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Exploratory Analysis of Biologicals in the Drug Treatment of Patients with Crohn's Disease using Administrative Claims Data

Master Thesis

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List of abbreviations

ATC	Anatomical Therapeutic Chemical (classification system for medications)
BIPS	Leibniz-Institute for Prevention Research and Epidemiology - BIPS GmbH
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
DDD	defined daily dose
DIMDI	German Institute of Medical Documentation and Information (*Deutsches Institut für Medizinische Dokumentation und Information)*
GePaRD	German Pharmacoepidemiological Research Database
HBI	Harvey Bradshaw Index
IBD	inflammatory bowel diseases
IBDQ	Inflammatory Bowel Diseases Questionnaire
IC	indeterminate colitis
ICD	International Classification of Disease
ICD-10-GM	German Modification of the International Classification of Disease in the 10th version
OPS	German Procedure Classification
SGB	code of social law (*Sozialgesetzbuch*)
SHI	statutory health insurance
UC	ulcerative colitis
WIdO	Scientific Institute of a main statutory health insurance (*Wissenschaftliches Institut der allgemeinen Ortskrankenkasse*)

Abstract

Background: Crohn's disease (CD) is a chronic relapsing inflammatory condition of the gastrointestinal tract. It is of public health relevance because of a high morbidity as well as psychosocial burden and the patients' need for a life-long intermittent medical treatment. New treatment options include biologicals (e.g. infliximab), which have a significant impact on CD management.

Aim: The aim of this study was to describe the types and proportions of medications dispensed to persons with CD as well as treatment patterns of CD patients receiving biologicals in order to reflect their drug treatment situation. Further, this study aimed to describe the rate of complications and the extent of CD-related health care utilization of CD patients receiving different treatment intensities.

Methods: Administrative claims data of two statutory health insurances with approximately 500.000 insurees were used to analyze the drugs dispensed to CD patients in annual cross-sectional designs (2004-2007). For 2007, the proportion of persons with complications and their health care utilization were assessed descriptively among CD patients receiving different treatment intensities. The description of treatment patterns of incident infliximab users was based on a longitudinal user cohort (2006-2007).

Results: In 2007, 855 CD patients were identified. Of these, 528 (61.8 %) had any dispensation of CD drugs in this year (total: 3.791 dispensations). Aminosalicylic acids accounted for 32.0 % of these dispensations, followed by immunosuppressants (28.4 %), systemic corticosteroids (20.5 %), budesonide (13.9 %), topical medication (3.1 %) and biologicals (2.1 %). Overall, 39.3 % of the 855 CD patients received aminosalicylic acids at least once in 2007, 26.7 % had at least one dispensation of systemic corticosteroids, 19.3 % of immunosuppressants, 15.4 % of budesonide, 4.6 % of topical medication and 1.9 % of biologicals. Among CD patients with immunosuppressants or biologicals as the most potent drugs in 2007, a higher proportion had fistulas and operations compared to patients with less potent drugs. The CD-related health care utilization (hospitalizations, duration of hospital stays, ambulatory physician contacts) was also higher. Seven CD patients started infliximab in 2006 or 2007. The majority (5) had received other CD drugs in the 365 days before onset of infliximab therapy. Infliximab was applied as monotherapy in one person, in combination with azathioprine in four patients. Mesalazine enemas as well as prednisolone were also concomitantly used. The time intervals between consecutive applications showed a wide range and no clear infliximab application scheme was found.

Conclusion: Aminosalicylic acids, systemic corticosteroids and immunosuppressants were important components in CD treatment, whereas biologicals were rarely dispensed. Patients with biologicals or immunosuppressants had more complications and showed a higher rate of health care utilization. Infliximab was mostly dispensed following the step-up approach and seemed to be applied on-demand.

1. Introduction

Crohn's disease (CD) is one of the major forms of inflammatory bowel diseases (IBD). It is characterized as a relapsing, transmural inflammatory condition, which can (discontinuously) affect any part of the intestine (1-3). On the contrary, ulcerative colitis (UC), another form of IBD, usually involves only the colonic mucosa (4). In approximately ten percent of IBD patients, the distinction between CD and UC based on standard clinical tests is not possible, which lead to the classification of a third form of IBD. According to the Montreal classification of CD this disease is named "inflammatory bowel disease, type unclassified", whereas the term "indeterminate colitis (IC)"[1] is used in the International Classification of Disease (ICD) (5-7).

During the last 50 to 60 years, the number of persons affected by IBD in general and by CD in particular increased significantly and CD accounts as the most common form of IBD in developed countries (8). In Europe, CD occurs more frequently in persons from northern regions and from countries with a higher gross domestic product (9).

This disease mainly affects persons in their working age and it is associated with a high psychosocial burden (10). For CD, a life-long intermittent medical treatment is required since there is no cure so far (11,12). The disease is of major public health relevance because of the increasing number of persons affected, the substantial individual burden as well as the need for medical services. From a health economic point of view, CD leads to considerable indirect costs due to work impairment and early retirement. Moreover, CD treatment such as physician consultations, medications, hospitalizations as well as operations cause significant direct costs to the health care system (9,13).

For CD, a wide range of medications is available to suppress the inflammation and to alleviate the disease's symptoms (13,14).

The introduction of biologicals namely anti-TNF-alpha-blockers into the treatment of CD had a significant impact on the management of the disease because these medications alter specific processes central to the inflammatory activity (12,15). Biologicals are medications, which are produced by living organisms using genetic or biological technology (16). Infliximab, a human-murine monoclonal antibody, was the first biological agent directed against TNF-alpha, which was introduced into CD therapy in 2001 and it is the main focus

[1] In this thesis, IC will be used for this form, which is in line with the ICD-coding system.
According to the Montreal classification, however, "the term "indeterminate colitis" should be reserved only for those cases where colectomy has been performed and pathologists are unable to make a definitive diagnosis of either Crohn's disease or ulcerative colitis after full examination." (5)

of this thesis (17). The second was adalimumab, a fully human, recombinant monoclonal antibody that was approved for CD in 2007 (18).

Most data about the actual medical care situation of patients with CD in Germany result from (cross-sectional) studies conducted in specialized gastroenterological practices. However, it is assumed that patients with mild disease rather seek medical care at their general practitioner and are not found in this setting (10).

On the contrary, statutory health insurance's (SHI) administrative claims data cover the whole outpatient provision of medical care by all panel doctors including specialists and general practitioners (19). Additionally, data about operations and procedures are available for the inpatient and for the outpatient care as well as data about medications. Moreover, SHI administrative claims data are available for the majority of the population (more than 85 percent of the German population) with limited risk of selection (20,21).

Therefore, administrative claims data are used in this thesis, which aims to describe the types and proportions of medications dispensed to persons with CD. Another aim is the description of the rate of complications and the extent of CD-related health care utilization among CD patients receiving different treatment intensities. Further, treatment patterns of CD patients receiving biologicals (infliximab) are analyzed in order to reflect their current drug treatment situation. Its results will provide important information in terms of the actual drug treatment situation of CD patients. This thesis may serve as a basis for further studies in health services research.

In the first part, the types and proportions of drugs applied in CD treatment are assessed in annual cross-sectional analyses. The same study design is used for the description of the rate of complications and the health care utilization among CD patients with different treatment intensities. The treatment patterns of CD patients receiving the biological agent infliximab are investigated in a longitudinal user cohort design.

2. Theoretical background

2.1 Crohn's disease

The etiology of CD is assumed to be multi-factorial including genetic and environmental aspects, but also behavioral risk factors like tobacco smoking (8,9,22).

Symptoms of CD are heterogeneous depending on its localization, extent and severity and can include, for example, chronic or recurring diarrhea, abdominal pain, weight loss and fever. The disease has a variable disease course and may be clinically active with various symptom-free periods in between (remission) (1,23).

CD is classified according to the Montreal classification, which considers the age at diagnosis, the location and the disease behavior (table 1).

Table 1: Montreal classification for CD

Age at diagnosis	A1 below 16 y
	A2 between 17 and 40 y
	A3 above 40 y
Location	L1 ileal
	L2 colonic
	L3 ileocolonic
	L4 isolated upper disease
Behaviour	B1 non-stricturing, non-penetrating
	B2 stricturing
	B3 penetrating
	P perianal disease modifier

Table adapted from Satsangi et al. 2006

CD is a chronic relapsing disease, which potentially affects any part of the intestine, but in most patients, the disease localization remains constant over time. Most commonly, it affects the ileum and/or the colon, whereas the upper part of the intestine is less often involved (23). Figure 1 illustrates parts of the gastrointestinal tract and the estimated percentage of patients with CD involvement in the marked area.

Figure 1: CD localization

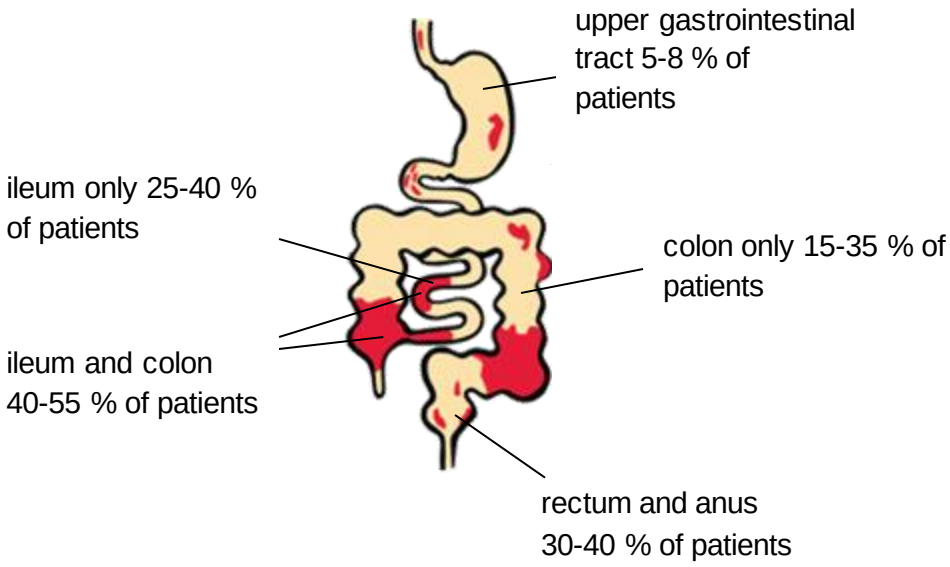


Figure adapted from Groß a. Dignass (n.y.), Reinshagen 2009

Complications, which are believed to result from persisting inflammation, comprise fistulas in more than one third of the patients and can include abscess formations as well as stenoses and small bowel obstruction (2,4,24-26).
CD may also be accompanied by extraintestinal manifestations, mainly skin lesions, eye and joint diseases. Further, CD is associated with primary sclerosing cholangitis, adenocarcinoma and lymphoma, although these are less frequent than in UC (27). The disease also causes significant morbidity in terms of psychosocial impairments including depressive symptoms (10).

There is no diagnostic procedure, which serves as "gold standard" for CD. Thus, it is diagnosed based on the patient's history and the clinical signs as well as a range of sonographical, endoscopic, radiological, histological and biochemical examinations. The correct identification of CD and the differentiation from other disorders with similar symptomatology is a complex process because CD shows very heterogeneous manifestations (13,28).

For clinical studies, validated indices assessing the disease activity are essential (23,29). Indices like the "Crohn's Disease Activity Index" (CDAI) or the "Harvey Bradshaw Index" (HBI) are frequently used for categorization, which commonly involves mild, moderate and severe disease (table 2) (13,15).

Table 2: Grading of CD disease activity

Mild	Moderate	Severe
Equivalent to a CDAI of 150-220 e.g. ambulatory, eating and drinking, < 10 % weight loss. No features of obstruction, fever, dehydration, abdominal mass, or tenderness.	Equivalent to a CDAI of 220-450 e.g. intermittent vomiting, or weight loss > 10 %. Treatment for mild disease ineffective, or tender mass. No overt obstruction.	Equivalent to a CDAI of > 450 e.g. Cachexia (BMI < 18 kg m^{-2}) or evidence of obstruction or abscess. Persistent symptoms despite intensive treatment.

Table taken from Van Assche et al. 2010

Remission, which means non-active or quiescent disease, is classified as a CDAI below 150 and achieving this is one of the aims in CD treatment (see below) (30).
A validated endoscopic index, in contrast to the non-endoscopic indices CDAI and HBI, is the Crohn's disease Endoscopic Index of Severity (CDEIS). More severe inflammatory parts of the intestine are rated with a higher number of points with 44 as the most severe inflammation (29).

Physician-based databases such as the General Practice Research Database in Great Britain contain the patients' digital medical files and provide essential information such as clinical parameters for the above-described indices (19). In contrast, neither the essential information for the calculation of the indices (e.g. symptoms) nor the indices itself are available in administrative claims data.

2.2 Epidemiology and costs of Crohn's disease

It is difficult to assess epidemiological data for CD because it is a relatively rare disease with a variety of symptoms and an often unspecific onset. Several studies in areas across Germany showed an incidence of 4 to 6 per 100.000 persons per year (9,31). The prevalence is assumed to be about 38 per 100.000 persons (28). However, considering this incidence and an average life expectancy, the prevalence is likely to be much higher and better estimated as 0.2 percent (9). This was also confirmed by a recent study assessing the CD prevalence based on administrative claims data. For 2009, the standardized CD prevalence by sex and age was 229 cases per 100.000 insurees. For women, the prevalence was higher (252/100.000 insurees) than for men (206/100.000 insurees) (32).

Most commonly, CD is first diagnosed in young adolescents, but it may affect people at all ages (9,13). According to a review (33), patients with CD had a slightly, but significantly higher mortality than the general population. The mortality was similar when deaths related to severe CD and its complications were excluded. CD complications included

postoperative complications, intraabdominal abscess, bowel perforation and gastrointestinal hemorrhage (33).

In Germany, a cross-sectional study in 24 specialized gastroenterological practices and two outpatient clinics showed that in total SHI spent 3767.3 € on average per CD patient and year. These costs ranged from 3089.9 € (remission) to 5348.2 € (active disease).
The costs for inpatient treatments were the second largest part in the direct costs (773.8 € per year). The main part, however, were medications which cost 2582.1 € on average per CD patient and year. The major proportion (57.8 %) of these costs was caused by biological TNF-alpha-blockers, followed by orally administered aminosalicylic acids (14.6 %), immunosuppressants (12.3 %) and orally administered budesonide (11.4 %) (34).
Apart from their clinical benefit, the rising application of biologicals is assumed to increase the direct medication costs of CD (10,13). However, infliximab therapy is associated with a significant reduction in hospitalizations, hospitalization days as well as inpatient procedures and surgeries, for example in patients with fistulizing CD (35). A Canadian study on health care use and costs for CD before and after infliximab therapy showed a significant reduction in resource use and costs, but an increase in total direct costs. This was caused by the costs for infliximab therapy. In countries with a higher cost structure for inpatient and outpatient treatment, however, infliximab may be cost-saving (36).

In an economic evaluation from the societal perspective, also the indirect costs of a disease are considered. CD may have a significant effect on the patients' ability to work and indirect costs arise for example from above average sick leave due to active disease, higher unemployment and the necessity for disability pension (37,38). It is estimated that these indirect costs of CD amount to approximately two billion Euro per year in Germany (13).

2.3 Treatment of Crohn's disease

Treatment of CD involves various drug treatment strategies as well as different surgical options.

The goals in CD therapy are, first of all, to induce and maintain steroid-free remission. This means reducing the inflammatory activity and symptoms of the disease, which is also associated with a substantially improved quality of life. Furthermore, the development of fistulas and stenoses is supposed to be prevented. Therapy of CD strives for reducing the need for surgery and hospitalizations and for sustaining the function of the intestine. Another important aim is to achieve mucosal healing and an acceptable balance between efficacy and safety of the therapy. Treatment of CD also aims to prevent disease-related mortality (13,15,39,40).

The therapeutic approach, which should be chosen in cooperation with the patient, depends on diverse aspects: the disease activity, the disease course, the affected regions of the intestine, extraintestinal manifestations, the patients' response to previous treatment as well as potential side effects of medications (13,41). There is also a group of patients with mild disease, for whom it is an option not to start active treatment. A systematic review of clinical trials showed that a considerable proportion of patients (18 %, 95 % CI 14-24 %) achieved remission under placebo (42). CD, however, is a chronic remitting disease with variable phases of activity, due to that these numbers must be reflected critically.

2.3.1 Drug treatment strategies

The current German guideline for CD drug treatment is based on the so-called "step-up-approach". In this approach, the therapy is intensified in case of more severe disease and in case of non-response to the treatment. The first step is the application of aminosalicylic acids followed by budesonide, systemic glucocorticoids, immunosuppressants and biologicals (43).

It is discussed whether biological anti-TNF-alpha antibodies may be able to alter the course and natural history of CD. The evidence suggests that patients benefit most from biological therapy early in the disease course, in the so-called "window of opportunity" (44). Therefore, some authors argue that biological anti-TNF-alpha antibodies may be applied earlier in CD treatment, before complications such as fibrostenosis or penetrating disease have developed ("top-down approach") (12,44-46). In this treatment approach, biologicals and immunosuppressants are used as first-line therapy and applied directly after diagnosis (figure 2) (43).

Figure 2: "step up-" and "top down-approach" in moderate to severe CD

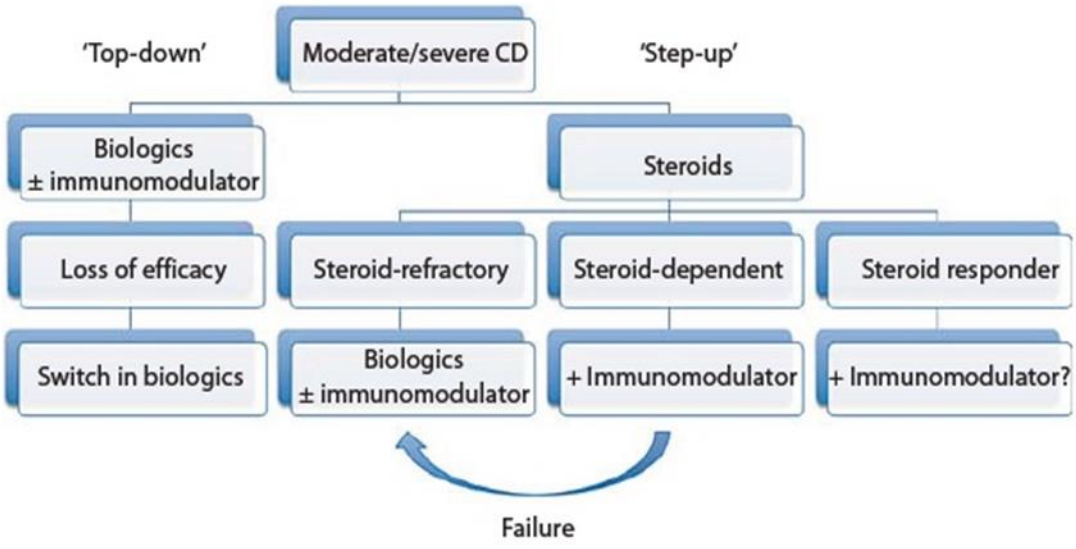


Figure taken from Nielsen et al. 2012

Another option within a general “step-up approach” is to identify patients with a high risk for a complicated disease course and to start an early treatment with anti-TNF-alpha blockers. There are data suggesting that high-risk patients may benefit from this initial treatment. The problem is, so far, to certainly identify these CD patients (45-47). The onset of disease before the age of 40, perianal lesions at time of diagnosis, the need for steroids in first relapse, several affected areas of the gastrointestinal tract and deep colon ulcers at time of diagnosis are discussed as risk factors for a potentially complicated disease course (48).

In a general “top-down-approach”, all patients are exposed to potent, but more toxic drugs and their related risks and costs (49). This would cause an overtreatment in 30 to 50 percent of the patients because they will not suffer from disabling disease within five years after diagnosis (50). In patients with mild disease, a “step-up-approach” could avoid these problems by starting baseline therapy and intensifying it in case of non-response (49). It is argued that a “step-up-approach” does not lead to disadvantages for CD patients with more severe disease if the treatment is rapidly intensified in case of non-response (51).
Therefore, a recently published review (46) concludes, that there is currently not enough evidence for a general application of a “top-down-approach” in clinical practice.

In CD treatment, it is distinguished between approaches to induce and approaches to maintain remission, although the transition from induction to maintenance treatment should be continuous for the patient (42). Another important aspect of CD treatment is the management of complications.

In general, CD therapy includes the following groups of medications, which are available in various formulations and can be used as monotherapy or in combination in different treatment approaches: aminosalicylic acids, systemic corticosteroids, budesonide, immunosuppressants and biological anti-TNF-alpha agents (13,52).

CD treatment is very complex and the treatment approaches as well as the application of individual drugs are controversial, partially because of inconsistent evidence about their efficacy and safety profile. For the reflection of the current drug treatment situation, information about the different drugs are essential, which are provided below.

2.3.1.1 Aminosalicylic acids

Active agents like mesalazine, sulfasalazine, olsalazine and balsalazide are classified as *aminosalicylic acid and similar agents* according to the WIdO ATC classification (53).

Aminosalicylic acids show a variety of anti-inflammatory and immunomodulatory effects, which are assumed to topically take action at the inflammation of the gastrointestinal mucosa rather than acting systemically (54-56). Therefore, aminosalicylic acids are a more

important component in the treatment of UC than in the treatment of CD, which extends beyond the mucosa.

Different formulations are available to deliver the drug to its point of action, the colonic mucosa. Oral formulations like tablets and micropellets can release the active drug pH-dependently as well as time-dependently (54,55). Additionally, aminosalicylic acids can be applied topically to the rectum using suppositories and enemas, which can be aerosols, liquids or gels (54).

Indication and dose

According to the German guideline, there is no general indication for the application of aminosalicylic acids in CD treatment. However, there is a high consensus among the experts to apply these drugs topically despite a lack of studies providing evidence concerning their efficacy (13).

Sulfasalazine is recommended at 3 to 6 g orally per day for the treatment of patients with a mild to moderate inflammation in the large intestine (Crohn's Colitis). Mesalazine may be used at 4 g orally per day in mild CD at ileocecal region (13).

Induction treatment

A pooled analysis of two studies including 263 patients with mildly to moderately active CD showed that sulfasalazine at 3 to 6 g per day was slightly more effective in inducing remission than placebo (RR 1.38; 95 % CI 1.02 to 1.87, P=0.04). This moderate effect was only reached in patients with Crohn's colitis.

In the comparison of sulfasalazine and systemic corticosteroids with 260 patients, sulfasalazine was found to be noticeably inferior for inducing remission (RR 0.66; 95 % CI 0.53 to 0.81, P<0.01) (55).

Mesalazine is usually applied orally three times a day with a total daily dose of 1.5 to 4 g (57). In 615 patients, controlled-released mesalazine at 4 g per day resulted in a statistically significant mean difference in CDAI of -17.5 (95 % CI -35 to -0.1, P=0.05). However, this mean reduction of CDAI is of questionable clinical relevance (55). In a trial with 182 patients, mesalazine was compared to budesonide and was less effective in inducing remission (RR 0.56; 95 % CI 0.40 to 0.78; P<0.01) (55).

Maintenance treatment

The efficacy of mesalazine for maintaining remission remains controversial because of inconsistent results from meta-analyses. For sulfasalazine and olsalazine, there is no evidence for their suitability for maintenance treatment. Hence, in general, aminosalicylic acids are not recommended for maintaining remission in CD (42).

Safety

The use of sulfasalazine is associated with side effects like allergic reactions, but also high rates of intolerance (up to 20 %) to the sulfapyridine part in the drug (54). Nausea, skin rash, headache and asthma are associated with sulfasalazine. Mesalazine has a different safety profile since it lacks the sulfapyridine component, but nausea, tiredness, abdominal pain and allergic reactions may also occur (57). The drug has extensive side effects and rarely, these also involve the kidneys (e.g. renal insufficiency) as well as the liver (e.g. hepatitis) (58).

Despite this modest benefit of aminosalicylic acids over placebo, mesalazine considerably contributed to the drug treatment costs before biologicals were introduced (59).

2.3.1.2 Systemic corticosteroids

Corticosteroids are a mainstay in the treatment of CD (60). The most commonly used systemic corticosteroids are prednisolone, prednisone and methylprednisolone (57).

Indication and dose

Systemic corticosteroids are recommended for Crohn's colitis as well as for moderate to severe inflammation in the ileocecal region, the small intestine or in the stomach. Explicitly, these drugs are not recommended for maintenance treatment due to ineffectiveness and an unfavorable safety profile (see below) (13,42).

Prednisone, prednisolone and methylprednisolone can be applied in a wide range of doses, which vary between less than 5 mg and more than 100 mg equivalent to prednisolone per day. Usually, in IBD these corticosteroids are administered orally in IBD (57). The initial dose of systemically acting corticosteroids is recommended at 1 mg per kg daily (61).

Betamethasone as well as hydrocortisone can be applied as topical therapy in patients with an affected large intestine. The dose of rectal foams is 5 mg bethametasone once per day or 1 mg hydrocortisone once to twice daily (57).

Induction treatment

The efficacy of systemic corticosteroids for inducing remission in CD has been demonstrated in several studies.

A randomized-controlled double-blind trial published in 1994 (62), for example, examined the efficacy and safety of prednisolone and budesonide. One group comprised of 88 patients with active ileal and ileocecal CD, who received 40 mg prednisolone per day for two weeks, then 30 mg daily and 25 mg for two weeks, respectively. Afterwards, the daily dose was reduced by 5 mg weekly for the remaining four weeks. At two weeks, 56 percent of the prednisolone group were in clinical remission defined as CDAI ≤ 150. After four

weeks, 67 percent of patients were in remission, 65 percent after eight weeks and 66 percent at ten weeks. The mean CDAI decreased from 279 to 136 during the ten-week treatment. In this study, budesonide was nearly as effective, but showed fewer side effects (see below) (62).

Maintenance treatment

The ability of systemic corticosteroids to maintain remission was assessed in another study with 109 CD patients, who were prospectively followed in Copenhagen from 1979 to 1987 (63). These patients received prednisolone as initial treatment at 1 mg per kg, which was reduced within weeks to 10 to 15 mg as maintenance therapy. This treatment was applied for 3.5 months. After 30 days of treatment, 48 percent of patients were in clinical remission and 32 percent reached partial remission defined as declining clinical symptoms, ≤ 2 bowel movements per day, no blood, pus or mucus in faeces, no abdominal pain, fever, weight loss, and extraintestinal manifestations. However, 20 percent did not show a response to treatment (steroid-resistant disease).

The remission rate was also assessed 30 days after steroid therapy was stopped. Nearly half of the persons in remission experienced a relapse. Among the patients with improved disease activity, 43 percent also had a relapse.

In summary, apart from the 20 percent of steroid-resistance, 44 percent had a prolonged response and 36 percent remained steroid-dependent (63). This means, that patients could not taper the drug below 10 mg equivalent to prednisolone per day within three months of starting steroids without having symptoms. Steroid-dependence also includes that patients experience a relapse within three months after they have withdrawn steroids (23,63,64).

Safety

Treatment with corticosteroids is associated with significant adverse events, which may occur even at low doses of 2.5 to 5 mg per day. These adverse events can involve any part of the body and may be irreversible (e.g. cataract or skin striae). Systemic corticosteroids may affect the musculoskeletal system (e.g. bone loss and osteoporosis), the metabolism (i.e. hypertension, diabetes), the central nervous system (i.e. emotional disturbances), the eyes (i.e. glaucoma) and the skin (i.e. acne). This treatment also increases the risk for infections and may lead to moon face, nausea, vomiting and heartburn as well as hair loss (60). These symptoms are summarized as Cushing's syndrome, which occurs when exceeding the Cushing threshold. This varies individually, but is generally at or above 7.5 mg equivalent to prednisolone per day (65).

Therefore, the duration of corticosteroid therapy is supposed to be kept as short as possible. It is necessary to withdraw the drug gradually, especially after a longer exposition to

corticosteroids, because a sudden end of treatment may lead to serious clinical consequences of adrenal insufficiency (60).

2.3.1.3 Budesonide

Budesonide is a glucocorticoid, which shows anti-inflammatory properties, but a limited systemic bioavailability because it is extensively metabolized in the liver (hepatic first-pass effect (14,66).

Indication and dose

According to the German guideline, budesonide is recommended for the treatment of mild to moderate inflammatory CD in the ileocecal region (13). The drug is administered orally and designed to have an effect in the terminal ileum and the ascending colon (14). Most commonly, it is applied three times a day at a dose of 3 mg (57,61). Another form of application are enemas, which contain 1 mg budesonide and are applied once daily (57).

Induction treatment

Budesonide was shown to be significantly more effective in inducing remission in CD patients than placebo in two randomized controlled trials included in a review (14). At the time points two, four and eight weeks, the pooled relative risk for remission (CDAI ≤ 150) was 2.97 (95 % CI, 1.67 to 5.29), 1.67 (95 % CI, 1.12 to 2.47) and 1.96 (95 % CI, 1.19 to 3.23) in favor of budesonide, respectively (14).

However, the comparison of budesonide with conventional corticosteroids based on eight randomized controlled trials with 750 patients demonstrated that budesonide was inferior in inducing remission at eight weeks (relative risk of 0.85, CI 95 % 0.75 to 0.97).

In patients with severe CD (CDAI ≥ 300) the pooled relative risk to induce remission in two randomized controlled trials, including 145 participants, was 0.52 (95 % CI, 0.28 to 0.95) in favor for conventional steroids, underlining the inferiority of budesonide to conventional corticosteroids (14).

Maintenance treatment

A review (66) on the ability of oral budesonide to maintain remission in CD (CDAI<150) showed a pooled relative risk of remission with 6 mg budesonide per day compared to placebo of 1.25 (95 % CI 1.00 to 1.58; P=0.05) at three months. At six months, the relative risk was 1.15 (95 % CI 0.95 to 1.39; P=0.14) and 1.13 (95 % CI 0.94 to 1.35; P=0.19) at twelve months. Similarly, budesonide at 3 mg per day was more effective in maintaining remission than placebo when remission state was assessed at three months (RR 1.31; 95 % CI 1.03 to 1.67; P=0.03). At six months, however, budesonide was not more effective

than placebo (RR 1.10; 95 % CI 0.81 to 1.50; P= 0.53). The same was observed at twelve months (RR 1.04; 95 % CI 0.84 to 1.30; P=0.70) (66).

Safety

There were no differences in adverse events between CD patients treated with budesonide and patients receiving placebo in two trials (RR 0.99, 95 % CI, 0.78 to 1.25, P=0.92). However, six trials with 709 patients in total showed significantly fewer corticosteroid-related adverse events in patients treated with budesonide than in patients using conventional corticosteroids (RR 0.64, 95 % CI 0.54 to 0.76) (14).

In general, despite their ability to induce remission in CD, it is assumed that systemic corticosteroids and budesonide are not able to improve mucosal lesions or to prevent recurrence of inflammation. Further, these medications are ineffective for maintaining remission (47,60). However, a long-term maintenance therapy is often needed, which can involve immunosuppressants, but also biologicals (see below) as steroid-sparing agents (47,67).

2.3.1.4 Immunosuppressants

Immunosuppressants are characterized as medications, which suppress one or more mechanisms of the immunosystem either completely, or partly (68).

Azathioprine/6-mercaptopurine

Most commonly, immunosuppressive therapy in patients with CD involves thiopurines like azathioprine, which is the prodrug of 6-mercaptopurine. Both drugs are purine analogues (61). 6-mercaptopurine, however, is generally unlicensed for the treatment of CD (42).

The drugs target nucleic acid synthesis and hinder the rapid cell proliferation that exacerbates most inflammatory processes (69). Alternatively, methotrexate, a classical immunosuppressant, can be used (see below) (61).

Indication and dose

In the German guideline, immunosuppressants (azathioprine/6-mercaptopurine and methotrexate in case of intolerance) are recommended for the treatment of severe inflammation in the ileocecal region, if an adequate treatment result could not be achieved with corticosteroids. For moderate to severe inflammation in the small intestine, an early application of immunosuppressants is indicated (13).
In general, immunosuppressants are effective steroid-sparing agents for maintaining remission (42). In an acute relapse during a rather stable remission under

immunosuppressants, steroids can be additionally used in short-term (61). The duration of maintenance treatment with immunosuppressants is supposed to be at least four years of remission without concomitant steroid use (13).
The recommended dose of azathioprine is 2.0 to 2.5 mg per kg orally and 6-mercaptopurine orally at 1.0 to 1.5 mg per kg. Lower doses are considered insufficient (61).

Induction treatment

The efficacy of azathioprine and 6-mercaptopurine for induction of remission in active CD was examined in a recently published review (70). This review included thirteen randomized placebo-controlled or active comparator trials with 1211 patients in total, published from 1971 to 2010. In five studies with 380 patients, there was no benefit of azathioprine or 6-mercaptopurine when compared to placebo for achieving clinical remission defined as CDAI < 150 or HBI ≤ 3 points (RR 1.23, 95 % CI 0.97 to 1.55).

Four additional studies used different endpoints like subjective improvement or non-validated outcomes. These studies were included in a pooled analysis which also showed no difference between azathioprine or 6-mercaptopurine and placebo, when the endpoint was clinical remission or improvement (434 patients, RR 1.26, 95 % CI 0.98 to 1.62). However, the underlying data for these conclusions were considered moderate to sparse (70).

It is assumed that treatment with immunosuppressants requires some time before the goal of remission can be achieved. When remission rates were assessed at 17 weeks or later, these were significantly higher in the azathioprine or 6-mercaptopurine group than in patients receiving placebo (RR 1.59, 95 % CI 1.05 to 2.41).

The right time for applying immunosuppressants in CD treatment is a topic of discussion and these medications play an important role in the “top-down-approach”. From 2001 to 2004, a randomized trial at 18 centers in Germany, Belgium and the Netherlands demonstrated the benefit of an early application of immunosuppressants. This trial showed that patients with newly diagnosed CD (less than four months) without previous exposure to corticosteroids, immunosuppressants or biologicals reached remission more quickly under a combined immunosuppression therapy (intermittently infliximab and azathioprine or methotrexate) than patients treated conventionally with corticosteroids (71).

Maintenance treatment

The ability of 6-mercaptopurine and azathioprine to maintain remission in patients with quiescent CD was also investigated in a review (69). This included eight randomized, controlled and double-blind trials with 208 patients receiving azathioprine, 47 with 6-mercaptopurine and 266 patients on placebo. For azathioprine, the overall remission rate

was 71 percent (95 % CI 64 % to 77 %), for 6-mercaptopurine, it was 51 percent (95 % CI 36 % to 66 %) and for placebo, 55 percent (95 % CI 49 % to 61 %) (69).

The steroid-sparing effect of azathioprine and 6-mercaptopurine in maintaining remission was examined in two very small studies published in 1971 and 1975. In these studies, 87 percent of patients receiving azathioprine as maintenance treatment could reduce or stop steroids (95 % CI 60 % to 98 %), but only 53 percent of patients from the placebo group (95 % CI 27 % to 79 %) (69). However, these confidence intervals are largely overlapping and show a wide range.

Safety

The profile of side effects is similar between azathioprine and 6-mercaptopurine (72,73).
Azathioprine is associated with adverse events that occur in approximately 15 percent of all patients receiving this drug. Side effects may involve disturbances in the immunosystem, the blood, the lymphatic system as well as in the gastrointestinal tract. Further, benign and malign tumors are of concern (72). Nausea, vomiting and abdominal pain were the most common adverse events in the azathioprine group (161 patients) of a randomized controlled trial. Nine cases of serious infections, one sepsis and two colon carcinoma also occurred (74).
For 6-mercaptopurine, a study of 396 IBD patients and approximately 1800 patient-years of follow-up published in 1989 reported infections in 7.4 percent of patients and pancreatitis in 3.3 percent. During treatment with 6-mercaptopurine neoplasm occurred in 3.1 percent, bone marrow suppression and allergy in 2.0 percent and drug-induced hepatitis in 0.3 percent of the patients. In a different study with 78 patients, published in 1991, an incidence of adverse events of ten percent was reported, which were considered as sufficiently severe to withdraw the medication (70).

The safety profile of azathioprine and 6-mercaptopurine was compared to the one of methotrexate: Patients using methotrexate were significantly more likely to experience an adverse event than patients taking azathioprine or 6-mercaptopurine as a pooled analysis of two studies showed (85 patients, RR 0.42, 95 % CI 0.21 to 0.82) (70).

Methotrexate

Methotrexate is a dihydrofolate reductase inhibitor that accounts as alternative treatment option to azathioprine and 6-mercaptopurine (67,75).

Indication and dose

According to the German guidelines, methotrexate is recommended if there is intolerance to azathioprine/6-mercaptopurine (see above). Methotrexate is administered parenterally,

which can be intramuscular, intravenous or subcutaneous (57). For induction of remission, a dose of 25 mg per week for a duration of approximately 16 weeks is recommended, whereas for maintaining remission, methotrexate is usually applied at 15 mg per week (57,61).

Induction treatment

A review (75) that comprised seven randomized controlled trials assessed the efficacy for induction therapy in CD. However, only one of these trials was sufficiently large enough to show the ability of intramuscularly administered methotrexate (25 mg per week) to induce remission without concomitant steroid use. This study was a randomized double-blind placebo-controlled trial with 141 chronically steroid-dependent CD patients published in 1995. After 16 weeks, 39.4 percent of patients on methotrexate were in remission defined as discontinuation of prednisone and CDAI score of < 150, but only 19.1 percent of patients receiving placebo (P=0.025). Overall, the mean CDAI score was significantly lower in the methotrexate group (P=0.002) after 16 weeks. Further, this group also needed less prednisone than the placebo-treated group (P=0.026). For induction of remission, there was no benefit for lower doses of methotrexate (less than 25 mg per week) and oral administration compared to placebo or azathioprine/6-mercaptopurine in two studies. These trials only included small numbers of patients and could not show a difference between treatment groups, which may be due to insufficient statistical power (75).

Maintenance treatment

The efficacy of methotrexate as maintenance therapy was also investigated in a review (67), which included three randomized controlled trials. The pooled analysis of two trials showed that after 36 to 40 weeks, methotrexate was significantly more effective in maintaining remission than placebo (OR 3.11, 95 % CI 1.31 to 7.41; P=0.01).

Safety

Methotrexate is associated with adverse events related to the gastrointestinal tract including nausea and anorexia, stomatitis and less often, diarrhea. Serious adverse events include bone marrow suppression and also, but rarely, hypersensitivity pneumonitis and opportunistic infections. Further, the occurrence of hepatotoxicity as well as liver fibrosis and cirrhosis is of major concern (76).

In a randomized double-blind placebo-controlled trial with 141 steroid-dependent CD patients, adverse events occurred at similar rates in the methotrexate and the placebo group (45 % vs. 42 %). The number of study withdrawal due to adverse events like nausea, vomiting and asymptomatic elevation of liver enzymes, however, was significantly higher in

patients on methotrexate (16 patients, 17 percent) than in patients receiving placebo (1 patient, 2 percent) (P=0.012). In this study, no serious adverse events occurred (75).
In most cases, minor side effects of methotrexate are successfully treated with concomitant folic acids (67,75)

In contrast to azathioprine, the benefit of combination therapy of methotrexate and infliximab or other biologicals still remains unclear (75).

2.3.1.5 Biologicals

In general, three different anti-TNF-alpha blockers are available for CD treatment, which are certolizumab pegol, infliximab and adalimumab. However, only the latter two have been approved in Germany. According to the German guidelines, these drugs currently serve as second-line medications in patients, who failed to respond to conventional nonbiologic therapy (see above) (13). Failure in drug therapy is characterized by primary non-response or loss of response over time, but also includes intolerance to drugs (77).

Infliximab

Infliximab is an intravenously administered, human-murine, monoclonal antibody, which is directed against TNF-alpha and neutralizes its functions (17).

Indication and dose

In addition to the above-mentioned indications, infliximab is also recommended for patients with active, fistulizing disease, if the conventional therapeutic approach including antibiotics, immunosuppressants and drainage did not lead to acceptable outcomes (17).
It is recommended to administer infliximab at 5 mg per kg at weeks 0, 2 and 6 as induction therapy (12,78). For maintenance therapy, infliximab should be given at 5 mg per kg every eight weeks. This strategy with regular infliximab is more effective in maintaining remission as well as response compared to an “on demand” application for many clinical endpoints (12,42,78,79). This was demonstrated regarding fistula closure, for example, in a multicenter, phase III, randomized, double-blind, placebo-controlled clinical trial (ACCENT II - A Crohn’s Disease Clinical Trial Evaluating Infliximab in a New Long-Term Treatment Regimen in Patients with Fistulizing Crohn’s Disease) (80).

Induction treatment

A twelve-week multicenter, double-blind, placebo controlled, randomized trial from 1997 investigated the ability of a single infusion of infliximab to induce remission in patients with moderate to severe CD who had failed standard therapy before (81). In this study, 108 patients were randomly assigned to three treatment groups (infliximab at 5, 10 or 20 mg per kg) or to a placebo group. At four weeks, significantly more patients treated with

infliximab were in remission (33 %) than patients on placebo (4 %, P=0.005). In this case, remission was defined as a reduction in CDAI of at least 70 points. Patients treated with infliximab also showed a higher mean decrease in CDAI (110 points at four weeks) than the patients in the placebo group (13 points) (81).

Maintenance treatment

In the pooled analysis of three randomized controlled trials, included in a review (82), infliximab was also superior to placebo for maintaining remission in CD patients (RR 2.50; 95 % CI 1.64 to 3.80, P < 0.0001). Further, infliximab was more effective than placebo in corticosteroid-free remission (RR 3.13; 95 % CI 1.25 to 7.81; P=0.01) as well as in complete healing of perianal and enterocutaneous fistulas (RR 1.87; 95 % CI 1.15 to 3.04; P=0.01) (82).

Infliximab also showed to be more effective in obtaining mucosal healing (83,84) and improvement in several dimensions of quality of life (79,85) when compared to placebo. Additionally, this drug is associated with a reduction in hospitalization rates, in mean duration of hospital stays as well as in need for surgical procedures (35).

Safety

While infliximab has been shown to be effective in several aspects of CD treatment, it is also associated with considerable side effects. These include infections (e.g. reactivation of latent tuberculosis), antibody formations to infliximab and antinuclear antibodies, malignancies (e.g. hepatosplenic T-cell lymphoma), demyelization (e.g. Guillain-Barré syndrome), cardiac abnormalities and skin eruptions (psoriasiform dermatitis). For patients receiving concomitant immunosuppressants like thiopurines, the risk for developing malignancies and infections is increased compared to patients on monotherapy (86).

The Crohn's Therapy, Resource, Evaluation and Assessment Tool (TREAT) registry, a prospective and observational registry, was initiated in 1999 in North America to assess the long-term clinical outcomes and safety of different treatment strategies. This registry included 3,764 patients who ever had received treatment with infliximab and were followed for at least five years (in total 17,712 patient years) (87).

At time of publication, the registry covered 53,003 infliximab infusions. In 1,571 infusions (3.0 % of all observed infusions) reactions were reported, which were most commonly headache (0.5 %) and arthritis (0.4 %). However, treatment with infliximab was also associated with an increased risk for serious mycobacterial and fungal infections (HR 1.43; 95 % CI 1.11 to 1.84, P=0.006). Whereas the mortality was similar in comparison to patients who had never received infliximab (0.58 vs. 0.59 per 100 patient-years follow-up) (87).

Treatment strategies

Infliximab was the first anti-TNF-alpha blocker approved for the treatment of CD in Germany in 2001. It is also the biological agent with the most clinical data and clinical experience in CD (47). Nonetheless, optimal treatment strategies are still discussed. In particular, the right time for starting, how to manage loss of response and whether to combine infliximab with an immunosuppressant remain controversial aspects (88).

Important arguments for the decision to apply anti-TNF-alpha blockers in combination with immunosuppressants include immunogenicity, efficacy as well as safety. Combined therapy is associated with decreased antibody formations against infliximab and decreased infusion reactions (12).

The SONIC trial (Study on Biologic and Immunomodulator Naive Patients in Crohn's disease) assessed the efficacy of infliximab, azathioprine or a combination therapy to induce and maintain remission (74). The randomized double-blind trial included 508 patients with a CDAI of 220 to 450. In this trial, significantly higher remission rates and higher rates of mucosal healing were achieved with combination therapy than with azathioprine or infliximab monotherapy. The safety profile was comparable between the three groups except that patients receiving combination therapy experienced infusion reactions significantly less frequently than patients in the infliximab group (74). Despite these findings it is still debated whether combination therapy enhances the efficacy of anti-TNF-alpha blockers because subgroup analyses showed conflicting results (12).

Two studies, which examined the efficacy of methotrexate in combination with infliximab compared to infliximab monotherapy for induction of remission, did not detect differences in remission rates (75). Furthermore, combination therapy is associated with an increased risk of rare, but serious toxic effects (74). Therefore, for children, young adults and the elderly in particular, these risks need to be taken into consideration (47).

The combination of infliximab with other immunosuppressants like cyclosporine or tacrolimus, but also other TNF-alpha-inhibitors is generally not recommended (78).

In an acute relapse during a rather stable remission under infliximab, steroids can be additionally used in short-term (61).

Loss of response and end of treatment

In case of diminished or suboptimal response to infliximab, it is recommended to either shorten the time interval between infusions, but not below four weeks, or to increase the dosage to 10 mg per kg (47,78). If this strategy does not lead to acceptable outcomes,

it may be beneficial for the patient to start treatment with a different anti-TNF-alpha-blocker (47).

As mentioned before, it is debated when or even whether infliximab therapy should be withdrawn in patients who reached stable remission. There are several reasons for striving to end treatment with infliximab such as costs and long-term safety aspects, but also other circumstances like pregnancies (88).

Adalimumab

Adalimumab is a subcutaneously administered fully human, recombinant monoclonal antibody, which binds to human TNF and neutralizes its biological functions. In Germany, this anti-TNF-alpha antibody was approved for treatment of severe and active CD in the third quarter of 2007 (18).

Indication and dose

Adalimumab is recommended for patients who did not show an adequate response or have intolerance to therapy with corticosteroids and/or immunosuppressants. For induction therapy, adalimumab should be combined with corticosteroids, but can also be given as monotherapy in case of intolerance to corticosteroids (18). The recommended induction dose of adalimumab at week 0 is 160 mg and 80 mg after two weeks. For maintenance therapy, 40 mg adalimumab are (self-) administered subcutaneously every other week (12).

Induction treatment

CLASSIC I (Clinical assessment of Adalimumab Safety and efficacy Studied as Induction therapy in Crohn's disease) was a randomized, double-blind, placebo-controlled dose-ranging trial including 299 patients with moderate to severe CD without previous exposure to an anti-TNF blocker (89). At four weeks, 36 percent of the patients with the highest adalimumab dose (160 mg/80 mg) were in remission compared to 24 percent receiving 80 mg/40 mg and 12 percent in the placebo group (P=0.004 for the difference among the three groups) (89).

Maintenance treatment

In CLASSIC II, a multi-center, randomized, double-blind, placebo-controlled trial, 55 infliximab-naive patients who had reached remission in CLASSIC I, were followed for 56 weeks (90). The patients were randomly assigned to receive either adalimumab 40 mg every other week, adalimumab 40 mg weekly or placebo. At week 56, 15 of 19 (79 %) patients in the adalimumab 40 mg every other week group remained in remission compared to 15 out of 18 patients (83 %) in the adalimumab 40 mg weekly group and 8 out of 18 patients (44 %) in the placebo group ($P < 0.005$ for each adalimumab group vs. placebo).

The remission rates of patients using concomitant immunosuppressants like azathioprine, 6-mercaptopurine or methotrexate were similar to patients receiving adalimumab monotherapy. An IBDQ score of ≥ 170 points, which corresponds to clinical remission, was maintained in the adalimumab treated groups, whereas there was a rapid decline in IBDQ scores in patients in the placebo group (90).

Apart from higher remission rates, adalimumab had a steroid-sparing effect and higher rates of fistula closure in a similar designed, but larger study (CHARM -Crohn's Trial of the Fully Human Antibody Adalimumab for Remission Maintenance) (91). Adalimumab was also associated with mucosal healing and maintenance of remission in EXTEND (Extend the Safety and Efficacy of Adalimumab through Endoscopic Healing) (92). In a meta-analysis, adalimumab was found to have a positive impact on the ability to work of patients with moderate to severe CD, which was reflected in a reduction of presenteesim, absenteeism and total work productivity impairment (38).

Safety

Besides its efficacy regarding different CD treatment aspects, adalimumab is also associated with various adverse events that are similar to the side effects related to infliximab therapy (see above).

The most common side effects associated with adalimumab reported in the above described studies were injection-site reactions, infections, headache and nausea. In CLASSIC I and II as well as in EXTEND, no opportunistic infections, lymphomas or deaths occurred (89,90,92).

In CHARM, 59.4 percent of all study participants experienced an adverse event during induction treatment with adalimumab that lead to study withdrawal in 6.3 percent. The most common adverse events in this study phase were also infections (15.2 %), headache (5.9 %) and nausea (5.3 %). Serious infections occured in 1.2 percent of the study participants during induction therapy with adalimumab. Further, one case of multiple sclerosis was reported.

Loss of response

If the response to adalimumab is suboptimal or diminishing, it can be applied weekly. It may be beneficial for patients to start therapy on a different anti-TNF-alpha agent, if weekly adalimumab does not lead to improvement. However, if a patient has lost response to an anti-TNF-alpha antibody, the chance for a response to a second one is also reduced (47). Therefore, also surgical options should be considered and discussed with the patient (42).

According to the London Position Statement of the World Congress of Gastroenterology on biological therapy for IBD, there are also contraindications for the use of biologicals.

These medications are not suitable for patients who have been vaccinated with live vaccines three months before the onset of biological therapy. Furthermore, patients suffering from infections are not eligible for biological therapy until the infection is treated and abscesses are drained. Moreover, before starting therapy with biologicals patients need to be examined regarding latent infections like tuberculosis, hepatitis B or immunodeficiency virus (47).

A problem with biologicals is non-response, which occurs in up to one third of all patients when using the first biologic agent ('primary non-response'), but also in patients, who showed a response and lose it over time ('secondary non-response') (40).
An option for preventing the loss of response and for increasing the therapeutic efficacy may be concomitant immunosuppression as applied in the SONIC trial (93). However, it is not clear whether the observed benefit from combined immunosuppression results from the suppression of immunogenicity, the additive effect of both drugs, the effect of azathioprine on the clearance of infliximab or from different numbers of persons with inflammation at baseline in the different treatment groups (74,93).

A study assessed the cost-effectiveness of biologicals from the perspective of the National Health Service in the United Kingdom using Markov models. The authors conclude that these medications are a cost-effective use of healthcare resources for patients with moderate to severe luminal CD and clinical response when used continuously (in contrast to on-demand application) for a limited time period (up to four years). This implies that the greatest clinical and cost advantages are achieved during the first few years of treatment considering the problem of loss of response over time. CD treatment with infliximab or adalimumab lasting for a patient's lifetime is, according to the model, not cost-effective and data on long-term use and safety are insufficient (94).

2.3.2 Surgical options

Surgery also accounts as therapeutic option for CD, which is indicated in case of failure in medical therapy, but also for arising complications (77,95). Failure in drug treatment may have several reasons including noncompliance or lack of treatment response (see above) (95). Complications arising in CD can be chronic (e.g. neoplasia) or acute such as bowel obstruction, perforation, abscesses, hemorrhage or toxic mega colon (95-97).

The surgical procedures most commonly applied in CD therapy encompass surgical resection, strictureplasty as well as drainage of abscesses (96). Another option for stenoses, which can be reached during endoscopy, is dilatation (23).

A resection operation in the small intestine and colon is indicated, if there are scarred stenoses in the small intestine or fistulas, abscesses and perforations, but is also possible if the inflammation did not respond to drug treatment (23).

In dependence of the disease's distribution and the patients' general condition, subtotal colectomy with ileorectal anastomosis, segmental colectomy, or total proctocolectomy can be applied (95). In contrast to UC, where a total proctocolectomy may cure the disease apart from extraintestinal manifestations, a resection of the affected parts is not curative for CD. For this disease, surgical resection may obtain control of symptoms and disease regression, but these goals may be reached only temporally (98).

In general, limited resection accounts as the preferred method. In this procedure, the most affected parts are removed and less affected areas left behind in order to avoid the occurrence of a short-bowel syndrome (see below) (95).

Strictureplasty, on the contrary, is the most common bowel-sparing procedure for strictures and stenoses. This procedure also avoids the occurrence of a short-bowel syndrome. It may be suitable for CD patients with multiple stenoses over a large length of the bowel, but also for patients who had undergone significant small bowel resection previously (97,98).
The decision for strictureplasty versus resection especially needs to consider the length of the remaining small bowel, because malabsorption, malnutrition and dependence on parenteral nutrition can result from small bowels shorter than 100 to 200 cm (short-bowel syndrome) (95). Laparoscopy, a minimally invasive technique, may be beneficial for CD patients, if resection is necessary (95).

During the disease course, 70 to 90 percent of the patients require an operation of the CD affected intestine and various surgical procedures may be necessary in the lifetime of a CD patient (23,95). Despite the potential of biologicals to avoid operations (see above), approximately one fifth of CD and UC patients using these medications still needs intestinal resection (77).

3. Aim and research questions

The aim of this study was to describe the health care situation of patients with CD with a special focus on the drug treatment.

It describes the types and proportions of medications dispensed to persons with CD as well as treatment patterns of CD patients receiving biologicals (infliximab) in order to reflect their drug treatment situation. Further, this study aimed to describe the rate of complications and the extent of CD-related health care utilization by CD patients receiving different treatment intensities.

The following research questions were examined:

1) Description of CD patients' treatment
    - What is the proportion of different types of medications including biologicals in the drug treatment of patients with CD?
    - What is the proportion of persons with complications such as fistulae and operations among CD patients with different treatment intensities?
    - How extensively do CD patients with different treatment intensities use CD-related health services defined as ambulatory physician contacts and hospitalizations?

2) Description of treatment patterns of infliximab users
    - How many CD patients begin therapy with infliximab per year?
    - Where does infliximab stand in the treatment cascade?
    - What is the time interval between consecutive applications of infliximab?
    - What drugs are used in combination with infliximab?

4. Methods

4.1 Data source

Routine data like SHIs' administrative claims data may serve as data source for studies in health services research (20).

The German law regulates the utilization of social data. For instance, in § 284 of the Code of Social Law (SGB) V it is described for which purposes SHIs are allowed to collect and store data of their insurees. The § 28 of the German Data Protection Act regulates the utilization of these data for research purposes. According to § 287 SGB V, SHIs and Associations of Statutory Health Insurance Physicians are allowed to analyze administrative claims data themselves for research and planning purposes. Further, according SGB X § 75, social data can be transferred to research institutes, if this is granted by the respective authority.

For this study, the German Pharmacoepidemiological Research Database (GePaRD) located at the Leibniz-Institute for Epidemiology and Prevention Research – BIPS GmbH (BIPS) served as underlying data source. For data protection reasons, the SHIs' data are first transferred to a trusted third party center and are pseudonymized before utilization for research purposes (21). A detailed data protection concept has been developed and is the basis for all research projects at BIPS involving data from GePaRD.

GePaRD contains data of four SHIs with more than 15 million insurees of all ages, which represent approximately 18 percent of the German population from all German regions (99-101). The data are available from the beginning of 2004, because since then, data on outpatient diagnoses and treatments of individual insurees are reported to SHIs in Germany (100).

Regarding the sex and age distribution as well as overall and disease-specific admission rates, GePaRD is in line with information about the general population in Germany which were published in official statistics (21).

This study is a subproject of the study "Versorgungsgeschehen und Sicherheit von Biologika in Deutschland". For this project, however, only the data of insurees from two out of four SHIs could be included because the approvals of the other two SHI had not been granted. The two included SHI are rather small and by the time of analysis, the data from 2004 to 2007 had been transferred to BIPS and was available in GePaRD.

This database contains individual-level data on sociodemographics, hospital stays, outpatient physician visits as well as ambulatory drug dispensations (figure 3) (99).

Figure 3: Structure and content of GePaRD

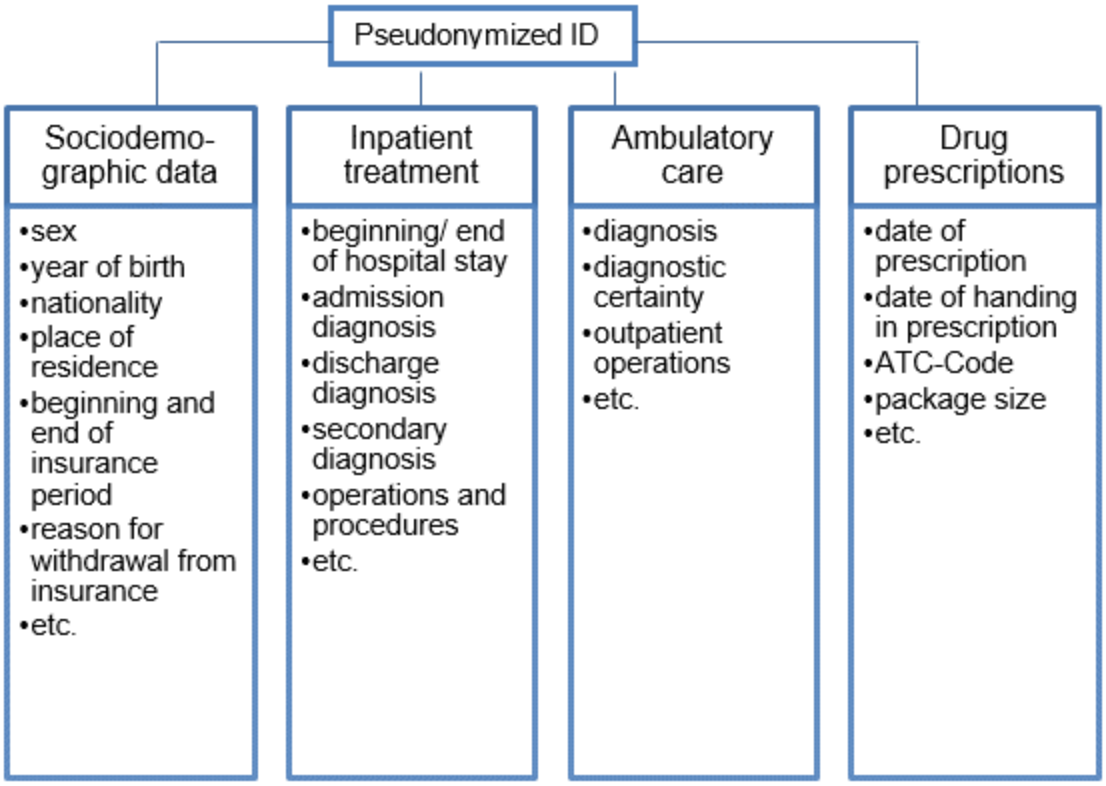


Figure adapted from Pigeot a. Ahrens 2008

4.1.1 Sociodemographic data

This part includes data, which are not related to medical care, but to the insuree's sociodemographic and insurance characteristics (102).

In GePaRD, sociodemographic data encompass the pseudonymized subject identification number (ID) (21).
Variables like the year of birth, the sex, the district of residence and the nationality (German vs. non-German) are available. There is also information on education, the occupational code and the employment status available. Sociodemographic data contain the date of entry to and exit from the SHI for different insurance periods. It is also recorded why a person is lost to follow up (e.g. changing SHI or death). Further, the insurance status (main insurance holder/relative) as well as the contribution group (obligatory, voluntary) are available (21,101).

In one of the two included SHIs, passive insurance periods are possible. This means that insurees can pause their health insurance, e.g. when spending time in foreign countries where a different health insurance coverage is required. During this time interval, the insurees are not able to claim benefits from their SHI.

4.1.2 Data from inpatient care

The type and scope of data from the inpatient sector which are transferred from hospitals to the SHIs is regulated in § 301 SGB V.

In GePaRD, data from the inpatient care include the dates of admission to and discharge from hospital for each treatment case. There are data available on admission and discharge diagnoses as well as secondary inpatient diagnoses, which are encoded using ICD-10-GM codes (21,99,101). GePaRD also contains information about a range of diagnostic and therapeutic procedures within hospitals with their respective date (99). Inpatient operations and procedures are reported using the Operations and Procedures Coding System (OPS) (100). OPS is a classification system, which is updated and published by the German Institute of Medical Documentation and Information (DIMDI) (102,103).

Medications, which are administered during a hospital stay, are generally not registered, except drugs falling into the OPS coding system, which has been the case for infliximab since 2005 (102). In 2004, however, there were no detailed OPS codes available for the application of specific medications. Thus, inpatient use of infliximab can only be analyzed from 2005 on.

4.1.3 Data from outpatient care

Data from the outpatient setting are generated by the claims of physicians who participate in the provision of medical services for the SHIs.

In § 295 of SGB V it is described what kinds of data are transferred electronically from physicians in private practice to the Associations of Statutory Health Insurance Physicians. The claims data is then forwarded in batches to the SHIs for reimbursement (21). Since the Healthcare Modernization Act has been implemented in 2004, the Associations of Statutory Insurance Physicians are required to transfer personal data of the patients to the respective SHI, which then can make the data available for research institutes (102).

In GePaRD, data from outpatient care contain outpatient treatments, procedures and diagnoses. Diagnoses are encoded with ICD-10-GM that is updated and published by DIMDI (99,104). ICD-codes usually comprise four digits, but medical specialists are required to provide a five-digit code in their field of work (102).
In general, specificity as well as sensitivity of ICD-codes from the outpatient sector are problematic, because in contrast to the inpatient sector the diagnoses are not crucial for reimbursement. In example, it is possible to classify a disease as "not specified" putting a "9" at the end of the code, which is used more frequently than the specific codes (102).
Diagnoses from the ambulatory care must include the physicians' diagnostic certainty since the second quarter of 2004. Four different kinds of diagnostic confidence can be added, which is "G" for an assured diagnoses and "A", if a disease can be excluded in a patient. If a patient has had a disease, but does not have symptoms anymore, "Z" meaning "past history of disease" needs to be added. The last category is suspected diseases and must be marked with "V" (102).
In one of the data contributing SHIs, the coding of diagnostic confidence of ambulatory CD diagnoses was analyzed in a previous feasibility study. In 2004, there were 170 CD diagnoses with missing diagnostic confidence and ten in 2005 until these were reduced to zero in 2006.

In the outpatient setting, the date of the diagnosis is not provided, but the quarter of the year. This is due to the reimbursement of physicians in quarters (99).

Outpatient procedures are recorded with their exact date and can be identified through the claim codes for outpatient services and procedures (EBM) (100). This number has been established by the Association of Statutory Health Insurance Physicians. Until the second quarter of 2005, these numbers had four digits and then five digits (102).

Operations are also possible in the ambulatory sector. These can be identified through the OPS-codes (103).

4.1.4 Drug dispensations

The reimbursement of prescribed drugs between pharmacies and SHIs as well as the transfer of data is based on § 300 of SGB V.

GePaRD contains data about drug prescriptions which are collected at pharmacies. Drugs, which are sold in pharmacies without a prescription (over the counter drugs) are not registered at SHIs and thus not available in GePaRD (21).

Data about dispensations of ambulatory prescribed medications are reported by the pharmacies to the pharmacies' electronic data processing centers. Then, these data are transferred to the SHI of the patient, where the ID is used to link it with the patients' sociodemographic as well as inpatient and outpatient data (21). The data include the date of prescription as well as the date of dispensation at the pharmacy, but also the specialty of the prescribing physician (21,101). The date of dispensation needs to be interpreted with caution because this is equal to the day when the pharmacy reports its claim to the pharmacies' electronic data processing centers, which usually happens once a week (21).

Medications are coded using a central pharmaceutical number, which describes a specific drug formulation and package size. Through this number, the data are linked with a reference database, where information about the drug's anatomical-therapeutic-chemical code (ATC-code), its package size, strength, formulation, generic and trade name as well as the defined daily dose (DDD) is available (21,101). For identification and classification of dispensed medications, the ATC-code published by the scientific institute of a main statutory health insurance (WIdO) is used in this study.

4.2 Study Design

In the first part, the proportions of drugs dispensed to persons with CD were investigated descriptively using annual cross-sectional designs from 2004 to 2007. The same design was applied for 2007 only to assess the rates of complications and the extent of CD-related health care utilization by CD patients with different treatment intensities.

In the second part, the description of treatment patterns of CD patients receiving infliximab was carried out in a longitudinal user cohort.

4.3 Definition of study population

Part I

Inclusion criteria

Insurees were required to be continuously[1] and actively[2] insured from Jan, 1st to Dec, 31st of the respective year and to have data on sex and age. An insuree was identified as CD patient if she/he fulfilled any of the following criteria:

- a main discharge diagnosis[3] of CD in the respective year OR
- a secondary inpatient diagnosis of CD in the respective year OR
- two ambulatory[4] diagnoses of CD in two different quarters of the same year OR
- an ambulatory diagnosis and a dispensation of a CD drug[4] in the same quarter

Note: [1] A continuous insurance period means that there were no more than 30 days between different insurance periods. This time interval was selected because 30 days after the end of an insurance period, the insuree is still able to claim benefits from the health insurance and data are generated if the insuree has contact to the health care system.

[2] An active insurance period is characterized by the possibility for the insuree to claim benefits from the health insurance in contrast to a passive insurance period. Passive insurance periods are only possible for insurees of one SHI who can pause their health insurance, e.g. when spending time in foreign countries where a different health insurance coverage is required.

[3] See appendix I: Definition of diagnoses, drugs and procedures. If the day of the ambulatory dispensation was missing, the day was set onto the 15th of the respective month.

[4] The ambulatory diagnoses were required to be either "assured" or with missing diagnostic certainty. In one SHI, the number of CD diagnoses with missing diagnostic certainty was assessed previously (see above), but since for the other SHI these numbers are unknown, ambulatory CD diagnoses with missing diagnostic certainty were included in addition to assured diagnoses. Since for ambulatory diagnoses only the quarter, but not the exact date is available, the date of the diagnosis was set to the middle of the quarter (15.2., 15.5., 15.8., 15.11.)

If an insuree fulfilled more than one criterion for CD within one year, the person was included in the presentation of results with the criterion which was assumed to have a higher specificity (main discharge diagnosis > secondary inpatient diagnosis > two ambulatory diagnoses in two different quarters > an ambulatory diagnosis and a dispensation of a medication). If a person fulfills a criterion more than once (e.g. if a person has more than one main discharge diagnosis), the first diagnosis within the respective year was selected (for inpatient diagnoses, the end of a hospital stay was used as the date of diagnosis).

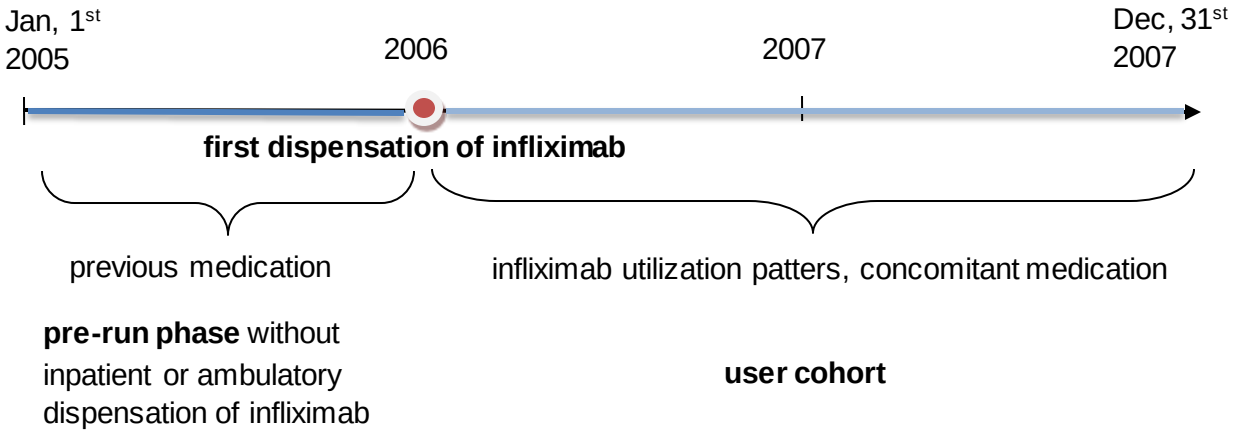
Exclusion criteria

To exclude patients with potential IC, patients fulfilling any of the four above described criteria also for UC were not considered in this study. It is possible, but rare, that the diagnosis of an IBD patient is classified as a different form over time (105). However, persons with diagnoses of both, CD and UC, may actually have IC. This was integrated in the German Modification of International Classification of Disease in the 10th version (ICD-10-GM) only in 2010 (7), so this disease cannot be specifically analyzed in administrative data before this date.

Part II

In this part, the frequency of CD patients beginning infliximab treatment per year was described as well as the previous and concomitant medications they received. From the cohort entry on, the CD patients' drug dispensations were investigated retrospectively for the pre-run phase (365 days) and prospectively until their cohort exit (figure 4).

Figure 4: User cohort design



Cohort entry

Patients entered the cohort on the date of the first ambulatory or inpatient dispensation of infliximab if they had been continuously and actively insured during the 365 days before this date and did not have a dispensation of infliximab in this time interval. Valid data on sex and age were required.

During the time interval of 365 days before the first dispensation of infliximab, the persons had to fulfill at least one of the above-described criteria for CD and none for UC. If a person fulfilled more than one criterion, the one with the higher specificity was used (see above). If a person fulfilled a criterion more than once within 365 days before cohort entry the most recent diagnosis was selected.

Cohort exit

Patients exited the cohort if their insurance period ended (either due to changing insurance or death) or at the end of the study period (Dec, 31st 2007).

4.4 Identification of medications and procedures

Part I

A broad spectrum of drugs for inducing and maintaining remission in CD treatment was chosen from a PubMed-based literature search as well as the current German guidelines (13) (see appendix I: definition of diagnoses, drugs and procedures). Medications for the treatment of acute symptoms (e.g. abdominal pain), complications or malnutrition were not considered.

The corresponding ATC-code (according to WIdO) was used for the identification of ambulatory dispensations in GePaRD. Dispensations of infliximab were also considered in the inpatient setting through its OPS code. The ATC and the OPS code for adalimumab were included in this analysis for 2007.

The diagnoses and procedures used for the assessment of complications and health care utilization were also extracted from literature and identified through ICD and OPS codes, respectively (see appendix I).

Part II

Dispensations of infliximab were considered from the outpatient as well as the inpatient setting (OPS codes). The application scheme was assessed as difference between two consecutive infusions (in- or outpatient) in days. The previously used drugs and the co-medications were analyzed using the drugs identified as CD drugs in part I of this study.

4.5 Statistical analysis

All analyses were conducted using the statistical analysis software SAS for Windows version 9.2.

4.5.1 Main analysis

Part I

The absolute and relative numbers of dispensations were analyzed for all agents. The analysis was also carried out by grouping the medications in line with Bokemeyer et al. 2012 (10) into aminosalicylic acids, budesonide, systemic corticosteroids, topical medication, immunosuppressants and biologicals (anti-TNF-alpha blockers). For the category topical medication, the drugs' form of application (i.e. rectal application forms) was considered in addition to their ATC code (see appendix I).

The proportion of CD patients using a specific type of medication was analyzed by using the grouped medications. It was also investigated how many patients received medications from more than one group of medications.

For the analysis of CD patients with a different treatment intensity in terms of sex, age, complications (fistulas, operations) and health care utilization (hospitalizations, duration of hospital stays, and physician contacts) the highest treatment intensity of a CD patient was selected within the respective year (topical medication < aminosalicylic acids < budesonide < systemic corticosteroids < immunosuppressants < biologicals). Mean and standard deviation were calculated for age. The sex-distribution was described by relative frequencies. Furthermore, the proportion of CD patients with complications such as at least one fistula diagnosis or at least one operation was analyzed. The utilization of CD-related health services was assessed as the proportion of CD patients with at least one hospitalization and at least one outpatient physician contact as well as in mean (+ standard deviation) and median number of physician contacts per patient. The duration of hospital stays was assessed as mean (+ standard deviation) and median duration over all hospital stays in days. The codes for operations and fistulas included in this analysis are listed in appendix I.

Part II

The number of CD patients starting infliximab treatment after a pre-run phase of 365 days was assessed in absolute frequencies per year. For the type of medication received before and during infliximab therapy, their absolute and relative frequencies as well as the number of infliximab users with at least one dispensation of the categorized drugs were calculated.

4.5.2 Sensitivity analysis

For 2007, the analysis of types and proportions of drugs dispensed to patients with CD was also performed using only the first three criteria of the above described algorithm. The criterion based on medications was excluded to assess if this alters the results regarding absolute and relative frequencies of prescribed medications. Apart from this aspect, the in- and exclusion criteria remained constant.

The cross-sectional analysis of the proportions of medications was conducted twice for 2007 (first and second quarter/third and fourth quarter) to specifically investigate the proportion of biologicals in CD treatment after the approval of adalimumab in the third quarter. For this analysis, only CD patients with any dispensation were considered.

5. Results

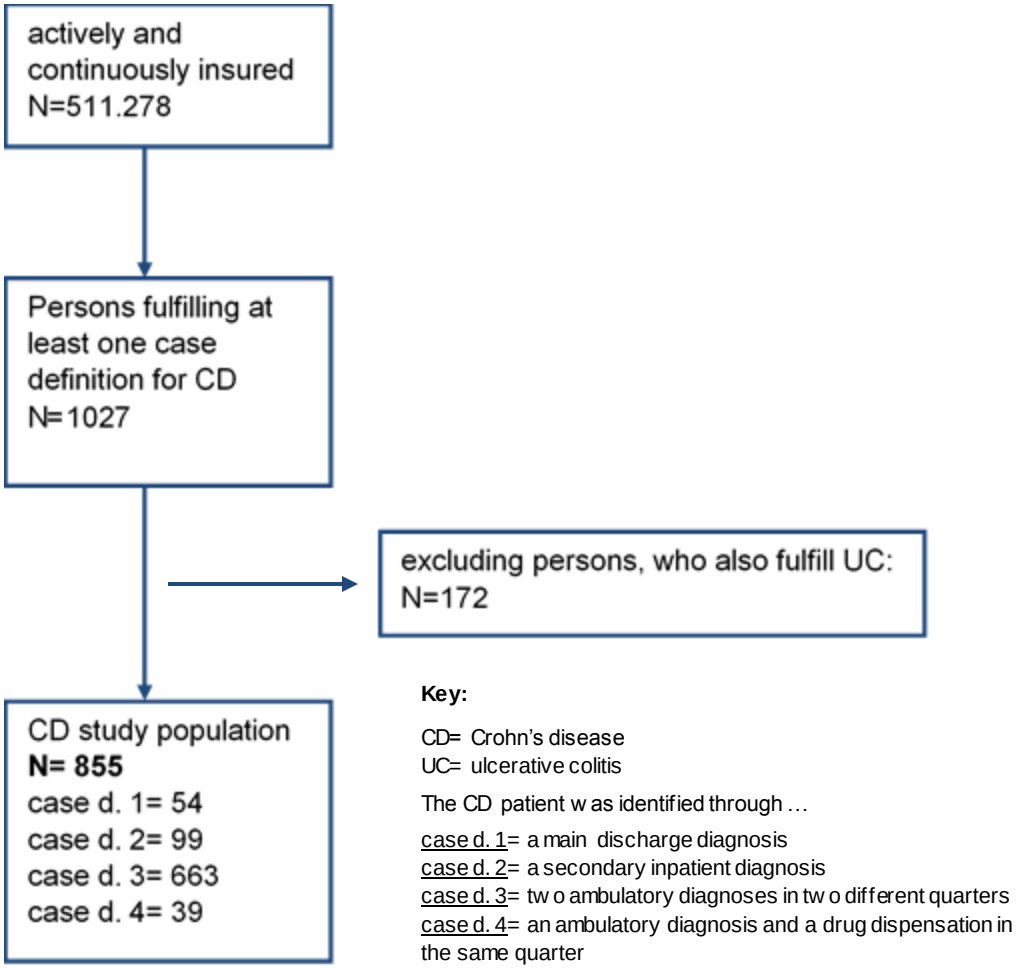
5.1 Description of CD patients' treatment

Study population

The number of actively and continuously insured persons increased steadily from 378.484 in 2004, to 386.231 (2005) and 393.638 in 2006. In 2007, 511.278 persons were included, which is due to a fusion of one of the included SHI with another SHI.

In 2004, 591 persons with CD were identified, 631 in 2005, 637 in 2006 and 855 in 2007 (figure 4). Most of the CD patients were recognized through the case definition of two outpatient CD diagnoses in two different quarters of the same year.

Figure 4: Impact of inclusion and exclusion criteria on study population (2007)



The majority of the study population was female, with 63.8 percent in 2004, 63.2 percent in 2005, 61.2 in 2006 and 60.1 percent in 2007.

The mean age in the study population was rather constant across the respective study populations. In 2004, the mean age was 46.5 years (SD 16.7) with a wide range of 90 years (6 to 96 years). In comparison, the mean age in 2007 was 45.7 years (SD: 16.0) including

a three year old person and with a lower age range than in the previous years (87; 3 to 90 years).

In the following, the results will be exemplarily described for 2007. For all other years, the trends were rather similar. These results are provided in appendix II.

The CD localization in the study population was assessed using the first diagnosis of the most specific criterion fulfilled in the respective year. In 2007, 153 persons were identified through an inpatient CD diagnosis and 702 with an ambulatory diagnosis. In the inpatient setting, the distribution of the CD diagnoses (small and large intestine, other or unspecified CD) was rather even.

On the contrary, most of the diagnoses from the outpatient setting were "CD unspecified" (table 3).

Table 3: Distribution of CD diagnoses in study population (2007)

Inpatient diagnoses		
Diagnosis	Frequency	Percent
CD small intestine (K50.0)	32	20.9
CD large intestine (K50.1)	39	25.5
Other CD (K50.8)	33	21.6
CD unspecified (K50.9)	49	32.0
Total	**153**	100.0
Ambulatory diagnoses		
Diagnosis	Frequency	Percent
CD small intestine (K50.0)	72	10.3
CD large intestine (K50.1)	97	13.8
Other CD (K50.8)	27	3.8
CD unspecified (K50.9)	506	72.1
Total	**702**	100.0

In 2007, 528 CD patients (61.8 percent of the study population) had at least one dispensation of the selected medications. The other 327 CD patients (38.2 %) did not have any outpatient dispensation or an inpatient dispensation of infliximab or adalimumab in 2007.

The 528 CD patients receiving medication were slightly younger (mean age: 43.6 years (SD:16.1)) and included more male patients (43.2 percent) than the general CD population in this study. Overall, there were 3.791 dispensations of CD drugs to these patients.

Approximately one third of these dispensations were aminosalicylic acids, followed by immunosuppressants, systemic corticosteroids and budesonide. Topical medications and biologicals had lower numbers of dispensations in 2007 (table 4).

Table 4: Absolute and relative frequencies of dispensed drugs in 2007

Name	ATC code/ OPS code	Frequency	Percentage of all dispensations
aminosalicylic acids		**1214**	**32.0**
olsazaline, oral	A07EC03	10	0.3
sulfasalazine, oral	A07EC01	65	1.7
mesalazine, oral	A07EC02	1139	30.0
budesonide (oral)		**528**	**13.9**
budesonide	A07EA06	528	13.9
systemic corticosteroids		**776**	**20.5**
betamethasone	H02AB01	4	0.1
dexamethasone	H02AB02	14	0.4
fluocortolone	H02AB03	10	0.3
methylprednisolone	H02AB04	32	0.8
prednisolone	H02AB06	584	15.4
prednisone	H02AB07	132	3.5
topical medication		**118**	**3.1**
hydrocortisone	A07EA02	33	0.9
betamethasone	A07EA04	4	0.1
sulfasalazine	A07EC01	1	<0.1
mesalazine	A07EC02	76	2.0
Budesonide, rectal	A07EA06	4	0.1
immunosuppressants		**1077**	**28.4**
methotrexate	L01BA01	11	0.3
mercaptopurine	L01BB02	72	1.9
tacrolimus	L04AD02	16	0.4
azathioprine	L04AX01	978	25.8
biologicals		**78**	**2.1**
infliximab**	L04AB02/ 8012u	56	1.5
adalimumab**	L04AB04/ 8012t	22	0.6
Total		**3.791**	**100.0**

** including inpatient dispensations, identified through OPS codes

Overall, more than one third of the 855 CD patients had at least one dispensation of aminosalicylic acids in 2007, followed by systemic corticosteroids and immunosuppressants. About 15 percent had at least one dispensation of budesonide, whereas the proportion of patients receiving topical medications or biologicals was considerably lower (figure 5 and table 5).

Figure 5: Proportion of CD patients with at least one dispensation of grouped medications in 2007

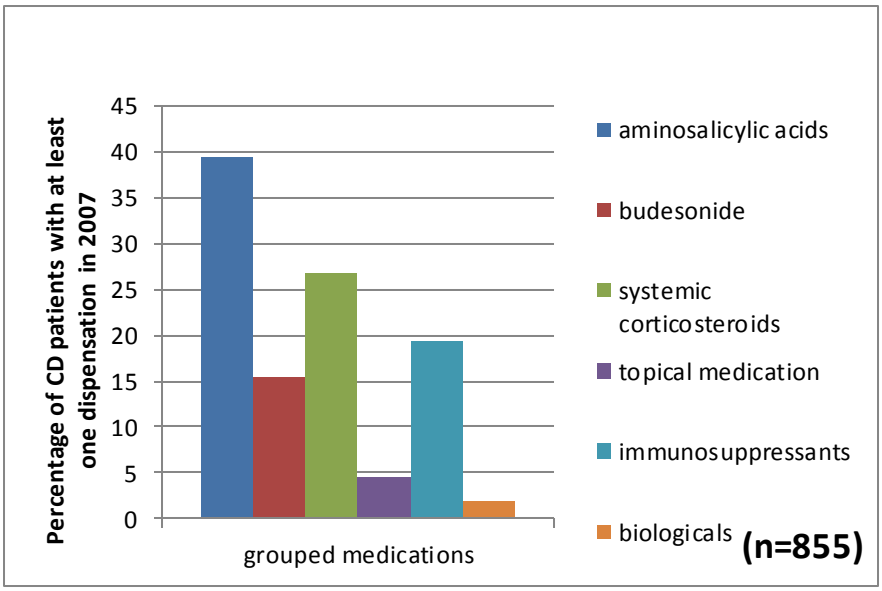


Table 5: Proportion of CD patients with at least one dispensation of grouped medications in 2007

Name of grouped medications	Number of persons with at least one dispensation	Percent of CD patients in 2007 (n=855)
aminosalicylic acids	336	39.3
budesonide	132	15.4
systemic corticosteroids	228	26.7
topical medication	39	4.6
immunosuppressants	165	19.3
biologicals	16	1.9

About half of the 528 patients receiving any medication in 2007 (266 persons, 50.4 percent) received medications from only one group compared to 31.1 percent (164 persons) with dispensations of drugs from two groups of medications. Medications from three different groups were dispensed to 73 persons (13.8 percent) and medications from four to 22 persons (4.2 percent) groups. Three persons (0.6 percent) received medications from five different groups of medications.

The analysis of the highest treatment intensity of the CD patients in 2007 identified, that the majority received immunosuppressants (27.9 %) or systemic corticosteroids (29.4 %), which were the most potent drugs. Topical medication and biologicals had a minor impact (1.3 % and 3.0 %, respectively). On average, CD patients, who received more potent drugs were younger compared to patients with less potent drugs. The proportion of females was lowest in the biological group. The proportion of patients with complications such as fistulae or an operation was also higher in the immunosuppressant and biological group than in the other four groups (table 6).

Table 6: Characteristics and disease complications in groups of highest treatment intensity in 2007

Highest treatment intensity in 2007	Number of CD patients (%) n=528	Mean age (SD)	Distribution of sex (%)	Number (proportion in %) of CD patients with at least one ambulatory fistula diagnosis	Number (proportion in %) of CD patients with at least one inpatient fistula diagnosis	Number (proportion in %) of CD patients with at least one operation
topical medication	7 (1.3)	49.9 (15.9)	female: 4 (57.1)	/	/	/
aminosalicylic acids	125 (23.7)	48.7 (17.1)	female: 67 (53.7)	5 (4.0)	/	4 (3.2)
budesonide	68 (12.9)	41.9 (14.6)	female: 37 (54.4)	/	1 (1.5)	4 (5.9)
systemic corticosteroids	155 (29.4)	46.4 (15.3)	female: 95 (61.3)	8 (5.2)	3 (1.9)	4 (2.6)
immuno-suppressants	157 (29.7)	37.8 (15.2)	female: 92 (58.6)	13 (8.3)	8 (5.1)	11 (7.0)
biologicals	16 (3.0)	39.3 (10.8)	female: 5 (31.3)	1 (6.3)	2 (12.5)	2 (12.5)

The utilization of CD-related health care such as hospitalizations and outpatient physician visits stratified by groups with different treatment intensity is shown in table 7.

In patients receiving immunosuppressants or biologicals as most potent drugs in 2007 a higher proportion with at least one hospitalization was observed. The mean duration over all hospital stays was also highest in the biological group. The same accounts for the median number of physician contacts per patient. The duration of hospital stays as well as the number of physician contacts varied widely within the groups as reflected in high standard deviations.

Table 7: Use of CD-related health care in groups of highest treatment intensity in 2007

Highest treatment intensity in 2007	Number of CD patients (%) n=528	Number (proportion in %) of CD patients with at least one hospitalization	Median duration over all hospital stays* of CD patients within 2007 (mean, SD)	Number (proportion in %) of CD patients with at least one outpatient physician contact (percent)	Median number of CD-related physician contacts per patient** (mean, SD)
topical medication	7 (1.3)	1 (14.3)	- (8***, -)	7 (100)	2 (2.4, 1.9)
aminosalicylic acids	125 (23.7)	15 (12.0)	9 (10.8, 8.1)	120 (96.0)	4 (4.5, 2.6)
budesonide	68 (12.9)	8 (11.8)	3 (8.3,13.3)	68 (100)	5 (5.8, 3.3)
systemic corticosteroids	155 (29.4)	35 (22.6)	8.5 (13.8, 17.3)	150 (96.8)	4 (5.7, 4.4)
immunosuppressants	157 (29.7)	38 (24.2)	3 (9.4, 15.8)	154 (98.1)	6 (7.0, 3.8)
biologicals	16 (3.0)	10 (62.6)	9 (18.6, 22.0)	15 (93.8)	6.5 (7.1, 4.4)

* hospitalizations with the same day of beginning and end where counted as 0 days

** defined as CD diagnosis by an outpatient physician

*** includes one observation only

Sensitivity analysis

The sensitivity analysis, which excluded the case definition “an ambulatory CD diagnosis and a dispensation of a CD drug in the same quarter”, identified 816 CD patients in 2007. Of those, 489 (59.9 percent) received at least one dispensation. The absolute and relative frequencies as well as the proportions of the grouped medications were not considerably different from the results described above (see table 26 and figure 16 in appendix II).

The separate analysis of dispensed medications in the first and second half in 2007 showed that 457 CD patients had any dispensation in the first or second quarter and 450 in the third or fourth quarter. The proportion of biologicals in the drug treatment of CD patients with any dispensation were not considerably different in the time intervals (see table 27 and 28 as well as figure 17 and 18 in appendix II). There were nine dispensations of adalimumab already in the first and the second quarter and 13 in the third and fourth quarter.

5.2 Description of treatment patterns of infliximab users

In the time period from Jan, 1st 2006 to Dec, 31st 2007, eleven persons (3 in 2006, 8 in 2007) started infliximab therapy.

However, one person had a UC as a secondary inpatient diagnosis within 365 days before the index date. Two persons had two outpatient UC diagnoses in two different quarters during the pre-run phase. Further, in this time interval, another person had an outpatient UC diagnosis and a dispensation of a medication in the same quarter. Therefore, these persons were excluded and seven persons remained in the infliximab user cohort.

Four persons of the remaining user cohort were identified through an outpatient dispensation of infliximab, whereas three persons received the drug in the hospital setting.

In the time period before cohort entry, two persons were classified as CD patients through a main discharge diagnosis and four through a secondary inpatient diagnosis. The seventh person had two outpatient CD diagnoses in two different quarters of the pre-run phase. For the description of the CD localization, the most recent diagnosis of the highest criterion before cohort entry was used. The distribution of CD diagnoses and the ICD codes as well as further characteristics of the infliximab user cohort are shown in table 8.

Table 8: Characteristics of infliximab user cohort

Characteristics	infliximab user cohort (n=7)
mean follow-up in days (SD, median)	259.4 (205.0, 195)
sex	female: 4
age group:	
30-39 years	2
40-49 years	1
50-59 years	2
60-69 years	1
70-79 years	1
inpatient diagnoses	**6**
CD large intestine (K50.1)	3
other CD (K50.8)	1
CD unspecified (K50.9)	2
outpatient diagnoses	**1**
CD unspecified (K50.9)	1

Medication in pre-run phase

In 365 days before cohort entry, five persons had any ambulatory dispensations of the chosen medications (see appendix) (59 dispensations in total). Most of these dispensations were azathioprine, followed by orally administered mesalazine and topically administered mesalazine (table 9).

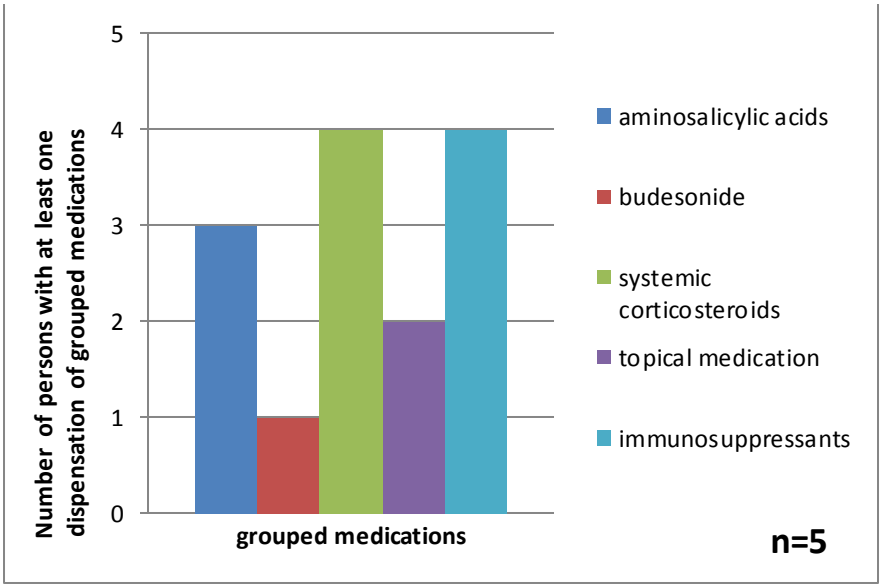
Table 9: Absolute and relative frequencies of drugs dispensed to infliximab users during the 365 days before cohort entry

Name	ATC code	Frequency	Percentage of all dispensations
aminosalicylic acids			
mesalazine, oral	A07EC02	**13**	**22.0**
budesonide (oral)			
Budesonide	A07EA06	**8**	**13.6**
topical medication			
mesalazine	A07EC02	**11**	**18.6**
systemic corticosteroids		**8**	**13.6**
prednisolone	H02AB06	5	8.5
prednisone	H02AB07	3	5.1
immunosuppressants			
azathioprine	L04AX01	**19**	**32.2**
total		**59**	**100.0**

In the pre-run phase, two persons received medications from two different groups, another two persons from three groups of medications and one person received drugs from four different groups.

The number of persons who received at least one dispensation from the respective group of medications is illustrated in figure 6.

Figure 6: Number of persons with at least one dispensation of grouped medications during the 365 days before cohort entry



Infliximab application scheme

The infliximab users had various numbers of infliximab dispensations during their time in the cohort. In total, the seven persons had 24 dispensations of infliximab. Their distribution is shown in table 10.

Table 10: Distribution of infliximab dispensations among CD patients in the cohort

Number of infliximab dispensations	Number of persons
1	1
2	1
3	1
4	2
5	2

Of these dispensations, half were applied in the inpatient and half in the outpatient setting. The dose of infliximab is recorded in administrative claims data differently for the in- and for the outpatient setting. In the inpatient setting, where infliximab is reimbursed using OPS codes, the dose is shown as range in mg, e.g. from 200 mg up to 300 mg (see appendix I: definition of diagnoses, drugs and procedures). In the outpatient setting, infliximab is dispensed as powder to establish an infusion solution, each unit containing 100 mg powder.

The frequency of the different doses is listed in table 11.

Table 11: Dose and frequency of infliximab dispensations

Dose of infliximab	Frequency
inpatient dose	
300 mg up to 400 mg	2
400 mg up to 500 mg	4
600 mg up to 700 mg	3
700 mg up to 800 mg	2
1.200 mg up to 1.400 mg	1
total	**12**
outpatient dose	
200 mg	6
300 mg	3
400 mg	3
total	**12**

Two persons had two dispensations on the same day (300 mg as well as 200 mg and 400 mg up to 500 mg as well as 1.200 up to 1.400 mg, respectively). Therefore, these dispensations were counted as one dispensation for the calculation of the time intervals between two consecutive infliximab dispensations.

These intervals (in days) had a wide range as reflected in interquartile range and standard deviation (table 12).

Table 12: Time interval between consecutive infliximab dispensations

N	Number of consecutive infliximab dispensations	Median number of days between infliximab dispensation (interquartile range)	Mean number of days between infliximab dispensations (SD)
6	1st and 2nd	45.5 (59)	74.3 (80.6)
5	2nd and 3rd	56 (50)	107.6 (132.8)
3	3rd and 4th	84 (41)	88.3 (20.8)
1	4th and 5th	-	57 (-)

Concomitant medication

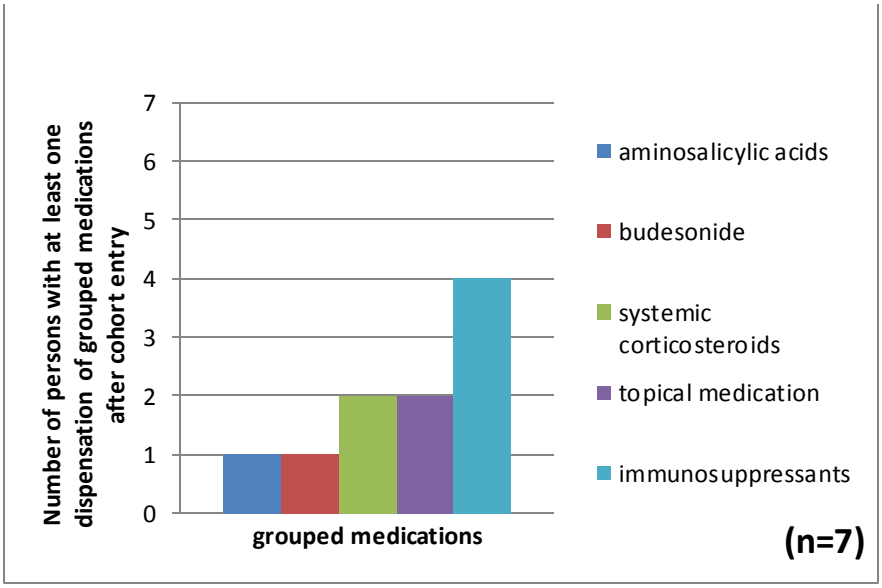
The absolute and relative frequencies of drugs (other than infliximab) dispensed to infliximab users after cohort entry is shown in table 13.

Table 13: Absolute and relative frequencies of drugs dispensed to infliximab users after cohort entry

Name	ATC code	Frequency	Percentage of all dispensations
aminosalicylic acids			
mesalazine, oral	A07EC02	**3**	**5.9**
budesonide (oral)			
Budesonide	A07EA06	**1**	**1.9**
topical medication			
mesalazine	A07EC02	**25**	**49.0**
systemic corticosteroids			
Prednisolone	H02AB06	**3**	**5.9**
immunosuppressants			
azathioprine	L04AX01	**19**	**37.3**
total		**51**	**100.0**

The number of persons with at least one dispensation of the grouped medications was highest for immunosuppressants, followed by systemic corticosteroids and topical medication (figure 7).

Figure 7: Number of persons with at least one dispensation of grouped medications after cohort entry



After cohort entry, one person received prednisolone and budesonide on the same day as the first dispensation of infliximab and exited the cohort 30 days later with no further drug dispensations.

Two persons received a combination therapy with azathioprine defined as various dispensations of this drug in between the dispensations of infliximab. The same accounts for two further persons with this combination therapy, but one person received regular mesalazine enemas in addition and the other had two dispensations of prednisolone in between the infliximab dispensations.

Mesalazine enemas were also dispensed to one person until cohort exit after this person had received two infliximab dispensations without concomitant medications.

Infliximab was applied as monotherapy in one person, who received four inpatient dispensations of infliximab, but no outpatient dispensation of CD drugs in between or until cohort exit.

6. Discussion

6.1 Summary of results

This study on the drug treatment situation of CD patients showed that almost two thirds of the 855 identified CD patients received any medication in 2007. About half of these patients had dispensations from only one category of drugs, but there were also persons with dispensations from two, three and four groups and few from five and six groups. More than one third of CD patients had no dispensation of any of the chosen medications in the observed time period.

In 2007, the medications most frequently dispensed to CD patients were aminosalicylic acids, predominantly mesalazine, followed by immunosuppressants with azathioprine as most important drug and systemic corticosteroids. Budenoside, topical medications and biological had the lowest proportion of all dispensations. Within the latter group of medications, infliximab was used more frequently than adalimumab.

On the individual level, the proportion of patients with at least one dispensation of the grouped medications was also highest for aminosalicylic acids followed by systemic corticosteroids, immunosuppressants and budesonide. Again, the proportion of CD patients with at least one dispensation of topical medication or biologicals was rather low.

CD patients were grouped according to the highest treatment intensity received in 2007 to assess the rate of complications as well as the health care utilization. The groups of medications most frequently used as highest treatment intensity were immunosuppressants and systemic corticosteroids, followed by aminosalicylic acids. Few CD patients received no more than topical medications or biologicals.

The patients with immunosuppressants or biologicals as most intensive treatment were, on average, younger than patients receiving topical medication, aminosalicylic acids, budesonide or systemic corticosteroids. In both groups, the proportion of patients with at least one CD complication such as a fistula (in- or outpatient fistula diagnosis) or an operation was higher compared to the other groups. The proportion of patients with a hospitalization as well as the mean duration of all hospital stays were also higher for patients with immunosuppressants or biologicals. However, the proportion of CD patients with an ambulatory physician contact in the biological group was lower than in the other groups. The mean number of CD-related physician contacts per patient was, again, highest in the immunosuppressant and the biological groups.

For the analysis of infliximab treatment patterns, a user cohort was selected. This included seven CD patients. Before cohort entry, topical medication, aminosalicylic acids, budesonide, systemic corticosteroids and immunosuppressants were dispensed to five persons. This is in line with the ”step-up-approach”, where less potent drugs are used before biologicals. However, two persons had no ambulatory dispensations of any of the chosen CD medications in 365 days before cohort entry, which may be in line with the “top-down-approach”. These persons had been in hospital several times before receiving infliximab, so it is possible that they received various medications in the inpatient sector, which were not registered through OPS codes (see below).

The analysis of the application scheme showed a wide range in time intervals between infliximab infusions and did not reveal a regularity concerning induction or maintenance treatment.

The persons in the user cohort were followed for different time periods. The most common concomitant medication of infliximab was azathioprine. Mesalazine enemas were also frequently used and prednisolone was dispensed twice. Infliximab was also used as monotherapy in one person.

6.2 Results in research context

Aminosalicylic acids

Despite their modest benefits over placebo in inducing remission, aminosalicylic acids take a considerable portion in the drug treatment of CD in clinical practice (49). This was also confirmed in this study as reflected in absolute and relative frequencies of dispensations as well as in the proportion of CD patients with at least one dispensation. The dominance of mesalazine within this group may be due to its different safety profile compared to sulfasalazine (see 2.3.1.1).

Methotrexate

On the contrary, methotrexate was rarely used in this study, especially in comparison to azathioprine (11 dispensations vs. 978 in 2007). This is in line with the German guideline (13), which only recommends methotrexate as treatment for patients, who do not show an adequate response or have side effects under azathioprine or 6-mercaptopurine. The low number of dispensations are also in line with a database study on medication use comprising 108,518 IBD patients in the USA between 1997 and 2009. There, methotrexate had the lowest prescription rates (76).

Azathioprine/6-mercaptopurine

Azathioprine was also more often used in this study than its prodrug 6-mercaptopurine (978 dispensations vs. 72 in 2007). In a pooled analysis of a review, more patients seemed to respond to azathioprine (71 % maintained remission) than to 6-mercaptopurine (51 % maintained remission). However, one of the included studies used a low dose of 6-mercaptopurine, which may lead to this result (69). The low dispensation rates may also be due to the fact that 6-mercaptopurine is not licensed for the use in IBD and azathioprine is an effective on-label alternative (42).

CD drug treatment in comparison to other studies

A study with a similar study design to the one presented in this thesis was based on administrative claims data of AOK Hesse. It investigated the medications dispensed to 582 CD patients in 2009. These patients had a mean age of 49 years and 44 percent were male (106). The population of the present study was slightly younger (mean age in 2007: 45.7) and included less males (39.9 percent).

In the AOK Hesse CD population, 64 percent of the identified patients received at least one medication, which is comparable with 61.8 percent in our study. In the AOK Hesse CD population, 36 percent received aminosalicylic acids and 17 percent topically acting corticosteroids. Glucocosteroids with a systemic mechanism were dispensed to 31 percent. Immunosuppressants were dispensed to 23 percent and one percent received 6-mercaptopurine (106). The proportion of CD patients receiving aminosalicylic and topical medication seem rather different from the results of our study. However, since the exact classification of the medications and the case identification algorithm were not reported, the results of both studies cannot be compared.

A cross-sectional study (10), which was conducted in 24 gastroenterology practices and two outpatient clinics, examined the clinical status, psychosocial impairments as well as the drug treatment of patients with IBD in Germany. From March 2006 to July 2007, data on various IBD-related aspects were documented in an online registry. The study population included 511 CD patients who were, on average, younger than this study population in 2007 (mean age: 40.3 years (SD:13.1) compared to 45.7 (SD:16.0)) and included slightly less males (37.4 % compared to 39.9 %). These differences may be coincidental, but also may be explained by younger patients, who experience a more severe disease course and require specialized treatment.

In general, the drug treatment was considerably different to our study. More than one third of CD patients did not have any drug dispensation in our analysis. However, in the study from the specialized setting, CD patients without drug treatment were not reported. Hence, in the comparison, from our study only CD patients with any dispensation in 2007 (n=528) are considered. Overall, the treatment intensity in the specialized practices and outpatient clinics was considerably higher than in our study as reflected in a higher proportion of CD patients receiving immunosuppressants or biologicals. Less potent drugs like aminosalicylic acids and topical medication were dispensed to a lower proportion of CD patients in the specialized setting. The same accounts for systemic corticosteroids (table 14).

Table 14: Drug treatment in research context I: Bokemeyer et al.

	Proportion of CD patients with at least one dispensation of grouped medications	
Group of medications	**Present study 2007 n=528**	**Bokemeyer et al. n=511**
Aminosalicylic acids	63.6	46.6
budesonide	25.0	22.9
systemic corticosteroids	43.2	22.9
topical medication	7.4	4.1
immunosuppressants	31.3	47.2
biologicals	3.0	8.2

Data taken from Bokemeyer et al. 2012

Another study from Germany (49) retrospectively included 162 patients from 14 outpatient gastroenterology practices applying the "step-up-approach" to assess the most intensive treatment during a median follow up of 43 months (January 2007 until May 2010).
In the specialized setting, aminosalicylic acids were more often used as most intensive treatment than in our study, although these were combined with initial corticosteroids in 8.6 percent of the patients. Again, the treatment intensity was generally higher than in our study as reflected in the proportion of CD patients receiving immunosuppressants or biologicals as most potent drugs. The proportion of patients who received not more than corticosteroids was considerably lower in the gastroenterology practices than in our study (table 15).

Table 15: Drug treatment in research context II: Kruis et al.

	Proportion of CD patients with grouped medications as highest treatment intensity in study period	
Group of medications	**Present study 2007 n=528**	**Kruis et al. n=162**
Aminosalicylic acids	23.7	33.3
budesonide	12.9	-
systemic corticosteroids	29.4	16.7
topical medication	1.3	-
immunosuppressants	29.7	38.9
biologicals	3.0	11.1

Data taken from Kruis et al. 2013

Various aspects may explain these differences. The demographic characteristics of the study populations could not be compared because only the age at diagnosis, but not the participants' age at time of the study was reported. Further, the categorization of the medications was different. In our study, a considerable proportion of patients received topical medication (1.3 %) or budesonide (12.9 %) as the most intensive treatment, whereas Kruis et al. did not explicitly consider these drugs.

The differences between the drug treatment in the specialized settings described above and in administrative claims data may be explained by patients with a more severe disease course who seek medical care at gastroenterological specialists. These patients require a more intensive treatment, which is linked to the higher percentage of patients receiving more potent drugs like immunosuppressants and biologicals and the lower percentages of CD patients with aminosalicylic acids or topical medication. Additionally, specialists may be more aware of the inconsistent evidence of aminosalicylic acids. They may more often consider the side effects of systemic corticosteroids and therefore, more often use immunosuppressants and biologicals as steroid-sparing agents, which would also explain the lower rates of corticosteroids in the study from gastroenterology practices.
This underlines the benefit of administrative claims data because these reflect the actual treatment situation of CD patients in contrast to only specialized settings.

Infliximab treatment patterns

A questionnaire among 292 Canadian gastroenterologists assessed the utilization of infliximab in IBD treatment under every day conditions. Medically refractory CD, fistulizing CD and steroid-dependent CD were mostly seen as indication for infliximab therapy (100 %, 98 % and 86 % respectively). In our study, it was not possible to analyze the indication for infliximab application because only the ICD-10 codes of the diagnoses were available, which do not contain information like treatment refractoriness or steroid dependence.

Most Canadian gastroenterologists (97 %) stated to start induction therapy with infliximab at 5 mg per kg and to follow a three-dose induction regimen (88 %). Maintenance therapy was named to be mostly applied every eight weeks (89 %), whereas five percent of the gastroenterologists stated to use infliximab on demand (107).
On the contrary, in this study, the dosage per kg could not be considered because administrative claims data do not contain information such as body weight. The dosages in this study had a wide range from 200 mg up to 2000 mg per application with higher doses in the inpatient setting.

An induction scheme with three doses at 0, 2 and 6 weeks could not be detected. In one person, who received infliximab in the inpatient setting, a kind of induction scheme was applied with the second infliximab infusion 18 days after the first and the third 28 days after the second. In another person, these intervals were 25 and 31 days, respectively.

A maintenance treatment scheme with infliximab every eight weeks was also not obvious in this study. The time intervals between the infusions varied widely, but only one person had two intervals of 56 and 57 days between two consecutive infusions. The other intervals were mostly longer than 56 days.

This variation in time intervals may be due to an on-demand application. Since the majority of persons had no regular time intervals, these results are in contrast to the study described above where only five percent stated to apply infliximab this way. However, the Canadian study used physicians' opinion, whereas our study showed the actual treatment patterns.

Concomitant immunosuppressants were applied by 80 percent of the Canadian gastroenterologists, which is in line with the majority of infliximab users in this study receiving azathioprine.

6.3 Strengths and limitations

First of all, administrative claims data have several advantages, which also account for this study. Data from several settings such as hospitals as well as outpatient physicians and specialists are available with limited risk of selection and missing data. Further, these data reflect the "real-life" situation as opposed to the artificial setting in clinical trials or specialized settings. Another important aspect is the avoidance of information or recall bias as it is a problem in surveys and interviews. Compared to most primary data studies, administrative claims data are available for a longer period of time and for larger study populations, but they do not require extensive funding (102). It is also feasible to extend the analysis when new data become available or another SHI agrees on the utilization of the data.

Sample size

For this study, however, only data of two relatively small SHI could be used because of missing approvals of the remaining two SHI in GePaRD by the time of analysis. This resulted in a rather small study population in general and in the extremely small infliximab user cohort. The findings from this cohort cannot be generalized. Nonetheless, this study provided information on the position of infliximab in the treatment cascade as well as concomitant medications and may serve as example for larger studies of its kind.

Selection

The structure of the insurees is different across German SHIs. In at least one of the two included SHIs the mean age of the insurees is higher than in SHIs‘ average and it is likely that women are slightly overrepresented (108).

The structure of the included SHI and the small sample size limit the generalizability of the results onto the German general population. Still, since both SHIs include insurees from north-west Germany, the results reflect the drug treatment of CD patients in this region.

By now, the utilization of the data has been agreed on by another SHI. This has a different structure and insurees from various German areas, so the analysis may be extended to these data in order to provide more generalizable results.

A major limitation of this study results from the selection of the CD study population because a considerable number of persons fulfilled criteria for both, CD and UC. In these cases, it is not feasible to classify patients as having CD, UC or IC on the data available because IC did not have an ICD-10-GM code during the study period. For increasing the validity of case identification in administrative claims data, other types of studies with informed consent of the insurees are essential (102). An external validation was beyond the scope of this study. However, by using the rather conservative approach of excluding all patients with criteria for CD and UC, the specificity of identifying CD patients is likely to be rather high.

Study design

Another limitation is the cross-sectional design in the first part of this thesis. It cannot be derived in which order the drugs were applied, i.e. following the “step-up-“ or “top-down-approach”. Further, the duration and the dosage of the drug exposition were not investigated. This is especially important for the dosage and exposure to steroids because continuous high-dose consumption is associated with significant side effects. This is related to the fact that the exact dosage recommended to the patient is not recorded in administrative claims data, but has to be estimated based on the DDDs, the package size and the number of dispensations.

The annual cross-sectional design was also a limitation in the description of complications and CD-related health care utilization among CD patients with different treatment intensities. It was not investigated, whether the complications arose before the application of the drug or despite the treatment. The groups receiving different treatment intensities were very different in size and overall, rather small, which limited this comparison to pure description instead of statistical tests. Consequently, no causal relation can be derived from this part of study.

Study period

The data of the two included SHI had been transferred to BIPS only for the time period from 2004 until 2007 at the time of analysis. During this period, only one biological was continuously available, which was infliximab that was approved for CD in 2001. The utilization of adalimumab in CD therapy was analyzed from its approval in the third quarter of 2007 on. By now, new data of the SHI until 2010 became available, so it is feasible to conduct the analysis for a longer period of time to provide more current results.

For the infliximab user cohort, the pre-run phase had to start in the beginning 2005, because the inpatient application of specific medications could not be analyzed in detail in 2004. From 2005 on, data about inpatient applications of infliximab became available through OPS codes.

This resulted in the rather short study period from 2006 to 2007. Regarding the position of infliximab in the treatment cascade ("step-up-" or "top-down-approach") another limitation was that data about inpatient medications are generally not available apart from medications identified through OPS codes.

Five out of seven infliximab users had received drugs from the "step-up-approach" before cohort entry, but two persons did not. Consequently, it could be assumed that in these patients, a top-down approach was applied. However, both had several hospital stays before cohort entry and it is impossible to analyze their previous medications.

The same accounts for the concomitant drugs of patients, who received infliximab in the hospital setting.

Further, during the rather short period of time and the flexible cohort entry, the times of follow-up varied widely and one person was lost to follow up shortly after the dispensation of infliximab. Intentionally, no follow-up time was required because the main focus was on medications received before cohort entry and the user cohort was expected to be rather small.

The variation of the time intervals between consecutive infliximab dispensations may be caused by the fact that the date of dispensations is not necessarily equal to the day of the drug application. The date of outpatient dispensation is generally equal to the date when pharmacies report their dispensations. Further, patients may have collected the medication at a pharmacy, brought it to the physicians practice on a different day and then received the infusion. Infliximab is dispensed at pharmacies as a powder, which does not require special handling apart from cooling. In general, patients also may have collected the drug for more than one application, which may also be a reason for the variation in time intervals.

It was rather unlikely to find persons who end infliximab therapy and switch to another biological (adalimumab) because of the limited time of two years (2006/2007) for the

analysis of the infliximab user cohort. This medication is usually applied for several years in practice before alternative strategies are considered.

Information

The disease patterns of CD were analyzed using the diagnoses and their respective ICD codes. On the contrary, disease-related information such as disease activity (according to CDAI, for example), disease course (stricturing, penetrating), behavior (steroid-dependent etc.) and severity (e.g. frequency of flares) are not available in administrative claims data. Moreover, there are no data about lifestyle factors such as tobacco smoking, which is assumed to have a negative impact on the disease course (e.g. frequency of flares and need for immunosuppressants) (9,102).

An important limitation in the analysis of the drugs dispensed to patients with CD is that medications cannot be categorized as applied for induction or maintenance treatment.

The data also do not provide information about the indication for which the drug is dispensed to the patient. Hence, it is possible that CD patients received the above-described drugs for other indications than CD because most of them are also indicated for other diseases like rheumatoid arthritis and psoriasis. There is evidence that these diseases occur more frequently in CD, but these diseases and co-morbidity were not a subject of this study.

Additionally, only medications that are prescribed by a physician and dispensed to the insuree by a pharmacist could be included in this study as self-medications are not recorded in administrative claims data (21,102). Therefore, based on administrative claims data, the exposition to medications is likely to be underestimated. The total extent of medication use can only be assessed using primary data like generated in surveys (102).

7. Conclusion

This study showed that the majority of CD patients required drug treatment defined as at least one drug dispensation within one year. Aminosalicylic acids, steroids and immunosuppressants were important components in CD treatment during the study period. On the contrary, biologicals like infliximab were rarely dispensed.

The evidence for the efficacy of aminosalicylic acids in CD treatment is still inconsistent, so further evidence is needed before reflecting the high rates of these drugs in this study.

The high percentage of patients receiving systemic corticosteroids in this study is of major relevance. Although the duration of the exposition to systemic corticosteroids was not investigated, the high proportion of patients receiving these drugs at least once per year is a hint for either a high number of disease flares, steroid-dependent disease courses in this study population or a higher need for these drugs because of a slow treatment

intensification. This aspect requires further analyses like the duration of steroid therapy and the prescribing physicians of these drugs.

For infliximab, a slight increase in the proportion of CD patients receiving this drug was observed from 2004 to 2007, although not statistically analyzed. For the detailed analysis of time trends, further analyses should consider a longer time period for statistical tests.

For the infliximab user cohort, the time under study should be extended to be able to analyze the duration of infliximab therapy and potential switches to other biologicals like adalimumab. It is also of major interest, whether CD patients ending infliximab therapy experience disease exacerbations defined as complications and hospitalizations.

The descriptive analysis of complications and CD-related health care utilization showed that persons with a more intensive treatment had, as expected, more complications and needed more health care. These findings should be investigated in analytic designs to determine factors for CD patients receiving more potent drugs.

Infliximab is associated with significant improvements in several aspects of CD, but also with considerable side effects and high costs for the health care system. On the contrary, it may be cost saving because it may be able to alter the disease course and reduce the need for hospitalizations and operations. This potential as well as the safety profile should be analyzed in detail in a longitudinal design with administrative claims data as suitable data source.

In conclusion, this study showed the general drug treatment situation of CD patients from two SHI in north-west Germany and may serve, at this stage, as a pilot study concerning the utilization patterns of infliximab in CD treatment. It might be used as methodological example regarding identification of CD patients as well as drug classes in administrative claims data. CD is a disease of major public health relevance and because of rising incidence and prevalence it is assumed that even more persons will be affected who need appropriate medical services as well as drug treatment in terms of (cost-)effectiveness and safety, but also in terms of avoiding disabling disease courses.

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Appendix I

Definition of diagnoses, drugs and procedures

Crohn's disease (ICD-codes)

K50 Crohn's disease

K50.0 Crohn's disease of small intestine

K50.1 Crohn's disease of large intestine

K50.8 other Crohn's disease

K50.9 Crohn's disease, unspecified

Ulcerative Colitis (ICD-codes)

K50 ulcerative colitis

K51.0 ulcerative (chronic) pancolitis

K51.1 ulcerative (chronic) ileocolitis

K51.2 ulcerative (chronic) proctitis

K51.3 ulcerative (chronic) rectosigmoiditis

K51.4 inflammatory polyps

K51.5 left sided colitis

K51.8 other ulcerative colitis

K51.9 ulcerative colitis, unspecified

Table 16: Drugs used for case identification (ATC codes)

Disease (CD/UC)	WidO ATC code	Active agent
CD/UC	A07EA06	budesonide
CD/UC	H02AB06	prednisolone
CD/UC	H02AB07	prednisone
CD/UC	H02AB04	methylprednisolone
CD/UC	A07EC01	sulfasalazine
CD/UC	A07EC02	mesalazine
CD/UC	L04AX01	azathioprine
CD/UC	L01BB02	mercaptopurine
CD	L01BA01	methotrexate
CD	L04AB02	infliximab* (part I only)
CD	L04AB04	adalimumab**
UC	L04AD01	cyclosporine
UC	L04AD02	tacrolimus

* For the treatment of UC, infliximab was approved in the first quarter of 2006 (109) and hence, it is only used for case identification in 2006 and 2007.

** Adalimumab has been approved for the treatment of CD in 2007 (18), therefore it is only used for case identification in 2007. For

UC, adalimumab was approved in 2012 (15) and hence, it is not applied for case identification.

Medications for description of CD patients' treatment (ATC-codes)

Aminosalicylates

A07EC01 sulfasalazine

A07EC02 mesalazine

A07EC03 olsazaline

A07EC04 balsalazide

(Systemic) corticosteroids

H02AB01 betamethasone

H02AB02 dexamethasone

H02AB03 fluocortolone

H02AB04 methylprednisolone

H02AB05 paramethasone

H02AB06 prednisolone

H02AB07 prednisone

H02AB08 triamcinolone

H02AB09 hydrocortisone

H02AB10 cortisone

H02AB11 prednylidene

H02AB12 rimexolone

H02AB13 deflazacort

H02AB14 cloprednol

Budesonide

A07EA06 budesonide (oral)

Topical medication

A07EA02 hydrocortisone (rectal)

A07EA04 betamethasone (rectal)

A07EC01 sulfasalzine (rectal)

A07EC02 mesalazine (rectal)

Besides the ATC code, the form of application is also considered. The medications are classified as topical medication, if their form of application in GePaRD is "Dosierschaum, Klistiere, Suppositorien, Suspension, Klysmen, Kombipackung, Rektalkapseln or Schaum". Further, betamethasone can be applied as "Rektal-Instillations- Lösung".

Immunosuppressants

L01BA01 methotrexate

L04AX01 azathioprine

L01BB02 mercpatopurine

L04AD01 cyclosporine

L04AD02 tacrolimus

L04AX02 thalidomide

Biologicals (anti-TNF-alpha-blockers)

L04AB02 infliximab

L04AB04 adalimumab

Biologicals (anti-TNF-alpha-blockers) OPS-Codes

2005/2006

8-012.7 infliximab, parenteral

- .70 100 mg bis unter 200 mg
- .71 200 mg bis unter 300 mg
- .72 300 mg bis unter 400 mg
- .73 400 mg bis unter 500 mg
- .74 500 mg bis unter 600 mg
- .75 600 mg bis unter 700 mg
- .76 700 mg bis unter 800 mg
- .77 800 mg bis unter 900 mg
- .78 900 mg bis unter 1.000 mg
- .79 1.000 mg bis unter 1.2000 mg
- .7a 1.200 mg bis unter 1.400 mg
- .7b 1.400 mg bis unter 1.600 mg
- .7c 1.600 mg bis unter 1.800 mg
- .7d 1.800 mg bis unter 2.000 mg
- .7e 2.000 mg und mehr

2007

8-012.u infliximab, parenteral

- .u0 50 mg bis unter 100 mg (Dieser Kode ist für Patienten mit einem Alter bei Aufnahme von unter 15 Jahren anzugeben)
- .u1 100 mg bis unter 150 mg (Dieser Kode ist für Patienten mit einem Alter bei Aufnahme von unter 15 Jahren anzugeben)
- .u2 150 mg bis unter 200 mg

.u3 200 mg bis unter 300 mg

.u4 300 mg bis unter 400 mg

.u5 400 mg bis unter 500 mg

.u6 500 mg bis unter 600 mg

.u7 600 mg bis unter 700 mg

.u8 700 mg bis unter 800 mg

.u9 800 mg bis unter 900 mg

.ua 900 mg bis unter 1.000 mg

.ub 1.000 mg bis unter 1.200 mg

.uc 1.200 mg bis unter 1.400 mg

.ud 1.400 mg bis unter 1.600 mg

.ue 1.600 mg bis unter 1.800 mg

.uf 1.800 mg bis unter 2.000 mg

.ug 2.000 mg und mehr

2005/2006

8-012.3 adalimumab, parenteral

.30 40 mg bis unter 80 mg

.31 80 mg bis unter 120 mg

.32 120 mg bis unter 160 mg

.33 160 mg bis unter 200 mg

.34 200 mg bis unter 240 mg

.35 240 mg bis unter 280 mg

.36 280 mg bis unter 320 mg

.37 320 mg bis unter 360 mg

.38 360 mg bis unter 400 mg

.39 400 mg bis unter 440 mg

.3a 440 mg und mehr

2007

8-012.t adalimumab, parenteral

.t0 10 mg bis unter 25 mg (Dieser Kode ist für Patienten mit einem Alter bei Aufnahme von unter 15 Jahren anzugeben)

.t1 25 mg bis unter 40 mg (Dieser Kode ist für Patienten mit einem Alter bei Aufnahme von unter 15 Jahren anzugeben)

.t2 40 mg bis unter 80 mg

.t3 80 mg bis unter 120 mg

.t4	120 mg bis unter 160 mg
.t5	160 mg bis unter 200 mg
.t6	200 mg bis unter 240 mg
.t7	240 mg bis unter 280 mg
.t8	280 mg bis unter 320 mg
.t9	320 mg bis unter 360 mg
.ta	360 mg bis unter 400 mg

Fistula diagnoses for comparison of biological-users and non-users (ICD-codes) adapted from (25)

K31.- Sonstige Krankheiten des Magens und des Duodenums

K31.6	Fistel des Magens und des Dudenums (Gastrojejunokolische Fistel, gastrokolische Fistel)

K38.- Sonstige Krankheiten der Appendix

K38.3	Appendixfistel

K60.- Fissur und Fistel in der Anal- und Rektalregion

K60.3	Analfistel
K60.4	Rektalfistel, Rektum-Haut-Fistel (exkl. Rektovaginalfistel N82.3, Vesikorektalfistel N31.2)
K60.5	Anorektalfistel

K63.- Sonstige Krankheiten des Darms

K63.2	Darmfistel (exkl. K60.-, K31.6, K38.3, N32.1, N82.2-4)

N32.- Sonstige Erkrankungen der Harnblase

N32.1	Vesikointestinalfistel (Vesikorektalfistel)

N82.- Fisteln mit Beteiligung des weiblichen Genitaltrakts

N82.2	Fistel zwischen Vagina und Dünndarm
N82.3	Fistel zwischen Vagina und Dickdarm (Rektovaginalfistel)
N82.4	sonstige Fisteln zwischen weiblichem Genital- und Darmtrakt (Intestinouterine Fistel)

Surgical procedures for comparison of infliximab users and non-users (OPS-codes) (adapted from (97))

5-453 Ausschaltung eines Darmsegmentes als selbstständiger Eingriff (z.B. bei zweizeitigen plastischen Operationen)

5-453.0	Duodenum
5-453.1	Jejunum oder Ileum

5-453.2 Kolon

5-453.x Sonstige

5-453.y nicht näher bezeichnet

5-454 Resektion des Dünndarmes

Inkl. Entnahme von Dünndarm zur Transplantation, Resektion bei kongenitaler Anomalie des Dünndarmes, Rekonstruktion und Ausleitung

5-454.0 Segmentresektion des Duodenums

5-454.1 Segmentresektion des Jejunums

5-454.2 Segmentresektion des Ileums

5-454.3 multiple Segmentresektion

5-454.4 (Teil-)Resektion des Duodenums

5-454.5 (Teil-)Resektion des Jejunums

5-454.6 (Teil-)Resektion des Ileums

5-454.x Sonstige

5-454.y nicht näher bezeichnet

5-455 Partielle Resektion des Dickdarmes

5-455.0 Segmentresektion

5-455.1 Multiple Segmentresektionen

5-455.2 Ileozäkalresektion

5-455.3 Zäkumresektion

5-455.4 Hemikolektomie rechts

5-455.5 Transversumresektion

5-455.6 Hemikolektomie links

5-455.7 Sigmaresektion

5-455.8 Resektion mehrerer benachbarter Dickdarmabschnitte (Subtotale Kolonresektion)

5-455.x Sonstige

5-455.y nicht näher bezeichnet

5-456 (Totale) Kolektomie und Proktokolektomie

Das Anlegen eines protektiven Enterostoma ist gesondert zu kodieren (5-462). Der Zugang ist in der 6. Stelle nach folgender Liste zu kodieren:

0 offen chirurgisch mit Ileostoma

1 offen chirurgisch mit ileorektaler Anastomose mit Reservoir (Pouch)

2 offen chirurgisch mit ileorektaler Anastomose ohne Reservoir (Pouch)

3 offen chirurgisch mit ileoanaler Anastomose mit Reservoir (Pouch)
4 offen chirurgisch mit ileoanaler Anastomose ohne Reservoir (Pouch)
5 laparoskopisch mit Anastomose mit Reservoir (Pouch)
6 laparoskopisch mit Anastomose ohne Reservoir (Pouch
7 laparoskopisch mit Ileostoma
8 Umsteigen laparoskopisch – offen chirurgisch
x Sonstige

5-456.0 Kolektomie (ohne Rektumextirpation)

5-456.1 Proktokolektomie (Kolon einschließlich Rektums)

5-456.2 Kolektomie mit Proktomuskosektomie

5-456.x Sonstige

5-456.y nicht näher bezeichnet

5-459 Bypass-Anastomose des Darmes

5-459.0 Dünndarm zu Dünndarm

5-459.1 Duodenum zu Duodenum

5-459.2 Dünndarm zu Dickdarm

5-459.3 Dickdarm zu Dickdarm

5-459.4 Mehrfache Anastomosen

5-459.x Sonstige

5-459.y nicht näher bezeichnet

5-460 Anlegen eines Enterostoma, doppelläufig, als selbstständiger Eingriff

5-460.0 Jejunostoma

5-460.1 Ileostoma

5-460.2 Aszendostoma

5-460.3 Transversostoma

5-460.4 Deszendostoma

5-460.5 Sigmoideostoma

5-460.x Sonstige

5-460.y nicht näher bezeichnet

5-461 Anlegen eines Enterostomas, endständig, als selbstständiger Eingriff

5-461.0 Zäkostoma

5-461.1 Aszendendostoma

5-461.2 Transversostoma

5-461.3 Deszendostoma

5-461.4 Sigmoideostoma

5-461.5 Ileostoma

5-461.x Sonstige

5-461.y nicht näher bezeichnet

5-462 Anlegen eines Enterostoma (als protektive Maßnahme) im Rahmen eines anderen Eingriffes

5-462.0 Jejunostoma

5-462.1 Ileostoma

5-462.2 Zäkostoma (Zäkale Lippenfistel)

5-462.3 Aszendostoma

5-462.4 Transversostoma

5-462.5 Deszendostoma

5-462.6 Sigmoideostoma

5-462.7 Appendikostoma

5-462.x Sonstige

5-462.y nicht näher bezeichnet

5-463 Anlegen anderer Enterostomata

5-463.0 Duodenostomie (Anlegen einer Ernährungsfistel)

5-463.1 Jejunostomie (Anlegen einer Ernährungsfistel)

5-463.2 Kolostomie, nicht näher bezeichnet

5-463.3 Bishop-Koop-Anastomose

5-463.x Sonstige

5-463.y nicht näher bezeichnet

5-464 Revision und andere Eingriffe an einem Enterostoma

5-464.0 plastische Erweiterung

5-464.1 plastische Einengung

5-464.2 Neueinpflanzung

5-464.3 Abtragung des vorverlagerten Teiles

5-464.4 Umwandlung in ein kontinentes Stoma (z.B. Kock-Pouch)

5-464.5 Korrektur einer parastomalen Hernie

5-464.x Sonstige

5-464.y nicht näher bezeichnet

5-465 Rückverlegung eines doppelläufigen Enterostoma

5-465.0 Jejunostoma

5-465.1 Ileostoma

5-465.2 Kolostoma

5-465.x Sonstige

5-465.y nicht näher bezeichnet

5-466 Wiederherstellung der Kontinuität des Darmes bei endständigen Enterostomata

5-466.0 Jejunostoma

5-466.1 Ileostoma

5-466.2 Kolostoma

5-466.x Sonstige

5-466.y nicht näher bezeichnet

5-467 Andere Rekonstruktion des Darmes

Exkl. Rekonstruktion des Rektums

5-467.0 Naht (nach Verletzung)

5-467.1 Verschluss einer Darmfistel, offen chirurgisch

5-467.2 Verschluss einer Darmfistel, endoskopisch

5-467.3 Erweiterungsplastik

5-467.4 Verschmälerungsplastik

5-467.5 Revision einer Anastomose

5-467.6 Dünndarmtransplantation

5-467.7 Anlegen eines Reservoirs, exkl. Anlegen eines Reservoirs zur Harnableitung

5-467.8 Revision eines Reservoirs

5-467.x Sonstige

5-467.y nicht näher bezeichnet

5-484 Rektumresektion unter Sphinktererhaltung

Inkl. Rektosigmoidektomie

5-484.0 anteriore Segmentresektion

5-484.1 posteriore Segmentresektion (Rectotomia posterior)

5-484.2 tubuläre Resektion unter Belassen des Paraproktiums

5-484.3 anteriore Resektion

5-484.4 hohe anteriore Resektion

5-484.5 tiefe anteriore Resektion

5-484.6 tiefe anteriore Resektion mit peranaler Anastomose

5-484.7 erweiterte anteriore Resektion mit Entfernung von Nachbarorganen

5-484.x Sonstige

5-484.y nicht näher bezeichnet

5-485 Rektumresektion ohne Sphinktererhaltung

5-485.0 abdominoperineal

5-485.1 abdominoperineal mit Entfernung von Nachbarorganen

5-485.2 abdominosakral

5-485.3 abdominosakral mit Entfernung von Nachbarorganen

5-485.4 sakroperineal

5-485.5 perineal

5-485.x Sonstige

5-485.y nicht näher bezeichnet

5-486 Rekonstruktion des Rektums

5-486.0 Naht (nach Verletzung)

5-486.1 plastische Rekonstruktion

5-486.2 Verschluss einer Rektum-Haut-Fistel

5-486.3 abdominale Rektopexie, offen chirurgisch

5-486.4 abdominale Rektopexie, laparoskopisch

5-486.5 Rektopexie durch Rectotomia posterior

5-486.6 extraanale Mukosaresektion (Rehn-Delorme)

5-486.x Sonstige

5-486.y nicht näher bezeichnet

5-489 Andere Operation am Rektum

5-489.0 Ligatur

5-489.1 Sklerosierung, peranal

5-489.2 Dilatation, peranal

5-489.b endoskopische Bougierung

5-489.c Endo-Loop

5-489.d endoskopisches Clippen

5-489.e endoskopische Injektion

5-489.g Einlegen oder Wechsel einer Prothese, endoskopisch

5-489.h Entfernung einer Prothese, endoskopisch

5-489.x Sonstige

5-489.y nicht näher bezeichnet

5-490 Inzision und Exzision von Gewebe der Perianalregion

5-490.0 Inzision

5-490.1 Exzision

5-490.x Sonstige

5-490.y nicht näher bezeichnet

5-491 Operative Behandlung von Analfisteln

5-491.0 Inzision (Spaltung)

5-491.1 Exzision

5-491.2 Fadendrainage

5-491.x Sonstige

5-491.y nicht näher bezeichnet

5-492 Lokale Exzision und Destruktion von erkranktem Gewebe des Analkanals

Inkl. Blutstillung

5-492.0 Exzision

5-492.1 Destruktion

5-492.2 Exzision, endoskopisch

5-492.3 Destruktion, endoskopisch

5-492.x Sonstige

5-492.y nicht näher bezeichnet

Appendix II

Results

Figure 10: Impact of inclusion and exclusion criteria on study population (2004)

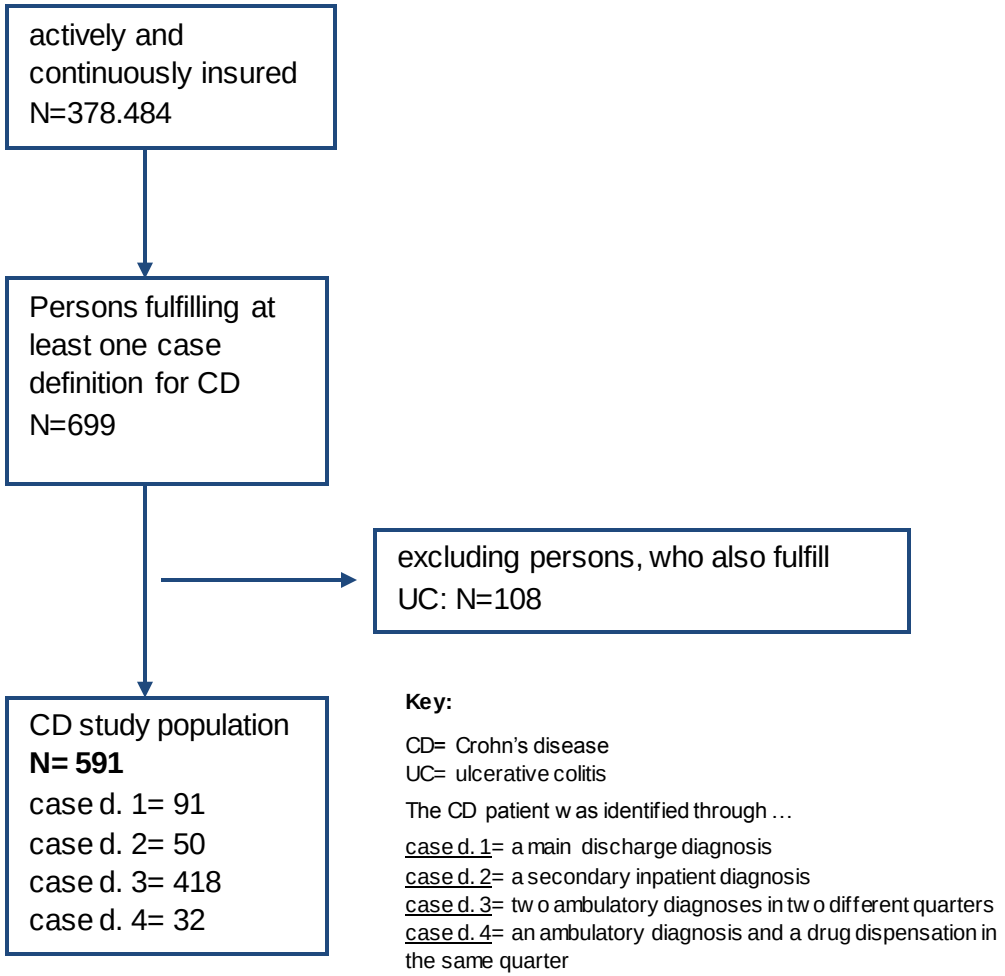

Table 17: Distribution of CD diagnoses in study population (2004)

Inpatient diagnoses		
Diagnosis	Frequency	Percent
CD small intestine (K50.0)	47	33.3
CD large intestine (K50.1)	39	27.7
Other CD (K50.8)	12	8.5
CD unspecified (K50.9)	43	30.5
Total	**141**	100.0
Ambulatory diagnoses		
Diagnosis	Frequency	Percent
CD small intestine (K50.0)	50	11.1
CD large intestine (K50.1)	71	15.8
Other CD (K50.8)	14	3.1
CD unspecified (K50.9)	315	70.0
Total	**450**	100.0

Table 18: Absolute and relative frequencies of dispensed drugs in 2004

Name	ATC code/ OPS code	Frequency	Percentage of all dispensations
aminosalicylic acids		**1076**	**38.7**
olsazaline, oral	A07EC03	2	< 0.1
sulfasalazine, oral	A07EC01	77	2.8
mesalazine, oral	A07EC02	997	35.8
budesonide (oral)		**352**	**12.7**
budesonide	A07EA06	352	12.7
systemic corticosteroids		**588**	**21.1**
dexamethasone	H02AB02	3	0.1
fluocortolone	H02AB03	7	0.3
methylprednisolone	H02AB04	27	1.0
prednisolone	H02AB06	395	14.2
prednisone	H02AB07	156	5.6
topical medication		**121**	**4.4**
hydrocortisone	A07EA02	23	0.8
betamethasone	A07EA04	3	0.1
prednisolone	H02AB06	1	<0.1
mesalazine	A07EC02	79	2.8
budesonide	A07EA06	15	0.5
immunosuppressants		**636**	**22.9**
mercaptopurine	L01BB02	32	1.1
cyclosporine	L04AD01	14	0.5
azathioprine	L04AX01	590	21.2
biologicals		**10**	**0.4**
infliximab**	L04AB02/ 8012u	10	0.4
Total		**2783**	**100.0**

** including inpatient dispensations, identified through OPS codes

Figure 11: Proportion of CD patients with at least one dispensation of grouped medications in 2004

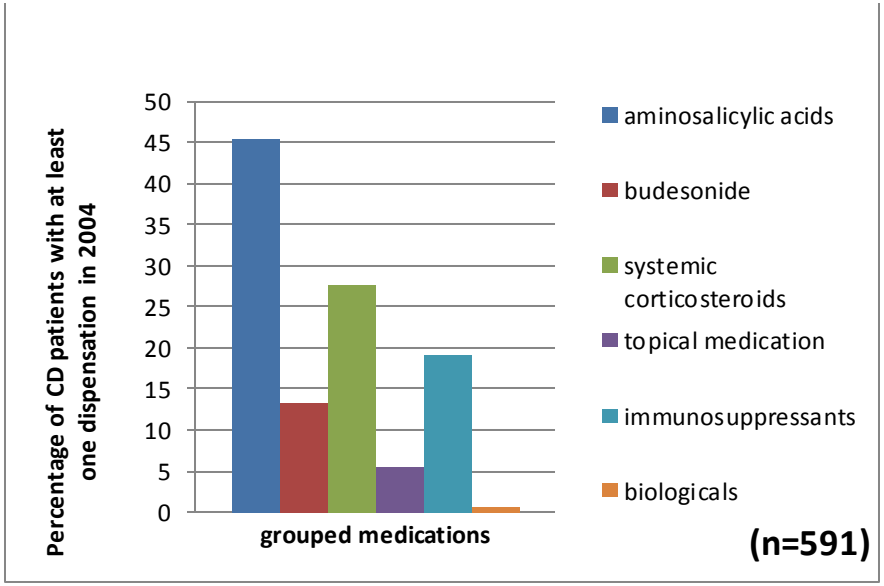

Table 19: Proportion of CD patients with at least one dispensation of grouped medications in 2004

Name of grouped medications	Number of persons with at least one dispensation	Percent of CD patients in 2004 n=591
aminosalicylic acids	269	45.5
budesonide	78	13.2
systemic corticosteroids	164	27.8
topical medication	33	5.6
immunosuppressants	113	19.1
biologicals	3	0.5

Figure 12: Impact of inclusion and exclusion criteria on study population (2005)

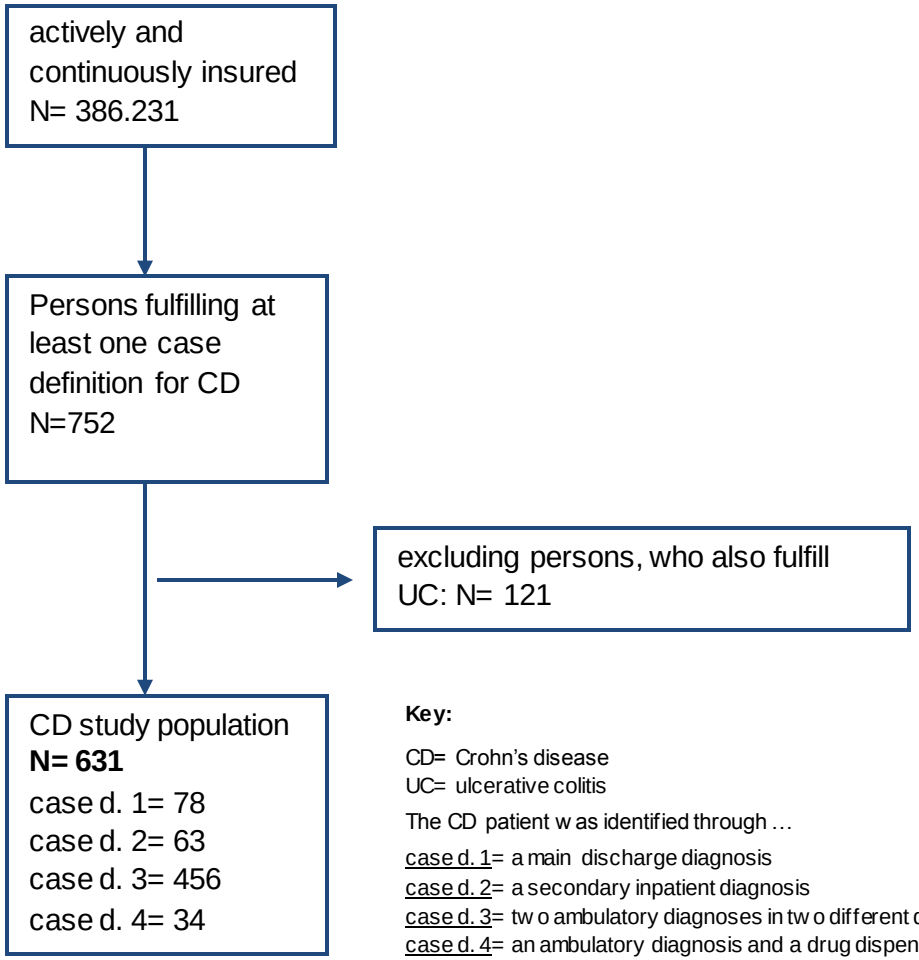

Table 20: Distribution of CD diagnoses in study population 2005

Inpatient diagnoses		
Diagnosis	Frequency	Percent
CD small intestine (K50.0)	44	31.2
CD large intestine (K50.1)	32	22.7
Other CD (K50.8)	18	12.8
CD unspecified (K50.9)	47	33.3
Total	**141**	100
Ambulatory diagnoses		
Diagnosis	Frequency	Percent
CD small intestine (K50.0)	47	9.6
CD large intestine (K50.1)	78	15.9
Other CD (K50.8)	20	4.1
CD unspecified (K50.9)	345	70.4
Total	**490**	100.0

Table 21: Absolute and relative frequencies of dispensed drugs in 2005

Name	ATC code/ OPS code	Frequency	Percentage of all dispensations
aminosalicylic acids		**1074**	**35.9**
olsazaline, oral	A07EC03	2	< 0.1
sulfasalazine, oral	A07EC01	74	2.5
mesalazine, oral	A07EC02	998	33.3
budesonide (oral)		**433**	**14.5**
budesonide	A07EA06	433	15.5
systemic corticosteroids		**615**	**20.5**
dexamethasone	H02AB02	7	0.2
methylprednisolone	H02AB04	17	0.6
prednisolone	H02AB06	455	15.2
prednisone	H02AB07	136	4.5
topical medication		**96**	**3.2**
hydrocortisone	A07EA02	16	0.5
betamethasone	A07EA04	3	0.1
mesalazine	A07EC02	65	2.2
budesonide	A07EA06	10	0.3
predonisone	H02AB07	1	< 0.1
prednisolone	H02AB06	1	< 0.1
immunosuppressants		**745**	**24.9**
mercaptopurine	L01BB02	30	1
cyclosporine	L04AD01	8	0.3
azathioprine	L04AX01	707	23.6
biologicals		**30**	**1.0**
infliximab**	L04AB02/ 8012u	30	1.0
Total		**2993**	**100.0**

** including inpatient dispensations, identified through OPS codes

Figure 13: Proportion of CD patients with at least one dispensation of grouped medications in 2005

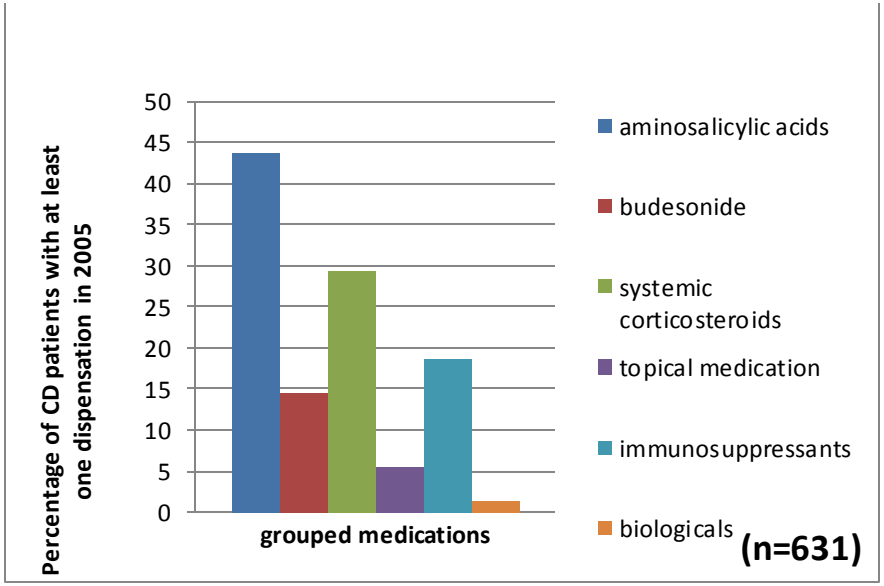

Table 22: Proportion of CD patients with at least one dispensation of grouped medications in 2005

Name of grouped medications	Number of persons with at least one dispensation	Percent of CD patients in 2005 n=631
aminosalicylic acids	276	43.7
budesonide	91	14.4
systemic corticosteroids	185	29.3
topical medication	34	5.4
immunosuppressants	117	18.5
biologicals	9	1.4

Figure 14: Impact of inclusion and exclusion criteria on study population (2006)

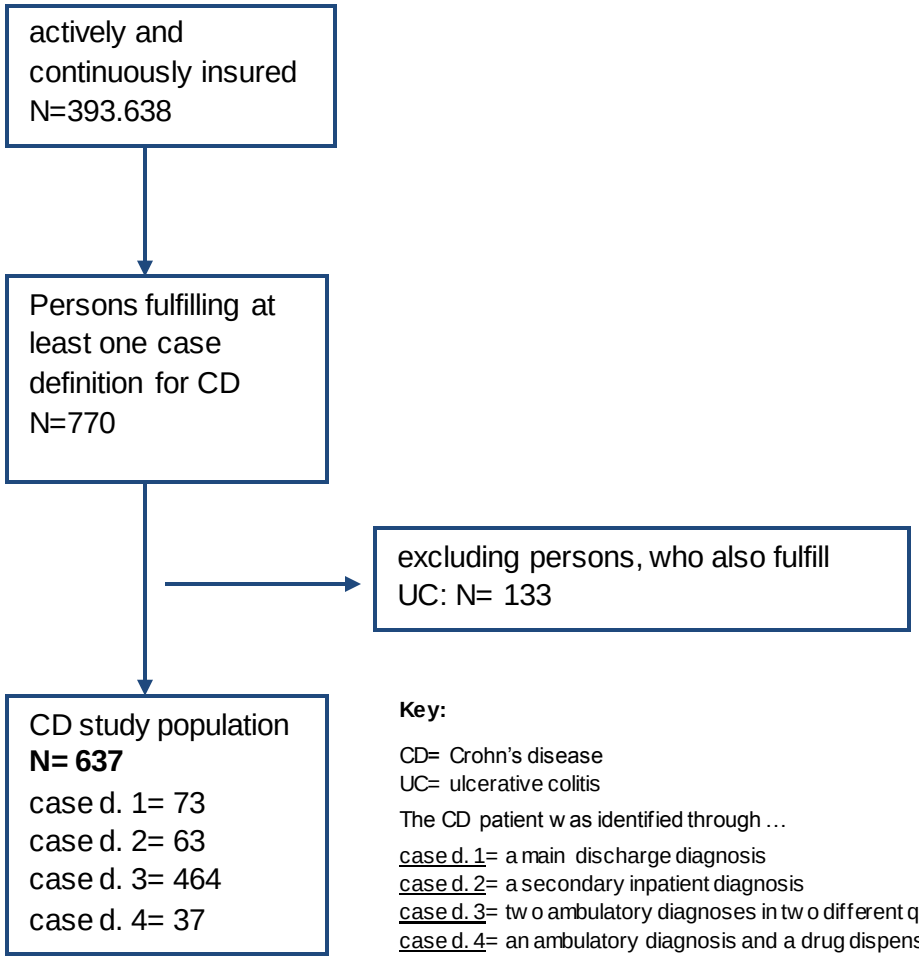

Table 23: Distribution of CD diagnoses in study population 2006

Inpatient diagnoses		
Diagnosis	Frequency	Percent
CD small intestine (K50.0)	36	26.5
CD large intestine (K50.1)	25	18.4
Other CD (K50.8)	20	14.7
CD unspecified (K50.9)	55	40.4
Total	**136**	100.0
Ambulatory diagnoses		
Diagnosis	Frequency	Percent
CD small intestine (K50.0)	44	8.8
CD large intestine (K50.1)	81	16.2
Other CD (K50.8)	18	3.6
CD unspecified (K50.9)	358	71.4
Total	**501**	100.0

Table 24: Absolute and relative frequencies of dispensed drugs in 2006

Name	ATC code/OPS code	Frequency	Percentage of all dispensations
aminosalicylic acids		**1132**	**37.6**
olsazaline, oral	A07EC03	4	0.1
sulfasalazine, oral	A07EC01	69	2.3
mesalazine, oral	A07EC02	1059	35.2
budesonide (oral)		**439**	**14.6**
budesonide	A07EA06	439	14.6
systemic corticosteroids		**589**	**19.6**
dexamethasone	H02AB02	1	< 0.1
fluocortolone	H02AB03	13	0.4
methylprednisolone	H02AB04	19	0.6
prednisolone	H02AB06	429	14.3
prednisone	H02AB07	125	4.2
triamcinolone	H02AB08	2	< 0.1
topical medication		**98**	**3.3**
hydrocortisone	A07EA02	26	0.9
betamethasone	A07EA04	1	< 0.1
mesalazine	A07EC02	65	2.2
budesonide	A07EA06	6	0.2
immunosuppressants		**718**	**23.9**
mercaptopurine	L01BB02	33	1.0
cyclosporine	L04AD01	8	0.3
azathioprine	L04AX01	677	22.5
biologicals		**32**	**1.0**
infliximab**	L04AB02/ 8012u	32	1.0
Total		**3008**	**100.0**

** including inpatient dispensations, identified through OPS codes

Figure 15: Proportion of CD patients with at least one dispensation of grouped medications in 2006

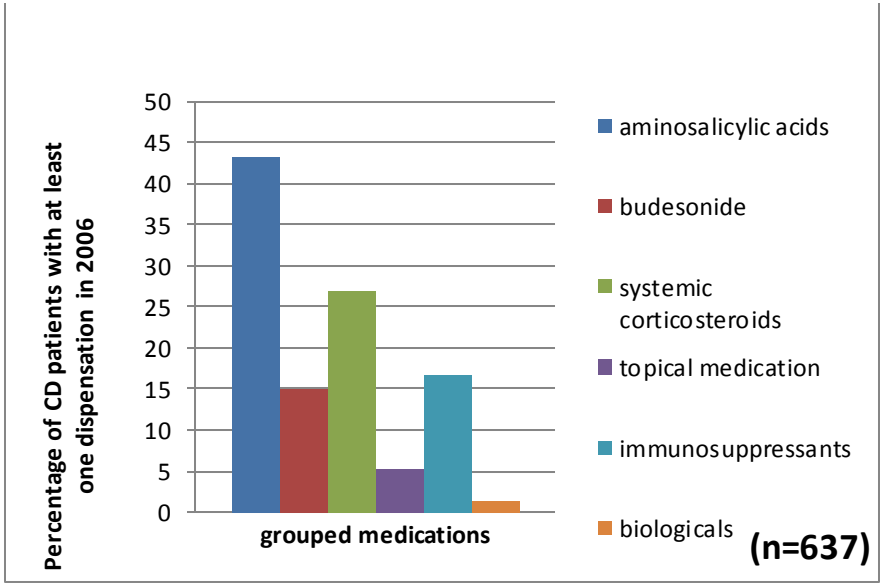

Table 25: Proportion of CD patients with at least one dispensation of grouped medications in 2006

Name of grouped medications	Number of persons with at least one dispensation	Percent of CD patients in 2006 n=637
aminosalicylic acids	276	43.3
budesonide	96	15.1
systemic corticosteroids	172	27.0
topical medication	33	5.2
immunosuppressants	107	16.8
biologicals	9	1.4

Table 26: Sensitivity analysis: absolute and relative frequencies of drugs dispensed to CD patients (case definitions 1-3) in 2007

Name	ATC code/ OPS code	Frequency	Percentage of all dispensations
aminosalicylic acids		**1169**	**32.1**
olsazaline, oral	A07EC03	10	0.3
sulfasalazine, oral	A07EC01	60	1.6
mesalazine, oral	A07EC02	1099	30.2
budesonide (oral)		**493**	**13.6**
budesonide	A07EA06	493	13.6
topical medication		**110**	**3.0**
hydrocortisone	A07EA02	33	0.9
betamethasone	A07EA04	4	0.1
mesalazine	A07EC02	69	1.9
budesonide	A07EA06	4	0.1
systemic corticosteroids		**737**	**20.3**
betamethasone	H02AB01	4	0.1
dexamethasone	H02AB02	9	0.3
fluocortolone	H02AB03	10	0.3
methylprednisolone	H02AB04	30	0.8
prednisolone	H02AB06	560	15.4
prednisone	H02AB07	124	3.4
immunosuppressants		**1060**	**29.1**
methotrexate	L01BA01	11	0.3
mercaptopurine	L01BB02	71	2.0
tacrolimus	L04AD02	16	0.4
azathioprine	L04AX01	962	26.4
biologicals		**70**	**1.9**
infliximab**	L04AB02/ 8012u	56	1.5
adalimumab**	L04AB04/ 8012t	14	0.4
Total		**3639**	**100.0**

** including inpatient dispensations, identified through OPS codes

Figure 16: Sensitivity analysis: Proportion of CD patients according to case definitions 1-3 with at least one dispensation of grouped medications in 2007

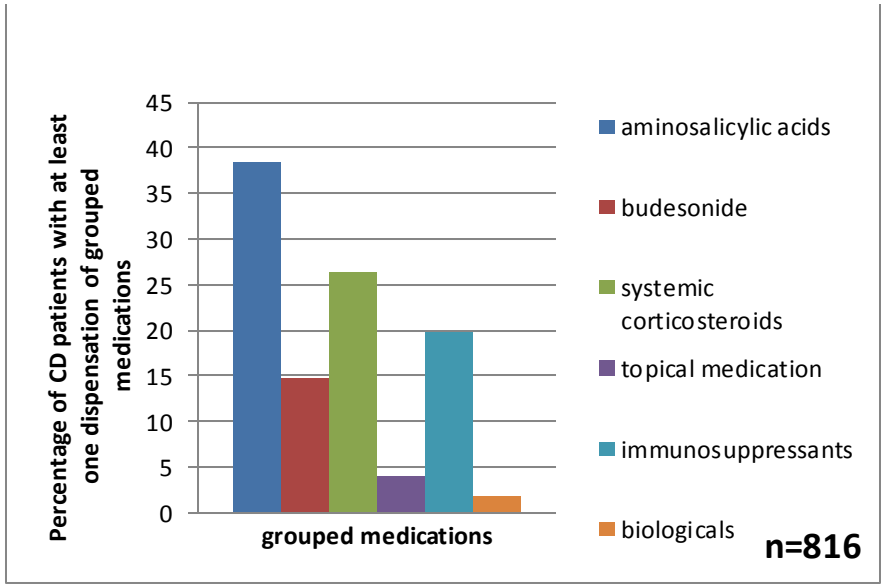

Table 27: Sensitivity analysis: absolute and relative frequencies of drugs dispensed to CD patients in the 1rst and 2nd quarter in 2007

Name	ATC code/ OPS code	Frequency	Percentage of all dispensations
aminosalicylic acids		**601**	**32.5**
olsazaline, oral	A07EC03	4	0.2
sulfasalazine, oral	A07EC01	29	1.6
mesalazine, oral	A07EC02	568	30.8
budesonide (oral)		**259**	**14.0**
budesonide	A07EA06	259	14.0
topical medication		**58**	**3.1**
hydrocortisone	A07EA02	10	0.5
betamethasone	A07EA04	2	0.1
mesalazine	A07EC02	43	2.3
budesonide	A07EA06	3	0.2
systemic corticosteroids		**374**	**20.3**
betamethasone	H02AB01	3	0.2
dexamethasone	H02AB02	5	0.3

Name	ATC code/ OPS code	Frequency	Percentage of all dispensations
fluocortolone	H02AB03	6	0.3
methylprednisolone	H02AB04	21	1.1
prednisolone	H02AB06	279	15.1
prednisone	H02AB07	60	3.3
immunosuppressants		**524**	**28.4**
methotrexate	L01BA01	5	0.3
mercaptopurine	L01BB02	36	2.0
azathioprine	L04AX01	483	26.2
biologicals		**31**	**1.7**
infliximab**	L04AB02/ 8012u	22	1.2
adalimumab**	L04AB04/ 8012t	9	0.5
Total		**1847**	**100.0**

** including inpatient dispensations, identified through OPS codes

Figure 17: Sensitivity analysis: Proportion of CD patients with at least one dispensation of grouped medications in 1+2 quarter 2007

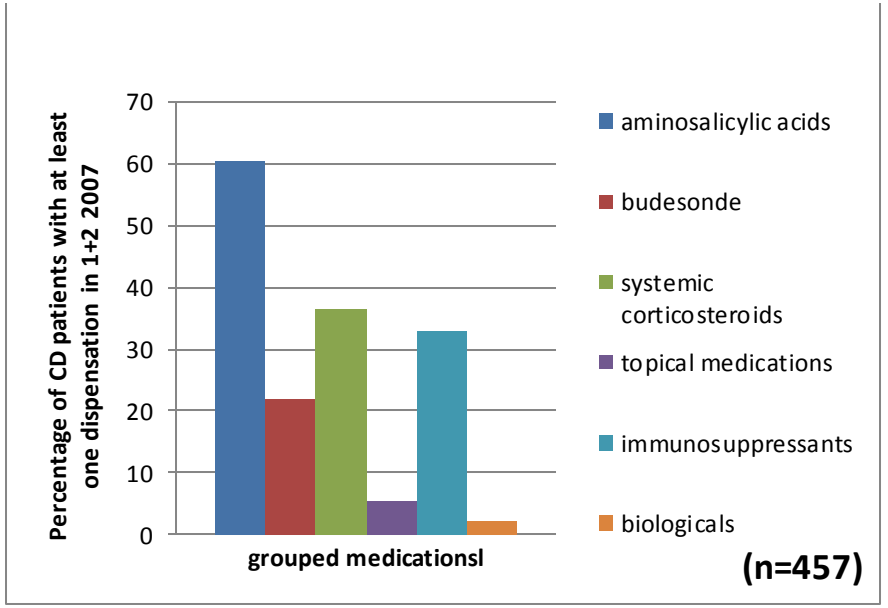

Table 28: Sensitivity analysis: absolute and relative frequencies of drugs dispensed to CD patients in the 3rd and 4th quarter in 2007

Name	ATC code/OPS code	Frequency	Percentage of all dispensations
aminosalicylic acids		**613**	**31.5**
olsazaline, oral	A07EC03	6	0.3
sulfasalazine, oral	A07EC01	36	1.9
mesalazine, oral	A07EC02	571	29.4
budesonide (oral)		**269**	**13.8**
budesonide	A07EA06	269	13.8
topical medication		**60**	**3.1**
hydrocortisone	A07EA02	23	1.2
betamethasone	A07EA04	2	0.1
mesalazine	A07EC02	33	1.7
budesonide	A07EA06	1	< 0.1
sulfasalazine	A07EC01	1	< 0.1
systemic corticosteroids		**402**	**20.7**
betamethasone	H02AB01	1	0.1
dexamethasone	H02AB02	9	0.5
fluocortolone	H02AB03	4	0.2
methylprednisolone	H02AB04	11	0.6
prednisolone	H02AB06	305	15.7
prednisone	H02AB07	72	3.7
immunosuppressants		**553**	**28.5**
methotrexate	L01BA01	6	0.3
mercaptopurine	L01BB02	36	1.9
	L04AD02	16	0.8
azathioprine	L04AX01	495	25.5
biologicals		**47**	**2.4**
infliximab**	L04AB02/ 8012u	34	1.8
adalimumab**	L04AB04/ 8012t	13	0.7
Total		**1944**	**100.0**

** including inpatient dispensations, identified through OPS code

Figure 18: Sensitivity analysis: Proportion of CD patients with at least one dispensation of grouped medications in 3+4 quarter 2007