumab	5 (1.0)	4 (1.5)	49 (20.0)	n/a
Infliximab	3 (0.6)	-	204 (80.0)	n/a
Mesalazine	24 (4.8)	34 (12.8)	144 (57.4)	n/a
Azathioprine	4 (0.8)	8 (3.0)	55 (21.9)	n/a
Mercaptopurine	4 (0.8)	1 (0.4)	37 (14.7)	n/a
Methotrexate	6 (1.2)	5 (1.9)	15 (6.0)	n/a
Corticosteroids	35 (6.2)	8 (3.0)	35 (13.9	n/a
Antibiotics	30 (6.0)	-	-	
Ileostomy supplies	266 (100)			
Hospitalisation	18 (3.6)	19 (7.1)	12 (4.8)	0.10
Surgery	7 (1.4)	3 (1.1)	1 (0.4)	0.45

CI, Confidence Interval; CT, Computer tomography; MRI, Magnetic Resonance Imaging; DXA, Dual-emission X-ray absorptiometry

*comparison between pouch and ileostomy

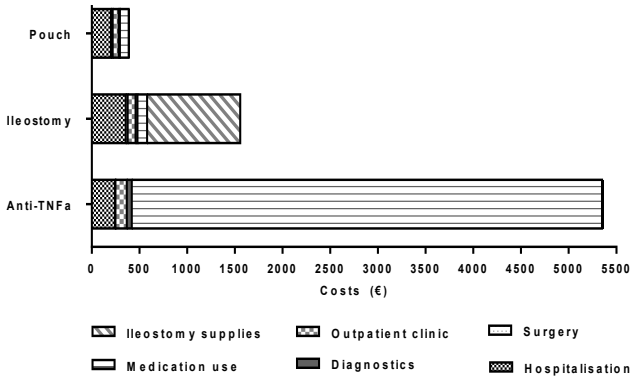


Figure 2. Mean three-monthly healthcare costs of UC patients with a pouch, ileostomy and anti-TNF therapy

cost drivers in ileostomy patients were ileostomy supplies (62%) and hospitalisation (23%). More information regarding healthcare costs is presented as supplementary tables S3-S5.

Productivity losses and patient costs

Productivity losses due to sick leave from paid work were higher in anti-TNF-treated patients than in pouch and ileostomy patients (€1,085 versus €483 and €377 [p<0.01]), Figure 3. Detailed data on sick leave is presented as Supplementary Table S6. Patient costs per 3 months were €42 in pouch patients, €51 in ileostomy group and €61 in the anti-TNF group (p=0.06). According to patient specifications, most expenditures were due to co-payments for medical costs not covered by the healthcare insurance, vitamins and other over-the-counter drugs (e.g. anti-diarrheal drugs, psyllium fiber) and travel costs.

Quality-of-life

We found no difference between the median (IQR) IBDQ score in pouch, ileostomy and anti-TNF-treated patients, 183 (156-198) versus 181 (165-199) and 181 (159-199), respectively [p=0.27]. However, as presented in Figure 4A and Table S7A, patients with a pouch had lower IBDQ subscores related to bowel symptoms compared to patients in the ileostomy and anti-TNF group [p<0.01].

Employing the EQ-5D index, QALYs were calculated for the three patients groups. Pouch patients were found to have a significant higher median (IQR) QALY (0.90 (0.78-1.00)), compared with ileostomy patients (0.84 (0.78-1.00)) and anti-TNF-treated patients (0.84

(0.69-1.00)) [p<0.01]. Figure 4B and Table S7B show the five dimensions of the EQ-5D-3L. Patients with an ileostomy were found to have more mobility-related problems [p<0.01], while anti-TNF-treated patients had higher pain and discomfort scores as compared to the other groups [p<0.01].

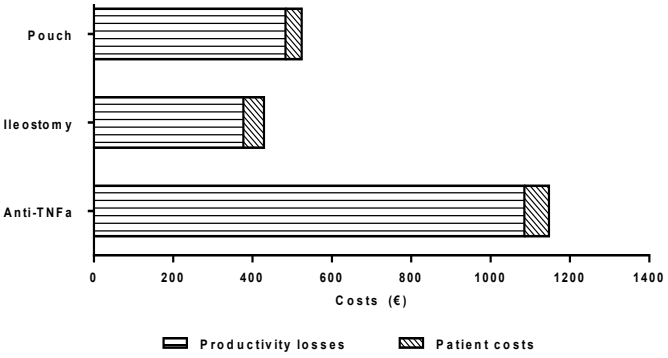
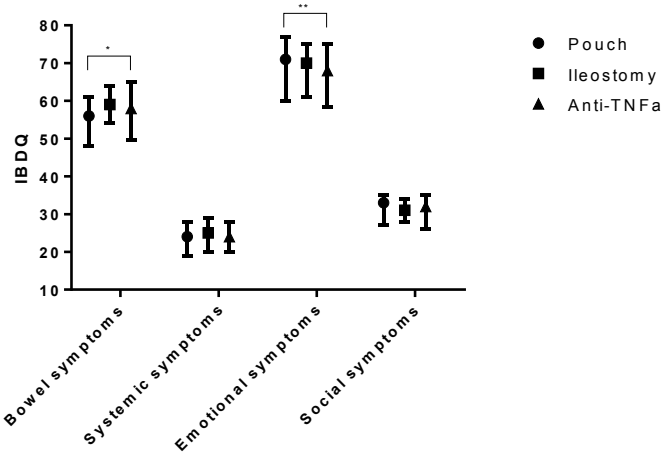


Figure 3. Mean three-monthly productivity losses and patient costs of UC patients with a pouch, ileostomy and anti-TNF therapy.



*Differences in bowel symptoms [p<0.01]
**Differences in emotional symptoms [p=0.07]

Figure 4A. IBDQ subscores in UC patients with a pouch, ileostomy and anti-TNF therapy (median and IQR)

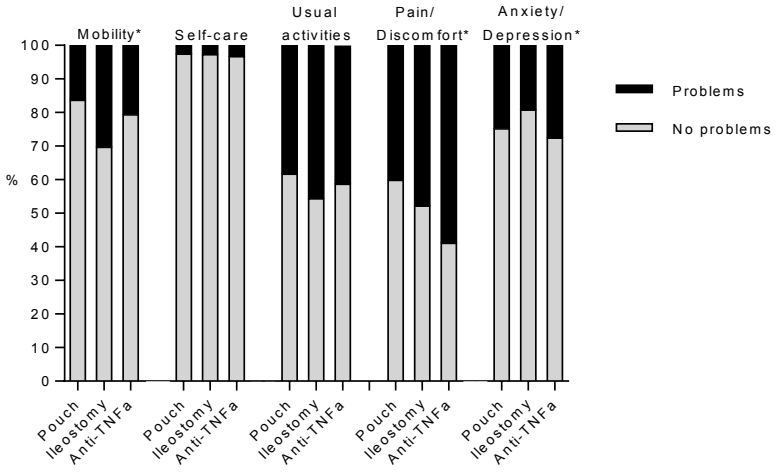


Figure 4B. Proportion of reported problems (%) by EQ- 5D in UC patients with a pouch, ileostomy and anti-TNF therapy

Figure legend: No problems (EQ-5D level 1: no problem), problems (EQ-5D level 2: some problems combined with EQ-5D level 3: extreme problems). *Significant differences for the dimensions mobility and pain/discomfort [p<0.01] .

DISCUSSION

Before the introduction of anti-TNF drugs, healthcare costs in UC patients who had previously undergone proctocolectomy were comparable with patients on maintenance medical therapy.[17] We expected the introduction of anti-TNF therapy for induction and maintenance of remission in UC to have profoundly influenced the balance of healthcare costs and quality-of-life in these treatment groups.

In this unique representative cohort to document the cost profiles of subgroups of UC patients, we confirmed that the average 3-monthly healthcare costs in UC patients treated with anti-TNF therapy were indeed substantively higher than in patients in whom a colectomy was performed. In addition, healthcare costs of ileostomy patients were 3-times as high as the costs in pouch patients, mainly due to hospitalization and costs of ileostomy supplies.

The high costs of patients on anti-TNF therapy did not come as a surprise. We recently reported that anti-TNF therapy, which was prescribed in just 4% of the 915 UC patients, was one of the major cost drivers, accounting for 31% of all healthcare costs.[2] Comparison with previous studies is difficult, because most studies have been conducted in the pre-biological era. For example, a recent study from Olmsted County showed com-

parable healthcare costs in medically and surgically treated UC patients.[17] However, anti-TNF therapy was prescribed in only one patient and most patients were in clinical remission on conventional therapy such as mesalazine and immunosuppressives. In line with our data, the authors from this study found that end-ileostomy was associated with higher healthcare costs, even without taking ileostomy supplies into account.Reported cumulative frequency rates of pouchitis 10-11 years after IPAA surgery range from 23% to 46%.[18,19] In our study, only 17% of pouch patients reported bowel complaints in a window of 2 years of follow-up. Even if pouchitis was underrepresented in our cohort due to selection bias, this could not have explained the difference in costs between the two post-surgery groups.

Obviously, this observational study was not based on comparable groups of patients. Especially the differences in the 'post-surgery' groups and the patients receiving anti-TNF therapy who still have disease activity preclude firm conclusions regarding the long-term consequences of the different treatment strategies. A randomized controlled trial would undoubtedly provide superior data, but will probably never be performed. Of note, in an earlier Olmsted county study an almost 50% drop of healthcare costs was observed after 2 years following surgery in UC patients who failed conventional therapy. [20] Obviously, a considerable decrease in healthcare costs is not anticipated in patients receiving anti-TNF-therapy who will continue therapy once they have achieved clinical remission.

Productivity losses due to sick leave of paid work were the highest among patients on anti-TNF therapy. These data should be interpreted with caution, given the differences in age and educational level between groups, with more anti-TNF patients within the working age group. Evidently, disease activity plays a major role in the loss of productivity in our patients, in particular in the anti-TNF treated group, as reported previously.[12, 21-23] Furthermore, we did not incorporate productivity losses due to work disability, as we did not know the cause of work disability. However, significantly more patients in the pouch and ileostomy groups were work disabled, therefore we have probably underestimated the productivity losses in these groups.

We found no differences in IBQD-scores between the three groups. There are no studies in which quality-of-life has been compared between anti-TNF therapy versus surgery. However, our findings are in line with a previous study, in which quality-of-life was compared in ileostomy versus pouch patients using the IBDQ.[24] However, employing the generic EQ-5D-3L, we found a difference between pouch and ileostomy patients. This is in contrast with previous studies (employing generic SF-36), in which no difference was found between pouch and ileostomy patients.[25,26] It could be that previous studies

were underpowered to detect differences in quality-of-life. Looking at the absolute QALY in pouch (0.90) and ileostomy (0.84) patients one might conclude that the overall quality-of-life-in the surgery group is good.

Due to our study design, the outcome could be biased by patient' preferences. UC patients occasionally decline restorative surgery after subtotal colectomy for a number of reasons, such as the risk of a decreased fecundity in young women, the risk of recurring pouchitis or perioperative complications, while, patients with an pouch often put up with the disadvantages and potential complications of a pouch because an ileostomy is not acceptable to them.

The strength of our study is the uniqueness of our cost data, and the detailed characterization of the patients and their cost profiles. Our findings might help to guide clinical decision-making in UC patients who fail conservative medical therapy and may be used for economic modelling. An important limitation of our study was the risk of confounding by indication. This is due to the fact that patients were not randomized for surgery or medical treatment. A randomized controlled trial would undoubtedly provide superior data, but will probably never be performed since most physicians consider pouch reconstruction the procedure of choice as reflected in the majority of international guidelines. To underscore the internal validity of our cohort, we performed a non-responder survey, and found no differences between responders and non-responders, as previous published.[2]

In conclusion, this is the first study aiming to provide an integrated assessment of the healthcare use, work absenteeism and associated costs, and the quality-of-life in UC patients with an ileostomy, pouch or on anti-TNF therapy. Despite some shortcomings we were able to demonstrate that UC patients treated with anti-TNF therapy had the highest healthcare expenditures. Remarkably, patients with an ileostomy had higher healthcare costs compared to the patients with a pouch.

REFERENCES

1. Dignass A, Lindsay JO, Sturm A, *et al.* Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 2: current management. J Crohns Colitis 2012;6: 991-1030.
2. van der Valk ME, Mangen MJ, Leenders M, *et al.* Healthcare costs of inflammatory bowel disease have shifted from hospitalisation and surgery towards anti-TNFalpha therapy: results from the COIN study. Gut 2012.
3. Oresland T, Bemelman WA, Sampietro GM, *et al.* European evidence based consensus on surgery for ulcerative colitis. J Crohns Colitis 2015;9:4-25.
4. Lohmuller JL, Pemberton JH, Dozois RR, Ilstrup D, van HJ. Pouchitis and extraintestinal manifestations of inflammatory bowel disease after ileal pouch-anal anastomosis. Ann Surg 1990;211: 622-627.
5. Salemans JM, Nagengast FM, Lubbers EJ, *et al.* Postoperative and long-term results of ileal pouch-anal anastomosis for ulcerative colitis and familial polyposis coli. Dig Dis Sci 1992;37:1882-1889.
6. Simchuk EJ, Thirlby RC. Risk factors and true incidence of pouchitis in patients after ileal pouch-anal anastomoses. World J Surg 2000;24:851-856.
7. Stahlberg D, Gullberg K, Liljeqvist L, *et al.* Pouchitis following pelvic pouch operation for ulcerative colitis. Incidence, cumulative risk, and risk factors. Dis Colon Rectum 1996;39:1012-1018.
8. Rajaratnam SG, Eglinton TW, Hider P, *et al.* Impact of ileal pouch-anal anastomosis on female fertility: meta-analysis and systematic review. Int J Colorectal Dis 2011;26:1365-1374.
9. Hahnloser D, Pemberton JH, Wolff BG, *et al.* Results at up to 20 years after ileal pouch-anal anastomosis for chronic ulcerative colitis. Br J Surg 2007;94:333-340.
10. Alves A, Panis Y, Bouhnik Y, *et al.* Subtotal colectomy for severe acute colitis: a 20-year experience of a tertiary care center with an aggressive and early surgical policy. J Am Coll Surg 2003;197: 379-385.
11. Hyman NH, Cataldo P, Osler T, *et al.* Urgent subtotal colectomy for severe inflammatory bowel disease. Dis Colon Rectum 2005;48:70-73.
12. van der Valk ME, Mangen MJ, Leenders M, *et al.* Risk factors of work disability in patients with inflammatory bowel disease--a Dutch nationwide web-based survey: work disability in inflammatory bowel disease. J Crohns Colitis 2014;8:590-597.
13. Drummond M, Manca A, Sculpher M. Increasing the generalizability of economic evaluations: recommendations for the design, analysis, and reporting of studies. Int J Technol Assess Health Care 2005;21:165-171.
14. Russel MG, Pastoor CJ, Brandon S, *et al.* Validation of the Dutch translation of the Inflammatory Bowel Disease Questionnaire (IBDQ): a health-related quality of life questionnaire in inflammatory bowel disease. Digestion 1997;58:282-288.
15. EuroQol--a new facility for the measurement of health-related quality of life. Health Policy 1990; 16:199-208.
16. Lamers LM, Stalmeier PF, McDonnell J, *et al.* Measuring the quality of life in economic evaluations: the Dutch EQ-5D tariff]. Ned Tijdschr Geneeskd 2005;149:1574-1578.
17. Holubar SD, Pendlimari R, Loftus EV, Jr., *et al.* Drivers of cost after surgical and medical therapy for chronic ulcerative colitis: a nested case-cohort study in Olmsted County, Minnesota. Dis Colon Rectum 2012;55:1258-1265.

18. Penna C, Dozois R, Tremaine W, *et al.* Pouchitis after ileal pouch-anal anastomosis for ulcerative colitis occurs with increased frequency in patients with associated primary sclerosing cholangitis. Gut 1996;38:234-239.
19. Fazio VW, Ziv Y, Church JM, *et al.* Ileal pouch-anal anastomoses complications and function in 1005 patients. Ann Surg 1995;222:120-127.
20. Holubar SD, Long KH, Loftus EV, Jr., *et al.* Long-term direct costs before and after proctocolectomy for ulcerative colitis: a population-based study in Olmsted County, Minnesota. Dis Colon Rectum 2009;52:1815-1823.
21. Siebert U, Wurm J, Gothe RM, *et al.* Predictors of temporary and permanent work disability in patients with inflammatory bowel disease: results of the swiss inflammatory bowel disease cohort study. Inflamm Bowel Dis 2013;19:847-855.
22. Boonen A, Dagnelie PC, Feleus 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.
23. Ananthakrishnan AN, Weber LR, Knox JF, *et al.* Permanent work disability in Crohn's disease. Am J Gastroenterol 2008;103:154-161.
24. Jimmo B, Hyman NH. Is ileal pouch-anal anastomosis really the procedure of choice for patients with ulcerative colitis? Dis Colon Rectum 1998;41:41-45.
25. Camilleri-Brennan J, Munro A, Steele RJ. Does an ileoanal pouch offer a better quality of life than a permanent ileostomy for patients with ulcerative colitis? J Gastrointest Surg 2003;7:814-819.
26. O'Bichere A, Wilkinson K, Rumbles S, *et al.* Functional outcome after restorative panproctocolectomy for ulcerative colitis decreases an otherwise enhanced quality of life. Br J Surg 2000;87: 802-807.

Supplementary Table 1 (see Chapter 3 - supplementary Table 1)

Supplementary Table 2. Number of responders per time point of UC patients with a pouch, ileostomy and anti-TNFα therapy.

	Number of patients		
Time point	**IPAA**	**Ileostomy**	**Anti TNFα**
3 months	81	48	34
6 months	58	32	26
9 months	57	35	34
12 months	63	29	34
15 months	63	33	33
18 months	61	31	35
21 months	62	31	30
24 months	51	27	25

Supplementary Table 3. Three-monthly healthcare resource use and associated costs of pouch patients (based on 496 questionnaires filled out by 81 patients).

	Number of questionnaires (%) n= 496	**Resource use - Mean (95% CI)**	**Costs - € Mean (95% CI)**
Outpatient clinic			
Gastroenterologist	134 (27.0)	0.34 (0.26-0.43)	43 (32-55)
Specialized nurse	53 (10.7)	0.21 (0.12-0.30)	9 (5-13)
Internist	3 (0.6)	0.01 (0.00-0.01)	1 (0-1)
Dietician	13 (2.6)	0.06 (0.01-0.11)	3 (0-5)
Surgeon	20 (4.0)	0.06 (0.03-0.09)	7 (3-11)
Rheumatologist	3 (0.6)	0.01 (0.00-0.02)	1 (0-2)
Dermatologist	4 (0.8)	0.01 (0.00-0.02)	2 (0-3)
Psychiatrist	2 (0.4)	0.03 (0.01-0.06)	2 (-1-5)
Occupational physician	3 (0.6)	0.01 (0.00-0.02)	1 (0-3)
Emergency room	14 (2.8)	0.03 (0.01-0.06)	5 (2-9)
General practitioner during day-time	26 (5.2)	0.07 (0.04-0.10)	2 (1-3)
General practitioner (during night/ weekend-time)	15 (3.0)	0.04 (0.02-0.06)	4 (2-5)
Subtotal			**80 (61-100)**
Diagnostics procedures			
Laboratory	31 (6.2)	0.10 (0.05-0.16)	2 (1-3)
Colonoscopy	11 (2.2)	0.03 (0.01-0.04)	9 (3-15)

Supplementary Table 3. Three-monthly healthcare resource use and associated costs of pouch patients (based on 496 questionnaires filled out by 81 patients). (continued)

	Number of questionnaires (%) n= 496	Resource use - Mean (95% CI)	Costs - € Mean (95% CI)
MRI scan	2 (0.4)	0.00 (0.00-0.01)	1 (0-2)
CT scan	3 (0.6)	0.01 (0.00-0.01)	1 (0-2)
Abdominal X-ray	4 (0.8)	0.01 (0.00-0.02)	0 (0-1)
Ultrasonography	4 (0.8)	0.01 (0.00-0.02)	0 (0-1)
DXA scan	7 (1.4)	0.01 (0.00-0.02)	1 (0-2)
Subtotal			**14 (7-21)**
Medication use			
None	302 (61.0)	n/a	n/a
Adalimumab	5 (1.0)	n/a	44 (5-82)
Infliximab	3 (0.6)	n/a	29 (-4-63)
Mesalazine	24 (4.8)	n/a	10 (6-14)
Azathioprine	4 (0.8)	n/a	1 (0-1)
Mercaptopurine	4 (0.8)	n/a	1 (0-1)
Methotrexate	6 (1.2)	n/a	3 (1-5)
Corticosteroids	35 (6.2)	n/a	4 (1-6)
Antibiotics	30 (6.0)	n/a	
Subtotal			**92 (40-144)**
Hospitalisation	18 (3.6)	9 (2-15)*	**201 (107-295)**
Surgery	7 (1.4)	n/a	**19 (3-34)**
Total healthcare costs			**407 (282-532)**

CI, Confidence Interval; CT, Computer tomography; MRI, Magnetic Resonance Imaging; DXA, Dual-emission X-ray absorptiometry

* mean number of days hospitalised (range)

Supplementary Table 4. Three-monthly healthcare resource use and associated costs of ileostomy patients (based on 266 questionnaires filled out by 48 patients).

	Number of questionnaires (%) n= 266	Resource use - Mean (95% CI)	Costs - € mean (95% CI)
Outpatient clinic			
Gastroenterologist	81 (30.5)	0.29 (0.21-0.36)	32 (25-40)
Specialized nurse	77 (28.9)	0.30 (0.20-0.40)	13 (9-18)
Internist	13 (4.9)	0.08 (0.02-0.13)	8 (3-14)
Dietician	16 (6.0)	0.08 (0.02-0.13)	4 (1-7)
Surgeon	27 (10.2)	0.17 (0.10-0.24)	17 (10-23)
Rheumatologist	10 (3.8)	0.04 (0.01-0.06)	5 (1-9)

Supplementary Table 4. Three-monthly healthcare resource use and associated costs of ileostomy patients (based on 266 questionnaires filled out by 48 patients). (continued)

	Number of questionnaires (%) n= 266	Resource use - Mean (95% CI)	Costs - € mean (95% CI)
Dermatologist	2 (0.8)	0.01 (-0.1-0.03)	1 (0-2)
Psychiatrist	3 (1.1)	0.01 (-0.1-0.03)	4 (-1-8)
Occupational physician	4 (1.5)	0.03 (0.00.-0.07)	4 (0-8)
Emergency room	14 (5.3)	0.07 (0.03-0.11)	11 (5-17)
General practitioner during day-time	16 (6.0)	0.05 (0.01-0.09)	3 (1-5)
General practitioner (during night/ weekend-time	15 (5.6)	0.08 (0.03-0.13)	7 (3-11)
Subtotal			**109 (84-134)**
Diagnostics procedures			
Laboratory	20 (7.5)	0.13 (0.06-0.21)	2 (1-4)
Colonoscopy	7 (2.6)	0.03 (0.01-0.05)	10 (3-17)
MRI scan	2 (0.8)	0.01 (-0.1-0.03)	2 (-1-5)
CT scan	3 (1.1)	0.02 (0.00-0.03)	2 (0-5)
Abdominal X-ray	2 (0.8)	0.01 (-0.01-0.03)	0 (0-1)
Ultrasonography	2 (0.8)	0.01 (0.00-0.02)	0 (0-1)
DXA scan	3 (1.1)	0.01 (0.00-0.02)	1 (0-2)
Subtotal			**19 (10-28)**
Medication use			
None	148 (70.2)	n/a	n/a
Adalimumab	4 (1.5)	n/a	66 (1-130)
Infliximab	-	-	-
Mesalazine	34 (12.8)	n/a	27 (18-36)
Azathioprine	8 (3.0)	n/a	3 (1-5)
Mercaptopurine	1 (0.4)	n/a	0 (0-1)
Methotrexate	5 (1.9)	n/a	5 (1-9)
Corticosteroids	8 (3.0)	n/a	1 (0-3)
Subtotal			**102 (38-166)**
Hospitalisation	19 (7.1)	8 (2-15)*	**357 (189-524)**
Surgery	3 (1.1)	n/a	**19 (-3-42)**
Ileostomy supplies	266 (100)	n/a	**975****
Total healthcare costs			**1,581 (1,377-1,786)**

CI, Confidence Interval; CT, Computer tomography; MRI, Magnetic Resonance Imaging; DXA, Dual-emission X-ray absorptiometry

* mean number of days hospitalised (range)

** [m] For patients with an ileostomy costs for caring for the stoma were based on a standard care package. This is based on the assumption of an exhange of base disk 4 times per week and of the ileostomy bag twice/day.

Supplementary Table 5. Three-monthly healthcare resource use and associated costs of anti-TNFα treated patients (based on 251 questionnaires filled out by 34 patients).

	Number of questionnaires (%) n= 251	Resource use - Mean (95% CI)	Costs - € mean (95% CI)
Outpatient clinic			
Gastroenterologist	116 (46.2)	0.61 (0.48-0.74)	61 (49-73)
Specialized nurse	92 (36.7)	0.43 (0.32-0.53)	19 (14-24)
Internist	17 (6.8)	0.10 (0.04-0.15)	8 (4-12)
Dietician	11 (4.4)	0.06 (0.02-0.10)	3 (1-5)
Surgeon	2 (0.8)	0.01 (-0.1-0.03)	1 (0-3)
Rheumatologist	12 (4.8)	0.06 (0.02-0.09)	6 (2-10)
Dermatologist	7 (2.8)	0.01 (-0.1-0.03)	4 (0-8)
Psychiatrist	-	-	-
Occupational physician	6 (2.4)	0.04 (0.00-0.08)	4 (0-9)
Emergency room	4 (1.6)	0.02 (0.00-0.04)	3 (0-6)
General practitioner during day-time	17 (6.8)	0.00 (0.00-0.01)	4 (2-5)
General practitioner (during night/weekend-time)	12 (4.8)	0.08 (0.02-0.13)	7 (2-11)
Subtotal			**120 (98-140)**
Diagnostics procedures			
Laboratory	38 (15.1)	0.38 (0.23-0.53)	7 (4-10)
Colonoscopy	28 (11.2)	0.12 (0.07-0.17)	41 (25-57)
MRI scan	2 (0.8)	0.01 (0.00-0.02)	1 (0-4)
CT scan	-	-	-
Abdominal X-ray	2 (0.8)	0.00 (0.00-0.01)	0 (0-1)
Ultrasonography	4 1.6)	0.02 (0.00-0.03)	1 (0-1)
DXA scan	4 (1.6)	0.02 (0.00-0.03)	1 (0-3)
Subtotal			**51 (33-70)**
Medication use			
Adalimumab	49 (20.0)	n/a	852 (636-1,067)
Infliximab	204 (80.0)	n/a	3,906 (3,666-4,145)
Mesalazine	144 (57.4)	n/a	122 (109-135)
Azathioprine	55 (21.9)	n/a	20 (15-25)
Mercaptopurine	37 (14.7)	n/a	13 (9-17)
Methotrexate	15 (6.0)	n/a	15 (8-22)
Corticosteroids	35 (13.9	n/a	3 (0-6)
Subtotal			**4,931 (4,897-4,965)**
Hospitalisation	12 (4.8)	10 (2-17)*	**242 (107-377)**
Surgery	1 (0.4)	n/a	**7 (-7 – 20)**
Total healthcare costs			**5,350 (5,191-5,510)**

CI, Confidence Interval; CT, Computer tomography; MRI, Magnetic Resonance Imaging; DXA, Dual-emission X-ray absorptiometry

* mean number of days hospitalised (range)

Supplementary Table 6. Three-monthly self-reported sick leave and associated productivity losses, and 3-monthly patient costs in UC patients with a pouch, ileostomy and anti-TNFα therapy.

	Number of questionnaires (%)				Number of days/patient Mean (95% CI)			3-monthly costs/ patient € - Mean (95% CI)			
	Pouch N=496	Ileostomy N=266	Anti-TNFα N=251	P-value	Pouch N=496	Ileostomy N=266	Anti-TNFα N=251	Pouch N=496	Ileostomy N=266	Anti-TNFα N=251	P-value
Productivity losses - sick leave	25/237 * (10.5)**	12/89* (13.5)**	32/134* (23.9)**	<0.01	2 (1-4)	5 (1-8)	7 (4-10)	**483 (230-736)***	**377 (126-629)***	**1,085 (589-1,581)***	<0.01
Patient costs	496/796	266/266	251/251		-	-	-	**42 (32-51)**	**51 (35-67)**	**61 (41-81)**	

CI, Confidence Interval;

*Number of employed patients
**p<0.01

Supplementary Table 7A. IBDQ total scores and subscores in UC patients with a pouch, ileostomy and anti-TNFα therapy

	Pouch	Ileostomy	Anti-TNFα	p-value
Total IBDQ –median [IQR]	183 [156-198]	181 [165-199]	181 [159-199]	0.14
Bowel symptoms	56 [48-61]	59 [54-64]	58 [50-65]	<0.01
Systemic symptoms	24 [19-28]	25 [20-29]	24 [20-28]	0.09
Emotional symptoms	71 [60-77]	70 [61-75]	68 [59-75]	0.07
Social symptoms	33 [27-35]	31 [28-34]	32 [26-35]	0.36

Supplementary Table 7B. Proportion of reported problems by EQ-5D dimension in UC patients with a pouch, ileostomy and anti-TNFα therapy

		No problems (%)	Some problems (%)	Severe problems (%)	p-value
Mobility	**Pouch**	83,6	16,4	0	<0.01
	Ileostomy	69,6	30,4	0	
	Anti-TNFa	79,3	19,8	0,8	
Self-care	**Pouch**	97,4	2,6	0	0.44
	Ileostomy	97,2	2,8	0	
	Anti-TNFa	96,6	3,1	0,3	
Usual activities	**Pouch**	61,6	36,6	1,8	0.19
	Ileostomy	54,3	44,2	1,5	
	Anti-TNFa	58,6	38,7	2,7	
Pain/discomfort	**Pouch**	59,8	38,5	1,6	<0.01
	Ileostomy	52,1	46	1,8	
	Anti-TNFa	41	54,4	4,6	
Anxiety/ depression	**Pouch**	75,1	23,1	1,8	0.12
	Ileostomy	80,7	18,7	0,6	
	Anti-TNFa	72,4	26,1	1,5	

Chapter 6

Cost-effectiveness analysis of anti-TNF versus corticosteroid-based therapy in Crohn's disease

Manuscript in preparation

ABSTRACT

Objective:

To estimate the cost-effectiveness of anti-TNF compounds versus corticosteroid-based therapy for inducing remission in active Crohn's disease (CD) within a two-year time horizon.

Methods:

In this prospective, nation-wide, web-based, cohort study with a two year follow-up, we compared two treatment strategies for remission induction of CD: anti-TNF therapy (adalimumab and infliximab) and corticosteroid-based therapy. Over a period of two years, patients filled-out a three-monthly questionnaire including data on healthcare costs, productivity losses, disease activity (SCDAI) and quality-of-life (EuroQol (EQ-5D-3L)). Cost-effectiveness analysis (CEA) was conducted, both from a healthcare and societal perspective within a two-year time horizon, using a mixed-effects linear regression analysis. CEA results were expressed as cost-effectiveness ratios showing the incremental costs per QALY gained, and the incremental costs per increased SCDAI-point. Bootstrapping was applied for deriving confidence intervals.

Results:

Of 1,307 CD patient initially included, 40 anti-TNF naive CD patients received anti-TNF treatment and 50 CD patients were treated with corticosteroid-based therapy because of active disease. The anti-TNF cohort had higher healthcare costs and societal costs than the corticosteroid-based treatment group, resulting in incremental healthcare and societal costs of €22,412 and €25,167, respectively. In addition, we found a negative incremental effect, in both QALY (-0.03) and SCDAI (-34). Therefore, in both healthcare and societal perspective, anti-TNF therapy was dominated by the corticosteroid-based therapy. This was confirmed by the bootstrapping results with less than 1% of the samples being cost-effective for anti-TNF.

Conclusion:

Remission-induction therapy with anti-TNF did not result in a better quality-of-life than corticosteroid-based, but was associated with higher healthcare costs. A finding that needs to be confirmed by future clinical studies.

INTRODUCTION

The last decade has been marked by an increased use of anti-TNF therapy in Crohn's disease (CD). Anti-TNF therapy is recommended for patients with moderate-to-severe CD who fail conventional therapy, such as mesalazine, immunosuppressives or corticosteroids.[1] Anti-TNF therapies are expensive, however, and were recently found to be the most important cost drivers in CD, accounting for up to two third of the total healthcare costs.[2-3] This led to a growing interest in economic evaluations to determine whether the increased drug costs associated with the use of anti-TNF therapy will be offset by a better quality-of-life at acceptable additional costs.

Cost-effectiveness analysis assesses the additional costs of the net effect, expressed as cost-effectiveness ratio showing costs per effect outcome, for example quality-adjusted life-year (QALY), for alternative interventions. A recent review on cost-effectiveness studies comparing anti-TNF therapy versus placebo or conventional therapy (mesalazine or corticosteorids with or without immunomodulators) identified only modelling studies, using either a Markov model or a decision tree.[4] To date, there is no cost-effectiveness study based on a clinical study comparing anti-TNF versus conventional treatment in patients with active CD.

In the current study, we investigated the cost-effectiveness of anti-TNF versus corticosteroid-based treatment in CD, based on data from the 'Cost of inflammatory bowel disease in the Netherlands' or COIN-study', utilizing a two-year time horizon and taking a healthcare payer and a societal perspective, respectively.

METHODS

Study design and data collection

Full details on the COIN-study have been described elsewhere.[3,5] Briefly, we identified all patients with IBD using diagnosis treatment combinations. Participating IBD patients were asked to fill-out a web-based questionnaire during two years of follow-up with a three month interval. The baseline questionnaire included data on demographic and disease specific characteristics, disease activity and quality-of-life. The three-month follow-up questionnaires included questions on self-reported healthcare uses, reduced productivity (e.g. sick leave, work disability), disease activity and quality-of-life. Patients were followed up for two years with a three month intercept. The study was centrally approved by the ethics committee of the University Medical Centre Utrecht.

Treatment strategies

For the current analysis, we selected and compared two treatment cohorts in CD patients with active disease. The first treatment cohort included CD patients with active disease, who were treated with anti-TNF therapy (adalimumab or infliximab) for the first time with or without immunomodulators *(referred hereafter as anti-TNF treatment)*. The second treatment cohort included CD patients with active disease who received corticosteroid-based therapy. Corticosteroid-based therapy was defined as remission-induction therapy with corticosteroids with or without immunomodulators *(referred hereafter as corticosteroid-based therapy)*. Disease activity was measured employing the well-validated Short Crohn's Disease Activity Index (SCDAI) for survey research.[6] Active disease was defined as a SCDAI score higher than 150.[6]

Effects

Treatment effect was measured using two outcome measurements: 1) disease activity using the SCDAI and 2.) quality-of-life expressed as QALYs. The SCDAI consists of three questions regarding stool, pain and general well being. SCDAI was assessed every three months during the two years of follow-up. The three monthly self-reported EuroQol-five dimension (EQ-5D-3L) measurements[7] were converted into a weighted health state index (utility), the so-called quality-adjusted life year (QALY) by applying scores from the EQ-5D preference weights elicited from a Dutch general population samples.[8] Two-year QALY indexes were calculated.

Costs

Self-reported healthcare resources were multiplied by corresponding unit prices. The healthcare costs consisted of costs due to surgery, hospitalization, visits to outpatient clinic, medication use and diagnostic procedures. Productivity losses were estimated by multiplying self-reported sick leave from paid work of patients between 18-64 years by age- and gender-specific corresponding unit prices using the human capital approach. Furthermore, we included patient's costs according to patient specifications. Costs were summed over the two-year time horizon and were presented as two-year costs expressed in 2011 Euros. Unit prices have been published elsewhere.[3]

Economic evaluation

In the cost-effectiveness analysis we compared anti-TNF therapy with corticosteroids-based therapy using a healthcare and a societal perspective. In the healthcare perspective only healthcare costs were considered. For the societal perspective all three cost categories (i.e. healthcare costs, productivity losses and patient costs) were included. The corticosteroid-based treatment was considered the reference arm as this used to be standard of care before the introduction of anti-TNF therapy. The underlying hypothesis

was that ant-TNF treatment dominates corticosteroid-based therapy mainly because of lower hospitalization and surgery rates, and an improved quality-of-life. Incremental cost-effectiveness ratios (ICERs) defined as the between-group difference in accumulated costs divided by the between-group differences in two-year QALYs (i.e. € per QALY gained) or SCDAI (i.e. € per increased SCDAI-point) were estimated. Discounting was not applied, neither for costs nor for effects (i.e. QALYs), given the limited time horizon of two years.

The WHO-guidelines were used to evaluate whether anti-TNF is cost-effective or not. [9] According to this guideline a strategy is considered highly cost-effective if ICER is less than 1x gross domestic product (GDP) per capita and cost-effective if ICER is less than 3xGDP per capita. The GDP per capita in the Netherlands in 2011 was €30,807.[10,11]

Statistical analysis

Data analysis was performed using SPSS version 20.0 and SAS version 9.2. Descriptive statistics were used to characterise patients with anti-TNF and corticosteroid-based treatment. We reported means with a standard deviation (SD) and medians with an interquartile range (IQR), when appropriate. Comparisons of baseline characteristics were analysed with the Student t-test for continuous variables and the Chi-squared test for dichotomous variables.

Costs were expressed as mean costs with 95% confidence interval (%). Cost-effectiveness analysis (CEA) was conducted using a mixed-effects linear regression analysis, including baseline characteristics (age, gender, disease duration, EQ-5D-3L and SCDAI scores). To estimate the uncertainty around the incremental costs, incremental effects, and cost-effectiveness ratio, non-parametric bootstrapping with 5000 iterations was used. Results were presented in a cost-effectiveness plane.

RESULTS

Initially, 1,307 CD patients were included in the COIN-study, of whom 40 met the inclusion criteria for the anti-TNF treatment cohort, and 50 met the criteria for the corticosteroid-based treatment cohort. Table 1 shows the baseline characteristics of both treatment cohorts. Patients with anti-TNF therapy had a shorter disease duration [p=0.03] and tended to have a lower QALY at baseline [p=0.07]. There were no differences between SCDAI scores. Patients with corticosteroid-based therapy more often underwent abdominal surgery in the past [p= <0.01]. Patients with anti-TNF therapy had more often colonic

Table 1. Baseline characteristics

	Anti-TNF treatment n=40	Corticosteroid-based treatment n=50	P-value
Male gender (%)	11 (27.5)	22 (44.0)	0.11
Age - years (± SD)	44.1 (11.7)	47.7 (13.0)	0.17
Disease duration - median (IQR)	13.8 (8.9)	19.2 (12.8)	0.03
Age of diagnosis	30.3 (11.4)	28.5 (10.5)	0.45
Disease localisation (%)			0.03
Colon	14 (35.0)	6 (12.0)	
Ileum	6 (15.0)	8 (16.0)	
Ileum and colon	19 (47.5)	36 (72.0)	
Unknown	1 (2.5)	-	
Penetrating disease course (%)	18 (45.0)	26 (52.0)	0.53
Abdominal surgery (%)	16 (40.0)	36 (72.0)	<0.01
SCDAI - mean (± SD)	200.3 (45.6)	205.8 (39.7)	0.54
QALY (EQ-5D-3L utility) – mean (± SD)	0.67 (0.26)	0.74 (0.20)	0.07
Medication (%)			n/a
Mesalazine	6 (15.0)	16 (32.0)	
Azathioprine	11 (27.5)	10 (20.0)	
Mercaptopurine	2 (5.0)	3 (6.0)	
Methotrexate	1 (2.5)	2 (4.0)	
Budesonide	1 (2.5)	72 (36)	
Prednisone	4 (10.0)	17 (34)	
Adalimumab	16 (40.0)	-	
Infliximab	24 (60.0)	-	
Work status (%)			0.73
Employed	14 (35.0)	17 (34.0)	
Fully (> 80%) disabled	13 (32.5)	13 (26.0)	
Partially (< 80%) disabled	5 (12.5)	8 (16.0)	

SD, Standard deviation; IQR, Interquartile range; SCDAI, Short Crohn's Disease Activity Index for survey research; EQ-5D-3L, EuroQol- 5 dimensions -3 levels

involvement, patients in the corticosteroid-based therapy-arm had more colonic and ileum involvement [p=0.03].

During two years of follow-up, 23% patients from the corticosteroid-based treatment cohort switched to anti-TNF treatment and 4% underwent surgery. In the anti-TNF treatment group, 84% was still on anti-TNF therapy and 5% underwent surgery. In the corticosteroid-based treatment group twice as many hospitalizations were encountered as compared to the anti-TNF group (6 versus 13).

The unadjusted two-year QALYs were 1.55 in the anti-TNF treatment and 1.58 in the corticosteroid-based treatment cohort. Unadjusted 2-year SCDAI scores were 145 and 125 for the anti-TNF and the corticosteroid-based treatment cohort. When comparing both treatment groups, the mean adjusted incremental effect in QALYs was 0.03 (NS). The same pattern was observed for SCDAI scores, with a mean adjusted incremental effect for SCDAI of -34 (NS).

Costs

The unadjusted two-year accumulated healthcare costs and societal costs were higher in the anti-TNF treatment cohort compared to the corticosteroid-based treatment cohort (€34,971 versus €12,559 and €39,136 versus €13,968), [p<0.01]. The adjusted mean incremental healthcare and societal costs were €24,839 and €22,241, respectively. Figure 1 shows the accumulated differences of the subcategories of costs. There were significant lower costs due to hospitalization in anti-TNF group compared to corticosteroid-based treatment group, €1,060 versus €2,875, with an adjusted mean differences of €1,815 [p=<0.01].

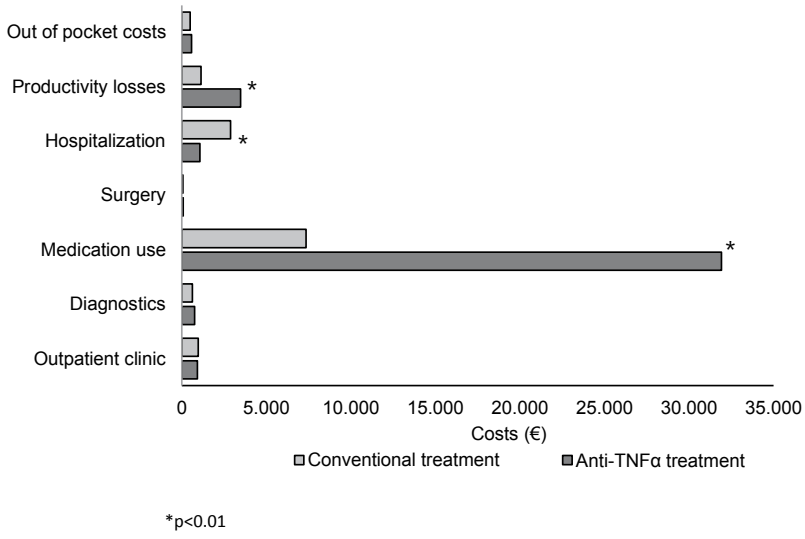
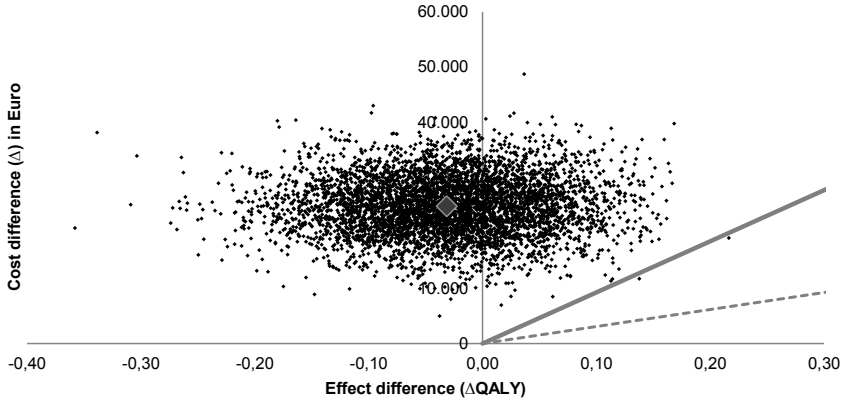


Figure 1. Mean two-years costs (€) by cost categories for anti-TNF versus corticosteroid-based treatment cohort

A. Healthcare perspective



B. Societal perspective

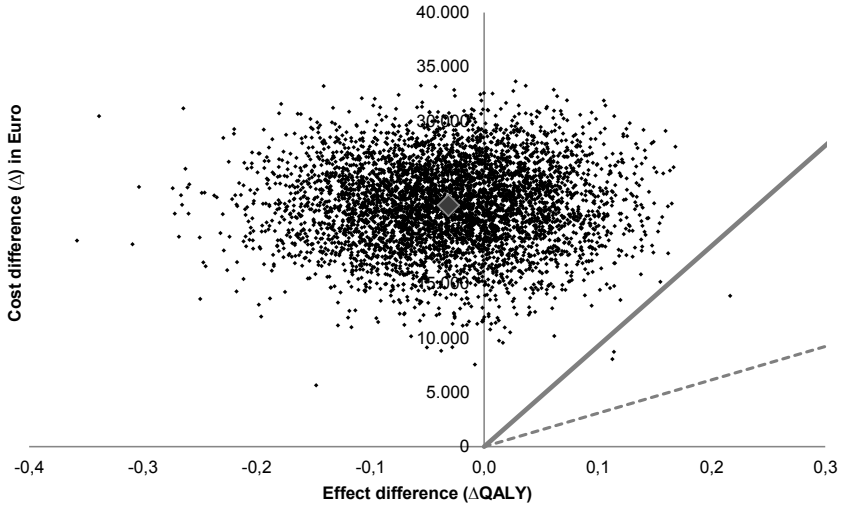
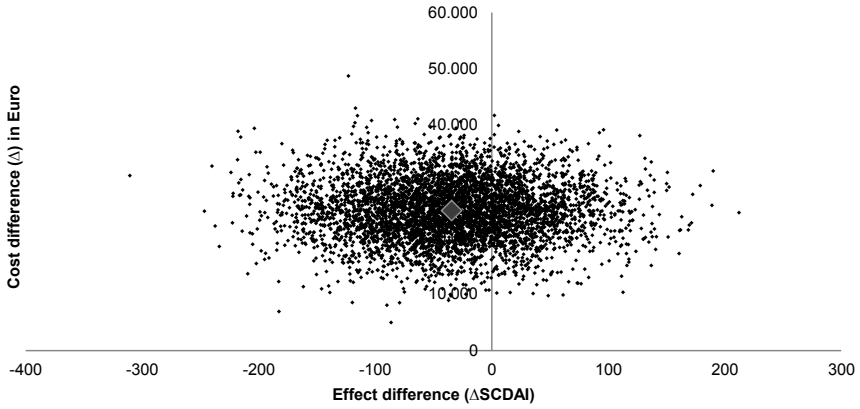


Figure 2. Cost-effectiveness plane for anti-TNF versus corticosteroid-based treatment using QALY as effect outcome and taking a healthcare payer perspective (A) and societal perspective (B)

Legend: Solid points represent incremental cost and incremental effects of 5000 bootstrapping samples. The blue point indicates the point estimate. Points estimates in the north-west quadrant (i.e. left upper quadrant) are in favour of the corticosteroid-based therapy(i.e. corticosteroid-based therapy dominates anti-TNF because anti-TNF is more expensive and less effective than the corticosteroid-based therapy). The dotted line represents the 1xGDP threshold (i.e. very cost-effective), and solid line represents the 3xGDP threshold (i.e. cost-effective). Points estimates in the north-west quadrant (i.e. right upper quadrant) are considered to be cost-effective if below the solid line, and are considered to be not cost-effective (because too costly per incremental effect) if above the solid line.

A. Healthcare perspective



B. Societal perspective

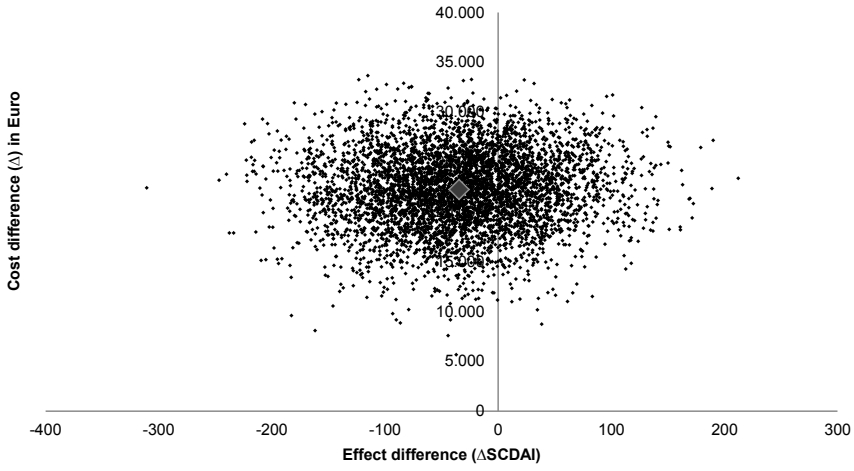


Figure 3. Cost-effectiveness plane for anti-TNF versus corticosteroid-based treatment using SCDAI as effect outcome and taking a healthcare payer perspective (A) and societal perspective (B)

Legend: Solid points represent incremental cost and incremental effects of 5000 bootstrapping samples. The blue point indicates the point estimate. Points estimates in the North-west quadrant (i.e left upper quadrant) are in favour of the corticosteroid-based therapy (i.e. corticosteroid=based therapy dominates anti-TNF because anti-TNF is more expensive and less effective than the corticosteroid-based therapy). Points estimates in the north-west quadrant (i.e. right upper quadrant) have a positive incremental effect above the conventional therapy at incremental costs. But there is no threshold defining at what additional costs an additional SCDAI point is considered being cost-effective and when not, as explained in Figure 2 for QALYs as outcome measure.

Incremental cost-effectiveness ratios

The anti-TNF therapy was dominated by the corticosteroid-based therapy. This strategy was found to be more expensive and less effective, both from the societal and healthcare perspective (Figure 2 and Figure 3). This result was confirmed by the bootstrapping results with less than 1% of the runs being cost-effective for anti-TNF (Figure 2).

DISCUSSION

In this observational, web-based cohort study, remission-induction and maintenance therapy with anti-TNF therapy compared to corticosteroid-based therapy in patients with CD was associated with higher incremental healthcare costs, and did not result in neither a better quality-of-life, nor an improved disease activity, nor in a reduction of productivity losses, when compared to corticosteroid-based therapy. A finding confirmed using bootstrapping with less than 1% of the samples being in favour of the anti-TNF therapy (i.e. anti-TNF therapy being cost-effective).

The high healthcare costs associated with anti-TNF therapy did not come as a surprise however. In our previous study we showed that anti-TNF therapy is the major cost-driver in patients with CD.[3] In fact, the a priori chance of anti-TNF therapy to be cost-effective with the current applicable thresholds (92,421/QALY) is low, because this requires an incremental effect of >0.24 QALY gained in two-years' time, or >0.12 QALYs gained per year which is most likely an unrealistic effect with a mean QALY of 0.67 at baseline (i.e. QALY at start of treatment) and presuming that also conventional therapy is not completely ineffective.

We are the first to report on cost-effectiveness of anti-TNF versus corticosteroid-based therapy using directly observed costs and effect data. Comparison with modelling studies, which are partly based on assumptions, is hampered by large methodological differences. Nevertheless, our data are in line with the findings of a recent review of the modelling literature by Tang et al.[4] This author concluded that maintenance therapy with infliximab and adalimumab was in general less likely to be cost-effective due to high healthcare costs.

Lessons can be learned from rheumatoid arthritis, a chronic inflammatory disease which primarily affects the joints, and in which anti-TNF therapy plays a pivotal role as well. The BeSt trial found the combination of methotrexate and infliximab in early rheumatoid arthritis to result in more QALYs and lower productivity losses, as compared to a strategy in which methotrexate, sulfasalazine and prednisone was initiated for remission induc-

tion,[12] and this was confirmed in a 5-year follow-up study.[13] In contrast, in methotrexate refractory rheumatoid arthritis, a treatment strategy in which infliximab was started resulted in higher healthcare costs with no differences between QALYs and productivity losses after 21 months as compared to a sulfasalazine + hydroxychloroquine-based strategy.[14] In contrast to the BeST study, we failed to show improvement of productivity losses. This could be due to the high percentage of work disability in our cohort at baseline, 45% in the anti-TNF and 42.0% in the corticosteroid-based treatment group. A two year follow-up period might be too short to fully acknowledge the improved health status resulting in new employment, and generate savings from the societal perspective. Furthermore, early initiation of combined immunosuppression might be more effective in younger patients, and might prevent, or at least reduce, sick leave and work disability.

An important finding is the lower hospitalisation costs in the anti-TNF treatment cohort in comparison to the corticosteroid-based treatment cohort. This strengthens our previous studies, in which we reported an overall decrease of hospitalization costs with increasing use of anti-TNF therapy.[3][15] In addition, unique data from the Netherlands showed that patients in the biological era had a lower hospitalization risk during follow-up compared to patients in the pre-biological era (34.4% vs. 51.4%).[16]

Apart from the higher medication costs, and the lack of cost savings due to reduced productivity losses, is our conclusion mainly driven by the absence of a positive between-group differences in QALYs and SCDAI. Clinical trials comparing anti-TNF maintenance therapy with placebo showed better remission rates in the first group (29-53%).[17–20] Observational studies, with data from clinical practice, report even higher remission rates, up to 74% after two-years of follow-up.[21,22] There are only few studies directly comparing anti-TNF therapy and corticosteroid-based therapy in CD.[23–25] The SONIC study showed higher one year remission rates in patients who received combination therapy versus azathioprine alone (46.2% versus 24.1%).[23] The same effect was seen in the 'top-down' study in which early combined immunosuppression was compared with corticosteroid-based therapy with 61.5% versus 42.2% patients in remission after one year.[24] However, no significant difference in remission rates after a two-year follow-up period was found, which might at least be partly attributed to the fact that up to 20% of patients in the step-up -arm received anti-TNF therapy after two years of follow-up. Ghazi et al compared step-up versus early anti-TNF therapy in clinical practice, and found no difference between the two groups.[25] However, in this retrospective study, patients receiving anti-TNF had a lower quality-of-life, a higher disease activity and more often perianal disease at baseline compared to the step up treatment group, thereby reflecting more severe disease activity.

The most important limitation of our study is selection bias. Due to the study design there were important differences in baseline characteristics. Patients receiving anti-TNF reported lower quality-of-life, to be expected to be an indirect marker of more severe CD. We addressed this limitation by adjusting for baseline characteristics using a mixed model. Furthermore and in line with the 'top-down' study, 23% of the patients in the corticosteroid-based treatment cohort received anti-TNF during the follow-up period, which probably levelled the SCDAI scores as well. Another limitation is the small sample size of 90 patients, which prevented subgroup analysis, such as short versus long disease duration.

In this study, we addressed the fundamental question as to whether anti-TNF therapy offers good value for money compared to corticosteroid-based therapy in patients with CD. Based on our data from the COIN study, we failed to show a positive incremental effect for disease activity and quality-of-life and found higher healthcare costs and productivity losses in patients on anti-TNF therapy compared to corticosteroid-based therapy. Prospective clinical trials reporting on efficacy, quality-of-life and costs should be initiated to address this important question.

REFERENCES

1 Dignass A, Van Assche G, Lindsay JO, *et al.* The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: Current management. *J Crohns Colitis* 2010;4: 28–62.

2 Kappelman MD, Rifas-Shiman SL, Porter CQ, *et al.* Direct health care costs of Crohn's disease and ulcerative colitis in US children and adults. *Gastroenterology* 2008;135:1907–13.

3 Van der Valk ME, Mangen M-JJ, Leenders M, *et al.* Healthcare costs of inflammatory bowel disease have shifted from hospitalisation and surgery towards anti-TNFalpha therapy: results from the COIN study. *Gut* 2014;63:72-9

4 Tang DH, Harrington AR, Lee JK, *et al.* A Systematic Review of Economic Studies on Biological Agents Used to Treat Crohn's Disease. *Inflamm Bowel Dis* 2013;19:2673-94.

5 Van der Valk ME, Mangen M-JJ, Leenders M, *et al.* Risk factors of work disability in patients with inflammatory bowel disease--a Dutch nationwide web-based survey: work disability in inflammatory bowel disease. *J Crohns Colitis* 2014;8:590–7.

6 Timmer A, Kemptner D, Takses A, *et al.* A survey-based index was validated for measuring disease activity in inflammatory bowel disease. An evaluation study. *J Clin Epidemiol* 2009;62:771–8.

7 EuroQol--a new facility for the measurement of health-related quality of life. *Health Policy* 1990; 16:199–208.

8 Lamers LM, Stalmeier PF, McDonnell J, *et al.* Measuring the quality of life in cost-utility analyses: the Dutch EQ-5D tariff. *Ned Tijdschr Geneeskd* 2005;149:1574–8.

9 Tan-Torres Edejer T, Baltussen R, Adam T, *et al. WHO guide to cost-effectiveness analysis*. 2003.

10 www.oecd.org (data available at http://www.oecd-ilibrary.org/economics/country-statistical-profile-netherlands-2013_csp-nld-table-2013-1-en)

11 www.oecd.org. (data available at https://data.oecd.org/conversion/exchange-rates.htm)

12 Van den Hout WB, Goekoop-Ruiterman YPM, Allaart CF, *et al.* Cost-utility analysis of treatment strategies in patients with recent-onset rheumatoid arthritis. *Arthritis Rheum* 2009;61:291–9.

13 Van den Hout W, Klarenbeek N, Dirven L, *et al*. Long-term cost-utility analysis of treatment strategies in patients with recent-onset rheumatoid arthritis - 5 year follow-up data from the BeSt study. *Ann Rheum Dis* 2012;71(Supp3):363.

14 Eriksson JK, Karlsson JA, Bratt J, *et al.* Cost-effectiveness of infliximab versus conventional combination treatment in methotrexate-refractory early rheumatoid arthritis: 2-year results of the register-enriched randomised controlled SWEFOT trial. *Ann Rheum Dis* 2015;74:1094–101.

15 Van der Valk ME, Mangen MJJ, van der Have M *et al.* Evolution of IBD-related costs over two years of follow up: increase of anti-TNF therapy related costs with a decline of hospitalization costs. *Abstr ECCO* 2015.

16 Jeuring SFG, van den Heuvel TRA, Zeegers MP *et al*. Long-term disease outcome of Crohn's disease in the biological era – Results from a Dutch population-based IBD cohort. *Abstr NVGE* 2015.

17 Panaccione R, Loftus EV Jr, Binion D, *et al.* Efficacy and safety of adalimumab in Canadian patients with moderate to severe Crohn's disease: results of the Adalimumab in Canadian SubjeCts with ModErate to Severe Crohn's DiseaSe (ACCESS) trial. *Can J Gastroenterol* 2011;25:419–25.

18 Panaccione R, Colombel JF, Sandborn WJ, *et al.* Adalimumab sustains clinical remission and overall clinical benefit after 2 years of therapy for Crohn's disease. *Aliment Pharmacol Ther* 2010; 31:1296–309.

19 Colombel JF, Sandborn WJ, Rutgeerts P, *et al.* Adalimumab for Maintenance of Clinical Response and Remission in Patients With Crohn's Disease: The CHARM Trial. *Gastroenterology* 2007;132: 52–65.
20 Hanauer SB, Feagan BG, Lichtenstein GR, *et al.* Maintenance infliximab for Crohn's disease: The ACCENT I randomised trial. *Lancet* 2002;359:1541–9.
21 van der Valk ME, van Oijen MGH, Ammerlaan M, *et al.* Crohn's disease patients treated with adalimumab benefit from co-treatment with immunomodulators. *Gut* 2012;*61:324-5*.
22 Peters CP, Eshuis EJ, Toxopeüs FM, *et al.* Adalimumab for Crohn's disease: Long-term sustained benefit in a population-based cohort of 438 patients. *J Crohn's Colitis* 2014;8:866–75.
23 Colombel JF, Sandborn WJ, Reinisch W, *et al.* Infliximab, azathioprine, or combination therapy for Crohn's disease. *N Engl J Med* 2010;362:1383–95.
24 D'Haens G, Baert F, van Assche G, *et al.* Early combined immunosuppression or conventional management in patients with newly diagnosed Crohn's disease: an open randomised trial. *Lancet* 2008;371:660–7.
25 Ghazi LJ, Patil S a, Rustgi A, *et al.* Step up versus early biologic therapy for Crohn's disease in clinical practice. *Inflamm Bowel Dis* 2013;19:1397–403.

Chapter 7

Crohn's disease patients treated with adalimumab benefit from co-treatment with immunomodulators

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ABSTRACT

Introduction:

Crohn's disease (CD) patients treated with infliximab benefit from co-treatment with immunomodulators, probably because of reduced antibody formation against this compound. Whether patients treated with adalimumab benefit from co-treatment with immunomodulators as well is still largely unknown. We aimed to explore the putative beneficial role of immunomodulators in a nationwide 'real practice' cohort of adalimumab-treated CD patients.

Methods:

Data were obtained from the 'ApotheekZorg' registry. This institution was responsible for the nationwide distribution of adalimumab in The Netherlands. All CD patients treated with adalimumab between 2004 and 2010 were included. Data on age, gender, hospital, dosing schedules, previous use of infliximab, and concomitant use of immunomodulators (azathioprine/ 6-mercaptopurine or methotrexate) were analyzed. Treatment success was defined as ongoing prescription of adalimumab on July 1, 2010. Multivariate logistic regression analysis was performed to assess the association between co-treatment with immunomodulators and treatment success of adalimumab.

Results:

In total, 2,860 CD patients were included (64% women, mean age 38 (SD 13) years). During follow-up, 771 (27%) patients discontinued treatment with adalimumab after a median period of 6 months. Co-treatment with either thiopurines (adjusted (adj.) odds ratio (OR) 0.35, 95%CI 0.28-0.43) or methotrexate (adj. OR 0.46, 95%CI 0.27-0.79), and male gender (adj. OR 0.69, 95%CI 0.57-0.83) were associated with a lower risk for discontinuation, whereas previous IFX treatment (adj. OR 1.38, 95%CI 1.56-1.64) and treatment in an academic setting (adj. OR 1.30, 95%CI 1.08-1.57) were associated with a higher risk for discontinuation.

Conclusion:

In a real practice population of all adalimumab users, 27% discontinued therapy. Concomitant use of immunomodulators was independently associated with a decreased risk of discontinuation.

INTRODUCTION

The beneficial role of co-treatment with immunomodulators in patients receiving infliximab maintenance therapy is widely accepted. Concomitant use of immunomodulators is associated with reduced disease activity and infliximab dose escalation, presumably through a lowered frequency of antibody formation.[1]

Although adalimumab is a 100% human anti-Tumour Necrosis Factor monoclonal antibody, it is not devoid of immunogenicity. Antibodies against adalimumab have been reported in 3-38% of patients treated for Crohn's disease (CD) or rheumatoid arthritis.[2–4] In only one observational study the effect of use of immunomodulators was evaluated in Crohn's disease patients treated with adalimumab who failed infliximab treatment.[5] In this study, co-treatment with immunomodulators did not affect treatment outcome and did not inhibit the induction of antibodies against adalimumab. Based on this study, the current paradigm is to treat CD patients with adalimumab monotherapy.[6]

However, the sample size of this clinical trial was most likely too small to detect significant differences between subgroups of patient with and without immunomodulators. Therefore we aimed to determine whether patients treated with adalimumab benefit from co-treatment with immunomodulators in a nationwide 'real practice' cohort of CD patients.

METHODS

Study population

Anonymous data were obtained from the 'ApotheekZorg' registry. ApotheekZorg is a company responsible for the nationwide distribution of adalimumab in the Netherlands. All CD patients in the Netherlands treated with adalimumab between 2004 and 2010 were included in this study. Data on age, gender, hospital setting, dosing schedules, previous use of infliximab, and concomitant use of immunomodulators were obtained from the database.

Concomitant use of immunomodulators was defined as the start or an ongoing prescription of azathioprine, 6-mercaptopurine or methotrexate at the time of initiation of adalimumab.

Outcome parameter

Our primary outcome parameter was treatment success. Treatment success was defined as an ongoing prescription of adalimumab on July 1, 2010. We considered discontinua-

tion of adalimumab as treatment failure. In the absence of response criteria based on clinical scores such as the Crohn's disease activity index, this probably most accurately reflected loss of response.

Statistical analysis

Data analysis was performed using SPSS version 18.0. Descriptive statistics were used to characterize patients with CD and UC. Comparisons between patients with treatment success and treatment failure were analysed with Student's t-test for continuous variables and χ^2 for categorical variables. We performed a uni- and multivariable logistic regression analyses to assess the association between co-treatment with immunomodulators and adalimumab treatment success.

RESULTS

Patient characteristics

A total of 2,685 CD patients who were treated with adalimumab between 2004 and 2010 were included. Of all CD patients, 63% were women with a mean (SD) age of 37 (13) years. In total, 967 (36%) of all patients were treated in academic setting. A total of 859 (32%) patients received co-treatment with thiopurines, 88 (3%) with methotrexate. Fifty-four percent (n=1149) had previously been treated with infliximab.

The induction dose of adalimumab was 160 milligrams (mgs)-80 mgs in 1,557 (58%) patients, 80mgs in 690 (26%) patients and 40mgs in 438 (16%) patients. After a median duration of adalimumab maintenance therapy of 12 months, 2,110 (79%) patients were on a 40mgs dose every other week, 18 (1%) patients on 80mgs every other week, and 557 (21%) patients on 40mgs weekly.

Treatment success

During follow-up, 700 (26%) patients failed treatment after a median (IQR) duration of 6 (range 3 – 10) months. A comparison of patients with treatment success versus treatment failure is shown in Table 1.

Predictors of treatment success

As shown in Table 2, co-treatment with thiopurines (adjusted (adj.) odds ratio (OR) 0.35, 95%CI 0.28-0.43) or methotrexate (adj. OR 0.42, 95%CI 0.24-0.79), and male gender (adj. OR 0.70, 95%CI 0.58-0.85) were independently associated with a lower risk of discontinuation, whereas previous infliximab treatment (adj. OR 1.32, 95%CI 1.10-1.58) and treatment

Table 1. Comparison of CD patients on adalimumab whit treatment success versus treatment failure

	Treatment success n=1985 (74%)	Treatment failure n=700 (26%)	P-value
Age (years ± SD)	38 (13)	37 (13)	0.85
Male gender (%)	774 (39)	210 (30)	<0.01
Academic center (%)	682 (34)	281 (40)	<0.01
Induction therapy 160-80-40 (%)	1154 (58)	403 (58)	0.82
Previous infliximab (%)	1023 (52)	426 (61)	<0.01
Methotrexate (%)	74 (4)	14 (2)	0.03
Azathioprine/ 6-mercaptopurine (%)	748 (38)	118 (17)	<0..01

SD, standard deviation

Table 2. Univariate and multivariate analysis of the association between demographic and treatment characteristics and treatment failure.

	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Increasing age (per year)	1.00 (0.99-1.00)	1.00 (0.99-1.00)
Male gender	0.67 (0.56-0.81)	0.70 (0.58-0.85)
Academic center	1.28 (1.07-1.53)	1.22 (1.01-1.48)
Induction therapy (160-80-40)	0.98 (0.82-1.16)	0.97 (0.80-1.17)
Previous infliximab	1.46 (1.23-1.74)	1.32 (1.10-1.58)
Methotrexate	0.53 (0.30-0.94)	0.42 (0.24-0.79)
A azathioprine/6-mercaptopurine	0.34 (0.27-0.42)	0.35 (0.28-0.43)

OR, Odds ratio; CI, confidence interval

at a academic centre (adj. OR 1.22, 95%CI 1.01-1.48) were independently associated with a higher risk for discontinuation.

Discussion

Here we report a beneficial effect of co-treatment with immunomodulators in CD patients with adalimumab. The success-rate of treatment with adalimumab in this unselected, nationwide cohort of CD patients was 73% after a median follow up of six months. We showed that co-treatment with immunomodulators (both thiopurines and methotrexate) were independently associated with a lower risk of discontinuation, whereas previous infliximab treatment was associated with a higher risk for discontinuation.

In literature, the overall remission rate at one year of follow-up is only 36-46%.[2,7] However, in open label studies, clinical response rates up to 67% are described, which more likely reflects the "real-life" situation.[8–11] In addition, previous study showed that treatment was less efficacious in patients who had already been treated with infliximab compared to infliximab-naive patients, which is also in line with our findings.[12]

The beneficial effect of immunomodulators could well be attributed to a reduced risk of antibody formation against adalimumab, as it is in infliximab. Another explanation could be that the induction phase of adalimumab is more effective with concomitant immunomodulators, causing a reduced inflammatory load. The reduction of adalimumab discontinuation in these patients might justify standard methotrexate or thiopurine co-treatment in clinical practice.

Our study has several strengths and some limitations. Using a nationwide registry of all CD patients treated with adalimumab, we minimalized the chance of selection bias. Furthermore, our data reflects 'real-life' practice. Finally, due to our large cohort we were able to analyse a large panel of risk factors in the multivariate analysis. However, there is also a downside of using an anonymised registry. We had no access to clinical or endoscopic disease parameters. Therefore we could not calculate response or remission rates, which makes comparison with previous literature challenging. We therefore assumed that an ongoing prescription of adalimumab implicated treatment success. In addition, due to the lack of clinical data, we might have missed other important predictors of treatment discontinuation, such as fistulizing disease, antibody formation, or important adalimumab-related side effects.

In conclusion, this is the first report on the beneficial effect of co-treatment with immunomodulators in CD patients treated with adalimumab. The highly significant reduction of adalimumab discontinuation in these patients might justify standard methotrexate or thiopurine co-treatment in clinical practice. A head-to-head comparison between adalimumab versus adalimumab plus an immunomodulator in patients with Crohn's disease is warranted.

REFERENCES

1 Sokol H, Seksik P, Carrat F, *et al.* Usefulness of co-treatment with immunomodulators in patients with inflammatory bowel disease treated with scheduled infliximab maintenance therapy. *Gut* 2010;59:1363–8.

2 Sandborn WJ, Hanauer SB, Rutgeerts P, *et al.* Adalimumab for maintenance treatment of Crohn's disease: results of the CLASSIC II trial. *Gut* 2007;56:1232–9.

3 Bartelds GM, Wijbrandts CA, Nurmohamed MT, *et al.* Clinical response to adalimumab: relationship to anti-adalimumab antibodies and serum adalimumab concentrations in rheumatoid arthritis. *Ann Rheum Dis* 2007;66:921–6.

4 West RL, Zelinkova Z, Wolbink GJ, *et al.* Immunogenicity negatively influences the outcome of adalimumab treatment in Crohn's disease. *Aliment Pharmacol Ther* 2008;28:1122–6.

5 Karmiris K, Paintaud G, Noman M, *et al.* Influence of Trough Serum Levels and Immunogenicity on Long-term Outcome of Adalimumab Therapy in Crohn's Disease. *Gastroenterology* 2009;137: 1628–40.

6 D'Haens GR, Panaccione R, Higgins PDR, *et al.* The London Position Statement of the World Congress of Gastroenterology on Biological Therapy for IBD with the European Crohn's and Colitis Organization: when to start, when to stop, which drug to choose, and how to predict response? *Am J Gastroenterol* 2011;106:199–212;

7 Colombel J-F, Sandborn WJ, Rutgeerts P, *et al.* Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. *Gastroenterology* 2007;132: 52–65.

8 Ho GT, Smith L, Aitken S, *et al.* The use of adalimumab in the management of refractory Crohn's disease. *Aliment Pharmacol Ther* 2008;27:308–15.

9 Seiderer J, Brand S, Dambacher J, *et al.* Adalimumab in patients with Crohn's disease--safety and efficacy in an open-label single centre study. *Aliment Pharmacol Ther* 2007;25:787–96.

10 Peyrin-Biroulet L, Laclotte C, Bigard M-A. Adalimumab maintenance therapy for Crohn's disease with intolerance or lost response to infliximab: an open-label study. *Aliment Pharmacol Ther* 2007; 25:675–80.

11 Hinojosa J, Gomollón F, García S, *et al.* Efficacy and safety of short-term adalimumab treatment in patients with active Crohn's disease who lost response or showed intolerance to infliximab: A prospective, open-label, multicentre trial. *Aliment Pharmacol Ther* 2007;25:409–18.

12 Sandborn WJ, Rutgeerts P, Enns R, *et al.* Adalimumab induction therapy for Crohn disease previously treated with infliximab: a randomized trial. *Ann Intern Med* 2007;146:829–38.

Chapter 8

Summary and discussion

SUMMARY AND DISCUSSION

Increasing healthcare costs worldwide have put current healthcare systems under pressure. In this thesis, we focused on the economic impact of the widespread and increasing use of anti-TNF therapy in inflammatory bowel disease (IBD). As cost studies are lacking since the introduction of anti-TNF, the general aim of the COIN-study was to determine the societal costs of IBD in the Netherlands and to evaluate the cost-effectiveness of anti-TNF therapy compared to corticosteroid-based therapy. In this chapter, the main findings of this thesis are summarized and their implications and future perspectives are discussed.

Healthcare costs

Up to 2000, i.e. before the introduction of anti-TNF drugs, the key cost drivers in IBD were hospitalisation and surgery accounting for more than half of total healthcare costs in the Netherlands.[1] Nowadays, medication costs, especially anti-TNF therapy, account for most of the healthcare costs, while costs related to hospitalization and surgery are substantially reduced as demonstrated in Chapter 3 and Chapter 4. During a two-year study period, healthcare costs remained stable over the two years of follow-up with annual healthcare costs of €6,326 in CD and €2,340 in UC (Chapter 4). Medication costs accounted for 81% and 65% of the healthcare costs for CD and UC respectively (Chapter 4). Our findings suggest that the increase in medication costs (and anti-TNF therapy) is at least partially compensated for by a decrease in costs due to hospitalization. This is in line with other studies reporting lower hospitalization rates since the introduction of anti-TNF therapy.[1,2] For example, recent data from the South-Limburg cohort in the Netherlands reported a lower hospitalization rate of IBD patients diagnosed in the anti-TNF era as compared to patients diagnosed in the pre-anti-TNF period (34% versus 51%). [2] A similar pattern has been observed in rheumatoid arthritis, with anti-TNF therapy playing a pivotal role as well. In two national registry cost-of-illness studies covering 20-years of follow-up, a downward trend for annual healthcare costs, apart from the costs for anti-TNF therapy has been reported.[3,4]

Our study provides valuable information, putting the high cost of anti-TNF therapy into perspective. With anti-TNF therapy being the most important cost driver, it might also be an important target when it comes to reducing healthcare costs. The recent introduction of biosimilars can be expected to have a significant impact in this respect. Biosimilars are copy versions of licensed anti-TNF compounds and have been approved for the treatment of both CD and UC. Currently, there are two infliximab biosimilars registered in the Netherlands, Remsima and Inflectra. One of the future study aims of the COIN-study is to assess the impact of the introduction of biosimilars on IBD-related healthcare costs.

Tailoring treatment to patients who can be expected to respond to anti-TNF drugs and discontinuing these drugs in a carefully selected subgroup of patients might also curb the increasing healthcare costs. The provisionally accepted consensus of the Dutch initiative on Crohn's and Colitis (ICC) state that anti-TNF/immunomodulator combination therapy should be continued for at least one year if the treatment is effective and well tolerated. After one year either the anti-TNF agent or the immunomodulator may be stopped, provided that this decision is made on an individual basis depending on the patient history and the presence of 'deep remission', based on clinical, biochemical and endoscopical assessment. Data from the STORI study has shown that the relapse rate is 15% in CD patients with no more than two risk factors, such as absence of surgery, male gender, C-reactive protein ≥5.0 mg/L or a fecal calprotectin level ≥300 µg/g.[5]

Another way to control healthcare costs is to optimize anti-TNF treatment. Patients should receive combination therapy with immunomodulators, which has been proven to be more effective than anti-TNF monotherapy. [6] We corroborated this finding in large cohort of patients receiving adalimumab in Chapter 7.

Finally, measurement of anti-TNF antibodies and trough levels might additionally increase the efficiency. A recently published randomized controlled trial showed that an algorithm based on combined trough and antibodies measurements significantly reduced average healthcare costs compared to routine dose escalation in patients. [7]

Productivity losses

The peak age of onset in IBD is in the second and third decade of life,[8] and therefore IBD has a major influence on the working career of a patient with IBD. Consequently, we found that the prevalence rates of work disability in CD and UC patients were higher as compared to the Dutch general population (Chapter 2). Increased age, low education, a state of depression, chronic back pain, joint manifestations and typical disease-related risk factors such as a penetrating disease course and abdominal surgery in the past were all found to be associated with work disability (Chapter 2).

Annual costs due to productivity losses were €1,335 in CD and €1,120 in UC (Chapter 4). Productivity losses due to IBD-related sick leave, accounted for 17% and 31% of the total societal costs in CD and in UC, respectively (Chapter 3 and 4). In Chapter 3 and 4 we did not take productivity losses of work disability into account. Although we used the human capital approach, we were not able to find out the specific cause of work disability. Therefore, the current estimates are an underestimation of the real productivity losses.

The observed high work disability rates and productivity losses warrant a coordinated approach from medical specialists and occupation physicians caring for these patients in order to prevent job losses and a further decline of productivity. However, to evaluate the effectiveness of this strategy, long-term prospective studies in patients with early IBD are needed to determine if this would result in the prevention of structural damage, improvement in work productivity (i.e. lower sick leave rates) and/or a reduction of work disability.

Anti-TNF versus surgery in UC patients

Economic evaluations in UC are particularly interesting in patients failing conservative treatment (mesalazine, corticosteroids with or without immunomodulators). It is still under debate whether, in the long term, anti-TNF therapy is a valid approach for "organ sparing", rather than an expensive way of delaying surgery. In Chapter 5 we compared costs and quality-of-life in three subgroups of UC, i.e. UC patients with a pouch reconstruction, an ileostomy and on anti-TNF therapy. Patients receiving anti-TNF-therapy reported the highest healthcare costs. In addition, healthcare costs were three times higher in ileostomy patients compared to pouch patients. We found no difference in IBDQ-scores, a measure for quality of life, but pouch patients were found to have slightly higher quality-adjusted life years (QALYs) than ileostomy patients and anti-TNF-treated patients. Obviously, due to the lack of randomization, this study was not based on comparable groups of patients. Especially the differences in both 'post-surgery' groups and patients receiving anti-TNFα therapy with continuing disease activity preclude firm conclusions.

Cost-effectiveness of anti-TNF therapy in CD patients

In chapter 6 we aimed to provide a clear answer as to whether anti-TNF therapy is more cost-effective as remission induction therapy than corticosteroid-based therapy in CD patients. Based on our data, we failed to show incremental positive effects for disease activity and quality-of-life but found higher incremental healthcare and societal costs in patients on anti-TNF therapy compared to corticosteroid therapy. Due to the lack of randomization, our study is limited by selection bias. There were for example important differences at baseline, i.e. a shorter disease duration and lower quality-of-life in the anti-TNF treatment group. In line with Chapter 3 and 4 we found lower hospitalization costs in the anti-TNF treatment group compared to the corticosteroid–based treatment group, but we failed to show an improvement of productivity (i.e. fewer sick leave, lower work disability) following anti-TNF treatment. This could be due to the high percentage of work disability in our cohort at baseline (45% in the anti-TNF group and 42.0% in the corticosteroid-based treatment group). It can be argued that a two-year follow-up is too short to fully acknowledge the improved health status resulting in new employment.

Prospective clinical trials reporting on efficacy, health-related quality-of-life and costs are required to address this important question.

MAIN CONCLUSIONS FROM THIS THESIS

- IBD is associated with an increase of work disability, which is more pronounced in CD than in UC.
- Risk factors for work disability in IBD include disease activity, abdominal surgery and penetrating disease course.
- The costs profile of IBD shifted since the introduction of anti-TNF therapy. Medication use, and especially anti-TNF therapy replaced hospitalisation and surgery costs as the major cost drivers.
- Costs of IBD remained stable over two years of follow up. During this period, the use of anti-TNF therapy further increased at the expanse of hospitalisations.
- Ileostomy patients are three times more expensive compared to pouch patients, mainly due to ileostomy supplies and hospitalizations.
- Anti-TNF therapy was not found to be associated with a positive incremental effect for disease activity and quality-of-life but led to incremental higher healthcare and societal costs compared to patients on corticosteroid-based therapy.

REFERENCES

1 Bernstein CN, Loftus E V., Ng SC, *et al.* Hospitalisations and surgery in Crohn's disease. Gut. 2012; 61:622–9.

2 Jeuring SFG, van den Heuvel TRA, Zeegers MP, *et al.* Long-term disease outcome of Crohn's disease in the biological era – Results from a Dutch population-based IBD cohort. *Abstr NVGE* 2015.

3 Kalkan A, Hallert E, Bernfort L, *et al.* Costs of rheumatoid arthritis during the period 1990-2010: a register-based cost-of-illness study in Sweden. *Rheumatology* 2014;53:153–60.

4 Huscher D, Mittendorf T, von Hinuber U, *et al.* Evolution of cost structures in rheumatoid arthritis over the past decade. *Ann Rheum Dis* 2015. Apr;74:738-45.

5 Louis E, Mary J-Y, Vernier-Massouille G, *et al.* Maintenance of remission among patients with Crohn's disease on antimetabolite therapy after infliximab therapy is stopped. *Gastroenterology* 2012;142:63–70

6 Colombel JF, Sandborn WJ, Reinisch W, *et al.* Infliximab, azathioprine, or combination therapy for Crohn's disease. *N Engl J Med* 2010;362:1383–95.

7 Steenholdt C, Brynskov J, Thomsen OO, *et al.* Individualised therapy is more cost-effective than dose intensification in patients with Crohn's disease who lose response to anti-TNF treatment: a randomised, controlled trial. *Gut* 2014;63:919-27.

8 Cosnes J, Gower-Rousseau C, Seksik P, *et al.* Epidemiology and natural history of inflammatory bowel diseases. *Gastroenterology* 2011;140:1785–94.

Chapter 9

Dutch summary/ samenvatting

Acknowledgments/ dankwoord

Curriculum vitae

List of publications

SAMENVATTING

De toename van kosten binnen de gezondheidszorg zet de huidige gezondheidszorg onder druk. In dit proefschrift hebben we ons gericht op de economische consequenties van het gebruik van anti-TNF therapie in inflammatoire darmziekten (IBD). De twee belangrijkste vormen van IBD zijn de ziekte van Crohn (ZvC) en colitis ulcerosa (CU). Deze chronische darmziektes kenmerken zich door terugkerende ontsteking van het maag- en darmkanaal. Om deze opvlammingen van de ziekte te voorkomen ontvangen de meeste patiënten onderhoudsmedicatie. De laatste tien jaar wordt in toenemende mate anti-TNF therapie gebruikt voor IBD. Alhoewel de effectiviteit van anti-TNF therapie in meerdere klinische studies bewezen is, gaat het gepaard met hoge kosten. Voorafgaand aan dit proefschrift waren er nog geen studies naar de kosten van IBD sinds de invoering van anti-TNF. Om die reden hebben we met behulp van de COIN studie de maatschappelijke kosten van IBD en de kosteneffectiviteit van anti-TNF therapie onderzocht.

Kosten van de gezondheidszorg

Tot 2000 – het tijdperk vòòr de invoering van anti-TNF therapie - werden de kosten van IBD vooral veroorzaakt door opnames en chirurgie. Deze twee kostenposten samen zorgden voor meer dan 50% van de IBD-gerelateerde kosten binnen de gezondheidszorg in Nederland. In hoofdstuk 3 en 4 laten we zien dat sinds de invoering van anti-TNF therapie medicatie het grootste deel van de kosten voor z'n rekening neemt. Daarentegen zijn de kosten door opnames en chirurgie aanzienlijk afgenomen. Gedurende de studieperiode van twee jaar blijven de totale kosten van IBD stabiel. De kosten per patiënt per jaar zijn €6,326 in het geval van de ZvC en €2,340 in het geval van CU (hoofdstuk 4). De medicatie kosten waren verantwoordelijk voor 81% van de kosten binnen de gezondheidszorg in de ZvC en 65% in CU (hoofdstuk 4). Daarentegen zien we een afname van kosten door opnames in zowel de ZvC als CU. Dit suggereert dat de stijging van de anti-TNF -gerelateerde kosten wordt gecompenseerd door een daling van opname kosten. De daling van opnames sinds de invoering van anti-TNF zien we ook terug in ander studies. Een goed voorbeeld hiervan is een recent onderzoek uit Zuid Limburg. In deze studie wordt aangetoond dat IBD patiënten bij wie de diagnose gesteld werd na de invoering van anti-TNF therapie minder vaak worden opgenomen dan patiënten uit het pre-anti-TNF tijdperk (34% versus 51%). Een vergelijkbaar patroon wordt waargenomen in reumatoïde artritis, een chronische inflammatoire aandoening van de gewrichten, waarbij anti-TNF therapie eveneens een belangrijke rol speelt. In twee nationale database studies over een tijdsbestek van 20 jaar wordt een duidelijke neerwaartse trend gezien van alle kosten binnen de gezondheidszorg, echter stegen de kosten door anti-TNF therapie.

Productiviteitsverliezen

De leeftijd waarop IBD zich meestal manifesteert ligt in het derde en vierde decennium van het leven. Dat is de periode waarin de basis wordt gelegd voor een gezin en carrière. In hoofdstuk 2 laten we zien dat de prevalentie van arbeidsongeschiktheid van patiënten met de ZvC en CU hoger ligt dan bij de algemene Nederlandse populatie. Daarnaast is het percentage arbeidsongeschiktheid hoger bij patiënten met de ZvC in vergelijking met CU. Een hogere leeftijd, lagere scholing, depressie, en chronische rugpijn en gewrichtsklachten blijken geassocieerd te zijn met een grotere kans op arbeidsongeschiktheid. Daarnaast zijn ook ziekte-specifieke kenmerken zoals ontstekingsactiviteit, abdominale chirurgie en een fistelende ziekte geassocieerd met arbeidsongeschiktheid.

In hoofdstuk 3 en 4 wordt onderzocht in hoeverre ziekteverzuim leidt tot productiviteitsverliezen (ook wel indirecte niet medische kosten genoemd). De aan ziekteverzuim gerelateerde kosten blijken aanzienlijk te zijn: op jaarbasis €1,335 en €1,120 voor patienten met respectievelijk de ZvC en CU (17% en 31% van de totale IBD-gerelateerde kosten). Deze percentages zijn waarschijnlijk een onderschatting van de werkelijke kosten, aangezien we niet de productiviteitsverliezen door arbeidsongeschiktheid hebben berekend. De reden hiervoor is dat we niet geïnformeerd waren over de reden van arbeidsongeschiktheid.

Een gezamenlijke aanpak van medisch specialisten en bedrijfsartsen zou een bijdrage kunnen leveren aan het verminderen van arbeidsongeschiktheid van IBD patiënten. Er zijn tot op heden geen studies gepubliceerd die het effect van een krachtige behandeling (zoals anti TNF medicatie) kort na de diagnose van IBD op het optreden van arbeidsongeschiktheid, ziekteverzuim en productiviteitsverliezen heeft onderzocht.

Anti-TNF therapie versus chirurgie bij CU patiënten

Tot op heden zijn er geen kosten studies verricht in CU patiënten bij wie conservatieve therapie (mesalazine, corticosteroïden met of zonder een immunomodulator) gefaald heeft. Er is dan ook nog geen duidelijkheid of anti-TNF of chirurgie in dit geval de beste therapie op de lange termijn is. In hoofdstuk 5 hebben we de kosten en kwaliteit van leven vergeleken in drie subgroepen van patiënten met CU, te weten patiënten met een ileo-pouch anale anastomose (pouch), patiënten met een ileostoma en patiënten die anti-TNF therapie krijgen. Het blijkt dat patiënten die anti-TNF therapie ontvangen de hoogste kosten genereren binnen de gezondheidszorg en dat patiënten met een ileostoma drie maal duurder zijn dan patiënten met een pouch. Dit laatste heeft met name te maken met de relatief hoge kosten van stomamaterialen en met frequentere opnames. We vonden geen verschil in de ziekte-specifieke kwaliteit van leven tussen de drie groepen, maar patiënten met een pouch bleken wel een hogere generieke kwaliteit

van leven te hebben. Een beperking van onze studie is een gebrek aan randomisatie. Randomisatie betekent dat de onderzoeksgroepen op willekeurige wijze, bijvoorbeeld door loting, zijn samengesteld. Door het gebrek aan randomisatie zijn de drie verschillende groepen niet geheel vergelijkbaar. Met name de verschillen tussen de pouch en ileostoma patiënten enerzijds, en de patiënten met anti-TNF met ziekteactiviteit belemmeren een betekenisvolle analyse.

Kosteneffectiviteit van anti-TNF therapie bij patiënten met de ZvC

In hoofdstuk 6 hebben we ons gericht op de vraag of anti-TNF medicatie kosteneffectief is als deze middelen ingezet worden als remissie-inductie therapie in patiënten met de ZvC. We hebben in deze analyse anti-TNF therapie vergeleken met een behandeling met corticosteroïden. Op basis van onze gegevens hebben we geen positief effect op ziekteactiviteit en kwaliteit van leven kunnen aantonen, maar gaat anti-TNF therapie wel gepaard met hogere kosten binnen de gezondheidszorg en met hogere productiviteitsverliezen. Ook hier wordt onze studie beperkt door selectie bias. Er waren bijvoorbeeld belangrijke verschillen aan het begin van de studie tussen de patiëntengroepen. Patienten die behandeld werden met anti-TNF therapie hadden een kortere ziekteduur en lagere kwaliteit van leven dan de patiënten die behandeld werden met corticosteroïden. In overeenstemming met hoofdstuk 3 en 4 vonden we wel lagere kosten door minder opnames in de anti-TNF therapie groep maar er kon geen afname van productiviteitsverliezen worden aangetoond. Dit kan worden verklaard doordat een groot deel van de patiënten al arbeidsongeschikt was, namelijk 45% in de anti-TNF-groep en 42% in de corticosteroïden-groep. Mogelijk is een studieduur van twee jaar te kort om effecten te mogen verwachten op de productiviteit van patiënten die reeds arbeidsongeschikt zijn (en mogelijk niet meer aan het werk kunnen door structurele schade van hun ziekte). Er zijn gerandomiseerde studies nodig waarbij er gekeken wordt naar de effectiviteit, kwaliteit van leven en kosteneffectiviteit van anti-TNF met een voldoende lange follow-up om deze vraag te kunnen beantwoorden.

Voorstellen voor een verbetering van de kosteneffectiviteit van anti-TNF therapie

Anti-TNF therapie is een belangrijke kostenpost, en daarmee een voor de hand liggend doel voor verdere rendementsverbetering in de zorg voor IBD patiënten. Hieronder bespreken we een aantal mogelijke manieren hoe dit te bereiken. Allereerst zijn recent de zogenoemde 'biosimilars' ingevoerd. Biosimilars zijn kopie versies van de huidige geregistreerde anti-TNF therapieën en zijn inmiddels goedgekeurd voor de behandeling van zowel ZvC als CU. In de praktijk is ondertussen gebleken dat biosimilars een stuk goedkoper zijn dan de eerdere anti-TNF preparaten. Eén van de vervolgstudies van de

COIN studie is om kijken wat het effect is van de invoering van biosimilars op de huidige kosten binnen de gezondheidszorg.

Om de IBD-gerelateerde gezondheidskosten te beteugelen is het van groot belang om dure middelen, zoals anti-TNF medicijnen, toe te dienen aan die patiënten van wie verwacht mag worden dat zij hier goed op reageren. Daarnaast zou er ook zorgvuldig gekeken moeten worden bij welke (zorgvuldig geselecteerde) groep patiënten de anti-TNF therapie op termijn gestopt kan worden. In de recent vernieuwde Nederlandse handleiding "Behandeling van IBD" wordt geadviseerd om anti-TNF/immunomodulator combinatietherapie gedurende ten minste één jaar voort te zetten indien de behandeling effectief en goed verdragen wordt. Na één jaar kan dan de anti-TNF-agent of de immunomodulator worden gestopt, mits er sprake is van zogenoemde 'diepe remissie' op basis van klinische, biochemische en endoscopische beoordeling.

Daarnaast is het van belang om de behandeling van anti-TNF therapie te optimaliseren. Patiënten die anti-TNF therapie ontvangen moeten in ieder geval combinatietherapie met een immunomodulator ontvangen. Dit is gebleken effectiever dan alleen monotherapie. Dit hebben we bevestigd in een groot cohort van ZvC patiënten die gedurende 2006-2010 adalimumab voorgeschreven kregen (hoofdstuk 7). Daarnaast kun je de behandeling van anti-TNF therapie optimaliseren door het meten van anti-TNF antilichamen en bloedspiegels. Uit een onlangs gepubliceerde, gerandomiseerde en gecontroleerde studie is gebleken dat een algoritme gebaseerd op de gecombineerde metingen van bloedspiegels en antilichaam metingen kosten
effectief is.

Belangrijkste conclusies van dit proefschrift

- IBD is geassocieerd met een toename in arbeidsongeschikt, waarbij patiënten met de ZvC vaker arbeidsongeschikt zijn dan patiënten met CU.
- Ziekte-specifieke risicofactoren voor arbeidsongeschiktheid zijn ontstekingsactiviteit, abdominale chirurgie en een fistelend ziektebeloop.
- Het kostenprofiel van IBD is veranderd sinds de invoering van anti-TNF therapie. De kosten door medicatiegebruik, met name anti-TNF therapie, hebben opnames en chirurgie vervangen als belangrijkste kostenpost.
- De totale kosten van IBD blijven stabiel gedurende twee jaar follow-up. Tijdens deze periode is er echter een toename van kosten door anti-TNF met een afname van kosten door opnames.
- CU patiënten met een ileostomie hebben gemiddeld drie keer hogere kosten binnen de gezondheidszorg in vergelijking met patiënten met een ileo-pouch anale

anastomose. Dit verschil ontstond met name door kosten van stoma materiaal en opnames.

- Remissie-inductie therapie met anti-TNF medicatie bij patiënten met de ZvC leidt niet tot een meetbaar diepere remissie of betere kwaliteit van leven in vergelijking met patiënten die behandeld werden met corticosteroïden. Wel ging de behandeling met anti-TNF gepaard met hogere gezondheidszorgkosten.

DANKWOORD

Soms heb je een harde deadline nodig om de klus te klaren. In mijn geval was dat het besluit dat Gijs en ik half april 2015 naar Zuid Afrika gingen verhuizen. Voor vertrek was de promotiedatum aangevraagd en met een "Valkse eindsprint" en met enorme druk op de ketel is het proefschrift afgeschreven. En mijn omgeving en co-promotoren hebben dat ook geweten, ook zij hebben gezweten. Gelukkig had ik de juiste mensen om me heen. Hieronder wil graag expliciet de personen bedanken die me de afgelopen jaren enorm geholpen hebben.

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Prof. Dr. P.D. Siersema. Mijn promotor, daarmee de eerste van de The Big Five. In eerste instantie leek er geen plek in het Utrechtse, maar u vertelde me dat het wel goed zou komen. U schoof me op een gegeven moment bij Bas de kamer in voor een sollicitatie-gesprek. Op onderzoeksgebied hebben we niet samen gewerkt, maar elke maand kwam ik even langs om de voortgang te bespreken. Deze werkoverleggen noemde u destijds vlammend, een soort monoloog van mijn kant. U gaf me altijd het gevoel dat het goed zou komen en soms is dat het enige wat je als promovenda wilt horen!

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Maar na bijna vier jaar was het tijd voor een nieuwe omgeving, en heb ik het Utrechtse verlaten voor het Jeroen Bosch Ziekenhuis.

Prof dr. P.J.H. Drenth en dr. M. van Kouwen. Mijn opleiders. Beste Joost en Mariëtte, het is heerlijk om in opleiding te zijn. Dank dat jullie mij hebben aangenomen en mij de ruimte hebben gegeven om mijzelf te ontwikkelen. Ik besef me dat het erg bijzonder is dat ik de opleiding voor twee jaar mag onderbreken om in Zuid Afrika als arts-assistent aan de slag te gaan. Mijn waardering is enorm!

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My fellow GIT registrars ("the GIT tribe") and the consultants from the GIT unit. Thank you for making my work at Groote Schuur Hospital so much fun and interesting. I am looking forward to the next two years at your department!

Collega onderzoekers. Wat hebben we toch enorm gelachen met z'n allen. De volgende dingen schieten me te binnen. Alleen maar vrouwelijke onderzoekers, met bijhorende gesprekken tijdens de lunch (Jan Steven en Erik, hoe hebben jullie dat volgehouden?). De borrels, bij Olivier, het Licht, de Poort, Oosterkade, die om 17.00 begonnen, altijd met kaasstengels (wat een uitvinding!) en waar we zonder eten doorgingen. De BBQs in Berkel Enschot bij Anke en Hein-Jan, Sinterklaas met de onderzoekers thuis, de Mike en Tim show, de mooie gedichten of sonnetten (met name Jan Steven), waar de aois

langskwamen als Sint (bleek mijn zwager uiteindelijk) en Piet (Wouter Hazen), aan Sinterklaas spelen voor de afdeling, met smijtpiet, met dwarse Sint (Max) en de eerste vrouwelijke Sint (Meike), aan het MDL voetbal team, waarmee we de afdeling Reiniging & Onderhoud hebben verslagen (wat een glorieuze overwinning), onze skitrips, de marathon in Berlijn met Lotte, Daisy en Vincent, want die staat zo goed op je CV, dat je zo groen kan zien (Vincent), aan de wekelijkse hardloopsessies (naja, bijna wekelijks), en aan de congressen, de ideale gelegenheid om de stad te leren kennen, dansend in de kosten koper, met alle collega's Tim aanmoedigen bij de hockey, en Tim, blij dat je nu zo gelukkig bent met Daisy! Mijn favoriete roze mascarpone taart van Huffels.

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Lieve Gijs, we hebben niet geluisterd naar de 'dreamstealers' en hebben onze droom waargemaakt. Ik geniet zo van ons leven in Kaapstad. Ontzettend lief hoe je me de afgelopen periode gesteund hebt! En met de zomer in aantocht kan het hier alleen maar beter worden!

Liefs Mirthe

CURRICULUM VITAE

Mirthe van der Valk werd geboren op 9 april 1984 te Dinxperlo. Na het behalen van haar gymnasium diploma, startte zij in 2002 met haar studie geneeskunde in Maastricht. Zij ronde haar studie af op de afdeling Maag-Darm- en Leverziekten van het Universitair Medisch Centrum Maastricht (prof. dr. A.A. Masclee en dr. S. Sanduleanu). Aansluitend werd zij aangenomen als arts-onderzoeker op de afdeling Maag-, Darm- en Leverziekten van het Universitair Medisch Centrum Utrecht. Onder begeleiding van prof. dr. P.D. Siersema, dr. B. Oldenburg en dr. M.J.J. Mangen deed ze promotieonderzoek naar de kosten van inflammatoire darmziekten in Nederland. Per 1 januari 2013 is ze in opleiding tot Maag-, Darm- en Leverarts (opleider prof. dr. J.P.H. Drenth en waarnemend opleider dr. M. van Kouwen). De vooropleiding heeft ze 31 maart 2015 afgerond in het Jeroen Bosch Ziekenhuis (opleider dr. W. Smit). Aansluitend is ze samen met haar partner Gijs Simon verhuisd naar Zuid Afrika. Daar is ze per 1 mei 2015 begonnen aan de vervolgopleiding tot Maag-, Darm- en Leverarts in het Groote Schuur Ziekenhuis, Kaapstad, Zuid Afrika (opleider prof. dr. S.R. Thomson). Per 1 april 2017 zal ze de opleiding tot Maag-, Darm- en Leverziekten in het Jeroen Bosch Ziekenhuis (opleider dr. I. van Munster) en Universitair Medisch Centrum st. Radboud vervolgen.

LIST OF PUBLICATIONS

van der Valk ME, Mangen MJJ, Severs M et al. Comparison of costs and quality of life in ulcerative colitis patients with an ileal pouch-anal anastomosis, ileostomy and anti-TNF therapy. *J Crohns Colitis. 2015 (in press)*

van der Have MJ, Fidder HH, Leenders M, Kaptein AA, van der Valk ME et al. Self-reported disability in patients with inflammatory bowel disease largely determined by disease activity and illness perceptions. *Inflamm Bowel Dis. 2015 Feb;21(2):369-77*

Lutgens M, van Oijen M, Mooiweer E, van der Valk ME et al. A risk-profiling approach for surveillance of inflammatory bowel disease-colorectal carcinoma is more cost-effective: a comparative cost-effectiveness analysis between international guidelines. *Gastrointest Endosc. 2014 Nov;80(5):842-8*

van der Valk ME, Mangen MJ, Leenders M et al. Risk factors of work disability in patients with inflammatory bowel disease - A Dutch nationwide web-based survey. *J Crohns Colitis. 2014 Jul 1;8(7):590-7*

van der Have M, Mangen MJ, van der Valk ME et al. Effect of Aging on Healthcare Costs of Inflammatory Bowel Disease: A Glimpse into the Future. *Inflamm Bowel Dis. 2014 Apr;20(4):637-45*

Van der Valk ME, Mangen MJJ, Leenders M et al. Healthcare costs of inflammatory bowel disease have shifted from hospitalization and surgery towards anti TNF therapy – results from the COIN study. *Gut. 2014 Jan;63(1):72-9*

Rondagh EJ, Masclee AA, van der Valk ME et al. Nonpolypoid colorectal neoplasms: Gender differences in prevalence and malignant potential. *Scand J Gastroenterol. 2012;47(1):80-8*

Van der Valk ME, van Oijen MGH, Ammerlaan M et al. Crohn's disease patients treated with adalimumab benefit from co-treatment with immunomodulators. *Gut. 2012;61(2):324-5.*

Addendum

The effect of aging on healthcare costs of inflammatory bowel disease: a glimpse into the future

Mike van der Have, Marie-Josée J Mangen, Mirthe E. van der Valk, Hugo M. Smeets, Ad A. van Bodegraven, Gerard Dijkstra, Herma H. Fidder, Dirk J. de Jong, Marieke Pierik, Cyriel Y. Ponsioen, Andrea E. van der Meulen-de Jong, C. Janneke van der Woude, Paul C. van de Meeberg, Mariëlle J.L. Romberg-Camps, Cees H.M. Clemens, Jeroen M. Jansen, Nofel Mahmmod, Clemens J.M. Bolwerk, J. Reinoud Vermeijden, Peter D. Siersema, Max Leenders, Bas Oldenburg, on behalf of the COIN study group and the Dutch Initiative on Crohn and Colitis

Inflamm Bowel Dis. 2014 Apr;20(4):637-45

ABSTRACT

Background:

Population aging is expected to result in a substantial additional burden on healthcare resources in the near future. We aimed to assess the current and future impact of aging on direct healthcare costs (DHC) attributed to inflammatory bowel disease (IBD).

Methods:

IBD patients from a Dutch multicenter cohort filled out three-monthly questionnaires for two years. Elderly (≥ 60 years) and younger (18-60 years) IBD patients were analyzed for differences in three-monthly DHC, productivity losses and out-of-pocket costs. Prevalence rates were obtained from a health insurance database. Estimates of annual DHC and prevalence rates were applied to the total Dutch adult population in 2011 and then projected to 2040, using predicted changes in population demography, prices, and volume.

Results:

IBD-attributable DHC were lower in elderly than in younger IBD patients with respect to three-monthly DHC (€359 versus €978, $p<0.01$), productivity losses (€108 versus €456, $p<0.01$) and out-of-pocket costs (€40 versus €57, $p<0.01$). Between 2011 and 2040, the percentage of elderly IBD patients in the Netherlands has been projected to rise from 24% to 35%. Between 2011 and 2040, DHC of the total IBD population in the Netherlands are projected to increase from €161 to €661 million. Population aging accounted for 1% of this increase, next to rising prices (29%), and volume growth (70%).

CONCLUSION:

Population aging has a negligible effect on IBD-attributable DHC of the IBD population in the near future, because the average costs incurred by elderly IBD patients are considerably lower than those incurred by younger IBD patients.

INTRODUCTION

Inflammatory bowel disease (IBD), encompassing Crohn's disease (CD) and ulcerative colitis (UC), is one of the most prevalent chronic gastrointestinal diseases in the Western world. Extrapolating the highest IBD prevalence rates to the populations of Europe and North America indicates that there were 3.7 million Europeans and 1.5 million North Americans diagnosed with IBD in 2011, accounting for respectively €17.9 and €7.4 billion annual direct healthcare costs.[1-4]

Currently, 16-27% of IBD patients is older than 60 years, hereafter referred to as "elderly IBD patients".[5] This subpopulation will expand as a result of the aging of the baby boom generation. Eurostat estimated that in Europe the elderly population will increase by 50%, from 116 million in 2010 to 175 million in 2040.[6] According to a recent survey of U.S. hospital discharges, elderly IBD patients accounted for a disproportionate number of hospitalizations and had a higher postoperative morbidity and mortality compared to younger patients.[7, 8] Therefore, the growing subpopulation of elderly IBD patients may increasingly burden healthcare resources.

In an era of budgetary constraints, more data on the economic impact of IBD are required for proper allocation of the limited healthcare resources. These data allow healthcare providers, policy makers and clinicians to create a Pareto optimum, defined in economics as a reallocation of resources for the benefit of all individuals.[9]

Previous cost-of-illness studies were mainly limited to single centers, reported only direct healthcare costs (DHC), and were conducted in a pre-biological era or relied on mathematic modelling.[10-16] Therefore, we initiated the "Costs Of Inflammatory bowel disease in the Netherlands" or "COIN" study in 2010.[4] We used the COIN database to compare the IBD-attributable DHC (DHC-IBD) and productivity losses of elderly IBD patients with those of younger IBD patients. Based on these data we estimated the 2011 DHC-IBD of the total adult IBD population in the Netherlands and projected those to 2040.

MATERIAL & METHODS

Patient population

Details on the patient population are available elsewhere.[4] Briefly, adult CD and UC patients from seven general and seven university hospitals were identified between 2007 and 2010, using Diagnosis-Treatment-Combination codes (DTC). DTC's are based on

the International Classification of Disease, Ninth Revision,[17, 18] and have been found to reliably identify IBD patients.[19, 20] In accordance with previous studies,[5, 7] patients ≥60 years were defined as "elderly IBD patients", whereas those <60 years were defined as "younger IBD patients". The study was centrally approved by the Medical Ethics Committee of the University Medical Center Utrecht.

Study protocol and measurements

A secured web-based questionnaire was developed to obtain baseline characteristics and three-monthly cost data during two years of follow-up. Demographic characteristics included gender, age, age at diagnosis, education level, work status, family history, and smoking status. Clinical characteristics included subtype of IBD, disease duration and localisation, penetrating disease course (perianal or other fistula), stoma or pouch and clinical disease activity. Clinical disease activity was measured by the well-validated Short Crohn's Disease Activity Index[21] and the Modified Truelove and Witts Severity Index[22, 23] for CD and UC patients, respectively. Finally, quality of life (QOL) was measured by the EQ-5D[23, 24] and the IBDQ-32.[25, 26]

DHC-IBD, productivity losses and out-of-pocket costs attributable to IBD

DHC-IBD were obtained and classified as: 1) outpatient visits, including the number of outpatient physician consultations; 2) diagnostic procedures, including endoscopies and radiological examinations; 3) medication use, including IBD-specific drugs (mesalazine, steroids, immunosuppressants and anti-TNFα antibodies); 4) stoma-related costs; 5) IBD-related hospitalizations, defined as the number of days hospitalized, and 6) IBD-related surgeries, including intestinal resections and perianal operations. In line with the Dutch guidelines for economic evaluations, patient's costs were calculated by multiplying self-reported units of resource utilization by their unit costs.[27]

To assess productivity losses we used sick leave of patients and their caregivers from both paid and unpaid work as outcome measure (absenteeism). Employed patients, partially disabled patients with a paid job and patients with an unpaid job (voluntary work) reported the number of sick leave days within the previous three months. In addition, patients were asked to report whether their caregivers were absent from paid work in order to take care of them, and if so, for how many days. Hours of work absence (paid and unpaid) of patients and caregivers was multiplied with the corresponding unit prices as reported previously.[4]

Patients reported IBD-related out-of-pocket costs within the previous three months, including patient's deductibles for healthcare insurance, over-the-counter drugs (vitamins, antidiarrheals, analgetics, probiotics, and minerals), travel costs and subscriptions

of patient organizations. More details on the calculation method are provided elsewhere. [4]

Non-responders

As reported previously,[4] there were no statistical differences between responders and non-responders from one participating center with regard to demographic (age, gender) and clinical characteristics (disease duration, penetrating disease course and abdominal surgery in the past).

Projection of prevalence rates and DHC-IBD of IBD

The projections were made as follows. First, IBD prevalence rates and annual DHC-IBD per person were generated for each age- (18-39, 40-59, ≥60 years), gender- and IBD subtype-specific group. The prevalence rate for each age-, gender- and IBD subtype-specific group was estimated by dividing the number of IBD patients by the total number of policy holders of the Agis Health Insurance Company[28] registered in July 1st 2011, and were conservatively assumed to remain constant between 2011 and 2040. Then, these prevalence rates were applied to the Census projections of population counts for the years 2011 to 2040 to generate the total IBD population for the years 2011 to 2040.[29] Finally, the DHC-IBD per person per three months were multiplied by four and by the corresponding number of IBD patients of the above-mentioned groups, to generate the total annual DHC-IBD of the IBD population for the years 2011 to 2040 (Supplementary Table 1).

In our base-case analysis we projected the DHC-IBD of the total IBD population from 2011 to 2040, taking into account the cumulative effects of population aging, rising prices and volume growth (increased healthcare utilization) on the DHC-IBD. Prices and volume of overall healthcare expenditure were assumed to increase at the same rate for the next 30 years: averaging an annual rate of 4.9% (2.2% due prices; 2.7% due to volume). But as the increase in volume is debatable, we conducted a scenario analysis, in which we only accounted for the effects of population aging and rising prices (2.2%) on the DHC-IBD.[30, 31]

Finally, one-way sensitivity analyses were performed, varying IBD prevalence rates and mean DHC-IBD of each age-, gender- and IBD subtype-specific group, using the lower and upper ends of the 95% CI, to assess the uncertainty of the projected DHC-IBD between 2011 and 2040. The projection method is described in full detail in Supplementary Methods.

Statistical analysis

Data analyses were performed using SPSS 20.0 and SAS 9.2. Descriptive statistics were used to characterize CD and UC patients according to their age. Means and medians were reported with a standard deviation (SD) and an interquartile range (IQR) respectively. Comparisons between elderly versus younger IBD were analysed with Student's t-test for continuous variables and $\chi 2$ or Fisher's exact test for dichotomous variables.

Costs were expressed as mean costs with 95% CI estimated using non-parametric bootstrap sampling. To identify cost drivers of high healthcare costs, we included demographic, clinical, and treatment-related characteristics into a two-part mixed model. This model takes into account that cost data are right-skewed with a substantial proportion of zero values and consists of two parts: 1) a generalised linear mixed model assessing the odds of costs being positive and; 2) a linear mixed model with log-normal link assessing the height of costs given that costs were actually incurred. To account for repeated measures within subjects, a random intercept was fitted to both parts of the model. Projections were modelled in MS Excel 2010.

RESULTS

Patient population

In total, 3,015 IBD patients filled-out the baseline questionnaire, including 1,551 patients with CD (51%), 1,051 patients with UC (35%) and 413 patients with either IBD-unspecified or "IBD-unknown" (14%). "IBD-unknown" included patients who did not know their IBD-subtype, reported UC with ileal involvement or fistulas. As there were no significant differences between patients with "IBD-unknown"/-unspecified and UC with regard to demographic (age, gender) and clinical characteristics (disease duration, abdominal surgery, stoma, pouch, and medication use), these groups were analyzed together (hereafter referred to as UC). Three-hundred seven out of 1,551 CD patients (20%) and 354 out of 1,464 UC patients (24%) were older than 60 years.

The proportion of patients lost to follow-up was comparable between elderly and younger IBD patients, namely 15.0% versus 15.4% ($p=0.78$). Both elderly and younger IBD patients who were lost to follow-up were more likely to be female ($p=0.02$), smoker ($p<0.01$), and had a lower education level ($p<0.01$) than those IBD patients who were not lost to follow-up.

Elderly CD patients were more likely to be male ($p<0.01$), had a higher probability of a positive history of abdominal surgery ($p<0.01$), and a current stoma ($p<0.01$) compared

Table 1. Main baseline characteristics of younger (< 60 years) versus elderly (≥ 60 years) CD patients

	Younger CD n = 1244	**Elderly CD n = 307**	p value
Demographic characteristics:			
Male gender (%)	408 (32.8)	164 (53.4)	0.00
Age – years (±SD)	42.2 (10.8)	66.0 (5.0)	0.00
Age at diagnosis – years (±SD)	26.7 (9.8)	40.2 (14.9)	0.00
Low education (%)	777 (62.5)	223 (72.6)	0.00
Positive family history (%)	265 (21.3)	71 (23.1)	0.50
Current smoker	279 (22.4)	49 (16.0)	0.01
Employment status (%)			
Employed	706 (56.8)	31 (10.0)	0.00
Fully work disabled	153 (12.3)	22 (7.2)	0.01
Partially work disabled	208 (16.7)	55 (17.9)	0.62
Retired	7 (0.6)	173 (56.4)	0.00
Homemaker	108 (8.7)	26 (8.5)	0.91
Student	62 (5.0)	-	0.00
Clinical characteristics:			
Disease duration – median (IQR)	13.9 (6.9-22.8)	24.9 (13.9-37.5)	0.00
Disease localization (%)			
Large bowel	335 (26.9)	92 (30.0)	0.29
Small bowel	241 (19.4)	66 (21.5)	0.40
Both large and small bowel	630 (50.6)	134 (44.6)	0.03
Unknown	38 (3.1)	15 (4.9)	0.11
Clinical disease activity – mean score on short – CDAI	146.5 (85.2)	119.5 (69.7)	0.01
IBDQ total – median (IQR)	177 (153-196)	176 (155-198)	0.48
EQ-5D VAS – median (IQR)	71 (61-80)	70 (60-80)	0.46
Penetrating disease course (%)	658 (52.9)	150 (48.9)	0.21
Stoma (%)	137 (11.0)	54 (17.6)	0.00
Pouch (%)	21 (1.7)	7 (2.3)	0.49
Treatment-related characteristics:			
Type of abdominal surgery in the past (%)	713 (57.3)	233 (75.9)	0.00
Ileocecal resection	281 (22.6)	79 (25.7)	0.17
Resection neo-terminal ileum	82 (6.6)	35 (11.4)	0.00
Partial small bowel resection	118 (9.5)	43 (14.0)	0.02
Partial large bowel resection	136 (10.9)	41 (13.4)	0.28
Subtotal resection	96 (7.7)	35 (11.4)	0.04
Medication use (%)[a]			
Mesalazine	221 (21.4)	67 (25.1)	0.20
Steroids	81 (7.8)	26 (9.7)	0.32
Immunosuppressants	359 (34.6)	59 (22.1)	0.00
Anti-TNFα antibodies	262 (25.3)	35 (13.1)	0.00

[a] = Medication use was obtained three months after inclusion. In total, 1035 younger CD patients and 267 elderly CD patients reported their medication use.

Table 2. Main baseline characteristics of younger (< 60 years) versus elderly (≥ 60 years) UC patients

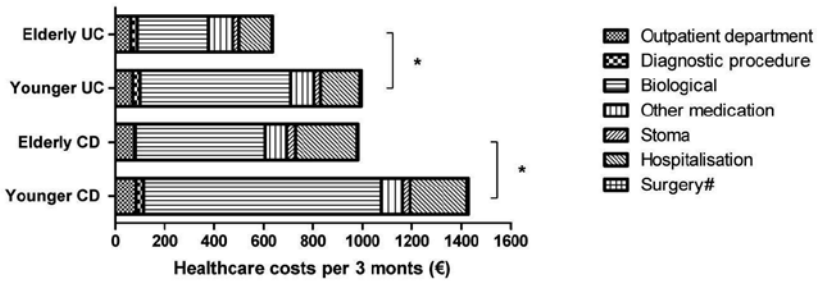
	Younger UC*[a] *n = 1110	***Elderly UC*[a] *n = 354***	p value
Demographic characteristics:			
Male gender (%)	503 (45.3)	245 (69.2)	0.00
Age – years (±SD)	44.1 (10.3)	66.7 (5.6)	0.00
Age at diagnosis – years (±SD)	30.8 (10.8)	48.2 (14.0)	0.00
Low education (%)	647 (58.3)	239 (67.5)	0.02
Positive family history (%)	224 (20.2)	76 (21.5)	0.44
Current smoker	127 (11.4)	28 (7.9)	0.06
Employment status (%)			
Employed	755 (68.0)	57 (16.1)	0.00
Fully work disabled	128 (11.5)	16 (4.5)	0.00
Partially work disabled	93 (8.4)	48 (13.6)	0.00
Retired	15 (1.4)	212 (59.9)	0.00
Homemaker	95 (8.6)	21 (5.9)	0.12
Student	24 (2.2)	-	0.00
Clinical characteristics:			
Disease duration – median (IQR)	11.2 (5.9-19.9)	16.3 (6.9-28.9)	0.00
Clinical disease activity – mean score on MTWSI (±SD)	4.2 (2.8)	3.8 (2.4)	0.01
IBDQ total – median (IQR)	184 (160-202)	189 (166-204)	0.01
EQ-5D VAS – median (IQR)	74 (65-81)	73 (65-80)	0.71
Stoma (%)	80 (7.2)	27 (7.6)	0.82
Pouch (%)	119 (10.7)	19 (5.4)	0.00
Treatment-related characteristics:			
Subtotal colectomy in the past (%)	126 (11.4)	23 (6.5)	0.01
Medication use (%)[b]			
Mesalazine	551 (59.3)	197 (62.5)	0.35
Steroids	44 (4.7)	18 (5.7)	0.59
Immunosuppressants	205 (22.1)	47 (14.9)	0.00
Anti-TNFα antibodies	49 (5.3)	7 (2.2)	0.04

[a] Including patients with UC and patients with IBD-unspecified/ "IBD-unknown"
[b] Medication use was obtained three months after inclusion. In total, 929 younger UC patients and 315 elderly UC patients reported their medication use.

to younger CD patients (Table 1). Younger CD patients were more likely to be smoker (p=0.01), had a higher incidence of clinical active disease (p=0.01), and were more frequently treated with immunosuppressants (p<0.01) and anti-TNFα antibodies (p<0.01). Elderly UC patients were more likely to be male (p<0.00) compared to younger UC patients (Table 2). Younger UC patients had a higher incidence of clinical active disease (p=0.01), were more frequently treated with immunosuppressants (p<0.01) and anti-TNFα antibodies (p=0.04).

DHC-IBD costs in CD and UC

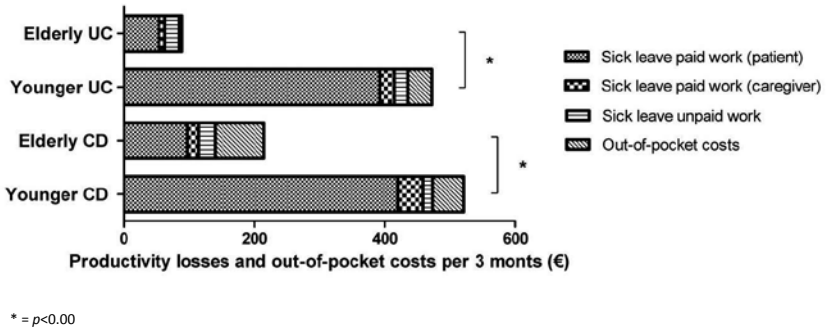
The mean DHC-IBD per patient per three months were lower in elderly than in younger IBD patients, i.e., €982 versus €1428 (p<0.01) in CD, and €637 versus €995 (p<0.01) in UC (Figure 1). Medication use was the major cost driver in both elderly CD and UC patients, accounting for 62% and 60% of total DHC respectively. The costs attributable to anti-TNFα antibodies were consistently lower in elderly than in younger IBD patients (€523 versus €962, p<0.01 in CD, and €287 versus €608, p<0.01 in UC).



* = *p*<0.00, # = Mean costs per three months related to surgery were €2, €6, €4, and €6 for respectively elderly UC, younger UC, elderly CD, and younger CD patients

Figure 1. Mean direct healthcare costs per three months in 2011 and cost drivers of both elderly and younger CD and UC patients.

In elderly CD, the only significant predictor of high costs was anti-TNFα therapy (Odds Ratio (OR) 15.30, 95% CI 12.61-18.56). Significant predictors of high costs in elderly UC were anti-TNFα therapy (OR 18.70, 95% CI 14.40-24.27), stoma use (OR 9.30, 95% CI 6.51-13.29), steroid therapy (OR 1.28, 95% CI 1.10-1.49), immunosuppressive therapy (OR 1.25, 95% CI 1.10-1.42), and current flares (OR 1.17, 95% CI 1.08-1.27).



* = p<0.00

Figure 2. Mean productivity losses and mean out-of-pocket costs per three months in 2011 of both elderly and younger CD and UC patients.

Productivity losses and out-of-pocket costs in CD and UC

Productivity losses due to sick leave of paid work were lower in elderly than in younger CD and UC patients (€97 versus €420 (p=0.04), and €54 versus €392 (p<0.01) respectively). Productivity losses due to sick leave of unpaid work were higher in elderly than in younger CD, but comparable between elderly and younger UC patients (€25 versus €14 (p<0.01), and €22 versus €20 (p=0.69) respectively). Out-of-pocket costs were lower in elderly than in younger CD and UC patients (€48 versus €75 (p<0.01), and €4 versus €37 (p<0.01) respectively) (Figure 2, Supplementary Table 2, Supplementary Table 3).

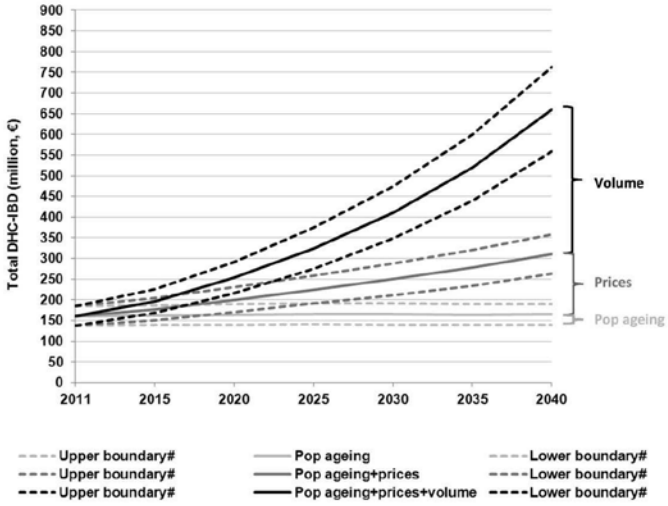
DHC-IBD costs in 2011

Costs were lower in elderly versus younger IBD patients with respect to three-monthly DHC-IBD (€359 versus €978, p<0.01), productivity losses (€108 versus €456, p<0.01) and out-of-pocket costs (€40 versus €57, p<0.01). Within elderly IBD patients, costs were higher in patients aged 60-70 years versus patients aged 70 years or older with respect to DHC-IBD (€432 versus €241, p=0.000), productivity losses (€119 versus €14, p=0.001), and out-of-pocket costs (€46 versus €19, p=0.001).

Projections of IBD population and DHC-IBD

The total IBD population in the Netherlands is expected to increase from 43,953 in 2011 to 46,894 individuals in 2040, an increase of 7%. The total number of elderly IBD patients will increase from 10,658 in 2011 to 16,323 in 2040, a growth of 53% (Supplementary Table 1).

According to our base-case analysis (population aging + rising prizes + volume), the DHC-IBD of the total adult IBD projection are projected to increase from €161 million



= The dotted lines represent the one-way sensitivity analysis, using the upper and lower boundaries of only the mean DHC-IBD

Figure 3. Projections of IBD-attributable direct healthcare (DHC-IBD) costs in the Dutch adult population from 2011 to 2040, considering the cumulative effects of population aging, rising prices, and volume growth.

to €661 million in 2040, a 4.1-fold increase. The contributions of population aging, price inflation and volume to this increase were respectively 1%, 29% and 70% (Figure 3).

According to our scenario analysis (population aging + rising prizes), the DHC-IBD of the total adult IBD projection are projected to increase from €161 million to €310 million in 2040, a 1.9-fold increase.

When using the low and high boundaries of the estimated DHC-IBD and the IBD prevalence rates in our base-case analysis, the projected DHC-IBD of the adult IBD population in 2040 varied between €559 and €763 million (Figure 3) and between €580 and €741 million respectively.

DISCUSSION

Healthcare costs have significantly increased over the recent years. This has been attributed to an overall increase in prices of healthcare expenditure, volume growth and population aging. The latter contributes to higher healthcare costs because of the

increasing likelihood of chronic illness with age and a general increased healthcare utilization. In IBD, however, we found that the impact of population aging on the DHC-IBD of the total adult IBD population, - presuming status quo in treatment - is mitigated by two factors: 1) the relatively low healthcare utilization by elderly IBD patients, and 2) a reduced proportion of relatively expensive middle-aged (40-60 years) IBD patients due to the declining birth rate since the baby boom.

COIN-cohort

Several reasons may explain the lower healthcare utilization, productivity losses and out-of-pocket costs in elderly IBD patients as compared with younger IBD patients. Consistent with previous studies, expensive anti-TNFα antibodies were less frequently prescribed for elderly than for younger IBD patients,[4, 32-34] which may suggest a milder disease course in elderly IBD patients. Accordingly, in our study elderly IBD patients reported a lower disease activity at baseline and a higher QOL at baseline and during follow-up than younger IBD patients (Supplementary Table 4). A milder disease course, when aged, has been reported by other authors showing lower requirements of immunosuppressants and anti-TNFα antibodies,[33, 35] reduced rates of hospitalization,[36, 37] and disease progression,[35, 38] and better treatment response.[39] Additionally, clinicians may hesitate to prescribe anti-TNFα antibodies in elderly patients, because of doubts related to the efficacy or the demonstrated increased risk of potential side effects of these compounds in elderly, such as (opportunistic) infections[40, 41] and cancer.[42]

Second, overall productivity losses were lower in elderly than in younger IBD patients, obviously because most elderly IBD patients were retired.

Third, most elderly IBD patients were captured at a later stage of their disease as reflected by the long median disease duration and were therefore exempted from high costs that are usually incurred in the first years after diagnosis.[43, 44]

Projection of IBD-attributable DHC until 2040

Productivity losses could not reliably be extrapolated due to ongoing policy changes with respect to retirement age and were therefore excluded. However, according to previous and current data, productivity losses contribute to only one-fourth of the total healthcare costs.[4] In line with recent data from high-incidence countries showing a stabilization of the IBD prevalence, we assumed that the current IBD prevalence will remain constant for the next 30 years.[3, 45]

Next to population aging, we assessed the impact of increasing prices and volume on the growth of DHC-IBD, thereby identifying potential targets for cost containment

interventions and putting the effect of population aging on the growing DHC-IBD into perspective.

According to our projections, the DHC-IBD would quadruple from €161 million to €661 million between 2011 and 2040. Only 1% of this growth is attributable to population aging. The limited effect of population aging on the DHC-IBD is due to the fact that elderly IBD patients utilize considerably less IBD-attributable healthcare compared to their younger counterparts. In addition, due to population aging the proportion of relative costly middle-aged (40-60 years) IBD patients will reduce from 43% in 2011 to 35% in 2040.

Another important finding was that 70% of the growth in DHC-IBD is attributable to volume. We suggest that technological innovations - frequently cited as a major volume-generating factor[46, 47] - are mainly responsible for this growth. In IBD, biologicals are considered important technological innovations. The expanding indications for the use of existing biologicals (mainly anti-TNFα antibodies) and the introduction of new compounds[48] may generate additional volume and, thereby, increase the DHC-IBD even more. Although biosimilars, that are generally priced 15-30% below their reference products, may reduce the total costs related to the use of biologicals/biosimilars,[49-51] in our opinion, this will likely have a minor effect on the expected utilization of these compounds in the future.

The future healthcare utilization of elderly IBD patients might increase for several reasons. First, as younger IBD patients will continue to use expensive biologicals while they age, more elderly IBD patients may be expected to use these compounds in the future. Second, as experience with the use of biologicals in elderly IBD patients grows, clinicians may be less concerned about potential side-effects and prescribe biologicals more frequently. Whether this increased healthcare utilization would disproportionately affect elderly IBD patients remains a matter of debate, and if so, the effect of population aging on DHC as we reported might be underestimated. However, we feel that more aggressive or treat-to-target treatment of younger IBD patients will also lead to a higher healthcare utilization in this subpopulation, which will counterbalance the potential increase in healthcare utilization in elderly IBD patients.

This study has several limitations. First, the web-based design of this study may be prone to sampling error, as elderly people may have a relatively limited access to internet. However, since 90% of elderly people in the Netherlands currently has access to internet,[52] we do not feel that this aspect has biased our study. Second, our projections may be subject to sampling error as our prevalence rates were based on information from a

health insurance database.[53] Yet, coding errors in this database are regularly excluded by random checks and auditing[28] and prevalence rates are consistent with those from surrounding countries in Europe and North America.[54, 55] Third, attrition bias may have occurred as patients who were lost to follow-up were more likely to be female, smokers, and had a lower education. Nevertheless, none of these characteristics were found to be significantly associated with higher costs. Fourth, indirect costs resulting from polypharmacy, drug-drug interactions or side effects of medications might have been missed. This may have led to an underestimation of total indirect healthcare costs, especially of those in elderly patients with IBD.

This study provides valuable information on current and future healthcare costs of elderly patients with IBD that will be useful to 1) inform decision makers as they plan to meet future healthcare demands in the elderly in general; 2) provide cost data to assess the cost-effectiveness of treatment strategies in elderly patients with IBD.

In conclusion, although population aging is generally considered an important cost driver, this does not hold true for IBD. In IBD, the impact of aging is mitigated, because of the lower ratio of DHC-IBD for elderly versus younger patients. This lower ratio may also be found in other immune-mediated inflammatory diseases (IMIDs) such as rheumatoid arthritis, where elderly patients are also less likely to receive expensive biological treatment.[56, 57] Therefore, we feel that our data may be generalizable to other IMIDs. Further comparative cost-of-illness studies are needed to confirm this state statement.

REFERENCES

1. Jacobsen BA, Fallingborg J, Rasmussen HH, et al. Increase in incidence and prevalence of inflammatory bowel disease in northern Denmark: a population-based study, 1978–2002. Eur J Gastroenterol Hepatol 2006;18:601–6.
2. Lapidus A. Crohn's disease in Stockholm County during 1990–2001: an epidemiological update. World J Gastroenterol 2006;12:75–81.
3. Loftus CG, Loftus EV Jr, Harmsen WS, et al. Update on the incidence and prevalence of Crohn's disease and ulcerative colitis in Olmsted County, Minnesota, 1940-2000. Inflamm Bowel Dis 2007; 13:254-61.
4. Van der Valk ME, Mangen MJ, Leenders M; on behalf COIN study group and the Dutch Initiative on Crohn and Colitis. Healthcare costs of inflammatory bowel disease have shifted from hospitalisation and surgery towards anti-TNFα therapy: results from the COIN study. Gut 2012 Nov 7. doi: 10.1136/gutjnl-2012-303376.
5. Piront P, Louis E, Latour P, et al. Epidemiology of inflammatory bowel diseases in the elderly in the province of Leige. Gastroenterol Clin Biol 2002;26:157-61.
6. Eurostat. http://epp.eurostat.ec.europa.eu/statistics_explained/index.php/Population_structure_and_ageingAccessed June 9th, 2013.
7. Page MJ, Poritz LS, Kunselman SJ, et al. Factors affecting surgical risk in elderly patients with inflammatory bowel disease. J Gastrointest Surg. 2002;6:606-13.
8. Ananthakrishnan AN, McGinley EL, Binion DG. Inflammatory bowel disease in the elderly is associated with worse outcomes: a national study of hospitalizations. Inflamm Bowel Dis 2009;15: 182-9.
9. Kaplan RM, Babad YM. Balancing influence between actors in healthcare decision making. BMC Health Serv Res 2011:19;11:85.
10. Hay JW, Hay AR. Inflammatory bowel disease: costs-of-illness. J Clin Gastroenterol 1992;14: 309–317.
11. Hay AR, Hay JW. Inflammatory bowel disease: medical cost algorithms. J Clin Gastroenterol 1992; 14:318–327.
12. Blomqvist P, Ekbom A. Inflammatory bowel diseases: health care and costs in Sweden in 1994. Scand J Gastroenterol 1997;32:1134–1139.
13. Bernstein CN, Papineau N, Zajaczkowski J, et al. Direct hospital costs for patients with inflammatory bowel disease in a Canadian Tertiary Care University Hospital. Am J Gastroenterol 2000;95: 677–683.
14. Silverstein MD, Loftus EV, Sandborn WJ, et al. Clinical course and costs of care for Crohn's disease: Markov model analysis of a population-based cohort. Gastroenterol 1999;117:49–57.
15. Bassi A, Dodd S, Williamson P, et al. Cost of illness of inflammatory bowel disease in the UK: a single centre retrospective study. Gut 2004;53:1471–8.
16. Odes S, Vardi H, Friger M, et al. Cost analysis and cost determinants in a European inflammatory bowel disease inception cohort with 10 years of follow-up evaluation. Gastroenterol 2006;131: 719–28.
17. Enthoven AC, van de Ven WP. Going Dutch—managed-competition health insurance in the Netherlands. N Engl J Med 2007;357:2421–3.
18. Tsiachristas A, Hipple-Walters B, Lemmens KM, et al. Towards integrated care for chronic conditions: Dutch policy developments to overcome the (financial) barriers. Health Policy 2011;101: 122–32.

19. Van Schaik FD, van Oijen MG, Smeets HM, et al. Thiopurines prevent advanced colorectal neoplasia in patients with inflammatory bowel disease. Gut 2012;61:235–40.
20. Baars JE, Looman CW, Steyerberg EW, et al. The risk of inflammatory bowel disease-related colorectal carcinoma is limited: results from a nationwide nested case-control study. Am J Gastroenterol 2011;106:319–28.
21. Timmer A, Kemptner D, Takses A, et al. A survey based index was validated for measuring disease activity in inflammatory bowel disease. An evaluation study. J Clin Epidemiol 2009;62:771-8.
22. Lichtiger S, Present DH. Preliminary report: cyclosporin in treatment of severe active ulcerative colitis. Lancet 1990;336:16–9.
23. Truelove SC, Witts LJ. Cortisone and corticotrophin in ulcerative colitis. Br Med J 1959;1:387-94.
24. Salén BA, Spangfort EV, Nygren AL, et al. The Disability Rating Index: an instrument for the assessment of disability in clinical settings. J Clin Epidemiol 1994;47:1423-34.
25. König HH, Ulshöfer A, Gregor M, et al. Validation of the EuroQol questionnaire in patients with inflammatory bowel disease. *Eur J Gastroenterol Hepatol* 2002;14:1205-15.
26. Guyatt G, Mitchell A, Irvine EJ, et al. A new measure of health status for clinical trials in inflammatory bowel disease. Gastroenterol 1989;96:804–10.
27. Russel MG, Pastoor CJ, Brandon S, et al. Validation of the Dutch translation of the inflammatory bowel disease questionnaire (IBDQ): a health-related quality of life questionnaire in inflammatory bowel disease. Digestion 1997;58:282–8.
28. Hakkaart-van Roijen L, Tan SS, Bouwmans CAM. Handleiding voor kostenonderzoek, methoden en standaard kostprijzen voor economische evaluaties in de gezondheidszorg. College voor zorgverzekeringen Geactualiseerde versie. 2010.
29. Smeets HM, Wit NJ de, Hoes AW. Routine health insurance data for scientific research: potential and limitations of the Agis Health Database. J Clin Epidemiol 2011;64:424-30. doi: 10.1016/j.jclinepi.2010.04.023.
30. Statistics Netherlands. http://statline.cbs.nl/StatWeb/selection/?DM=SLNL&PA=80745NED&VW=T. Accessed June 9th, 2013.
31. Statistics Netherlands. http://statline.cbs.nl/StatWeb/publication/default.aspx?DM=SLEN&PA=71311eng&D1=01&D2=0%2c137141%2c144&D3=64%2c77%2c90%2c103%2c116%2c129%2c142%2c155%2c168%2c181%2c194%2c219%2c232&LA=EN&HDR=G1%2cT&STB=G2&VW=D. Accessed June 9th, 2013.
32. Luijben AHP, Kommer GJ. Tijd en Toekomst. Deelrapport van de Volksgezondheid Toekomst Verkenning 2010 Van Gezond naar Beter. RIVM-rapport 270061008. Bilthoven: RIVM, 2010.
33. Juneja M, Baidoo L, Schwartz MB, et al. Geriatric inflammatory bowel disease: phenotypic presentation, treatment patterns, nutritional status, outcomes, and comorbidity. Dig Dis Sci 2012;57:2408-15. doi: 10.1007/s10620-012-2083-x.
34. Benchimol EI, Cook SF, Erichsen R, et al. International variation in medication prescription rates among elderly patients with inflammatory bowel disease. J Crohns Colitis 2012 Sep 24. pii: S1873-9946(12)00402-3.
35. Charpentier C, Salleron J, Savoye G, et al. Natural history of elderly-onset inflammatory bowel disease: a population-based cohort study. *Gut* 2013 Feb 13. [Epub ahead of print]
36. Kappelman MD, Porter CQ, Galanko JA, et al. Utilization of healthcare resources by U.S. children and adults with inflammatory bowel disease. Inflamm Bowel Dis. 2011;17:62-8.
37. Heresbach D, Alexandre JL, Bretagne JF, et al. Crohn's disease in the over-60 age group: a population based study. *Eur J Gastroenterol Hepatol* 2004;16:657-64.

38. Lakatos PL, David G, Pandur T, et al. IBD in the elderly population: results from a population-based study in Western Hungary, 1977-2008. *J Crohns Colitis* 2011;5:5-13. doi:
39. Ha CY, Newberry RD, Stone CD, et al. Patients with late-adult-onset ulcerative colitis have better outcomes than those with early onset disease. Clin Gastroenterol Hepatol 2010;8:682-687.e1.
40. Cottone M, Kohn A, Daperno M, et al. Advanced age is an independent risk factor for severe infections and mortality in patients given anti-tumor necrosis factor therapy for inflammatory bowel disease. Clin Gastroenterol Hepatol 2011;9:30-5.
41. Toruner M, Loftus Jr EV, Harmsen WS, et al. Risk factors for opportunistic infections in patients with inflammatory bowel disease. Gastroenterol 2008;134:929–36.
42. Siegel CA, Hur C, Korzenik JR, et al. Risks and benefits of infliximab for the treatment of Crohn's disease. Clin Gastroenterol Hepatol 2006;4:1017–24.
43. Bernstein CN, Longobardi T, Finlayson G, et al. Direct medical cost of managing IBD patients: a Canadian population-based study. *Inflamm Bowel Dis* 2012;18:1498-508.
44. Longobardi T, Bernstein CN. Utilization of health-care resources by patients with IBD in Manitoba: a profile of time since diagnosis. Am J Gastroenterol. 2007;102:1683-91.
45. Kappelman MD, Moore KR, Allen JK, et al. Recent trends in the prevalence of Crohn's disease and ulcerative colitis in a commercially insured US population. Dig Dis Sci. 2013;58:519-25.
46. Okunade AA, Murthy VNR. Technology as 'major driver' of health care costs: a cointegration analysis of the newhouse conjecture. J Health Econ 2002;21:147–159.
47. Gelijns A, Rosenberg N. The dynamics of technological change in medicine. Health Aff (Millwood) 1994;13:28-46.
48. Danese S. New therapies for inflammatory bowel disease: from the bench to the bedside. Gut 2013;61:918-32.
49. Gecse KB, Khanna R, van den Brink GR, et al. Biosimilars in IBD: hope or expectation? Gut 2013;62: 803-7.
50. Malik NN. Controlling the cost of innovative cancer therapeutics. Nat Rev Clin Oncol 2009;6:550-2.
51. S1695: Biologics Price Competition and Innovation Act of 2007Congressional Budget Office cost estimate. http://www.cbo.gov/ftpdocs/94xx/doc9496/s1695.pdf. Accessed June 9th, 2013.
52. Statistics Netherland.2013. http://www.cbs.nl/enGB/menu/themas/dossiers/eu/publicaties/archief/ 2012/2012-3636-wm.htm. Accessed June 9th, 2013.
53. Wilchesky M, Tamblyn RM, Huang A. Validation of diagnostic codes within medical services claims. J Clin Epidemiol 2004;57:131-41.
54. Burisch J, Jess T, Martinato M, et al; on behalf of ECCO -EpiCom. The burden of inflammatory bowel disease in Europe. J Crohns Colitis 2013;7:322-37.
55. Loftus EV Jr. Clinical epidemiology of inflammatory bowel disease: Incidence, prevalence, and environmental influences. Gastroenterology. 2004;126:1504-17.
56. Radovits BJ, Fransen J, Eijsbouts A, et al. Missed opportunities in the treatment of elderly patients with rheumatoid arthritis. Rheumatology (Oxford). 2009;48:906-10.
57. Tutuncu Z, Reed G, Kremer J, et al. Do patients with older-onset rheumatoid arthritis receive less aggressive treatment? Ann Rheum Dis. 2006;65:1226-9.

SUPPLEMENTARY METHODS:

Projections of IBD prevalence rates

Prevalence rates of IBD were estimated with data from the Agis Health Database (AHD). The Agis Health Insurance Company is one of the largest health insurance companies in the Netherlands. It provides healthcare coverage for more than 1.5 million policy holders. Random samples from this database have been shown to be representative for the Dutch population with regard to gender and age distribution. The AHD contains data on demographics, diagnostic and therapeutic provisions, pharmaceutical prescriptions and Diagnosis-Treatment-Combination (DTC) codes. Coding errors within this database are excluded by random checks and a comprehensive program of material auditing.[1]

The DTC codes were used to identify patients with either Crohn's disease or ulcerative colitis. The prevalence rate for each age-, gender- and IBD subtype-specific group was estimated by dividing the corresponding number of IBD patients by the total number of policy holders registered in July 1st 2011. Prevalence rates were then applied to the Census projections of population counts for the years 2011 to 2040 to generate the total IBD population for the years 2011 to 2040. Projected population counts for the years 2011 to 2040 were obtained from the 2010 population projections of the Dutch population generated by the Dutch Census Bureau (Statistics Netherlands).[2] The 2010 population projections are based on assumptions about future changes in fertility, life expectancy, and migration and were generated by a cohort-component model.[3]

Projection of direct healthcare costs

The data source for generating projections of direct healthcare costs of IBD was the current "Costs Of Inflammatory bowel disease in the Netherlands" or "COIN" study.[4] The direct healthcare costs per person per three months in 2011 for each age-, gender- and IBD subtype-specific group were estimated using a two-part mixed model. This model takes into account that cost data are right-skewed with a substantial proportion of zero values and consists of two parts: 1) A generalised linear mixed model assessing the odds of costs being positive and; 2) a linear mixed model with log-normal link assessing the height of costs given that costs were actually incurred. To account for repeated measures within subjects, a random intercept was fitted to both parts of the model. Direct healthcare costs per person per three months were then multiplied by four and applied to the Census projections of IBD population for the years 2011 to 2040 to generate the total annual direct healthcare costs of the IBD population for the years 2011 to 2040.

In our base-case analysis we projected the DHC-IBD of both the total IBD population from 2011-2040, taking into account the cumulative effects of population ageing, rising prices and volume growth on the DHC-IBD of both populations. Prices and volume of

overall healthcare expenditure were expected to increase at the same historical rate (2001-2011) for the next 30 years: averaging an annual rate of 4.9% (2.2% due prices; 2.7% due to volume). But as the increase in volume is debatable, we conducted a scenario analysis, whereby we only accounted for the effects of population ageing and rising prices (2.2%) on the DHC.[5,6]

Finally, one-way sensitivity analyses were performed, varying IBD prevalence rates and mean DHC-IBD of each age-, gender- and IBD subtype-specific group, using lower and upper bound of the 95% CI, to assess the uncertainty of the projected DHC-IBD between 2011 and 2040. The model used to project IBD-DHC at population level for the years 2011 up to 2040 was built in MS Excel 2010.

REFERENCES

1. Smeets HM, Wit NJ de, Hoes AW. Routine health insurance data for scientific research: potential and limitations of the Agis Health Database. J Clin Epidemiol 2011;64(4):424-30.
2. Statistics Netherlands. http://statline.cbs.nl/StatWeb/selection/?DM=SLNL&PA=80745NED&VW=T**.** Accessed June 9th, 2013.
3. Beer J de, Alders M (1999) Probabilistic population and household forecasts for the Netherlands. Joint Economic Commission for Europe–EUROSTAT Work Session on Demographic Projections, Perugia, May 3rd–7th, working paper 45. Geneva: Economic Commisson for Europe.
4. Van der Valk ME**,** Mangen MJ**,** Leenders M**;** on behalf COIN study group and the Dutch Initiative on Crohn and Colitis**.** Healthcare costs of inflammatory bowel disease have shifted from hospitalisation and surgery towards anti-TNFα therapy: results from the COIN study. Gut 2012 Nov 7. doi: 10.1136/gutjnl-2012-303376.
5. Statistics Netherlands. http://statline.cbs.nl/StatWeb/publication/default.aspx?DM=SLEN&PA=71311eng&D1=0-1&D2=0%2c137141%2c144&D3=64%2c77%2c90%2c103%2c116%2c129%2c142%2c155%2c168%2c181%2c194%2c219%2c232&LA=EN&HDR=G1%2cT&STB=G2&VW=D**.** Accessed June 9th, 2013.
6. Luijben AHP, Kommer GJ. Tijd en Toekomst. Deelrapport van de Volksgezondheid Toekomst Verkenning 2010 Van Gezond naar Beter. RIVM-rapport 270061008. Bilthoven: RIVM, 2010.

Supplementary Table 1. Projections of Dutch adult population with IBD and total DHC-IBD from 2011 to 2040 according to gender (male/female), disease subtype (CD/UC) and age group (18-39/40-59/≥60 years)

		IBD	CD						UC					
			Male			Female			Male			Female		
Year	**Estimate**	**All**	**18-39**	**40-59**	**≥60**	**18-39**	**40-59**	**≥60**	**18-39**	**40-59**	**≥60**	**18-39**	**40-59**	**≥60**
2011	Prevalence [a]	167	152	132	104	257	275	143	120	178	195	137	213	136
	Dutch pop (million) [b]	12.73	2.09	2.46	1.69	2.07	2.42	2.00	2.09	2.46	1.69	2.07	2.42	2.00
	IBD patients	43,953	3,177	3,243	1,762	5,326	6,666	2,866	2,508	4,373	3,304	2,839	5,163	2,726
	Mean DHC-IBD [c,d]	917,33	1,534	1,398	1,164	1,748	1,142	763	714	427	316	581	503	296
	Total costs (million, €)	161.29	19.50	18.13	8.21	37.24	30.45	8.75	7.16	7.47	4.17	6.60	10.38	3.23
2015	Prevalence [a]	167	152	132	104	257	275	143	120	178	195	137	213	136
	Dutch pop (million) [b]	13.04	2.07	2.44	1.88	2.05	2.43	2.17	2.07	2.44	1.88	2.05	2.43	2.17
	IBD patients	44,816	3,145	3,223	1,959	5,268	6,688	3,097	2,483	4,347	3,672	2,808	5,180	2,946
	Mean DHC [c]	1100,17	1,858	1,692	1,410	2,117	1,383	924	864	517	382	704	609	359
	Total costs (million, €)	197.23	23.37	21.82	11.05	44.61	37.00	11.44	8.58	9.00	5.62	7.90	12.61	4.23
2020	Prevalence [a]	167	152	132	104	257	275	143	120	178	195	137	213	136
	Dutch pop (million) [b]	13.37	2.12	2.32	2.12	2.09	2.34	2.38	2.12	2.32	2.12	2.09	2.34	2.38
	IBD patients	45,611	3,218	3,068	2,205	5,384	6,430	3,405	2,540	4,137	4,135	2,870	4,980	3,238
	Mean DHC [c]	1387,88	2,359	2,149	1,791	2,689	1,757	1,173	1,097	657	485	894	773	456
	Total costs (million, €)	253.22	30.37	26.38	15.80	57.90	45.18	15.98	11.15	10.87	8.03	10.26	15.40	5.90
2025	Prevalence [a]	167	152	132	104	257	275	143	120	178	195	137	213	136
	Dutch pop (million) [b]	13.69	2.17	2.17	2.37	2.15	2.21	2.62	2.17	2.17	2.37	2.15	2.21	2.62
	IBD patients	46,253	3,305	2,864	2,463	5,524	6,065	3,742	2,610	3,863	4,618	2,945	4,697	3,559
	Mean DHC [c]	1752,09	2,997	2,731	2,275	3,416	2,232	1,490	1,394	835	617	1,135	982	579
	Total costs (million, €)	324.16	39.63	31.29	22.41	75.48	54.14	22.31	14.55	12.90	11.39	13.37	18.45	8.24

Supplementary Table 1. Projections of Dutch adult population with IBD and total DHC-IBD from 2011 to 2040 according to gender (male/female), disease subtype (CD/UC) and age group (18-39/40-59/≥60 years) (continued)

		IBD				CD				UC				
				Male			Female			Male			Female	
2030	Prevalence [a]	167	152	132	104	257	275	143	120	178	195	137	213	136
	Dutch pop (million) [b]	13.86	2.17	2.05	2.57	2.15	2.10	2.82	2.17	2.05	2.57	2.15	2.10	2.82
	IBD patients	46,510	3,302	2,700	2,678	5,515	5,765	4,037	2,607	3,641	5,021	2,940	4,465	3,839
	Mean DHC [c]	2206,67	3,807	3,469	2,890	4,339	2,835	1,893	1,771	1,060	783	1,442	1,247	735
	Total costs (million, €)	410.54	50.29	37.47	30.95	95.71	65.37	30.57	18.47	15.45	15.73	16.96	22.28	11.29
2035	Prevalence [a]	167	152	132	104	257	275	143	120	178	195	137	213	136
	Dutch pop (million) [b]	13.95	2.13	2.01	2.69	2.11	2.06	2.95	2.13	2.01	2.69	2.11	2.06	2.95
	IBD patients	46,654	3,239	2,655	2,793	5,418	5,668	4,219	2,557	3,580	5,236	2,888	4,390	4,012
	Mean DHC [c]	2781,63	4,835	4,405	3,670	5,510	3,600	2,404	2,249	1,347	995	1,831	1,584	934
	Total costs (million, €)	519.09	62.64	46.78	40.99	119.42	81.61	40.57	23.00	19.28	20.84	21.16	27.81	14.99
2040	Prevalence [a]	167	152	132	104	257	275	143	120	178	195	137	213	136
	Dutch pop (million) [b]	13.99	2.10	2.05	2.69	2.08	2.10	2.97	2.10	2.05	2.69	2.08	2.10	2.97
	IBD patients	46,894	3,197	2,712	2,793	5,356	5,788	4,250	2,524	3,657	5,237	2,855	4,483	4,042
	Mean DHC [c]	3521,68	6,136	5,590	4,657	6,992	4,569	3,051	2,854	1,709	1,263	2,324	2,010	1,185
	Total costs (million, €)	660.56	78.46	60.65	52.03	149.79	105.76	51.87	28.81	25.00	26.45	26.54	36.04	19.16

a) Age- and gender-specific IBD prevalence rates as estimated based on Agis Health Database[1]

b) Dutch adult population (in million)[2]

c) Age- and gender-specific mean annual DHC-IBD based on the COIN study[4]

d) The 2011 cost-estimates were corrected for inflation and volume[5,6]

Supplementary Table 2. Productivity losses (€) and out-of-pocket costs (€) in younger (<60 years) and elderly CD (≥60 years) patients

	Number of patients (%)		*Mean number of days (95% CI)*		*Mean costs (€) per 3 months per patient (95% CI)*		
	Younger CD n = 1244	**Elderly CD n = 307**	**Younger CD n = 1244**	**Elderly CD n = 307**	**Younger CD n = 1244**	**Elderly CD n = 307**	**P value**
Sick leave of paid work (patients)	289/915 (31.6)	17/86 (19.8)	4.3 (3.4-5.2)	4.1 (1.2-7.1)	419.9 (360.6-479.2)	96.7 (40.6-152.8)	0.04
Sick leave of paid work (caregivers)	129 (10.4)	15 (4.9)	1.0 (0.7-1.3)	1.1 (0.3-1.9)	39.1 (27.3-50.8)	17.5 (8.0-26.9)	0.05
Sick leave of unpaid work (patients)	414 (33.3)	162 (52.8)	0.06 (0.05-0.07)	0.05 (0.03-0.07)	14.4 (10.3-18.5)	24.7 (13.3-36,0)	<0.00
Total productivity losses	-	-	-	-	473.4 (412.4-534.4)	138.9 (79.2-198.5)	<0.00
Out-of-pocket costs	-	-	-	-	75.0 (44.4-105.6)	47.7 (38.0-57.4)	<0.00

Supplementary Table 3. Productivity losses (€) and out-of-pocket costs (€) in younger (<60 years) and elderly UC (≥60 years) patients

	Number of patients (%)		*Mean number of days (95% CI)*		*Mean costs (€) per 3 months per patient (95% CI)*		
	Younger UC n = 1110	**Elderly UC n = 354**	**Younger UC n = 1110**	**Elderly UC n = 354**	**Younger UC n = 1110**	**Elderly UC n = 354**	**P value**
Sick leave of paid work (patients)	231/848 (27.2)	6/105 (6.7)	4.1 (3.2-5.1)	5.7 (-3.3-14.7)	392.3 (283.6-497.6)	53.5 (23.2-94.2)	<0.00
Sick leave of paid work (caregivers)	68 (6.1)	6 (1.7)	1.1 (0.7-1.5)	0.9 (-0.2-2.0)	23.1 (-1.8-47.9)	8.7 (-2.7-20.0)	0.04
Sick leave of unpaid work (patients)	385 (34.7)	198 (55.9)	0.05 (0.04-0.06)	0.03 (0.02-0.04)	19.5 (10.5-28.4)	21.6 (2.4-41.3)	0.69
Total productivity losses	-	-	-	-	437.0 (243.8-630.2)	81.1 (-7.2-169.4)	<0.00
Out-of-pocket costs	-	-	-	-	36.9 (23.8-50.0	4.2 (-2.9-11.3)	<0.00

Supplementary Table 4 a & b. Clinical outcomes of younger (< 60 years) versus elderly (≥ 60 years) CD and UC patients as observed during two years of follow-up in the COIN-study. Clinical outcomes included the number of IBD-related hospitalisation, self-reported flares and IBD-related surgery, and quality of life (total score on the IBDQ)

a. Crohn's disease

	OR	*95% CI*	*p value*
IBD-related hospitalization	0.89	0.55-1.09	0.54
Self-reported flare	0.79	0.62-1.02	0.07
HRQOL	2.71[a]	0.39-5.04	0.02

b. Ulcerative colitis

	OR	*95% CI*	*p value*
IBD-related hospitalization	0.54	0.33-0.87	0.01
Self-reported flare	0.73	0.58-0.91	0.01
IBD-related surgery	0.26	0.08-0.86	0.03
HRQOL	4.31[a]	2.15-6.47	<0.00

[a] Absolute reduction in the total score on the IBDQ in elderly versus younger IBD patients