

Work Loss in Relation to Pharmacological and Surgical Treatment for Crohn's Disease: A Population-Based Cohort Study

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Purpose: Patients with Crohn's disease have increased work loss. We aimed to describe changes in work ability in relation to pharmacological and surgical treatments.

Patients and Methods: We linked data from the Swedish National Patient Register, The Swedish Quality Register for Inflammatory Bowel Disease SWIBREG, The Prescribed Drug Register, The Longitudinal Integrated Database for Health Insurance and Labour Market Studies, and the Social Insurance Database. We identified working-age (19–59 years) patients with incident Crohn's disease 2006–2013 and population comparator subjects matched by sex, birth year, region, and education level. We assessed the number of lost workdays due to sick leave and disability pension before and after treatments.

Results: Of 3956 patients (median age 34 years, 51% women), 39% were treated with aminosalicylates, 52% with immunomodulators, 22% with TNF inhibitors, and 18% with intestinal surgery during a median follow-up of 5.3 years. Most patients had no work loss during the study period (median=0 days). For all treatments, the mean number of lost workdays increased during the months before treatment initiation, peaked during the first month of treatment and decreased thereafter, and was heavily influenced by sociodemographic factors and amount of work loss before first Crohn's disease diagnosis. The mean increase in work loss days compared to pre-therapeutic level was ~3 days during the first month of treatment for all pharmacological therapies and 11 days for intestinal surgery. Three months after treatment initiation, 88% of patients treated surgically and 90–92% of patients treated pharmacologically had the same amount of work loss as before treatment start. Median time to return to work was 2 months for all treatments.

Conclusion: In this regular clinical setting, patients treated surgically had more lost workdays than patients treated pharmacologically, but return to work was similar between all treatments.

Keywords: inflammatory bowel disease, sick leave, disability pension, TNF inhibitor, aminosalicylate, immunomodulator

Introduction

Crohn's disease is chronic and affects young individuals, and therefore one important goal of treatment for both patients and society is to maintain work ability. Pharmacological treatments traditionally used in Crohn's disease include corticosteroids, aminosalicylates (even though aminosalicylates are recommended only in specific clinical situations such as in a postoperative setting), and immunomodulators. Tumor necrosis factor (TNF) inhibitors, initially recommended only for patients with inadequate response to conventional therapy, are nowadays used

earlier during the disease course,¹ sometimes in a top-down-approach, rather than step-up.²

Clinical trials have evaluated the effects of TNF inhibitors on work productivity mainly by the Work Productivity and Activity Index^{3–10} ([Supplementary Table 1](#)). Data from clinical trials have shown a decrease in patient-reported absenteeism during treatment with TNF-inhibitors^{3–7,9,10} in selected populations with short follow-up (weeks or months).^{3–6,8,9} However, the long-term effect of TNF-inhibitors in routine clinical practice is not known, and data on work ability during other treatments, including surgery, are sparse.

The aim of this study was to assess work loss before and after the start of pharmacological treatments and surgery in a population-based cohort of working-age patients with Crohn's disease, where objectively assessed day-to-day information on work loss was available for each individual, as well as detailed information on disease characteristics, medication, and surgeries. A secondary aim was to describe work loss in patient subgroups, stratified by demographic characteristics and previous work loss.

Materials and Methods

Setting

In 2015, Sweden had a population of 9.7 million.¹¹ The Swedish health-care system is tax funded and offers universal access, with prescription drugs provided free of charge above an annual threshold of SEK 1800 (approximately \$190 in June 2019). The Swedish social insurance system provides compensation for sick leave and disability pension, both of which can be partial or complete. During the study period, the first day of sick leave was not compensated, and days 2–14 paid by the employer.¹² Sick leave episodes exceeding 2 weeks were paid by the Social Insurance Agency, as well as disability pension, which was compensated from the first day in individuals with permanently reduced work capacity by at least 25%. Periods of sick leave could be compensated during a time not covered by disability pension. Unemployed individuals could receive both sick leave and disability pension. Retirement age in Sweden was 61–67 years, most commonly 65 years.

Data Sources

The unique personal identity number, issued to all Swedish residents¹³ was used to link data from the following registers:

The Swedish National Patient Register which contains information on dates of hospital care (nationwide from 1987) and specialized outpatient visits (from 2001) with International Classification of Diseases (ICD) codes for diagnoses and surgical procedure codes according to the Swedish version of the Classification of Surgical Procedures (NOMESKO), with a population coverage exceeding 99%.¹⁴ SWIBREG is the national quality register for inflammatory bowel disease and was founded in 2005 and holds data on start- and stop-date of biologic treatment. The national coverage of prevalent patients with Crohn's disease was estimated to be 73% in 2015.¹⁵ The Prescribed Drug Register holds information on names and Anatomical Therapeutic Chemical (ATC) Classification of prescribed drugs dispensed from pharmacies in Sweden from 1 July 2005 and onwards. The coverage of the register is complete for prescriptions in ambulatory care (both specialist and primary care), while in-hospital drug treatment is generally not recorded on a patient level.^{16,17} The Longitudinal Integrated Database for Health Insurance and Labour Market Studies (LISA) contains data on socioeconomic factors for all Swedish citizens by calendar year since 1990.¹² The Micro Data for Analysis of the Social Insurance Database (MiDAS) contains nationwide administrative data on compensation for lost workdays with information on exact dates and the proportion compensation (25%, 50%, 75%, or 100% for each day).¹⁸ We had access to data from MiDAS until October 2015. The Total Population Register records dates of emigration and death of all residents in Sweden and is continuously updated.¹¹

Study Design

We performed a cohort study, assessing days of sick leave and disability pension before and after different treatments in working-age patients with incident Crohn's disease compared to matched general population comparator subjects.

Identification of Patients with Incident Crohn's Disease

Working-age (19 to 59 years) patients with Crohn's disease were identified through the Patient Register requiring that the first 2 diagnoses of IBD were Crohn's disease (K50)¹⁹ and occurred between July 1st 2006 and Sep 30th 2013. The time period was chosen to ensure at least 1 year of look-back in the Prescribed Drug Register and a minimum follow-up of 2 years for all participants (work loss data

available until Sep 30th 2015). Patients with listings of inflammatory bowel disease before July 1st 2006 were excluded ([Supplementary Table 2](#)).

General Population Reference Individuals

Up to five population reference individuals without a diagnosis of inflammatory bowel disease before index date or during follow-up were matched to each patient by age, sex, health-care region, calendar year, and highest achieved education level at match date. Each comparator was assigned a pseudo-date of diagnosis of the matched case.

Assessment of Treatment (Exposure)

Data on first dispensing of disease-related medications (aminosalicylates, immunomodulators, and TNF inhibitors) were abstracted from the Prescribed Drug Register ([Supplementary Table 3](#)). For TNF inhibitors administered in-hospital, data were also collected from the Patient Register based on ATC-codes, and from the quality register SWIBREG. Start and stop date for TNF inhibitor treatment was set for each substance. During the years when treatment exposure was measured, infliximab and adalimumab were widely used. Newer targeted therapies such as golimumab, vedolizumab and ustekinumab were rarely used, and natalizumab and certolizumab were not approved. Procedure codes for intestinal surgery were abstracted from the National Patient Register ([Supplementary Table 4](#)). For descriptive purposes, we also evaluated occurrence of procedure codes for perianal surgery ([Supplementary Table 4](#)).

Assessment of Sick Leave and Disability (Outcome)

For all study participants, the exact dates of sick leave and disability pension were retrieved from the social insurance database. The net number of lost workdays due to sick leave and/or disability pension per time unit (month or year) was calculated by multiplying the number of days by the proportion of compensation received.¹⁹

Covariates

Patients' phenotypes were defined by location and behaviour according to ICD-codes in the National Patient Register ([Supplementary Table 6](#)) or from information in SWIBREG. Extraintestinal manifestations were defined as diagnosis of primary sclerosing cholangitis, inflammatory arthritis, iridocyclitis, erythema nodosum, pyoderma gangrenosum, or Sweet's syndrome ([Supplementary Table 5](#)). Prescribed doses of corticosteroids were converted into prednisolone equivalents.²⁰

Statistics

The mean number of lost workdays in patients and comparators were computed per month in relation to start of treatment, and 95% confidence intervals (CIs) were estimated by non-parametric bootstrapping. We estimated lost workdays separately for each type of IBD treatment (aminosalicylate, immunomodulator, TNF inhibitor, and intestinal surgery) in all patients starting treatment, which can be viewed as an intention to treat-analysis. We also estimated lost workdays in those not switching to other therapy (as treated-analysis), by censoring patients at the time of initiation of an additional or other treatment in the step-up treatment ladder (aminosalicylate → immunomodulator → TNF inhibitor). In the "as-treated" subanalyses the patients with aminosalicylate treatment were censored at date of first immunomodulator, TNF inhibitor, or surgery. Patients with immunomodulator treatment were censored at date of TNF inhibitor or surgery. Patients with TNF inhibitor use were censored at date of a new line TNF inhibitor or surgery, and patients undergoing intestinal surgery were censored at date of TNF inhibitor or new intestinal surgery (excluding surgical procedures occurring within the same hospital admission).

The mean difference in lost workdays between patients and population comparators was estimated per year from 5 years before to 5 years after treatment initiation in all patients starting treatment (intention-to-treat) as well as in those continuing (as treated).

Separate assessments were done with stratification for the mean number of lost workdays per month during the 2 years preceding first Crohn's disease diagnosis (0, 1–14, 15–29, ≥30 days), and by sex, age, and educational level. We also describe lost workdays by categories (the proportion of patients affected): no work loss (0 days per month), <50% work loss (1–14 days per month), >50% work loss (15–29 days per month), total work loss (≥30 days per month), and with the 75th and 90th percentile.

The mean change in work loss days from pre-therapeutic level (baseline was set to 6 to 5 months before treatment initiation) was calculated in a within-subject pre-post analysis in all patients starting treatment with aminosalicylate, immunomodulator, TNF inhibitor, and intestinal surgery. The difference in mean days is presented at 3, 6, 9, and 12 months with 95% CI calculated with the Wald method. We present the proportion of patients had returned to pre-therapeutic work loss level or lower at these time points. Among patients with increased work loss before

treatment initiation that returned to work within 12 months, we calculated the mean and median time to return to work. We compared time to return to work between treatment groups with the Kruskal Wallis test.

All statistical tests were two-sided, and $p < 0.05$ was considered statistically significant. We used statistical software from SAS (version 9.2; SAS Institute Inc., Cary, NC, USA) Stata (release 12.0; StataCorp, College Station, TX, USA), and R (version 3.5.0).

Ethics

The regional ethics committee in Stockholm approved the study (DNR 2007/785-31/5; 2011/1509-32; 2012/601-32; 2015/0004-31; 2015/615-32; 2015/1030-32).

Results

Baseline Characteristics

We identified 4823 patients who had their first 2 ever diagnoses of Crohn's disease in the Patient Register July 1st 2006- Sep 30th 2013. Of those, 867 patients had a dispensing of aminosalicylate, immunomodulator, or TNF inhibitor prior to first diagnostic listing of Crohn's disease and were excluded. The 3956 remaining patients were matched to 19,777 comparator subjects from the general population on sex, age, geographical region, and education level ([Supplementary Figure 1](#)).

Median age at diagnosis was 34 years and 51% were women. Time between first and second Crohn's disease diagnostic listing was in median 49 days (IQR: 21–122). Median follow-up time was 5.3 (range 0–9.2) years in the patients and 5.4 (0–9.2) years in the comparators, and 1.7% of the patients and 0.5% of the comparators died during follow-up ($p < 0.0001$). Of all patients 29% were ever treated with aminosalicylate, 52% with immunomodulator, 22% with TNF inhibitor, and 18% went through intestinal surgery at some point during follow-up ([Supplementary Table 7](#)).

Disease Characteristics Up to Start of Treatment

Median time from diagnosis to start of treatment with aminosalicylate was 30 (IQR: 3–139) days, for immunomodulator 125 (41–409) days, and for TNF inhibitor 419 (146–967) days. Time to first intestinal surgery was in median 217 (47–735) days. The majority of patients starting aminosalicylate treatment had not used other medication before, whereas the majority of patients starting TNF inhibitor had already used immunomodulator (75%) or

aminosalicylate (38%). Patients starting TNF inhibitor treatment had more complicated disease behavior (B2/B3: 6.4%), more perianal disease (14%) and more joint manifestations (6.3%) than those starting immunomodulator or aminosalicylate treatment. The highest proportion of patients with severe disease behavior (12.7%) was found in the group undergoing intestinal surgery ([Table 1](#)).

Mean Number of Lost Workdays per Month Before and After Treatment Start

In the patients starting aminosalicylate treatment, the mean number of lost workdays 6 months before first dispensation was 3.7 days per month (2.0 days in the matched comparators). Work loss increased to 6.2 days during the first month after treatment start and declined thereafter. One year after start of treatment, the mean number of lost workdays in all patients starting treatment with aminosalicylate was 4.2 days, and 3.8 days in the patients not adding treatment with immunomodulator, TNF inhibitor, or undergoing intestinal surgery (65% of all) ([Figure 1](#) and [Supplementary Table 8](#)).

In patients starting immunomodulator treatment, the mean number of lost workdays 6 months before first dispensation was 3.8 days per month (1.9 days in the matched comparators). Work loss increased to 6.5 days during the first month after treatment and declined to 4.1 days at 1 year in all patients starting treatment, and to 3.5 days in the patients not adding treatment with TNF inhibitor or undergoing intestinal surgery (75% of all).

Patients starting first-line TNF inhibitor treatment had 4.4 lost workdays 6 months before treatment start (1.9 days in the matched comparators). Work loss increased to 7.2 days during the first month of treatment and declined to 4.9 days at 1 year in all, and to 4.2 days in patients not starting second line TNF inhibitor treatment or undergoing surgery (78% of all).

Patients starting second line TNF inhibitor treatment had 5.6 lost workdays before treatment start (2.1 days in the matched comparators). Work loss increased to 6.2 days during the first month of treatment and was virtually unchanged at 1 year- 6.1 days – in all patients. Work loss in patients continuing second line treatment, ie not starting third line TNF inhibitor treatment or undergoing surgery, declined rapidly and was 3.5 days per month at 1 year (56% of all).

Patients who underwent intestinal surgery had 5.5 lost workdays 6 months before surgery (2.6 days in the matched comparators) and increased to 16.9 days during the first

Table I Characteristics of 3956 Patients with Incident Crohn's Disease (2006–2013 and Followed Until October 2015) Up to Start of Treatment with Aminosalicylate, Immunomodulator, TNF Inhibitor, and Intestinal Surgery

	Aminosalicylate	Immunomodulator	TNF Inhibitor	Intestinal Surgery
Number of patients [†]	1547	2043	853	719
Female sex, n (%)	814 (53)	1033 (51)	414 (49)	354 (49)
Education Level at Diagnosis, n (%)				
≤9 years	224 (14)	315 (15)	140 (16)	139 (19)
10–12 years	824 (53)	1117 (55)	475 (56)	383 (53)
≥13 years	474 (31)	575 (28)	222 (26)	184 (26)
Unknown	25 (1.6)	36 (1.8)	16 (1.9)	13 (1.8)
Age at diagnosis (years)	33 (25–46; 19–59)	32 (24–44; 19–59)	30 (23–41; 19–59)	36 (26–49; 19–59)
Median (25th–75th; min–max)				
Time from diagnosis to treatment start (days)	30 (3–139;	125 (41–409; 0–3294)	419 (146–967;	217 (47–735;
Median (25th–75th; min–max)	0–2781)		0–3246)	0–2935)
Previous Treatment from Date of Crohn's Disease Diagnosis,[‡] n (%)				
Aminosalicylate		647 (32)	322 (38)	164 (23)
Immunomodulator	171 (11)		641 (75)	288 (40)
TNF inhibitor	46 (3.0)	111 (5.4)		123 (17)
Intestinal surgery	90 (5.8)	195 (9.5)	109 (13)	
Perianal surgery	15 (0.97)	72 (3.5)	91 (11)	31 (4.3)
Cumulative dose of Prednisolone equivalents (mg) from date of Crohn's disease diagnosis[‡]	0 (0–500;	500 (0–1000;	1000 (125–2000;	500 (0–1500;
Median (25th–75th; min–max)	0–12,581)	0–13,743)	0–16,367)	0–16,000)
0	1089 (70)	892 (44)	210 (25)	327 (45)
>0–<1500	338 (22)	788 (39)	315 (37)	189 (26)
1500–<3000	88 (5.7)	244 (12)	199 (23)	116 (16)
3000–<4500	19 (1.2)	81 (4.0)	71 (8.3)	46 (6.4)
≥4500	13 (0.84)	38 (1.9)	58 (6.8)	41 (5.7)
Phenotype,[‡] n (%)				
L1	157 (10)	300 (15)	68 (8.0)	62 (8.6)
L2	225 (15)	214 (11)	66 (7.7)	20 (2.3)
L3/LX	1165 (75)	1529 (75)	719 (84)	637 (89)
B1	1511 (98)	1935 (95)	798 (94)	628 (87)
B2/B3	36 (2.3)	108 (5.3)	55 (6.4)	91 (12.7)
P	27 (1.8)	110 (5.4)	117 (14)	50 (3.1)
Extraintestinal Manifestations,[‡] n (%)				
Primary sclerosing cholangitis	6 (0.39)	3 (0.15)	2 (0.23)	2 (0.28)
Joint manifestations	18 (1.2)	39 (1.9)	54 (6.3)	15 (2.1)
Any manifestation	34 (2.2)	62 (3.0)	73 (8.6)	23 (3.2)

Notes: [†]The sum of treated patients exceeds the total number of patients, since the same patient can receive several treatments. [‡]Up to start of treatment.

month after surgery. One year after surgery the mean number of lost workdays in all patients was 5.8 days, and 5.2 days in the patients not starting TNF inhibitor treatment or undergoing further intestinal surgery (81% of all).

Work Loss Up to 5 Years Following Treatment

When estimating lost workdays from 5 years before start of treatment to 5 years after, the mean difference between patients later starting treatment with

aminosalicylate and their matched comparators was +16 days per year 5 years before treatment start, and +18 days per year 5 years after. The mean difference between patients not started on other treatments (45% of all) and the comparators was +13 days per year 5 years after treatment start (Figure 2).

Five years before start of immunomodulatory treatment, patients with Crohn's disease had +12 more lost workdays than comparators, and the difference was +21 days 5 years after within the 5th calendar year in all

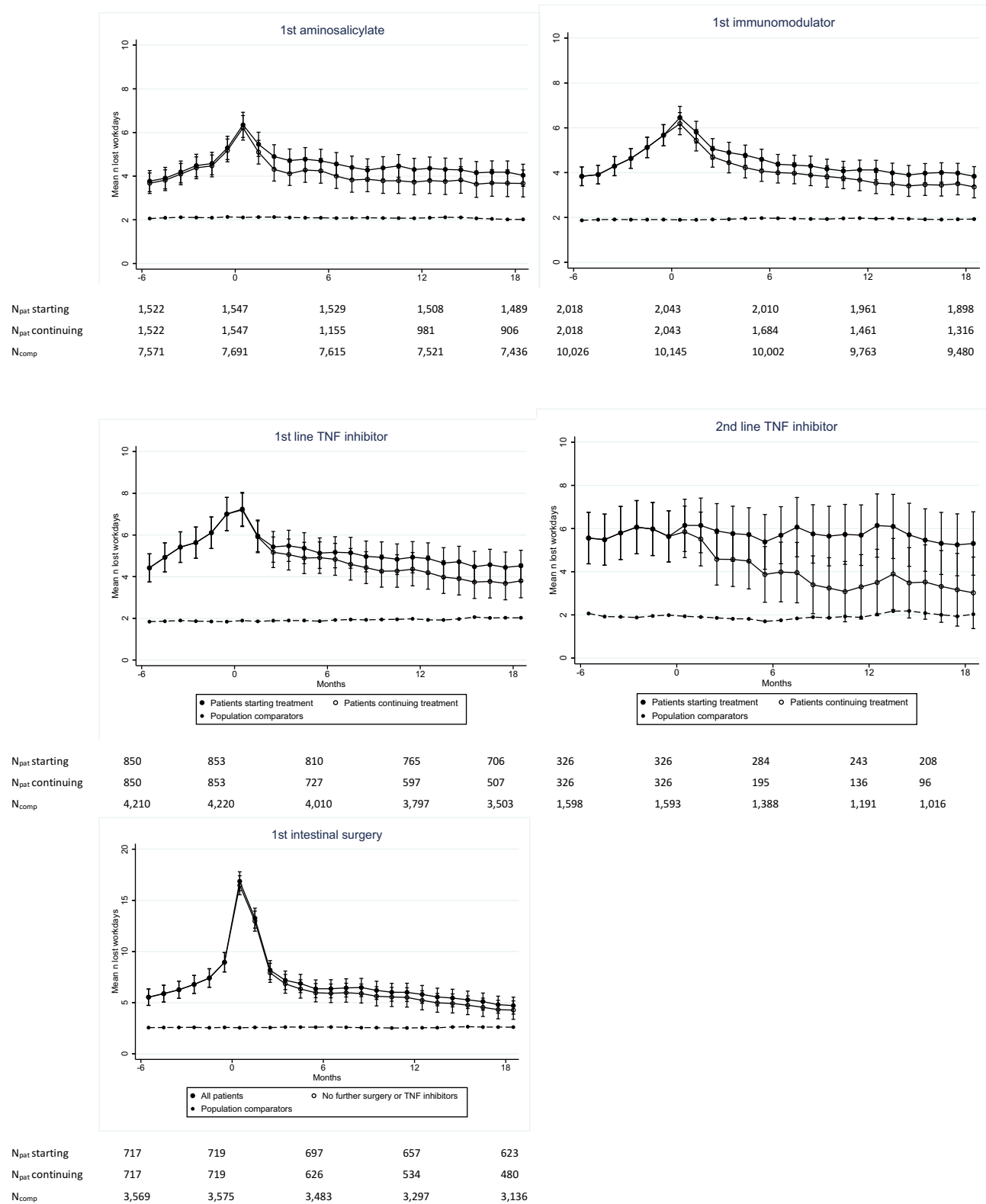


Figure I Mean number of lost workdays per month in patients with Crohn's disease from 6 months before to 18 months after start of treatment with aminosalicylate, immunomodulator, first and second line TNF inhibitor, and intestinal surgery, with and without censoring at addition of other treatment, or surgery.

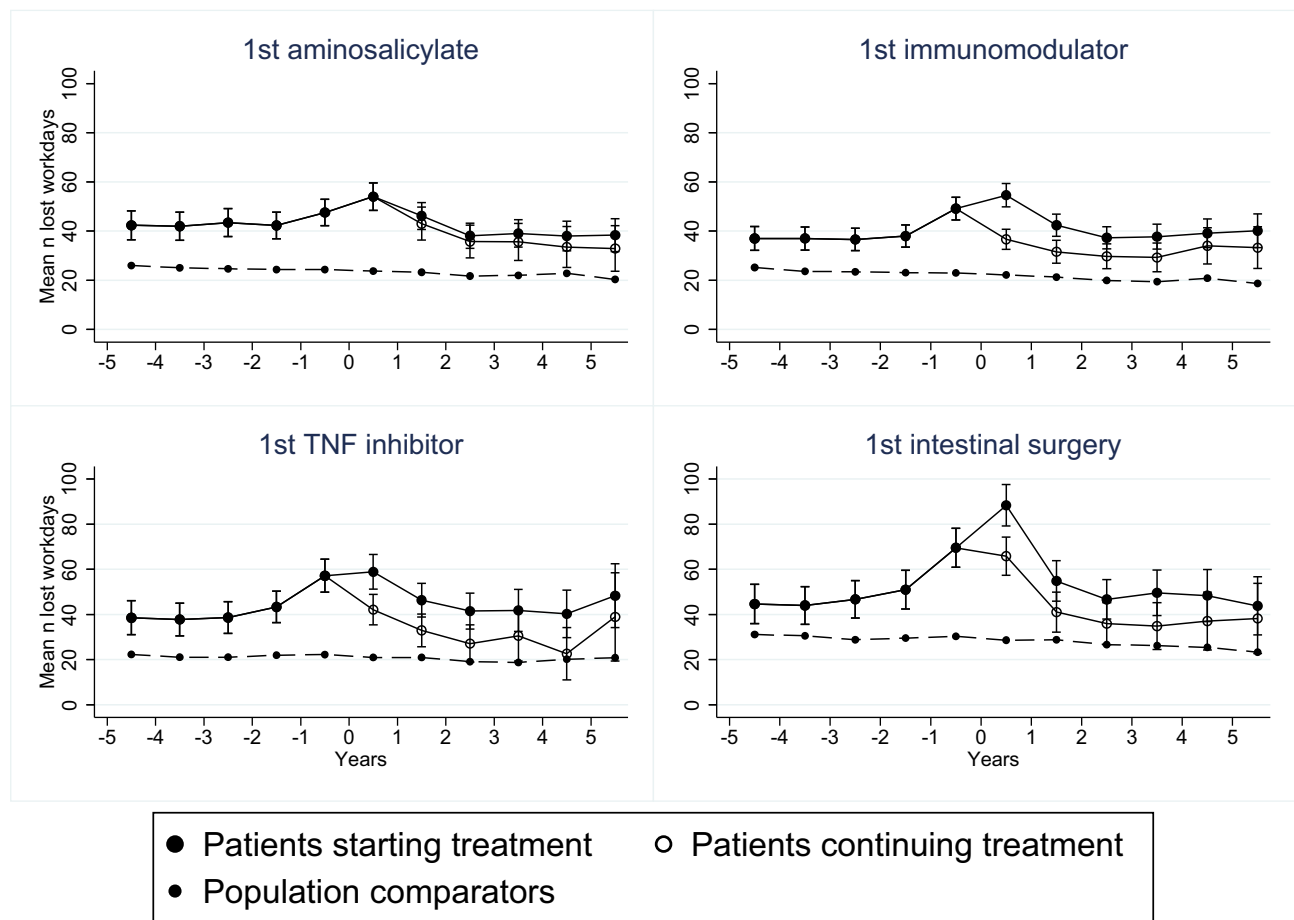


Figure 2 Mean number of lost workdays per year in patients with Crohn's disease from 5 years before to 5 years after first aminosalicylate, immunomodulator, TNF inhibitor, and intestinal surgery, with and without censoring at addition of other treatment, or surgery.

patients, and +15 days difference in patients not adding other treatment (55% of all).

Patients starting treatment with TNF inhibitor had +16 more lost workdays than comparators 5 years before treatment start, and the difference was +27 days during the 5th year after. The mean difference between patients not started on second line TNF inhibitor or undergoing surgery (39% of all) and the comparators was +15 days.

Patients undergoing intestinal surgery had +13 more lost workdays than comparators 5 years before treatment start, and +20 more days the 5th year after (mean difference +15 days between patients not started on other treatments and the comparators, 55% of all).

Proportion Work Loss Before and After Treatment Start

The proportion of patients with no lost workdays was 82% 3 to 2 months before start of aminosalicylate treatment, 79% before immunomodulator, 76% before TNF inhibitor,

and 72% before intestinal surgery (Figure 3). In all treatments, the proportion of patients without work loss was smallest during the first month following treatment start (aminosalicylate: 73%, immunomodulator: 72%, TNF inhibitor: 69%, intestinal surgery: 29%), but in all treatments a recovery was seen within 3–4 months to levels similar to 3 to 2 months before initiation of treatment.

Factors Influencing Work Loss

When stratifying patients by mean number of lost workdays during the 2 years preceding first Crohn's disease diagnosis (≥ 30 days, 15–29, 1–14 or 0 days per month) most patients remained within the same category both before and after treatment start in all treatment groups (Figure 4). The increase in work loss days around treatment start was most prominent in patients with no or little previous work loss.

The mean number of lost workdays differed between sociodemographic subgroups in both patients and

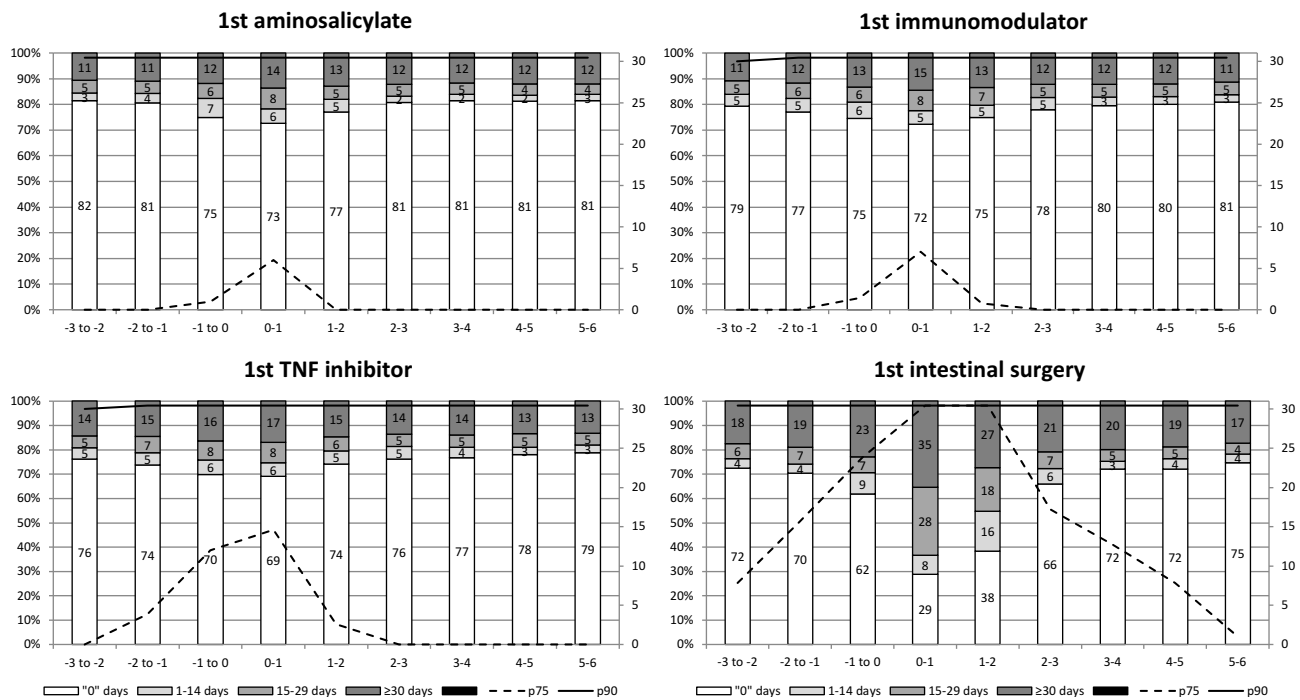


Figure 3 Proportion (left y-axis) with lost workdays per month from 3 months before to 6 months after first aminosalicylate, immunomodulator, TNF inhibitor, and intestinal surgery in patients with Crohn’s disease. The dashed line shows the 75th percentile, and the line the 90th percentile of lost workdays per month (right y-axis).

population comparators. Women had more lost workdays than men, individuals with shorter education had more lost workdays than individuals with longer education, and older individuals had more lost workdays than younger.

At treatment initiation with aminosalicylate or immunomodulator, women with Crohn’s disease had 2.0 more lost workdays per month than the men with Crohn’s disease starting the same treatment, and female patients starting TNF inhibitor had 3.4 more lost workdays than male patients. Individuals with shorter education had 5.3 more lost workdays during the month of treatment initiation with aminosalicylate, 5.7 more lost workdays at start of immunomodulator and 4.8 more days at start of TNF inhibitor than patients with longer education.

The difference in lost workdays between patients and comparators both before and after treatment initiation was also most pronounced in women, individuals with short education, and those aged 50–59 at diagnosis ([Supplementary Figures 2–5](#)).

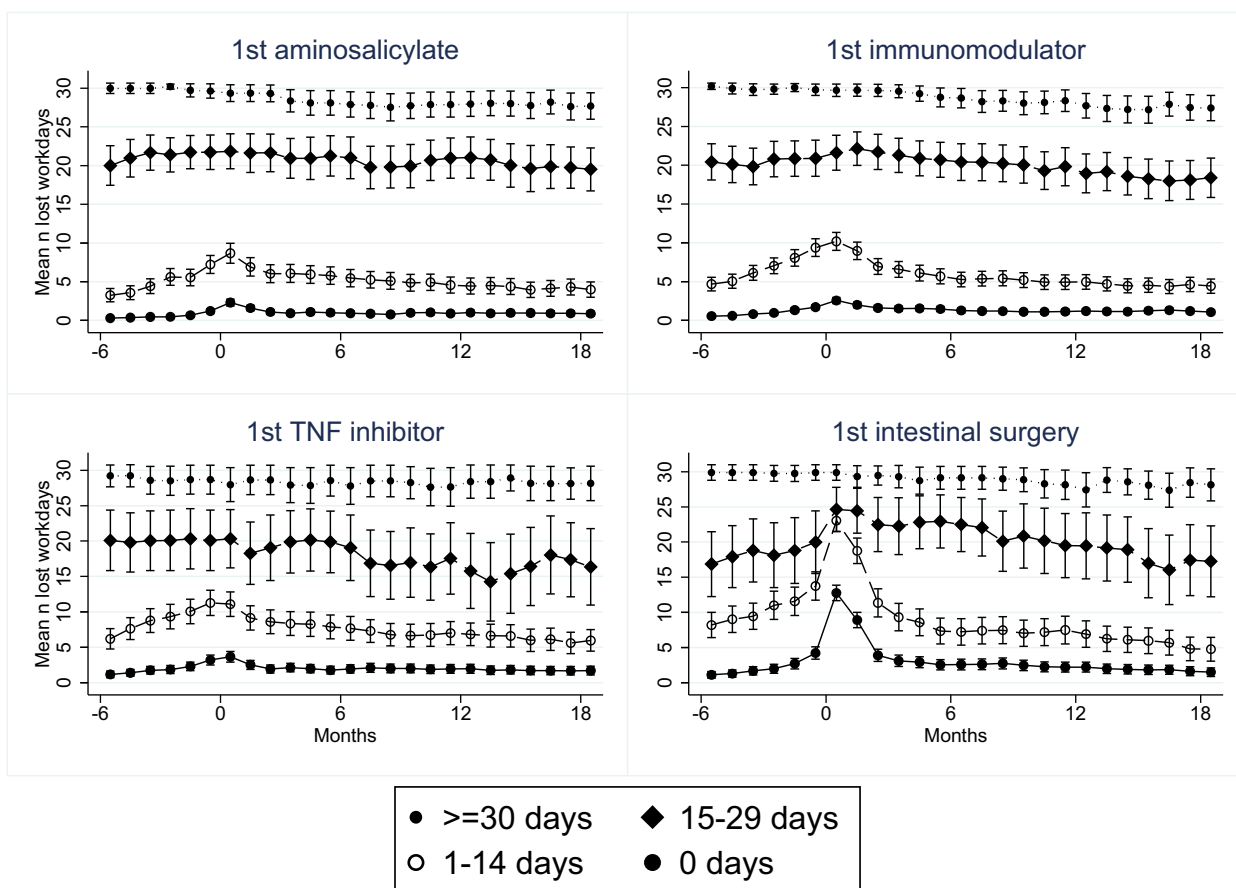
Return to Pre-Therapeutic Work Loss

When comparing work loss days in a within-subject pre-post analysis, the mean increase from 6 months before to treatment initiation was largest in patients undergoing intestinal surgery (+11.2 days during the month after

surgery) and 70% of the patients had increased work loss ([Figure 5](#) and [Table 2](#)). For pharmacological treatments, the increase was 2.8 to 3.4 days and 27–30% of the patients had increased work loss. Three months after treatment start, 88% of patients treated surgically and 90–92% of the patients treated pharmacologically had the same number of lost workdays (or lower) as before treatment start and 91–93% at 1 year. Among patients that experienced increased work loss around treatment start and had returned to pre-treatment level within 1 year, the median time to return was 2 months for all treatments.

Discussion

Our study shows that the mean number of lost workdays increased up to treatment initiation and decreased thereafter for all common treatments for Crohn’s disease. The mean increase in days of work loss compared to pre-therapeutic level was approximately 3 days during the first month of treatment for all pharmacological therapies and 11 days for intestinal surgery. Three months after treatment initiation 88% of patients treated surgically and 90–92% of patients treated pharmacologically had the same amount of work loss as before treatment start. Improvement in work ability during the first 18 months after treatment initiation was more pronounced in patients



Mean n of lost workdays/month during the 2 years before diagnosis	Aminosalicylates n patients (%)	Immunomodulators n patients (%)	TNF inhibitor n patients (%)	Intestinal surgery n patients (%)
0 days	1,021 (66)	1,372 (67)	567 (67)	463 (65)
1-14 days	361 (23)	479 (24)	213 (25)	171 (24)
15-29 days	59 (3.8)	76 (3.7)	26 (3.1)	26 (3.6)
30 days	97 (6.3)	106 (5.2)	43 (5.1)	54 (7.6)

Figure 4 Mean number of lost workdays per month from 6 months before to 18 months after start of treatment with aminosalicylate, immunomodulator, TNF inhibitor, and intestinal surgery, stratified by mean number of lost workdays per month during the 2 years before first Crohn’s disease diagnosis.

not adding or switching to other treatments, indicating that these patients probably responded to the treatment.

Assessing work loss before and after initiation of different treatments in an observational study requires caution when interpreting the results. Disease activity is the indication for treatment, and therefore the patient populations differ between treatment groups, and the number of work loss days cannot be compared cross-sectionally. Data from Table 1 clearly show the strong adherence to the “treatment ladder” in that TNF inhibitor treatment was in most patients started more than a year after diagnosis and two-thirds of those patients were already treated with immunomodulator. The use of aminosalicylate treatment

was high, 39%, and treatment was initiated early, in median 30 days from diagnosis. Clearly, in routine medical care and contrary to international guidelines, many gastroenterologists use aminosalicylate as first-line treatment in patients with Crohn’s disease.

When comparing work loss between treatments, patients undergoing intestinal surgery had the largest increase in work loss (+11 days per month compared to around +3 for medical treatments) but return to work was similar between treatments. However, the increase in work loss before start of treatment constituted only a minor part of the work loss experienced by the patients. For all treatments, the mean number of lost workdays was higher in

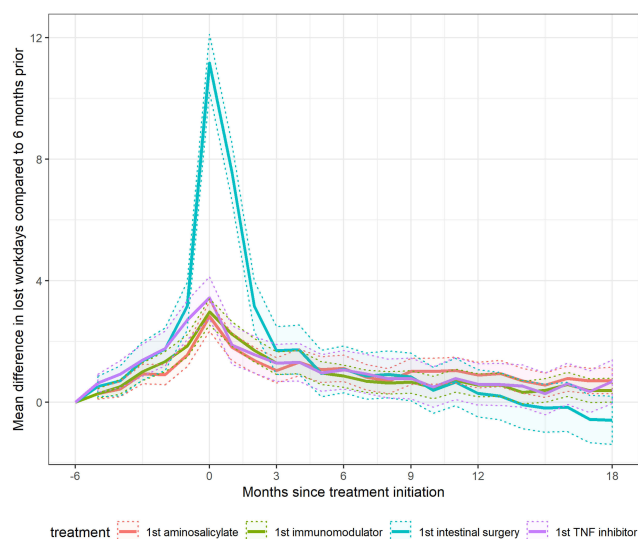


Figure 5 Change in lost workdays per month from pre-treatment level (6 months before treatment initiation) in patients treated with aminosalicylate, immunomodulator, TNF inhibitor, and intestinal surgery. Dotted lines are pointwise 95% confidence intervals for the mean change.

patients with Crohn’s disease compared to the general population both before and after interventions, irrespective of treatment. That patients with Crohn’s disease have increased work loss, and that such work loss heavily depends on sociodemographic factors has been shown before, in both incident²¹ and prevalent patients.²²

In patients starting treatment with TNF inhibitor, individuals with short education had 4.8 more lost workdays per

month (ie twice as many) as individuals with long education, whereas when comparing patients starting treatment with TNF inhibitor (believed to have more severe disease) with patients starting aminosalicylate treatment (believed to have less severe disease), those starting TNF inhibitor treatment only had 1 more lost workday than those starting treatment with aminosalicylate. Socioeconomic factors thus seem to have a greater impact on work loss than disease severity.

In population-based studies, treatment with TNF inhibitors^{22–24} and surgery^{24–28} have been identified as risk factors for work disability. This association likely represents confounding by indication, in that disease severity and behaviour are associated with both the work disability and the treatment.

Two randomized controlled trials have reported a 10% reduction in absenteeism in mixed patient populations (bio-naïve and bio-experienced) after 20 weeks of adalimumab⁹ and 26 weeks of certolizumab treatment,⁴ which concurs with results from a meta-analysis of four studies with 20 to 52 weeks of adalimumab treatment estimating a 9% (7–10%) reduction in absenteeism over a year.⁷ In the present study, the reduction in absenteeism from start of first line TNF inhibitor treatment to 24 weeks was 7% (24% to 17%; from 7.2 to 5.2 lost workdays per month). In analyses where patients needing additional or other treatment were excluded (ie restricted to “responders”) the reduction was 8% (24% to 16%; 7.2 to 4.8 lost workdays per month).

Table 2 Mean Difference in Work Loss Days and Proportion Patients with an Equal or Lower Number of Sick Leave Days Compared to 6 Months Before Treatment Start. The Bottom Row Shows Time to Return to Pre-Treatment Work Loss Level in Patients Who Had Increased Work Loss at Treatment Start and Returned to Pre-Treatment Work Loss Level Within 1 Year

		Aminosalicylate N=1547	Immunomodulator N=2043	TNF Inhibitor N=853	Intestinal Surgery N=719
At treatment start	Mean difference Days (95% CI) % with equal or lower work loss	2.8 (2.3–3.3) 73.2	3.0 (2.5–3.4) 72.8	3.4 (2.7–4.1) 69.5	11.2 (10.2–12.1) 30.3
At 3 months after treatment start	Mean difference Days (95% CI) % with equal or lower work loss	1.0 (0.6–1.5) 92.0	1.3 (0.9–1.7) 90.7	1.3 (0.7–1.9) 89.8	1.7 (0.0–2.5) 87.6
At 6 months after treatment start	Mean difference Days (95% CI) % with equal or lower work loss	1.1 (0.7–1.5) 82.1	0.9 (0.5–1.2) 82.1	1.1 (0.4–1.7) 79.1	1.1 (0.3–1.9) 75.8
At 9 months after treatment start	Mean difference Days (95% CI) % with equal or lower work loss	1.0 (0.6–1.4) 82.9	0.7 (0.3–1.0) 83.3	0.8 (0.1–1.5) 80.4	0.8 (0.1–1.6) 77.1
At 1 year after treatment start	Mean difference Days (95% CI) % with equal or lower work loss	0.9 (0.5–1.3) 92.5	0.6 (0.2–0.9) 93.1	0.6 (–0.1 to 1.3) 91.5	0.3 (–0.5 to 1.1) 91.0
Time to return to pre-treatment work loss level (months)	Number of patients Mean (SD) Median (IQR)	208 2.3 (2.2) 2 (1–2)	282 2.9 (2.3) 2 (1–4)	127 2.6 (2.3) 2 (1–3)	351 2.5 (1.8) 2 (2–2)

For second line TNF inhibitor treatment absenteeism went from 20% to 19% in our study (from 6.2 to 5.7 lost workdays per month) over 6 months in all patients starting treatment, and from 19% to 13% (from 5.8 to 4.0 lost workdays per month) in “responders”. Other studies have reported a reduction in absenteeism from 25% to 6% and from 23% to 11% from baseline to 26 weeks of second line certolizumab treatment,⁵ and a 7% reduction after 20 weeks of second line adalimumab.³

Studies on work ability after surgical treatment for Crohn’s disease are scarce. In the only randomized study comparing surgery and TNF inhibitor treatment, patients treated surgically had more sick leave days (3.4 vs 1.4 days), but long-term results were similar,²⁹ in line with our results. A Swedish study of patients undergoing one or more intestinal resections found that 73% of the patients had full working capacity up to 15 years after surgery.³⁰

A major strength of the present study is the population-based design and access to data from routine clinical practice entered prospectively in virtually complete registers. In contrast to most other studies, we did not rely on patient-reported data on lost workdays.

Limitations include lack of complete information on TNF inhibitor use, since infusion drugs given in-hospital are not registered by all Swedish counties. However, the quality register SWIBREG has information on biological treatment, and data on TNF inhibitor use were extracted from all available data sources. Albeit this, the true number of patients in this study receiving infliximab treatment is likely higher and some patients treated with aminosalicylate and immunomodulator may therefore have been misclassified as not having needed additional treatment, leading to an overestimation of the proportion “responders” in those treatment groups, and an underestimation of the decrease in work loss days after treatment initiation in analyses where patients needing additional or other treatment were excluded.

Estimations of work loss over a 10-year time period should be interpreted with caution, since many patients were censored due to age or end of follow-up, and therefore few patients were followed over the entire time period.

Also, the mean number of lost workdays is an underestimation since the register does not include sick leave episodes <14 days. This exclusion, however, applied to all participants.

Social systems differ among countries regarding the maximum duration of sick leave and the amount of compensation received, therefore our results in absolute terms may not be generalizable to countries with other social systems. However, the observed relative differences between treatments and

between patients and comparators should be generalizable, as long as the same treatment paradigms are applied.

Conclusion

In Swedish routine health care, where decisions on medical and surgical treatment for Crohn’s disease were taken according to regional and national guidelines (ie depended mainly on disease activity) return to work was similar between all treatments, including surgery.

Abbreviations

IBD, inflammatory bowel disease; ICD, International Classification of Diseases; ATC, Anatomical Therapeutic Chemical; LISA, The Longitudinal Integrated Database for Health Insurance and Labour Market Studies; MiDAS, The Micro Data for Analysis of the Social Insurance Database; CI, confidence interval.

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Author Contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Disclosure

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