

Title

Regional differences in anti-TNF- α therapy and surgery in the treatment of inflammatory bowel disease patients: A Norwegian nationwide cohort study

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Short title

Anti-TNFs and surgery in the treatment of IBD

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ABSTRACT

Background and Aims

During the last decades, substantial progress has been made in both medical and surgical treatment of inflammatory bowel disease (IBD). The aim of this study was to determine the use of anti-TNFs and surgery during the first three years after diagnosis in IBD patients across the four health regions in Norway using nationwide patient registry data.

Methods

This study used nationwide data from the Norwegian Patient Registry. Cumulative incidence of anti-TNF exposure and major surgery was calculated for patients diagnosed in 2010-2012. The analyses were stratified by diagnosis and health region. All patients were followed for an equal period of 3 years.

Results

The study population included 8257 IBD patients first registered between 2010 and 2012, of whom 2829 were diagnosed with Crohn's disease (CD) and 5428 with ulcerative colitis (UC). Across Norway's health regions, the cumulative incidence of major surgery after three years varied from 11.4% to 17.1% for CD and from 4.6% to 6.9% for UC. The cumulative incidence of anti-TNF exposure varied from 20.9% to 31.4% for CD and from 8.0% to 13.5% for UC.

Conclusions

Cumulative incidence of anti-TNF exposure and surgery varied across Norway's health regions during the three first years after IBD diagnosis.

1. Introduction

During the last two decades, several new drugs, including anti-TNF- α agents (anti-TNFs) and anti-integrins, have been introduced for treatment of inflammatory bowel disease (IBD).

Biologic therapies have changed the management of IBD through their ability to induce and maintain remission.^{1,2} However, the effect on the disease's long-term course is not sufficiently clarified and remains an active research area.³⁻⁵ A substantial proportion of patients do not achieve remission with biologics; others lose response or experience adverse reactions. Failure of medical therapy is the most common indication for surgery, but surgery can also be an option without having failed medical therapy.^{6,7,8}

Extensive research conducted on variations in the use of healthcare highlights that considerable variation is unwarranted because it is not explained by illness or patient preference.^{9,10}

Treatment of IBD patients can be classified as 'preference-sensitive care' when more than one generally accepted treatment option is available, such as elective surgery or medical therapy for patients with moderate to severe IBD. Variations in healthcare are found across geographic regions, institutions, and even among individual physicians within single institutions.¹¹ Practice variation is important because of its potential impact on cost and outcomes, but there has been limited focus on such variation in the treatment of IBD.¹² Previous studies have described treatment patterns based on nationwide registries in other countries, but there is very limited research on intra-country variation.¹³⁻¹⁵

The aim of this study was to determine the use of anti-TNFs and surgery during the first three years after diagnosis in IBD patients across the four health regions in Norway using nationwide patient registry data.

2. Materials and Methods

Data source

In Norway, all citizens have free access to a tax-supported healthcare system. Norway's specialist healthcare system consists of four regional health authorities (Central, North, South-East and North) which are state enterprises responsible for specialist healthcare in the different health regions (Figure 1). All in- and outpatient hospital contacts are registered in the Norwegian Patient Registry (NPR), and it is mandatory to report diagnoses and clinical procedures. In addition, all biological drugs (both intravenous and subcutaneous preparations) can only be prescribed at hospitals and are registered in the NPR by their ATC codes. The registry dates back to 1997, and unique personal identification numbers were added in 2008, which made it possible to follow individual patients over time. The dataset in this study included every in- and outpatient hospital event for all patients who received an IBD diagnosis (ICD-10 code K50 or K51) at least once between 2008 and 2015. The dataset included information about gender, hospital, birth year (5-year intervals), date of contact (month and year) and procedure- and ATC-codes

Defining the cohort

The study cohort was defined as all patients with at least two registered K50 or K51 events during their three year follow-up. Two or more diagnoses were required based on a recent Swedish validation study which reported a positive predictive value for correct IBD diagnosis of 93% using this definition.¹⁶ The date of diagnosis was set to the earliest record of an IBD diagnosis in the registry. For individuals who received both UC and CD diagnoses the last registered diagnosis was used as the main diagnosis. Patients first observed with an IBD diagnosis in 2008 and 2009 were excluded to reduce the risk of misclassifying prevalent IBD

cases as incident IBD. Patients first observed between 2013 and 2015 were excluded since they had less than three years of observational information. Patients with registered events in multiple health regions during the follow-up time were excluded in order to enable comparison between the regions (Figure 2).

Anti-TNF therapy

The drugs included in the analysis were the TNF- α inhibitors infliximab, adalimumab and golimumab. Other biologics were not included as they were not accepted as IBD treatment in Norway until after 2015(?). All patients with at least one registered event of anti-TNF use after their first IBD diagnosis were considered anti-TNF recipients (anti-TNF exposure).

Surgery

The Norwegian patient registry stores all surgical procedure codes for each individual hospital contact. The NOMESCO Classification of Surgical Procedures (NCSP) was used to define major surgery, which included resections, colectomies, strictureplasty and intestinal obstruction repair (Supplementary Table 1).

Statistical analysis

Cumulative incidence of ever use of anti-TNFs and major surgery was estimated by constructing time-to-event curves (1 - Kaplan-Meier). All patients were followed for an equal period (three years) and no censoring occurred as the data did not include time of death. There is no uncertainty around the estimates as it is descriptive statistics for a limited period with complete follow-up.

Ethical considerations

The study was approved by the Norwegian Patient Registry, the Norwegian Data Protection Authority and the Regional Committees for Medical and Health Research Ethics.

3. Results

Study population

The study population included 8257 IBD patients first registered between 2010 and 2012, of whom 2829 (34.3%) were diagnosed with CD and 5428 (65.7%) with UC (Figure 2). Crohn's patients had a median age of 42 years at diagnosis and UC patients had a median age of 47 years. The analyses were stratified by diagnosis and health region (Table 1).

Surgery

Crohn's disease

The cumulative incidence of major surgery in Norway was 13.8% after three years. Across the four health regions, surgery varied between 11.4% (Central) and 17.1% (North) after three years. The South-East and West regions had cumulative incidences of 13.0% and 15.6% (Figure 3).

Ulcerative colitis

After three years, 5.2% of UC patients received surgery in Norway. The cumulative incidence of surgery varied from 4.6% (South-East) to 6.9% (Central) between the health regions. The North and West regions had cumulative incidences of 5.2% and 5.5% (Figure 3).

Anti-TNFs therapy

Crohn's disease

Among the CD patients, 28.8% received at least one anti-TNF three years after diagnosis. The anti-TNF exposure in each of the four health regions ranged from 20.9% (Central) to 31.4% (South-East). The North and West regions had cumulative incidences of 26.1% and 28.9%

(Figure 4). The Central region had administered anti-TNFs to 11.5% of the CD patients after one-year, which was approximately half the result for the other regions (20.1%-21.3%).

Of the 391 CD patients who underwent surgery, 173 (44.3%) received anti-TNFs. Across the health regions, between 11.3% and 36.8% received anti-TNF prior to surgery and 15.5%-36.8% after surgery. For patients that did not receive surgery, the proportion receiving anti-TNFs varied from 20.9%-28.5% (Figure 5).

Ulcerative colitis

Among the UC patients, 11.8% received at least one anti-TNF after three years. The anti-TNF exposure in each of the four health regions ranged from 8% (Central) to 13.5% (South-East). The West and North regions had cumulative incidences of 10% and 12.2% (Figure 4).

Of the 282 UC patients who underwent surgery, 107 (38.0%) received anti-TNFs. Across the health regions, between 18.5% and 46.2% received anti-TNF before surgery and 1.9%-8.8% after surgery. In patients that did not receive surgery, the proportion receiving anti-TNFs was between 7.2% and 11.9% (Figure 5).

4. Discussion

In this nationwide registry study of 8257 IBD patients, we found that both surgery and anti-TNF exposure varied across Norway's health regions. We also found that patient characteristics - age and gender - were comparable across regions (Table 1).

This indicates that the explanation for the differences is not due to differences in patient characteristics, but other factors such as the preferences and beliefs of the physicians and the patients. The management of IBD patients is challenging because of a complex disease spectrum and rapidly changing treatment options, which make it prone to unwarranted variation. Anti-TNFs have shown to reduce the need for surgery in the short term, but their effect in the long term is uncertain.¹⁷⁻¹⁹ Biologic agents and surgery are complementary therapies, and consensus on the roles of the different treatments is still being developed. This uncertainty may create differences in beliefs and variations in treatment practice.

Large hospitals treat the majority of IBD patients in all the Norwegian health regions. This makes the treatment landscape more susceptible to the treatment preferences of key opinion leaders. Lower utilization of anti-TNFs and more surgery might indicate that the Central region was more conservative in giving the more severe cases of IBD anti-TNFs and instead opted for surgery or other medical therapy. This hypothesis was further strengthened by the variation in the proportion of patients receiving anti-TNF before and after surgery which show that the Central region gave less anti-TNFs to the patients who underwent surgery. In CD patients, the Central region had administered anti-TNFs to half as many patients as the other regions within one year after diagnosis. The low use of anti-TNF therapy were accompanied by the highest surgery rates

among the regions for both UC and CD. When examining patients not receiving surgery, the proportion of patients receiving anti-TNFs were more similar across the regions (figure 5).

In a prospective follow-up study from Norway (the IBSEN Study) conducted before anti-TNFs were introduced, the surgery rates for UC were 3.5% after one year and 9.8% after 10 years.²⁰ For CD, the surgery rates were 13.6%, 27% and 37.9% after one, five and 10 years, respectively.²¹ The cumulative probabilities of surgery were lower in our study than in the IBSEN study in all regions. Given that the IBSEN cohort was diagnosed between 1990 and 1994 (in the prebiologic era), our results indicate a reduction in IBD surgery over time in Norway. Our results are in line with a nationwide cohort study from Denmark showing a decrease in major and minor surgery over time alongside an increase in the use of anti-TNFs, although a causal connection between the two could not be established.¹⁴ Other studies have found no change in surgery rates in the post-biologic era.^{3,4}

As the data did not include time of death, the analyses assumed that no patients died during the three-year follow-up time. Since the follow-up period is short, it is unlikely that this affected the cumulative incidences. Furthermore, the IBSEN study found no significant evidence of excess mortality for IBD patients after 20 years.^{22,23}

As with any diagnosis, there is a risk of coding errors during hospital admission. However, when requiring two IBD diagnoses within three years, we believe the number of false positive IBD diagnoses to be very low. No known validation studies of the IBD diagnoses in the NPR exists.

Registration of anti-TNFs should be accurate since hospital trusts are reimbursed for each registered ATC-code.

In conclusion, this study has shown that the cumulative incidence of anti-TNF exposure and surgery varied across Norway's health regions during the first three years after IBD diagnosis.

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Figure Legends

Figure 1: The four health regions in Norway

Figure 2: Definition of the IBD cohort

Figure 3: Cumulative probability of receiving anti-TNFs over time by diagnosis and region (%)

Figure 4: Cumulative probability of first major surgery over time by diagnosis and region (%)

Figure 5: Cumulative probability of first minor surgery over time in Crohn's disease by region (%)