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Clinical Course, Treatment Strategies, Social and Economic Impact of Ulcerative Colitis: An Overview

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Abstract

The aim of this paper is to provide an overview of the clinical course, predictive factors, and treatment strategies for ulcerative colitis (UC) as well as the social and economic impacts of the disease. Based on review of population-based and observational studies as well as drug trials we state:

1. Extensive colitis, a young age at diagnosis, and the need for glucocorticosteroids at diagnosis are risk factors for requiring surgery.

2. During the past 10-15 years, the advances in the treatment of UC have been characterised by the more widespread use of immunosuppression/immunomodulation. In particular, TNF- α inhibitors and thiopurines are used to treat UC. TNF- α inhibitors are currently the drug of choice. Topically active GCSs have emerged as valuable and safer alternatives to standard GCSs in moderate to severe colitis; however, GCSs have no role in maintenance therapy. For mild and moderate UC, local or oral 5-ASA is still the drug of choice, and the use of probiotics still is controversial.

3. The risk of colectomy is much lower than reported in studies completed prior to 1990. The surgery rates at 10 years after diagnosis are between 4 and 10% in recent studies, and the colectomy rate for patients with severe UC who require hospitalisation has remained stable at 27%.

4. The potential of medical and surgical care to decrease morbidity, thus improving quality of life and reducing associated indirect costs, is expected to have a significant impact upon the economics of IBD. This effect, however, remains to be evaluated.

Keywords: Ulcerative colitis; Course; Treatment; Socioeconomic factor

Introduction

Ulcerative colitis (UC) is characterised by chronic or recurrent inflammation of the large bowel in genetically susceptible individuals exposed to environmental risk factors [1]. Disease onset usually occurs in young adults [2]. Symptoms vary from mild to serious, and the disease course is unpredictable. Aggressive UC is associated with a high relapse rate, the need for surgery, the possibility of developing colon cancer, and the presence of extra-intestinal manifestations [3].

Given the prospect of a life with many years of illness, information about short term and long term prognosis is important and requested by the patients [4]. The natural progression of the disease, the medical treatment and possible side effects, and the probability of surgery at a young age are key issues that gastroenterologists are faced with. The medical treatment for UC has become more individualised during the past 10-20 years, and biological treatment has been introduced. In addition, the understanding of this disease and its heterogeneous clinical course has expanded. Ambulatory treatment is now more common, and the number of hospitalisations has been reduced [5,6].

Most cross sectional and prospective studies on UC are based on selected populations from drug trials or specialist centres and, thus, might give heavily biased results that only represent a part of the truth. Population-based studies and real-life cohorts are necessary to

increase the knowledge on the whole spectrum of this disease, and to determine effects of treatments when used outside trial settings.

The “natural course” in UC might be different in 2014 compared to the situation for instance in the 1980’s, and there are at least two reasons for this: we now have better tools to diagnose the condition in an earlier phase, and we have new therapeutic agents that hopefully will alter the course of the disease.

The present review aims to summarize the change in epidemiology of UC and the predictive factors for clinical course and outcome, with focus on population based studies. We also summarize the recent established medical treatment by assessing randomized controlled trials (RCT) and review articles.

Epidemiology

The epidemiology of IBD varies worldwide, both within and between countries [7,8]. Since the highest incidence rates have been found in northern and western Europe and North America, IBD has traditionally been considered a disease of the northern and western hemisphere [9].

However, there has been a rapid increase in the incidence of both UC and CD (Crohn’s disease) in several geographic areas the last 50 years [10], typically in countries that have been “westernized”.

The incidence of UC in Northern Europe has more or less plateaued [11,12]. The incidence of IBD is still increasing in many countries, especially in children and due to the increase in the incidence of CD [13]. For many countries reliable prevalence data are still not available. The highest incidence rates for UC are estimated to be from 19.2 to 24.3 per 100,000 in the Western world and 6.3 per 100,000 in Asia and the Middle East [10]. The strongest environmental associations identified are cigarette smoking and appendectomy, although neither alone explains the variation in incidence of IBD worldwide. Urbanization of societies, associated with changes in diet, antibiotic use, hygiene status, microbial exposures, and pollution, have been implicated as potential environmental risk factors for IBD [8].

UC is usually diagnosed at a young age, with a peak during the second and third decades, although individuals of any age can be affected [2]. There is no gender difference in the prevalence of UC [2,14,15].

In summary, the incidence of UC is still increasing and onset is usually observed in young adults, with an equal distribution between sexes. Changes in diet and living conditions are suggested as potential causal mechanisms while non-smoking are the factor that has shown the strongest association with developing UC.

Impact of Clinical Presentation for the Prognosis

UC almost always affects the rectum and extends proximally. The combination of the disease location and the severity of the inflammation influence the clinical presentation and prognosis.

The reported extent of the disease at the time of diagnosis in UC patients have varied in early studies, with a frequency of 22% to 55% for proctitis alone and 19% to 38% for extensive colitis [16-18].

In more recent studies, assessment of disease extension was based on colonoscopy and not barium enemas and proctosigmoidoscopy. In a Norwegian population-based study one third of the patients had proctitis, one third left sided and one third extensive colitis. In a population-based Danish cohort 30% had proctitis, 47% had left-sided colitis, and 27% had extensive colitis [2,19].

Predictive factors for an unfavourable prognosis at the time of diagnosis have been investigated in several European population-based studies [16,20-23]. Extensive colitis at presentation (defined as macroscopic lesions with an upper limit proximal to the splenic flexure) has consistently been shown to be the most important and independent predictor of the need for a colectomy within the first 10 years after diagnosis [16,20,24,25].

The predictive effect of age at time of diagnosis for relapse frequency remains unclear. Two studies have shown trends towards more frequent relapses after disease onset at young age [21,22]. The population-based IBSEN cohort, which showed an association between age above 50 at diagnosis with a decreased risk of relapse and colectomy [20] confirm these data. The EC-IBD study, however showed an increased risk of relapse in patients diagnosed at older age than 80 years [22], while the Copenhagen study could not find an association between age at diagnosis and the disease course at all [26]. Increased colectomy risk is associated with disease distribution past the left flexure (extensive colitis), the presence of deep colonic

ulcerations upon admission, elevated concentrations of C-reactive protein (CRP), and the need for hospitalisation [27,28]. In patients who do not respond to three to five days of intensified treatment with corticosteroids, the colectomy rate has been observed to be as high as 85%. Findings of more than six daily stools, the presence of blood in the stool, and elevated C-reactive protein levels (>40) has further more been shown to be separate high risk factors for increasing the colectomy rates [29].

Accurate disease classification and the assessment of the risk for progression at diagnosis are important factors in therapy stratification and optimising the patient's outcome. Furthermore, an accurate classification is important with respect to patient counselling and consequently increased treatment compliance and follow-up [29]. Clinicians should, in daily practice, classify UC patients using existing phenotypic classification systems such as the Montreal classification. Such classification of UC patients could help clinicians to recognise clinical and endoscopic predictors of the clinical outcome and initiate appropriate treatment options [22].

Mucosal healing (assessed by endoscopy) after one year of medical treatment, has shown to be significantly associated with a decreased risk of colectomy within 10 years of diagnosis [30].

Attempts have been made to develop a risk matrix model for the prediction of a future colectomy by using data from a well-defined population-based cohort [27]. In this model the risk of colectomy ten years after diagnosis in UC patients was 15 times higher in patients who had all of the following risk factors at diagnosis: age < 30 years, extensive colitis, erythrocyte sedimentation rates and CRP more than 30, and need for corticosteroids at diagnosis compared to those without these risk factors. This model predicts the need for a future colectomy correctly in 90.3% of cases. These results indicate that a prediction matrix could be helpful to identify, at the time of diagnosis, patients at risk of future surgery.

In summary, one-third of UC patients have extensive colitis at diagnosis and risk factors initially for colectomy are age below 40 years, extensive disease, elevated CRP, hospitalization and high disease activity at diagnosis.

Medical Treatment

The treatment goals for UC should include the maintenance of steroid-free remission, prevention of hospital admission and surgery, mucosal healing, improved quality of life, and avoidance of disability. The mainstay medical treatment consists of 5-aminosalicylic acid (5-ASA), glucocorticosteroids (GCSs), immune modulating drugs (thiopurines), and monoclonal antibodies against TNF- α (biological therapy). Cyclosporine could be an alternative to anti TNF- α inhibitors in patients with severe risk of surgery. Probiotics are not yet part of the mainstay medical treatment. The treatment outcome is dependent on a correct indication (induction vs. maintenance, mild disease vs. severe disease, extent of colonic involvement), optimisation of dosage, and patient drug adherence.

Mesalamine

Sulfasalazine (SASP) was the first amino salicylic acid shown to have a positive effect in the treatment of UC. However, its use is restricted by adverse effects highly dependent on increasing dosage

[31]. Oral 5-ASA preparations were developed to avoid the adverse effects of SASP while maintaining its therapeutic benefits. These drugs can be given as oral preparations or local treatments as suppository, enema, or rectal foam.

Feagan and MacDonald evaluated the efficacy, dose-responsiveness, and safety of oral 5-ASA for the induction of remission in patients with mild and moderate active UC in a review of 48 studies with 7776 patients [32]. 5-ASA was found to be significantly more effective in inducing remission than placebo, there was no significant difference in efficacy or adherence to therapy between the conventional (twice daily) and once daily dosages of 5-ASA or in efficacy between high-dose (4.8 g/d) and low-dose (2.4g/d) Asacol treatment. A smaller study did, however, show a better effect of high-dose (4 g/d) than low-dose (2.25 g/d) Pentasa (75% improvement vs. 43%, RR 0.44; 95% CI 0.27-0.71) [33]. No differences in adverse events between 5-ASA and placebo were found. Another review [34], found a significant superiority of 5-ASA over placebo for the maintenance of clinical or endoscopic remission in UC (41% vs. 58% relapse, respectively, RR 0.69, 95% CI 0.62-0.77). A Cochrane review by Marshall et al. evaluated 38 studies to assess the effect of rectal 5-ASA compared to placebo and oral 5-ASA on distal colitis [35]. They conclude that rectal 5-ASA is effective and safe for maintenance of remission if mild to moderate UC. A combination therapy with oral 5-ASA and 5-ASA enemas for patients with distal colitis seems to have an even better effect than either of them.

In summary, 5-ASA is still the basis of the treatment regimen for inducing and maintaining remission in patients with mild and moderate UC. However, the treatment should be individualised and based on the extent and severity of the disease and eventually if failure on previous maintenance treatment. Patients with distal disease additionally benefit of local treatment. Patients with moderate active colitis may benefit from using higher dose of 5-ASA than previously recommended both to induce and maintain remission. Oral and topical treatment seems to work better than mono therapy.

Glucocorticosteroids (GCSs)

If symptoms do not improve quickly after the initiation of 5-ASAs, treatment with oral steroids is the next therapeutic step. A meta-analysis by Ford et al. concluded that GCSs are superior to placebo in inducing remission in UC patients [36]. There are few population-based data available, but an older study (from the pre-biologic era) including 64 patients showed that 70% responded to the first course of GCSs, 22% developed steroid dependency during the first year of treatment, and only 49% maintained steroid-free remission [37]. For the initial GCS dosage, oral prednisolone 1.0 g per kg daily is usually sufficient and should be maintained until a significant clinical improvement is achieved. No randomised trials have assessed the optimum duration of GCS treatment, but the tapering protocol to maximise its effectiveness is suggested to be 5 mg per week. All the time the aspect of corticosteroid dependency has to be taken into consideration. Topically active GCSs (e.g., budesonide) have emerged as valuable and safe alternatives in mild and moderate UC [38-40]. Patients with severe colitis should be hospitalised for treatment with intravenous corticosteroids [41]. After the first course of corticosteroids, the rate of colectomy during the next year is approximately 30% [41,42]. Once-daily budesonide MMX® 9 mg has

shown to be safe and also more effective than placebo in inducing remission in patients with active, mild to moderate UC [39].

In summary, GCSs are still the mainstay treatment for inducing remission in patients with moderate to severe UC, but GCSs have no role in maintenance therapy. Topically active GCSs have emerged as valuable and safe alternatives for the treatment of mild and moderate disease. The early identification of patients for whom intravenous corticosteroids are likely to be ineffective, careful monitoring by gastroenterologists and surgeons, and the early introduction of rescue treatments for patients with steroid-refractory disease are crucial to minimise morbidity and mortality.

Thiopurines

The evidence-based data concerning the use of thiopurine drugs (azathioprine and mercaptopurine) for both induction and maintenance therapy in UC is limited.

Data from a well-conducted study on steroid-dependent active UC demonstrated that 53% of the patients on azathioprine achieved steroid-free clinical and endoscopic remission after 6 months, compared with 21% on Mesalamine (OR 4.78, 95% CI 1.57-14.5) [43]. However, the colectomy rate was similar in both groups (8-10%). An observational cohort study that included 42 steroid-dependent patients reported steroid-free remission with azathioprine at 12, 24, and 36 months in 55%, 52%, and 45% of the patients, respectively [44]. Therefore, thiopurines are recommended as the first choice of therapy for patients who experience flare-ups when steroids are withdrawn. Thiopurines should be started in steroid-dependent and steroid-refractory patients. However, anti-TNF α therapy must also be considered in cases of severe disease [45]. A meta-analysis from 2009 concluded that thiopurine drugs are more effective than the placebo for maintenance (the prevention of relapse) in UC patients (number needed to treat (NNT) of 5 and an absolute risk reduction of 23%) [46]. This conclusion was confirmed in a recent Cochrane review that, however, also states that currently, there is not sufficient evidence to conclude that thiopurines is superior to standard maintenance therapy with 5-ASA or SASP [47].

The proper duration of thiopurine treatment is uncertain. In a retrospective analysis, UC patients who received azathioprine for at least 6 months with mean treatment duration of 634 days had a remission rate of 87% [48]. The proportions of patients remaining in remission at one, three, and five years after treatment was started (UC and CD together) were 0.95, 0.69, and 0.55, respectively. The remission rates one, three, and five years after the withdrawal of azathioprine were 0.63, 0.44, and 0.35, respectively. These results confirm the findings of an old study by Hawthorne et al., who were the first to show that azathioprine discontinuation is associated with a high rate of relapse [49]. Patients who have previously been treated with cyclosporine or tacrolimus for a severe flare-up can also be given azathioprine to maintain remission [46,47].

In summary, there is evidence that thiopurines are effective as maintenance therapy and apparently effective treatment for those who are steroid dependent.

Biological treatment

Outpatients with moderately active UC who do not respond to

conventional treatment can be given the TNF α -inhibitors infliximab, adalimumab or golimumab, either alone or in combination with thiopurines.

Infliximab has been established as an effective treatment for moderate to severe UC. Infliximab is given intravenously at 5 mg/kg at 0, 2, and 6 weeks and every 8 weeks thereafter. The ACT-1 and ACT-2 randomised controlled trials assessed the ability of infliximab to induce and maintain remission in patients with moderate to severe ulcerative colitis [50,51]. In the ACT-1 and ACT-2 trials, 69.4% and 64.5% of infliximab-treated patients (5 mg/kg), respectively, had a short-term clinical response, compared with 37.2% and 29.3% of those who received placebo. A higher dose of 10 mg/kg did not improve the response rate. Combining both ACT trials, the one-year colectomy rate in the infliximab-treated arm was 10% vs. 17% in the placebo arm. However, the ACT trials did not include acute severe colitis cases that were refractory to intravenous GCSs.

A comparative effectiveness trial showed that infliximab in combination with azathioprine was more effective than either drug alone [52]. Combination treatment is therefore the preferred strategy for most patients.

Adalimumab is administered as subcutaneous injections. Two RCTs have shown that adalimumab is effective in inducing remission in patients with moderate to severe UC (in the dose 160 mg at week 0, 80mg at week 2 and thereafter 40 mg every second week). At week 8, 18.5% of patients were in remission, compared with 9.2% in the placebo group ($p = 0.031$) [53]. The second study showed that overall rates of clinical remission at week 8 were of 16.5% vs. 9.3% on placebo ($P = .019$) and also showed an effect on remission with remission rates at week 52 of 17.3% vs. 8.5% for placebo ($P = .004$) [54]. The obvious differences in remission rates in the infliximab and the adalimumab studies were mainly due to differences in study endpoint. In the ACT studies response was defined as a decrease in the Mayo score of at least 3 points and at least 30 percent, while in the adalimumab studies the primary efficacy endpoint was clinical remission defined as Mayo score ≤ 2 with no individual sub score >1 .

Golimumab is the newest, subcutaneous anti-TNF available. Recent results have shown that golimumab is effective in inducing remission (clinical response at 6 weeks was 51% as compared to 30.3% for placebo, $P > 0.001$) [55] and maintaining remission (clinical response was maintained through week 54 in 47.0% of patients receiving 50 mg golimumab, 49.7% of patients receiving 100 mg golimumab, and 31.2% of patients receiving placebo ($P = 0.010$ and $P < .001$, respectively) [56].

Vedolizumab, a recombinant humanized, anti $\alpha 4\beta 7$ integrin monoclonal antibody, which regulates the movement of leucocytes to the gastrointestinal tract, has been shown to be effective in moderate to severe UC [57]. The substance has been approved by the Food and Drug Administration in the US in 2014. Two integrated randomized, double blind, placebo controlled trials with induction therapy with 300 mg vedolizumab at week 0 and 2, and maintenance therapy with the same dose every 4 or 8 weeks, showed higher clinical response rates than placebo with clinical remission at week 6 (47.1% vs. 25.5% with placebo), and at week 52 (44.8% after treatment every 4 weeks and 41.8% after treatment every 8 weeks vs. 15.9% with

placebo) [58]. Other biologic agents have so far not been approved for the treatment of UC.

The increasing use of infliximab as a second-line medical treatment for severe UC to avoid colectomy has been based on the high effectiveness of this drug [59]. After a single dose of 5 mg/kg infliximab or placebo, the colectomy rates after 3 months of follow-up for severe UC refractory to steroids were 7/24 and 14/21, respectively (OR 4.9, 95% CI 1.4-17, $p = 0.017$). Long-term follow up for 3 years showed colectomy rates of 50% and 76%, respectively [60]. Medical rescue therapy should be utilised as the first-line treatment for acute severe colitis before colectomy in most patients for whom corticosteroids failed and who do not present with acute surgical abdomen or toxic mega colon [61].

An observational cohort study found substantially higher short-term clinical response rates for both adalimumab and infliximab, both above 80%, with no difference between the two drugs [62]. Data on the long-term effect of anti-TNF treatment are sparse. However, an extension study from the ACT-1 and ACT-2 studies reported long-term outcomes (disease activity, use of corticosteroids, and quality of life) of patients with less severe UC treated with infliximab [51]. Out of the primary responders to infliximab in the ACT-1 and ACT-2 studies, 181 patients were followed for 1 year, and 92 were followed for 2 years. The rates for little or no activity at weeks 56 and 104 were 92% and 97%, respectively. Data on adalimumab treatment beyond 1 year for UC are not available, but the maintenance of the effect in those who maintain a response to anti-TNF therapy after 1 year can be expected with continued treatment. No study of the withdrawal of anti-TNF therapy has been reported for UC patients.

In summary, anti-TNF- α drugs are effective in inducing and maintaining remission. There is, however, still a lack of long-term follow-up studies.

Cyclosporine and tacrolimus

Cyclosporine is highly effective in inducing short-term clinical improvement of active UC, with response rates of approximately 60–80%. However, the use might be limited by serious adverse events, and the number of observed cases is limited [63,64]. In a recent study in 130 patients with steroid-refractory UC the authors concluded that tacrolimus was safe and efficient, but data on this drug in this setting are limited [65]. Although the short-term response rate is good, approximately 50% of responders will eventually require colectomy when the drug is discontinued, typically after 4 months [66-68]. The likelihood of colectomy is reduced if cyclosporine is used as a bridging medication to thiopurines which therefore should be administered [69]. With regard to dose, the Leuven group compared cyclosporine given intravenously at a dose of 2 mg/kg or 4 mg/kg per day for 1 week and then orally at doses of 8 mg/kg, with the doses adjusted to maintain trough serum concentrations between 150 and 300 ng/ml. There was no sign of an improved effect in the high-dose group [70].

Whether the optimal rescue treatment for patients with severe steroid-refractory colitis is cyclosporine or infliximab is still unclear. A randomised trial showed similar short-term response rates for both drugs (cyclosporine 85.4% vs. infliximab 85.7%; $p = 0.97$) and no difference in colectomy rates after 3 months (18% vs. 21%; $p = 0.66$) [71,72]. In view of these similar outcomes, infliximab might

be preferred over cyclosporine because it can be continued as a maintenance treatment in responding patients, particularly in those for whom azathioprine has been ineffective [73,74].

In summary, cyclosporine might be a bridging therapy to thiopurines in acute severe colitis, but adverse effects, necessity of continuous monitoring of serum concentrations and the continuing high colectomy rates would still justify the question regarding applicability.

Probiotics

Mounting evidence suggests an important role for intestinal dysbiosis in chronic mucosal inflammation, which has been identified in these patients. However, randomised controlled trials of probiotics for the management of IBD are still limited [75].

A systematic review by Jonkers et al. included a small number of clinical intervention studies with probiotics for the management of IBD in adults [76]. The overall risk ratio of 2.70 (95% CI 0.47-15.33) for inducing remission in patients with active UC with Bifido fermentated milk versus placebo or no additive treatment were promising, but studies were small. A somewhat weaker effect was found (RR 1.88; 95% CI 0.96,-3.67) for VSL#3 versus placebo. Most convincing effect for VSL#3 versus placebo was found for preventing relapse in patients with inactive UC and ilea-anal pouch anatomises (IPAA) (RR 0.17; 95% CI 0.09- 0.33). One meta-analysis of randomised controlled trials (RCTs) comparing probiotics to placebo or another intervention for the maintenance of remission in UC patients was published by Naidoo et al. in 2011, but this study did not demonstrate a statistically significant difference between probiotics and 5-ASA [77]. They concluded, however, that the small numbers of patients in the studies gave insufficient evidence regarding the efficacy of probiotics for the maintenance of remission in UC patients.

In summary, the results of some studies on the effect of probiotics are promising, but larger randomised controlled trials are needed to reach firm conclusions.

Surgery for UC

Surgery is defined as urgent in cases of severe inflammation and non-response to medical treatment. Emergencies may occur in cases of spontaneous colon perforations or toxic colitis. Long-term active or relapsing UC without a satisfactory medical treatment response or an increasing risk for malignancy indicate the need for elective surgery [78]. Overall, the risk for surgery in UC seems to be decreasing [79, 80], nevertheless, 10-20% of UC patients today are expected to need surgery during their lifetime [19,20].

In a recent European study of patients diagnosed in the early 1990s, the overall 10-year cumulative colectomy rate was 8.7%, with substantial regional differences. The 10-year colectomy rate in Denmark was 25.7%, versus 8.2% in Norway and the Netherlands, whereas the 10-year colectomy rate in southern Europe (Greece, Italy, Spain, and Israel) was 3.9% [80]. In a Norwegian prospective, population-based study including 424 UC patients the cumulative colectomy rates were 3.5%, and 9.7%, at the 1- and 10-year follow-up respectively [20]. A more recent publication reported even lower colectomy rates in a population-based cohort from western Veszprem in Hungary (n=914), where the overall colectomy rates for

UC patients were 1.6% and 3.7% after 5 and 10 years, respectively [81]. The lower colectomy rates in population-based studies might reflect the inclusion of more subjects with milder disease than in studies of selected patient populations.

The decreasing colectomy rate in general may be a consequence of a more restrictive attitude towards surgery, as, has been seen in Denmark [19,81] or the result of the increasing number of effective medical treatment options, such as immune modulators and TNF- α inhibitors [60,82]. However, the short-term colectomy rate in hospitalised patients with severe UC has remained stable at 27% [79].

Although mortality related to severe attacks of UC has substantially decreased to less than 1% in recent decades [41], delay in time until surgery beyond 5-7 days can increase the risk of postoperative complications and mortality [83].

In a Canadian study from 2011[84] 666 patients with UC underwent colectomy from 1996 to 2009. A postoperative complication occurred in 27 % of the patients and the mortality rate was 1.5%. Elderly patients with multiple comorbidities were found to have increased risk of developing complications postoperatively.

In summary, the risk of colectomy seems decreasing compared to studies completed prior to 1990. The surgery rates 10 years after diagnosis are between 4 and 10 % in recent studies while the colectomy rate for patients with severe UC who require hospitalisation still remains 27%.

Colorectal Cancer

Colorectal cancer (CRC) accounts for 10-15% of deaths in IBD, and the 5-year survival rate in CRC in UC patients is about 50 % [85]. A study from Belgium found that 73 % of the patients developed their tumours in areas of colon affected by inflammation [86]. Jess et al performed a meta-analysis of population-based cohort studies and found the overall risk of CRC among patients with UC to be comparable with the risk in the background population (RR 1.07; 95 % CI 0.95-1.121) [87]. Patients diagnosed in childhood/adolescence, those with PSC, and those with a long duration of disease were at increased risk. The authors conclude that a diagnosis of UC no longer seems to increase the patients' risk of CRC, although subgroups of patients remain at increased risk. The decreasing risk for CRC might result from improvement in therapy but this has yet to be shown.

Health-Related Quality of Life (HrQoL)

Patient-reported outcomes such as HRQoL are important in chronic diseases such as UC. The current knowledge of HRQoL for unselected, population-based UC cohorts is limited [88]. However, data from selected UC populations indicate that, in general, UC patients have HRQoL scores (as measured with the SF-36) in line with those of the general population. An exception is reduced scores for the general health dimension [89-91]. UC patients overall report better HRQoL than CD patients [91,92]. Disease activity seems to be the most important factor determining HRQoL in UC patients [90,93-97]. However, factors such as female sex, the use of corticosteroids, smoking, and unemployment/work disability and sick leave are associated with reduced HRQoL scores [89,98,99]. The presence of fatigue also seems to be independently associated with a reduced HRQoL [97].

In summary, UC patients seem to have HRQoL comparable to the general population. However, female gender, disease symptoms and treatment with corticosteroids as well as excess from the labour market is associated with reduced HRQoL.

Work Disability

A reduced ability to work or study is a serious consequence of UC. A substantial amount of the health care costs of UC are due to sick leave, work disability and early retirement [100-102]. Comparison of disability rates across countries is challenging due to differences in economy and political systems.

In the Norwegian IBSEN cohort 18.8% of the UC patients received a disability pension 10 years after diagnosis. Elevated CRP or ESR levels at diagnosis, the need for corticosteroids at one year follow up, early relapse, and early colectomy was associated with an increased risk of receiving disability pension [103].

A Swedish population-based prevalence study found a disability rate of 15% in UC patients, compared with 11% in age-, sex- and education-matched healthy individuals [104]. The rate of sick leave episodes was also increased in the UC cohort. A Dutch study found a lower age-adjusted employment rate for males only and the disability rate was dependent on education status [105].

Health Care Costs

In UC the contribution of direct costs for medicine and healthcare and indirect costs due to productivity losses varies internationally depending on variable price settings for healthcare and productivity loss. A cross-sectional study estimated the total cost for IBD in Sweden in 1994 to be 85.9 million US dollars [100]. Over 30% of the UC expenditures were indirect costs. In a European cohort, the price for medical treatment for UC was rather low in remission (€34/patient-month) and mild disease (€91/patient-month) [106]. In a retrospective study of commercially insured UC patients in the US, the mean annual medical expenditure was US\$15020 [101], while the average total health care costs for 242 German UC patients were €1015 per month with a proportion of 54% indirect costs [102]. The first cost-of-illness study after the introduction of anti-TNF- α treatment was performed in the Netherlands with 937 patients with UC [107]. The mean total healthcare costs for 3 months were €595, and the mean costs for productivity losses for 3 months were €395, which is still a substantial part of the total cost. The largest part of the healthcare costs was the medication (€136 for 5-ASA and €197 for anti TNF α), although only 4% of the included patients used infliximab or adalimumab.

In summary, productivity loss accounts for a substantial part of the disease-related costs for UC, especially in Europe. Anti-TNF- α therapy has become an increasingly important factor in healthcare costs related to UC, although the number of patients receiving this medication is still limited.

Summary Statements for UC: Clinical Presentation, Treatment, Health-Care Costs and Quality of Life

1. Initial classification is important and has implications for individualised treatment stratification, the clinical course,

and the outcome. Extensive colitis, young age and the need for glucocorticosteroids at diagnosis are risk factors for requiring surgery.

2. During the past 10-15 years, the advances in the treatment of UC have been characterised by the more widespread use of immunosuppressives. In particular, TNF- α inhibitors and thiopurines have gained increasing application in UC. TNF- α inhibitors in severe UC are currently the drug of choice. Topically GCSs have emerged as valuable and safe in mild and moderate distal colitis while orally GCSs should not be used as maintenance therapy. For mild and moderate UC, oral 5-ASA is the drug of choice with an even better effect in combination with topical treatment. Temporarily increasing the oral dose up to more than 3-4 g could in some cases achieve and maintain remission.

3. The risk of colectomy seems to be lower than reported in studies completed prior to 1990. Data from population-based studies as well as improved medical treatment options account for this difference. The surgery rates at 10 years after diagnosis are between 4 and 10% in recent studies, and the colectomy rate for patients with severe UC who require hospitalisation has remained stable at 27%.

4. The potential of medical and surgical care to decrease morbidity, thus improving quality of life and reducing associated indirect costs, is expected to have a significant impact upon the economics of IBD. This effect, however, remains to be evaluated.

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