THE RATE AND IMPORTANCE OF HOSPITALIZATIONS AND ITS ROLE IN THE PREDITIONS OF OUTCOMES IN INFLAMMATORY BOWEL DISEASES IN A POPULATION-BASED INCEPTION COHORT

PhD Thesis

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Introduction

The pathogenesis of Crohn's disease (CD) and ulcerative colitis (UC) has only been partly understood. Inflammatory bowel diseases (IBD) are multifactorial, potentially debilitating diseases with probable genetic heterogeneity. In addition, several environmental risk factors (e.g. diet, smoking, measles, or appendectomy) may contribute to the pathogenesis.

During the past two decades, the incidence pattern of IBD has changed significantly. The disease course is reported to be highly variable.

New imaging techniques, tools and guidelines are available for the diagnosis.

The phenotypic classification of IBD based on clinical features plays an important role in patient management, and may help with predicting the clinical course in patients. Current practice guidelines from ECCO advocate the use of the Montreal classification in both CD and UC. Using the Vienna classification system, it has been shown first in referral IBD cohorts that there can be a significant change in disease behavior over time, whereas disease location remains relatively stable.

The medical management changed in the last 20-40 years, including increasing and earlier use of immunosuppressives and biological and tight patient monitoring.

Other significant adverse outcomes include need for hospitalization and surgery/reoperations. Hospitalization and surgery are considered to be markers of disease severity in CD and are associated with high costs. There are relatively limited data available on hospitalization trends (especially from population-based studies) and the interpretation of the data is complicated by local management strategy and reimbursement issues.

Objectives

Limited data are available on the hospitalization and surgery rates in population-based studies. Since this is a very important outcome measure, the aim of our studies were to prospectively analyze the hospitalization, the early hospitalization, the surgery rates and whether the early limited surgery is associated with the changed medical management in a population based inception cohort in the Veszprem province database between 1977 and 2012.

1. **Has there been a change in the natural history of Crohn's disease? Surgical rates and medical management in a population-based inception cohort from western Hungary between 1977 – 2009**

   Medical therapy for Crohn's disease (CD) has changed significantly over the past 20 years with increasing use of immunosuppressives. In contrast, surgery rates are still high and there is little evidence that disease outcomes for CD have changed over the past decades. The objective of this study was to analyze the evolution of the surgical rates and medical therapy in the population-based Veszprem province database.

2. **Is early surgery associated with a more benign disease course in Crohn's disease? Surgery rates in a population-based inception cohort from Western Hungary between 1977-2009**

   Crohn's disease (CD) is a chronic relapsing inflammatory bowel disease (IBD) most frequently affecting the terminal ileum and right colon, with a high rate of stricturing or penetrating complications. Early surgery may represent a valid alternative to medical therapy, particularly in patients with isolated stenotic ileocaecal CD. Our aim was to analyze the disease course and need for surgery in patients with (within the year of diagnosis) and without an early resective surgery in the population-based Veszprem province database.

3. **Is hospitalization predicting the disease course in Crohn's disease? Prevalence and predictors of hospitalization and re-hospitalization in Crohn's disease in a population based inception cohort between 2000-2012**

   Limited data are available on the hospitalization rates in population-based studies. Since this is a very important outcome measure, the aim of this study was to prospectively analyze if early hospitalization is associated with the later disease course as well as to determine the prevalence and predictors of hospitalization and

re-hospitalization in a population based inception cohort in the Veszprem province database between 2000 and 2012.

4. **Is hospitalization predicting the disease course in UC? Prevalence and predictors of hospitalization and re-hospitalization in ulcerative colitis in a population-based inception cohort between 2000-2012**

   Limited data are available on the hospitalization rates in population-based studies. Since this is a very important outcome measure, the aim of this study was to prospectively analyze if early hospitalization is associated with the later disease course as well as to determine the prevalence and predictors of hospitalization and re-hospitalization in the population-based UC inception cohort in the Veszprem province database between 2000 and 2012.

Methods

The well-characterized cohort of patients in the population-based database from Veszprem-province, Hungary was included in our studies.

IBD patient data were collected every year from the seven general hospitals and gastroenterology outpatient units (internal medicine, surgery, pediatric departments, as well as outpatient units), each staffed by at least one gastroenterologist or internist with special interest in gastroenterology, as well as family physicians. The majority of patients (76% of UC and 94% of CD patients) were monitored at the Csolnoky F. Province Hospital in Veszprem. This hospital also serves as a secondary referral center for IBD patients in the province. Data collection was prospective since 1985, while prior to that, only data collected in Veszprem was prospective. In other sites throughout the province, data for this period (1974-1985) were collected retrospectively in 1985. Both inpatients and outpatients permanently residing in the investigated area were included in the study. Most patients had regular follow-up. Diagnoses (based on hospitalization records, outpatient visits, endoscopic, radiological, and histological evidence) generated in each hospital and outpatient unit were reviewed thoroughly, using the Lennard-Jones criteria. The provincial IBD register data were centralized in Veszprem. The disease phenotype was assessed by a questionnaire completed by the clinician at the time of diagnosis, and updated yearly, as necessary.

Ethical permission

The study was approved by the Semmelweis University Regional and Institutional Committee of Science and Research Ethics and by the Csolnoky F. Province Hospital Institutional Committee of Science and Research Ethics. The numbers of the ethical permissions: TUKEB 193/2004 and TUKEB 1207/2009, the Csolnoky F. Province Hospital Institutional Committee of Science number: 2009/001 (2009.12.07).

Results

1. Has there been a change in the natural history of Crohn's disease? Surgical rates and medical management in a population-based inception cohort from western Hungary between 1977 – 2009

A well-characterized Hungarian cohort of 506 incident cases with CD (male/female:251/ 255, age at diagnosis: 31.5 years, SD 13.8 years) diagnosed between 1 January 1977 and 31 December 2008 were included. Follow-up data were collected through 31 December 2009. According to the year of diagnosis the patients were divided in three groups Cohort A: 1977-1989, Cohort B: 1990-1998 and Cohort C: 1999-2008.

Overall, AZA, systemic steroid, and biological (available only after 1998) exposure was 45.8, 68.6, and 9.5 %, respectively. Total AZA exposure increased in the subsequent cohorts despite shorter follow- up. The 1- and 5-year probability of AZA use were 3.2 and 6.2 % in cohort A, 11.4 and 29.9 % in cohort B, and 34.8 and 46.2 % in cohort C. In a multivariate Cox-regression analysis, decade of diagnosis, age at onset, disease behavior at diagnosis, and need for systemic steroids were significantly associated with the time to initiation of AZA therapy. Early AZA use was significantly associated with the time to intestinal surgery in CD patients; in a multivariate Cox analysis and after matching on propensity scores for AZA use. In the present study, the authors assessed the time trends in medical therapy and need for surgery in the population-based Veszprem province database, including incident patients diagnosed between 1977 and 2008. The present study has shown that the recent reduction of surgical rates was independently associated with increased and earlier (< 1.5 or < 3 years from diagnosis) AZA use in this Eastern European CD cohort. To the best knowledge of the authors, this is the first time that the associations between AZA use and surgical requirements were studied after matching on propensity scores. To minimize the bias, the authors focused predominantly on first intestinal surgery, and appropriate use of immunosuppressive drugs before surgery. In addition, the total anti-TNF exposure was low, and the majority of the cases received induction only or episodic therapy. Regular maintenance with anti-TNFs has only been reimbursed in Hungary since 1 December 2008.

In conclusion, this population-based study has demonstrated a significant change in the natural history of CD over the last three decades, fewer cases with complicated disease behavior at diagnosis, reduced probability of disease behavior change, and reduced rates of surgery independently associated with increased and earlier AZA use.

2. Is early surgery associated with a more benign disease course in Crohn's disease? Surgery rates in a population-based inception cohort from Western Hungary between 1977-2009

Five hundred six residents in Veszprem province were diagnosed with Crohn's disease in the 32-year period from 1977 to 2008. There were 74 patients in Cohort A (diagnosed 1977-1989), 199 in Cohort B (diagnosed 1990-1998), and 233 in Cohort C (diagnosed 1999-2008). Follow-up information was collected up to December 31, 2009, equaling 5758 patient-years of follow-up.

There were a total of 204 (40.7%) patients who had at least one resective surgery (patients with resective surgery due to malignant disease were excluded from analysis, n=5). Further 36 (7.1%) patients had other surgical procedures (abscess drainage or fistulectomy). Forty-two (8.4%) patients had two resections and seventeen (3.4%) had three or more operations for Crohn's disease during follow-up. Ileocecal resection was the most common procedure overall.

Overall 73 patients (14.4%) required resective surgery within the year of diagnosis. Ileal or ileocolonic disease location, stricturing or penetrating disease behavior at diagnosis and tendencially early age at onset were associated with the need of early resective surgery in a multivariate analysis. Time to surgery was significantly longer in patients with early limited resection as an index intervention. In a multivariate Cox-regression analysis, early resective surgery, ileal or ileocolonic disease location and stricturing or penetrating disease behavior at diagnosis were significantly associated with the time to intestinal resection/reoperation after excluding cases with extensive early resections. In addition, early limited resective surgery was significantly associated with the time to intestinal surgery in CD patients after matching on propensity scores for the need for early resection.

This population-based inception cohort has shown that early limited resective surgery may be associated with a more benign disease course after index surgery, requiring less surgical interventions during follow-up compared to patients without an early resection.

3. Is hospitalization predicting the disease course in Crohn's disease? Prevalence and predictors of hospitalization and re-hospitalization in Crohn's disease in a population based inception cohort between 2000-2012

Data of 304 incident CD patients diagnosed between January 1, 2000 and December 31, 2010 were analyzed (mean age at diagnosis: 32.2; SD: 15.4years). Both in- and outpatient records were collected and comprehensively reviewed.

Probabilities of first hospitalization and first re-hospitalization were 54.9%, 72% 76% and 22.8%, 34%, 52.3% after 1, 2 and 5 years of follow-up in Kaplan-Meier analysis. Main reasons for hospitalization in the first year were diagnostic procedures (48.5%), IBD-related surgery (29.9%) and disease activity (14.3%). Non-inflammatory disease behavior at diagnosis was the only factor significantly associated with time to hospitalization while both non-inflammatory disease behavior at diagnosis and disease behavior change were associated with time to first re-hospitalization in multiple Cox-regression analysis. Early hospitalization (within the year of diagnosis) was associated with age at onset, non-inflammatory disease behavior at diagnosis, internal fistulizing disease and it was predictive for need for immunosuppressives and need for surgery/multiple surgeries during the disease course.

Early hospitalization was associated with clinically significant outcomes (need for immunosuppressives and surgery). Hospitalization and re-hospitalization rates were still high in this population-based cohort. Non-inflammatory disease behavior at diagnosis was identified as the pivotal predictive factor for both hospitalization and re-hospitalization.

4. Is hospitalization predicting the disease course in UC? Prevalence and predictors of hospitalization and re-hospitalization in ulcerative colitis in a population-based inception cohort between 2000-2012

Data of 347 incident UC patients diagnosed between January 1, 2000 and December 31, 2010 were analyzed (m/f: 200/147, median age at diagnosis: 36, IQR: 26-50 years, duration: 7, IQR 4-10 years). Both in- and outpatient records were collected and comprehensively reviewed.

Probabilities of first UC-related hospitalization 28.6%, 53.7% and 66.2% and first re-hospitalization were 23.7%, 55.8% and 74.6% after 1-, 5- and 10- years of follow-up. Main UC-related causes for first hospitalization were diagnostic procedures (26.7%), disease activity (22.4%) or UC related surgery (4.8%), but a significant percentage was unrelated to

IBD (44.8%). In Kaplan-Meier and Cox-regression analysis disease extent at diagnosis or at last follow-up, need for steroids, azathioprine and anti-TNF were associated with the risk of UC-related hospitalization. Early hospitalization was not associated with a specific disease phenotype or outcomes, however 46.2% of all colectomies were performed in the year of diagnosis.

Hospitalization and re-hospitalization rates were relatively high in this population-based UC cohort. Early hospitalization was not predictive for the later disease course.

Conclusions

Inflammatory bowel disease (IBD) is a multifactorial, life-long, relapsing condition, developing in genetically predisposed individuals triggered by environmental factors. IBD is usually treated at gastroenterology ambulances, but in some cases besides the medical treatment hospitalizations and surgery are also needed. In Crohn's disease, surgery is not curative, but an important treatment step. Surgery can be lifesaving in severe cases but it can be also a therapeutic decision in some cases. Colectomy in ulcerative colitis is curative, but as in a significant proportion of the patients complications may develop as pouchitis or cuffitis, the tight monitoring of the patients can not be ceased. In the last two decades there was a paradigm shift both in medical and surgical treatment. The medical strategies have changed towards a more frequent use of the accelerated step up or the step down therapeuric approach to prevent disease complications. Especially in those patients with negative predictive factors as young age, smoking, perianal disease, weight loss, extensive disease, need for steroid at diagnosis. Due to the change in medical therapy the natural history of IBD has changed. There was a paradigm shift in IBD-surgery, as well. The indications of surgery have also changed. Nowadays, not only lifesaving surgical procedures are performed but surgery can be also a therapeutic decision in some cases. Patients with early limited resective surgery needed less medication, less relapses and had a better quality of life. The hospitalization rates both in CD and in UC are still high. The hospitalization rates are the highest in the year of the diagnosis and proceeded in part of the diagnostic procedures. The resective surgery and colectomy rates are the highest in the year of the diagnosis. The predictive factors are non-inflammatory disease behavior and pancolitis. IBD is a complex disease. The multidisciplinary approach is necessary in patient management to avoid disease complications and improve the quality of life. The gastroenterologist, surgeon, dermatologist, rheumatologist, radiologist and the phycologist all have a great importance in leading the patient. A good and confident long-term doctor-patient relationship is needed in the management of this chronic, life-long disease.

Major novel findings of the present PhD thesis:

1. Our study group confirmed that the natural disease behavior of Crohn's disease has changed in the last 30 years.
2. The incidence of complicated disease behavior at diagnosis and the development of disease complications decreased.
3. Surgical resection rates for Crohn's disease decreased in Veszprem province from 1977 to 2009.
4. Multivariate Cox-regression analysis has shown that decade of diagnosis, age at onset, disease behavior at diagnosis, and need for systemic steroids were significantly associated with the time to initiation of AZA therapy.
5. Multivariate Cox-regression analysis, and a proportional Cox hazard model adjusted propensity scores for azathioprine use, have shown that early azathioprine use and colonic location were associated with lower rates of intestinal surgery, while complicated disease behavior at diagnosis was associated with higher rates of intestinal surgery.
6. Early limited resective surgery may be associated with a more benign disease course. Patients needed less steroid treatment after the index surgery.
7. The prevalence of hospitalization is still high even in the biologic area. Half of the hospitalizations were in the year of the diagnosis. In 46%, hospitalization was indicated due to the diagnostic procedures, in the year of the diagnosis.
8. The days of the hospitalization were the highest in the year of diagnosis and decreased over the years.
9. Non-inflammatory disease behavior at diagnosis was identified as the pivotal predictive factor for both hospitalization and re-hospitalization.
10. Early hospitalization was associated with the clinical outcome and it was predictive for the need for immunosuppressives and need for surgery/multiple surgeries during the disease course.
11. Main UC-related causes for first hospitalization were diagnostic procedures, disease activity or UC related surgery, but a significant percentage was unrelated to IBD. Early hospitalization was not associated with a specific disease phenotype or outcomes, however half of the colectomies were performed in the year of diagnosis.

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