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aAgaplesion Markus Hospital, Frankfurt/Main, Germany; bAdelphi Real World, Bollington, UK; cPfizer Inc, Groton, USA; dPfizer Inc, New York, USA; ePfizer Germany GmbH, Berlin, Germany; fHGC Healthcare Consultants GmbH, Dusseldorf, Germany

ABSTRACT

Aims: To investigate treatment of moderate-to-severe ulcerative colitis (UC) using real-world German health insurance claims data.

Materials and methods: A retrospective, longitudinal cohort study was conducted from a German statutory health insurance database for adult patients with UC indexed on biologic therapy initiation (2013–2015). Anonymized data were evaluated for 12 months prior to (baseline) through 24 months after (follow-up) indexing. Biological dose escalations, steroid and immunosuppressant use, healthcare resource utilization (HCRU) and direct healthcare costs were evaluated, with significant differences assessed across and between index biologics. Descriptive statistics, chi-square or Fisher’s exact tests, and analysis of variance were performed.

Results: The analysis included 304 patients (adalimumab, n = 125; golimumab, n = 47; infliximab, n = 114; vedolizumab, n = 18). Demographic and clinical characteristics were similar across biologics. Dose escalations occurred in 58% of patients (73% of patients receiving adalimumab), with 41% receiving subsequent de-escalation. Steroids were used during follow-up by 74% of patients; 25% received steroids >14 weeks after indexing. Overall, 41% of patients received an immunosuppressant during follow-up. Steroid and immunosuppressant use were similar across biologics. Total direct healthcare costs were higher during follow-up than baseline and differed significantly across treatments (p < .05), with highest costs for golimumab. Biologic costs contributed to a major portion of follow-up costs. HCRU and costs for most resources were higher in the first 12-month follow-up period than baseline. All resource use except gastroenterology visits returned to, or below, baseline levels 13–24 months post-index date.

Limitations: There was potential for inappropriate inclusion/exclusion due to miscoding. Patients may have received biologics >12 months prior to the index date. Biologic originators and biosimilars could not be differentiated.

Conclusions: These data suggest that control with current biologics is suboptimal. Further treatment options that provide sustained steroid-free remission for this patient population without the need for dose escalations or concomitant therapies may be warranted.

Original Research

JOURNAL OF MEDICAL ECONOMICS

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Introduction

Ulcerative colitis (UC) is a chronic, relapsing-remitting, inflammatory bowel disease, characterized by continuous mucosal inflammation starting in the rectum and extending proximally to the colon. A systematic review of the global epidemiology of UC, including 60 studies from 1990 or later, found that reported prevalence varied from 2.4 to 505 cases per 100,000 people, being more common in the industrialized nations, while the incidence of UC ranged from 0.15 to 57.9 per 100,000 person-years. Since the recognition of UC, the global incidence has increased, with recent studies suggesting that the incidence in the western world has stabilized, but is increasing in newly industrialized countries. Estimates of the magnitude of increase in incidence vary; a systematic review reported an annual increase of 2.4–18.1% in studies that showed a significant rise in incidence while a more recent review reported annual increases of 14.9% between 1988 and 2012 in Brazil and of 4.8–6.2% between 1998 and 2008 in Taiwan.

Treatment options for UC include aminosalicylates (5-ASA), corticosteroids, immunosuppressants, biologics (tumor necrosis factor inhibitors and anti-integrins), calcineurin inhibitors, the JAK inhibitor tofacitinib, and surgery as an option for non-responsive patients. Guidelines recommend that treatments are selected based on disease site, severity and current activity.

Topical and/or oral 5-ASA is generally used as 1st-line treatment to induce remission in mild-to-moderate UC, with
the addition of topical/oral steroid treatment if there is insufficient response. In moderate-to-severe UC, systemic steroids are the most common 1st-line treatment. In patients showing inadequate response, or developing a dependency on steroids to maintain remission, 2nd-line therapy is usually an immunosuppressant or biologic 9. Severe disease is treated with biologics and immunosuppressants. For patients in remission, maintenance treatment options include topical and/or oral 5-ASA, immunosuppressants or biologics if these have been used in inducing remission.

Not all patients receiving biologics achieve treatment targets, and some patients receiving immunosuppressive and/or biologic treatment respond initially, but then lose response 13,14. Estimates of the level of primary non-response vary, depending on the definition of response. The number of patients with acute refractory UC failing to show a response (≥3 point and ≥30% decrease in Mayo score, and ≥1 point decrease in rectal-bleeding subscore or absolute rectal-bleeding subscore of ≤1) to infliximab after 8 weeks of treatment in two phase III studies was reported to be 30–40% 15. A systematic review and clinician survey conducted in the UK and France reported that 19–48% of patients fail to respond to treatment with infliximab 13. A systematic review and meta-analysis of the efficacy of infliximab, adalimumab, golimumab and vedolizumab in moderate-to-severe UC reported that, with a pooled placebo rate for clinical remission (Mayo score ≤2 with no individual subscore >1) of 10%, 68–84% of patients receiving biologics failed to achieve clinical remission 16.

Secondary loss of response to biologics is often due to the development of anti-drug antibodies, which has been reported from a systematic literature review (SLR) to occur in up to 41% of patients with UC receiving biologics 17. The shortest observation period for the detection of anti-drug antibodies in this SLR was 10–14 days, the longest up to month of treatment 17.

Safety concerns also lead to patients stopping biologic therapy, with a systematic review reporting 4.1–13.1% of patients receiving infliximab, adalimumab, or golimumab for moderate-to-severe UC discontinuing therapy due to adverse events 16. In the event of a loss of response, switching to an alternative biologic is dependent on the reason for switching treatment, which can be secondary failure or primary failure. Based on the reasons for switching, a switch to an alternative biologic in the same class or to an alternative mode of action may be implemented. A systematic review and network meta-analysis reported that a change from one tumor necrosis factor (TNF) antibody to another TNF antibody is only associated with a small chance of success in approximately 30% of cases of primary failure and 45% of cases of secondary failure 18. Other studies indicate that a change to a treatment with an alternative mode of action results in a better response than a change to a treatment in the same class 13,19.

UC carries high humanitarian and economic burdens, with active UC resulting in impaired health-related quality of life (HRQoL) 20–22, reduced productivity 20,21,23 and increased healthcare resource utilization (HCRU) and healthcare costs 20,24,25. Suboptimal treatment response, loss of treatment response and changes to treatment are associated with increases in HCRU and costs 20.

The short-term aim of treatment in UC is to improve symptoms by reducing mucosal inflammation 27, with mucosal healing now considered an achievable treatment goal 1, and European, German and US guidelines all recommending sustained steroid-free remission as an appropriate target of treatment 9,10,12. Sustained remission is associated with a reduced need for surgery, and a decreased risk of colorectal cancer, as well as improved HRQoL 12,27. While patients with uncontrolled moderate-to-severe UC experience extremely unpleasant symptoms and very poor HRQoL, and patients refractory to pharmacologic treatment are likely to require surgery, controlled UC has been observed to present little in the way of disease burden 21,22,28, although long-term biologic use carries a substantial economic burden.

Despite the importance of effective long-term treatment in UC, medication changes observed in substantial proportions of patients are suggestive of suboptimal treatment response. In one US study of patients receiving 5-ASA, steroids, immunosuppressants or biologics as monotherapy, treatment changes (including discontinuation, switching, or dose escalation) were reported in 80% of patients within 12 months of initiating therapy 26, and a dose increase of >50% was observed in almost half of patients receiving adalimumab in a retrospective analysis of German prescription data 29.

There is a lack of comparative data on the implications of incomplete response to biologic therapies in moderate-to-severe UC for HCRU and healthcare costs; improved understanding of the impact of this relationship may help inform UC disease management strategies. This study was designed to assess key questions regarding treatment of moderate-to-severe UC from a German healthcare system and societal perspective, using real-world, representative claims data. The primary objectives of the analysis were to estimate the frequency and extent of dose escalations and subsequent dose de-escalations among patients using biologic therapy, to examine the patterns of concomitant steroid and immunosuppressants use among patients using biologic therapy, and to estimate HCRU and direct healthcare costs among patients using biologic therapy. The secondary objectives of the analysis were to compare HCRU, direct healthcare costs and steroid/immunosuppressant use prior to and following biologic therapy initiation.

**Methods**

**Study design**

Claims data for the period from January 2012 to December 2017, inclusive, were obtained from a German statutory health insurance (SHI) database containing >4.5 million patients from over 60 SHIs nationwide (from a total of 118). Data on health claims are transferred directly from healthcare providers to specialized data centers owned by SHIs, where all data are anonymized before entering the database. The sample is representative of the German population in terms
of age and sex, and is widely used for real-world evaluation of morbidity, drug use and healthcare costs\textsuperscript{30,31}.

A retrospective, longitudinal cohort analysis was conducted of data from patients with UC newly initiating biologic therapy between January 2013 and December 2015, with the date of initiation referred to as the index date and the therapy starting at that time referred to as the indexed biologic (Figure 1). Patient characteristics, dose escalations, concomitant use of steroids and immunosuppressants, and HCRU and direct healthcare costs were evaluated for the entire 12-month period prior to the index date (baseline) and the entire 24-month period after the index date (follow-up). An intention-to-treat approach was adopted, i.e. analysis based upon the treatment group the patient was initially assigned to; therefore, patients may have discontinued the indexed biologic at some point within the follow-up period, but their outcomes were still assessed throughout the entire follow-up period.

**Patients**

Patients had to be aged \( \geq 18 \) years on the index date, continuously insured by the SHI from January 2012 to December 2017, and have \( \geq 1 \) primary or secondary inpatient diagnosis code or confirmed outpatient diagnosis code of UC (K51) in the 12 months prior to or including the index date, using the International Classification of Diseases, 10\textsuperscript{th} Revision, German Modification (ICD-10-GM). They were also required to have an outpatient prescription or administration of one of the following biologic therapies between January 2013 and December 2015: adalimumab – Anatomical Therapeutic Chemical (ATC) of L04AB04 or Operationen- und Prozedurenschlüssel (OPS) of 6-001.d; golimumab – ATC of L04AB06 or OPS of 6-005.2; infliximab – ATC of L04AB02 or OPS of 6-001.e; or vedolizumab – ATC of L04AA33 or OPS of 6-008.5. Patients were excluded from the analysis if they had prescription or administration of two or more of any of the specified biologic therapies on the index date; \( \geq 1 \) prescription or administration of one of the specified biologic therapies in the baseline period; \( \geq 1 \) confirmed outpatient or inpatient primary or secondary diagnosis code for Crohn’s disease (CD; ICD-10-GM of K50) in the baseline or follow-up period.

**Outcomes**

Dose escalation: Daily doses were calculated as the quotient of the dose prescribed and duration between prescriptions/administrations; therefore, at least two prescriptions/administrations were required. Dose escalations were defined as an increase in daily dose following the induction period of \( \geq 50\% \) compared with the recommended maintenance daily dose (adalimumab: 2.86 mg [40 mg/2 weeks], golimumab: 3.57 mg [100 mg/4 weeks], infliximab: 6.25 mg [5 mg/kg/8 weeks – assuming patient weighs 70 kg], vedolizumab: 5.36 mg [300 mg/8 weeks]). De-escalations were defined as a daily dose equal to or below the recommended maintenance daily dose. Time-to-dose escalation (from start of maintenance) and subsequent de-escalation were calculated.

Steroid/immunosuppressant use: Concomitant use of steroids and immunosuppressants was assessed in the follow-up period. Four mutually exclusive patient subgroups were defined: biologic monotherapy (i.e. no steroids or immunosuppressants prescribed in the follow-up period), biologic + steroid(s) only, biologic + immunosuppressant(s) only, and biologic + steroid(s) + immunosuppressant(s). As some patients might continue to receive steroids prescribed prior to biologic initiation during the follow-up period as the dose is tapered prior to stopping steroid treatment, steroid users were further stratified by steroid use in or after the first 14 weeks following biologic initiation. Immunosuppressant users (and steroid users) were further stratified by whether or not an immunosuppressant (or steroid) had been prescribed in the baseline period, i.e. existing users or new users.

HCRU and direct healthcare costs: All-cause (i.e. for any reason) HCRU and associated direct healthcare costs were assessed in the baseline and follow-up periods. Medications (biologic, steroid and immunosuppressant therapy), outpatient appointments, hospital stays, visits to the emergency room (ER) and any surgeries or procedures related to the lower digestive tract were considered and reported, and associated costs were summated to determine the total direct health care cost.

**Analysis**

Analysis was descriptive for all outcomes and reported using frequencies and percentages for categorical variables, and counts, means, medians, and standard deviations for continuous variables. Data protection requirements established by the board of SHIs prevent the reporting of data from a sample size \(< 5 \) (other than 0).
Statistical significance ($p < .05$) of outcomes across index biologics (i.e. omnibus tests) was assessed using either chi-squared or Fisher’s exact tests (if expected cell count was $\leq 5$) for comparisons of categorical data, and analysis of variance for continuous variables. Bonferroni-adjusted pairwise statistical tests were also conducted between indexed biologics following a statistically significant omnibus test (for both categorical and continuous variables). Bonferroni-adjusted $p$-values were multiplied by the number of pairwise comparisons and a significance level of .05 used.

Time-to-dose escalation from start of maintenance was reported using Kaplan-Meier estimates accounting for right-censored observations, and statistical significance across index biologics was assessed using the log-rank test.

All analysis was performed using Stata, version 15.1 or later.

Ethics

This was a retrospective analysis of data, involving no decisions regarding patient interventions or the omission of interventions and all patient-level data were de-identified; complying with German data protection regulations. Hence, institutional review board/ethics approval and patient informed consent were not needed.

Results

Eligible patients

Of the 4.8 million individuals with data available during the study period, 304 met all the criteria for inclusion in the analysis (Figure 2).

Treatment, demographics and disease characteristics

Demographic and clinical characteristics were similar for patients receiving each of the biologics (Table 1).

Escalations of biologic dose

Data on two or more biologic prescriptions during the maintenance period were available to calculate dose escalations for 169 patients, and almost 60% of those patients had a dose escalation (Figure 3). There were significant differences in the proportions of patients with a dose escalation.

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**Figure 2.** Consort flow-diagram. Abbreviations. CD, Crohn’s disease; UC, ulcerative colitis.
between treatments, with patients receiving adalimumab being most likely to have their dose-escalated, and patients receiving golimumab least likely. The differences between golimumab and adalimumab and between golimumab and infliximab were significant (Bonferroni-adjusted p < .001 for both). There was a significant difference between treatments in the time-to-dose escalation (measured from start of maintenance), with the median survival time being shortest in patients receiving adalimumab (0.7 months) and longest in patients receiving vedolizumab (18.7 months), although differing administration frequencies between biologics limits interpretation of this finding (Figure 3(b)). Mean doses following dose escalations for patients initiated on adalimumab, golimumab, infliximab and vedolizumab were 2.8, 3.7, 4.4 and 1.8 times, respectively, the recommended maintenance dose.

Overall, 41% of patients having a dose escalation had a subsequent de-escalation. Of patients receiving infliximab and adalimumab, 53% and 31% (Bonferroni-adjusted p = .039), respectively, had a de-escalation following a dose escalation. The mean time from dose escalation to de-escalation was 103 days and 32 days, and doses were reduced to 77% and 84% of the recommended maintenance dose for infliximab and adalimumab, respectively; the difference in time to de-escalation was not statistically significant. Data regarding dose de-escalations for patients receiving golimumab or vedolizumab could not be reported as fewer than 5 patients in each treatment group had de-escalations.

A sensitivity analysis reported that 92%, 37%, 80% and 56% of patients receiving adalimumab, golimumab, infliximab, and vedolizumab, respectively, had dose escalations of >20% (p < .001), which was consistent with the findings of the main analysis.

**Use of steroids and immunosuppressants**

Steroid use decreased slightly from the baseline to follow-up period, but remained high, with 74% of all patients requiring steroids at some time after initiation of a biologic (Table 2). When only patients receiving steroids >14 weeks after initiation of a biologic were considered, this reduced to 25%. Overall, 11% of all patients receiving steroids in the follow-up period had not received steroids during the baseline period, and therefore required a new course of steroids during treatment with a biologic (Table 2). Of patients receiving steroids in the follow-up period, prednisolone was the most commonly used steroid, received by 80% of patients overall receiving steroids in the follow-up period, but remained high, with 74% of all patients requiring steroids at some time after initiation of a biologic (Table 2).

Use of both steroids and immunosuppressants in the baseline and follow-up periods was broadly similar across biologic treatment groups (Table 2).

When considering steroids taken at any time during the follow-up, the majority of patients received a biologic therapy in combination with a steroid, or a steroid and immunosuppressant; this was observed regardless of which biologic

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**Table 1. Patient demographics and disease characteristics.**

<table>
<thead>
<tr>
<th></th>
<th>Total n = 304</th>
<th>ADA n = 125</th>
<th>GOL n = 47</th>
<th>INF n = 114</th>
<th>VED n = 18</th>
<th>p-value*</th>
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<tbody>
<tr>
<td><strong>Age at index date (years)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>N</td>
<td>304</td>
<td>125</td>
<td>47</td>
<td>114</td>
<td>18</td>
<td>.346</td>
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<tr>
<td>Mean (SD)</td>
<td>42.9 (15.2)</td>
<td>42.7 (13.8)</td>
<td>46.3 (17.4)</td>
<td>42.0 (15.9)</td>
<td>40.3 (13.7)</td>
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<tr>
<td>Median</td>
<td>42.5</td>
<td>43.0</td>
<td>47.0</td>
<td>40.5</td>
<td>38.5</td>
<td></td>
</tr>
<tr>
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<td>18, 84</td>
<td>18, 76</td>
<td>19, 66</td>
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<tr>
<td>Sex, n (%)</td>
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<td></td>
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<td></td>
<td></td>
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<tr>
<td>Female</td>
<td>133 (44%)</td>
<td>53 (42%)</td>
<td>19 (40%)</td>
<td>52 (46%)</td>
<td>9 (50%)</td>
<td>.861</td>
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<tr>
<td>Male</td>
<td>171 (56%)</td>
<td>72 (58%)</td>
<td>28 (60%)</td>
<td>62 (54%)</td>
<td>9 (50%)</td>
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<tr>
<td>Baseline CCI</td>
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<td></td>
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<td></td>
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<td>125</td>
<td>47</td>
<td>114</td>
<td>18</td>
<td>.339</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>0.8 (1.3)</td>
<td>1.0 (1.2)</td>
<td>0.9 (1.5)</td>
<td>0.7 (1.3)</td>
<td>0.6 (1.2)</td>
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<tr>
<td>Median</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Min, max</td>
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<td>0, 6</td>
<td>0, 7</td>
<td>0, 7</td>
<td>0, 5</td>
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<tr>
<td>Categorised, n (%)</td>
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<td></td>
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<tr>
<td>0</td>
<td>178 (59%)</td>
<td>63 (50%)</td>
<td>28 (60%)</td>
<td>74 (65%)</td>
<td>13 (72%)</td>
<td>.139</td>
</tr>
<tr>
<td>1–2</td>
<td>95 (31%)</td>
<td>49 (39%)</td>
<td>12 (26%)</td>
<td>30 (26%)</td>
<td>4 (22%)</td>
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<tr>
<td>3–4</td>
<td>26 (9%)</td>
<td>12 (10%)</td>
<td>6 (13%)</td>
<td>8 (7%)</td>
<td>0 (0%)</td>
<td>.339</td>
</tr>
<tr>
<td>5+</td>
<td>5 (2%)</td>
<td>1 (1%)</td>
<td>1 (2%)</td>
<td>2 (2%)</td>
<td>1 (6%)</td>
<td></td>
</tr>
<tr>
<td>Baseline disease extent, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Pancolitis</td>
<td>96 (32%)</td>
<td>35 (28%)</td>
<td>14 (30%)</td>
<td>43 (38%)</td>
<td>4 (22%)</td>
<td>.097</td>
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<tr>
<td>Left-sided</td>
<td>16 (5%)</td>
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<td>0 (0%)</td>
<td>8 (7%)</td>
<td>0 (0%)</td>
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<tr>
<td>Proctosigmoiditis</td>
<td>17 (6%)</td>
<td>5 (4%)</td>
<td>4 (9%)</td>
<td>7 (6%)</td>
<td>1 (6%)</td>
<td></td>
</tr>
<tr>
<td>Proctitis</td>
<td>19 (6%)</td>
<td>6 (5%)</td>
<td>4 (9%)</td>
<td>5 (4%)</td>
<td>4 (22%)</td>
<td></td>
</tr>
<tr>
<td>Other/Unknownb</td>
<td>156 (51%)</td>
<td>71 (57%)</td>
<td>25 (53%)</td>
<td>51 (45%)</td>
<td>9 (50%)</td>
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<tr>
<td>Inflammatory polyps</td>
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<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Other ulcerative colitis</td>
<td>54 (18%)</td>
<td>25 (20%)</td>
<td>8 (16%)</td>
<td>19 (17%)</td>
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<tr>
<td>Ulcerative colitis, unspecified</td>
<td>155</td>
<td>70</td>
<td>25</td>
<td>51</td>
<td>9</td>
<td></td>
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</tbody>
</table>

*aIndicates difference across treatments.

*bIncludes ICD-10-GM codes for “inflammatory polyps”, “other ulcerative colitis”, and “ulcerative colitis, unspecified”. Patients could have multiple diagnosis codes recorded in the baseline period therefore, percentages may sum to more than 100%.

Abbreviations. ADA, adalimumab; CCI, Charlson Comorbidity Index; GOL, golimumab; INF, infliximab; SD, standard deviation; VED, vedolizumab.
Figure 3. Dose escalation. *An increase in daily dose of >50% compared to the recommended maintenance dose was considered a dose escalation; ^Omnibus p-value shown indicates difference across treatments; Bonferroni-adjusted pairwise p-values between treatments: ADA vs GOL, p<.001 (Odds ratio [95% CI] = 12.2 [3.8–38.9]); ADA vs INF, p=.999 (1.5 [0.7–3.2]); ADA vs VED, p=.419 (2.8 [0.9–8.5]); GOL vs INF, p<.01 (0.1 [0.0–0.4]); GOL vs VED, p=.153 (0.2 [0.1–0.9]); INF vs VED, p>.999 (1.9 [0.7–5.3]). Abbreviations. ADA, adalimumab; GOL, golimumab; INF, infliximab; SE, standard error; VED, vedolizumab.
they were prescribed (Figure 4). When only steroids taken >14 weeks post-index date were considered, ≤15% of patients received therapy consisting of a biologic in combination with a steroid +/− an immunosuppressant (Figure 4).

**Direct healthcare costs**

Total direct healthcare costs in the 24-month follow-up period differed significantly across biologic therapies ($p<.05$), driven by the significantly higher costs incurred by patients receiving golimumab than those receiving vedolizumab (Bonferroni-adjusted $p<.01$) (Figure 5(a)). Mean total direct healthcare costs during the baseline period were comparable across biologic treatments (Figure 5(b)). Direct healthcare costs in the first 12 months after initiation of a biologic were substantially higher than in the 12 months prior to initiation with all biologic therapies, and were significantly different dependent on treatment received, again due to the significantly higher costs with golimumab vs vedolizumab ($p<.05$; Figure 5(b)). Although costs decreased in the second 12-month period after the index date, they remained considerably higher than during the baseline period (Figure 5(b)).

Biologic medication costs contributed a major portion of the costs in the follow-up period (Table 3). However, the mean cost for all resources was higher in the first 12 months

---

### Table 2. Use of steroids and immunosuppressants.

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>ADA</th>
<th>GOL</th>
<th>INF</th>
<th>VED</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 304</td>
<td>125</td>
<td>47</td>
<td>114</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Patients receiving steroid treatment, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>256 (84%)</td>
<td>106 (85%)</td>
<td>40 (85%)</td>
<td>96 (84%)</td>
<td>14 (78%)</td>
</tr>
<tr>
<td>Follow-up – all steroid treatment (&lt;14 weeks and &gt;14 weeks post-index date)</td>
<td>224 (74%)</td>
<td>98 (78%)</td>
<td>36 (77%)</td>
<td>78 (68%)</td>
<td>12 (67%)</td>
</tr>
<tr>
<td>Follow-up – steroid treatment &gt;14 weeks post-index date only</td>
<td>77 (25%)</td>
<td>28 (22%)</td>
<td>17 (36%)</td>
<td>27 (24%)</td>
<td>5 (28%)</td>
</tr>
</tbody>
</table>

Mean (SD) average daily dose of steroid* – prednisolone equivalent, mg

**Baseline**

- ADA: 15.4 (17.7)
- GOL: 14.8 (14.4)
- INF: 15.8 (13.9)
- VED: 14.7 (20.5)

**Follow-up**

- ADA: 17.9 (54.8)
- GOL: 26.8 (87.1)
- INF: 13.5 (8.8)
- VED: 10.9 (9.6)

Newly initiated steroid treatment in follow-up, n (%)b

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>ADA</th>
<th>GOL</th>
<th>INF</th>
<th>VED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>24 (11%)</td>
<td>11 (11%)</td>
<td>&lt;5</td>
<td>7 (9%)</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Follow-up</td>
<td>126 (41%)</td>
<td>59 (47%)</td>
<td>17 (36%)</td>
<td>46 (40%)</td>
<td>&lt;5</td>
</tr>
</tbody>
</table>

Newly initiated immunosuppressant treatment in follow-up, n (%)c

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>ADA</th>
<th>GOL</th>
<th>INF</th>
<th>VED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>162 (53%)</td>
<td>71 (57%)</td>
<td>28 (60%)</td>
<td>57 (50%)</td>
<td>6 (33%)</td>
</tr>
<tr>
<td>Follow-up</td>
<td>126 (41%)</td>
<td>59 (47%)</td>
<td>17 (36%)</td>
<td>46 (40%)</td>
<td>&lt;5</td>
</tr>
</tbody>
</table>

*Excluding budesonide.

bAs a % of patients taking steroids in follow-up.

cAs a % of patients taking immunosuppressants in follow-up.

Abbreviations. ADA, adalimumab; GOL, golimumab; INF, infliximab; SD, standard deviation; VED, vedolizumab.

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Figure 4. Treatment groups in the 24-month follow-up. <5 patients received VED in combination with a steroid >14 weeks post-index. Abbreviations. ADA, adalimumab; GOL, golimumab; INF, infliximab; VED, vedolizumab.
Figure 5. Direct healthcare costs\(^a\). \(^a\)Costs include the costs of outpatient visits, hospital stays, surgeries and medication; \(^b\)Omnibus \(p\)-value shown indicates difference across treatments; Bonferroni-adjusted pairwise \(p\)-values between treatments: ADA vs GOL, \(p=\) .338; ADA vs INF, \(p>\) .999; ADA vs VED, \(p=\) .154; GOL vs INF, \(p=\) .176; GOL vs VED, \(p=\) .008; INF vs VED, \(p=\) .262; \(^c\)No difference between treatments during baseline or M13–24 follow-up period; omnibus \(p\)-value of \(p<\) .05 for difference across treatments during M0–12 follow-up period; Bonferroni-adjusted pairwise \(p\)-values between treatments during M0–12 follow-up period: ADA vs GOL, \(p=\) .217; ADA vs INF, \(p>\) .999; ADA vs VED, \(p=\) .395; GOL vs INF, \(p=\) .350; GOL vs VED, \(p=\) .019; INF vs VED, \(p=\) .308. Abbreviations. ADA, adalimumab; CI, confidence interval; GOL, golimumab; INF, infliximab; VED, vedolizumab.
after initiation of a biologic than the 12 months prior to initiation, with the exception of dermatology visits, steroids and immunosuppressants (Table 3). Although the costs of steroids and immunosuppressants decreased from baseline to follow-up, these costs remained high, decreasing to 80% and 63% of baseline levels, respectively, in the first follow-up period. During the second follow-up period, steroid costs remained at 60% of baseline, and immunosuppressant costs increased from the initial post-baseline level to 72% of baseline costs (Table 3).

Table 3. Breakdown of direct healthcare costs.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Follow-up</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Median</td>
<td></td>
</tr>
<tr>
<td>General practice visits, €</td>
<td>292.5 (206.1)</td>
<td>254.6</td>
<td>344.3 (271.6)</td>
</tr>
<tr>
<td>Resource users, n (%)</td>
<td>301 (99%)</td>
<td>295 (97%)</td>
<td>298 (98%)</td>
</tr>
<tr>
<td>Gastroenterology OP visits, €</td>
<td>104.4 (140.4)</td>
<td>28.5</td>
<td>198.7 (254.9)</td>
</tr>
<tr>
<td>Resource users, n (%)</td>
<td>187 (62%)</td>
<td>211 (69%)</td>
<td>200 (66%)</td>
</tr>
<tr>
<td>Psychology/psychiatry OP visits, €</td>
<td>46.8 (265.9)</td>
<td>0.0</td>
<td>81.3 (414.1)</td>
</tr>
<tr>
<td>Resource users, n (%)</td>
<td>20 (7%)</td>
<td>25 (8%)</td>
<td>26 (9%)</td>
</tr>
<tr>
<td>Dermatology OP visits, €</td>
<td>25.1 (73.7)</td>
<td>0.0</td>
<td>25.1 (56.3)</td>
</tr>
<tr>
<td>Resource users, n (%)</td>
<td>104 (34%)</td>
<td>114 (38%)</td>
<td>114 (38%)</td>
</tr>
<tr>
<td>Ophthalmology OP visits, €</td>
<td>18.6 (94.0)</td>
<td>0.0</td>
<td>31.3 (132.7)</td>
</tr>
<tr>
<td>Resource users, n (%)</td>
<td>76 (25%)</td>
<td>0.0</td>
<td>66 (22%)</td>
</tr>
<tr>
<td>Rheumatology OP visits, €</td>
<td>24.9 (89.2)</td>
<td>0.0</td>
<td>33.0 (126.6)</td>
</tr>
<tr>
<td>Resource users, n (%)</td>
<td>38 (13%)</td>
<td>38 (13%)</td>
<td>42 (14%)</td>
</tr>
<tr>
<td>ER visits, €</td>
<td>855.2 (2443.6)</td>
<td>0.0</td>
<td>1764.0 (6016.0)</td>
</tr>
<tr>
<td>Resource users, n (%)</td>
<td>68 (22%)</td>
<td>77 (25%)</td>
<td>47 (15%)</td>
</tr>
<tr>
<td>Surgery, €</td>
<td>1047.2 (2685.5)</td>
<td>0.0</td>
<td>3542.1 (12159.0)</td>
</tr>
<tr>
<td>Resource users, n (%)</td>
<td>104 (34%)</td>
<td>116 (38%)</td>
<td>57 (19%)</td>
</tr>
<tr>
<td>Inpatient stays, €</td>
<td>1928.8 (3894.0)</td>
<td>0.0</td>
<td>4176.9 (9461.6)</td>
</tr>
<tr>
<td>Resource users, n (%)</td>
<td>119 (39%)</td>
<td>132 (43%)</td>
<td>90 (30%)</td>
</tr>
<tr>
<td>Steroids, €</td>
<td>218.3 (380.3)</td>
<td>0.0</td>
<td>173.3 (296.4)</td>
</tr>
<tr>
<td>Resource users, n (%)</td>
<td>256 (84%)</td>
<td>197 (65%)</td>
<td>138 (45%)</td>
</tr>
<tr>
<td>Immunosuppressants, €</td>
<td>305.9 (1105.7)</td>
<td>0.0</td>
<td>192.9 (516.9)</td>
</tr>
<tr>
<td>Resource users, n (%)</td>
<td>34.7</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Biologic therapies, €</td>
<td>162 (53%)</td>
<td>0.0</td>
<td>108 (36%)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>0.0 (0.0)</td>
<td>23191.9 (11499.9)</td>
<td>15109.4 (12985.3)</td>
</tr>
<tr>
<td>Median</td>
<td>0.0</td>
<td>24457.5</td>
<td>15109.4 (12985.3)</td>
</tr>
<tr>
<td>Adalimumab, €</td>
<td>0.0 (0.0)</td>
<td>23886.7 (10907.1)</td>
<td>15980.5 (12665.5)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>0.0</td>
<td>25228.6</td>
<td>15980.5 (12665.5)</td>
</tr>
<tr>
<td>Median</td>
<td>0.0</td>
<td>26354.5</td>
<td>15980.5 (12665.5)</td>
</tr>
<tr>
<td>Golimumab, €</td>
<td>0.0 (0.0)</td>
<td>24828.9 (8633.2)</td>
<td>16791.0 (12814.1)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>0.0</td>
<td>26508.6</td>
<td>16791.0 (12814.1)</td>
</tr>
<tr>
<td>Median</td>
<td>0.0</td>
<td>27811.8</td>
<td>16791.0 (12814.1)</td>
</tr>
<tr>
<td>Infliximab, €</td>
<td>0.0 (0.0)</td>
<td>26621.0 (13347.8)</td>
<td>12219.2 (12512.7)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>0.0</td>
<td>27811.8</td>
<td>12219.2 (12512.7)</td>
</tr>
</tbody>
</table>

Paired t-tests: *p < .05 between baseline and M0–12 of follow-up; †p < .05 between baseline and M13–24 of follow-up; ‡p < .05 between M0–12 and M13–24 of follow-up.

Means and medians are based on total population, not just resource users.

Abbreviations. ER, emergency room; OP, outpatient; SD, standard deviation.


**Healthcare resource utilization**

Utilization of all reported healthcare resources increased during the first 12-month period after initiation of a biologic, with all resource use except for outpatient gastroenterology visits returning to levels at or below baseline levels in the second part of the follow-up period (Figure 6(a)). The length of hospital stays also increased in the 12 months after the index date before returning to pre-index levels (Figure 6(b)).

The maximum duration of both individual and total hospital stays were higher during the follow-up period compared with the baseline period; although not formally tested this could have contributed to the increased mean length of stay.

There were few differences in HCRU between patients receiving the different biologics, and where there was a significant difference, this was usually seen during both baseline and follow-up periods, suggesting there was no association of the biologic received with HCRU.
**Discussion**

In this retrospective, longitudinal cohort analysis of German claims data, unmet needs, indicated by dose escalations, concomitant use of steroids and immunosuppressants, and high levels of HCRU, were observed in patients receiving biologic treatment for UC. A proportion of patients receiving adalimumab, infliximab, vedolizumab and golimumab required dose escalations (19–73%) and treatment switching (31–32% for adalimumab, infliximab and vedolizumab). Concomitant use of steroids (12–21%), immunosuppressants (7–11%), and steroids + immunosuppressants (10–15%), when only considering steroids received after the likely period for steroid tapering, together with 11% of patients newly initiating steroids during follow-up period, all speak to the suboptimal response to biologic therapy in a proportion of patients. The significant level of unmet need that remains despite the availability of a number of biologic treatment options in UC has been recognized previously. Dose escalations of >50% were reported for some patients receiving each of the four indexed biologics, with 50% or more of patients receiving adalimumab, infliximab and vedolizumab, and 19% of patients receiving golimumab, having this level of increase. The extent of dose escalation in patients receiving adalimumab seen in the current analysis, with 74% of patients having a dose increase of >50% within 2 years of initiation, exceeded that seen in a previous analysis of German prescription data, in which dose escalations of >50% were observed within 12 months in 45% of patients receiving adalimumab and in a UK study, in which 55% of patients had an increase in adalimumab dose of >50% during an undefined period. In a retrospective analysis of US claims data for patients receiving adalimumab, infliximab, golimumab, certolizumab pegol, or natalizumab, >50% dose escalation within 2 years of initiation of treatment was reported in 40% of patients. The relatively low frequency of dose escalation in patients receiving golimumab seen in the current analysis (19%) may reflect the fact that dose escalation was not allowed in the product label, and hence physicians might have been concerned about potential issues with reimbursement if they were to increase the dose.

Overall, 74% of patients in our analysis received a steroid after the index date, with 25% receiving steroids more than 14 weeks after the index date; 11% of patients received steroids post-index, having not received them in the baseline period. Immunosuppressants were received by 41% of patients during the 24 months after initiation of a biologic. We observed infliximab to be taken with an immunosuppressant in 40% of patients (with the immunosuppressant being initiated during follow-up in 37% of patients). As German guidelines state that infliximab should preferably be given in combination with a thiopurine, these numbers may indicate treatment practices that do not align with recommendations. However, monotherapy should be the preferred therapeutic regime in patients with milder disease due to the safety issues associated with combined immunosuppressive therapies. The concomitant use of steroids and immunosuppressants that we observed is high compared with reports in the literature. Medical records for patients with UC in Europe and Canada indicated initiation, or a dose increase, of a non-biologic treatment in combination with adalimumab or infliximab for 21% of patients within 2 years of starting biologic treatment, and analysis of US claims data reported concomitant use of a non-biologic treatment within 1 year of initiation of a biologic in 23% of patients.

An increase in medication and associated costs following initiation of a biologic might be anticipated, given the purchase cost of these agents and the resource use involved in their administration, but utilization of almost all healthcare resources increased in the 12 months after patients commenced biologic treatment, as did both total and constituent direct healthcare costs. These findings are in contrast to a US retrospective chart review that reported significantly lower resource utilization during infliximab treatment compared with the pretreatment period; the difference in findings might reflect differences in the patient population in this published study compared with our analysis population. An open-label parallel-group, randomized trial comparing infliximab and cyclosporine in treating steroid-resistant UC in the UK reported a considerably higher total cost for infliximab than cyclosporine, supporting our finding of high costs associated with biologic therapy. The high cost of biologic therapy is expected to be offset to some degree by reductions in indirect costs, such as those associated with impaired productivity and sick leave; while sick leave was assessed, it was included in an alternative publication. Dose escalations in biologics being used to treat UC have been shown to be associated with increases in drug costs in both an analysis of German prescription data and a Spanish observational study, while an analysis of US insurance claims data has shown treatment switching, dose escalation and the need for combination therapy all result in increases in HCRU and costs.

Some limitations of this analysis are acknowledged. Privately insured patients are not covered within the database, but as these equate to around 10% of the German population, it is not felt this will impact extrapolation of the findings to the general population in Germany. The identification of patients with UC was made via the use of ICD-10-GM diagnosis codes, with potential for miscoding, which might have led to inappropriate inclusion or exclusion of patients from the analysis. The magnitude of miscoding is likely small, and would not be expected to affect the outcome of the study. The database provides data from a 6-year window, which limited the potential data accessed, and drove the duration of the baseline and follow-up periods. The study cohort identified may not reflect the broader population of patients with UC given some of the assumptions made in the study design, for example severity of UC was determined using treatment history and not symptoms. The small number of patients receiving vedolizumab likely reflects its approval for use in Europe in 2014 and the time lag due to this being claims data. Although patients using biologics in the 12-month baseline period prior to initiation of a biologic were excluded from this analysis, some patients may have received biologic therapy more than 12 months prior to the index date and would not be biologic-naïve at
the time of initiation of the indexed biologic. Decisions to escalate or de-escalate biologic dose might have been clinically based or due to biologic trough levels; reasons for dose decisions were not available from the data source. It was not possible to distinguish between originators and biosimilars in this analysis. Out-of-pocket and indirect costs were excluded from the analysis. Type of hospital (e.g. regional or academic) and type of treating physician (e.g. academic or non-academic) was not captured in the SHI claims data. Finally, the number of patients included in some analyses was low, with only 27 and 18 patients receiving golimumab and vedolizumab, respectively; findings must, therefore, be interpreted with care.

Despite these limitations, this analysis confirmed a continuing unmet need in UC, although a number of biologic treatment options are available. Treatment options other than new biologics might have advantages: the secondary loss of response to biologics is a potential issue, as a discrete-choice study has shown that in UC long-term symptom control is the attribute most valued by both physicians and patients; biologics require parenteral administration, and there is evidence that oral administration is preferred by patients with UC; and numerous studies have shown biologics to have poor cost-effectiveness.

In conclusion, continuing research is needed to identify whether either utilization of existing treatments or novel treatments for UC that provide sustained steroid-free remission, are cost-effective, and that align with patient preferences.

Transparency

Declaration of funding

The study was sponsored by Pfizer Inc.

Declaration of financial/other relationships

Axel Dignass served as consultant for AbbVie, Celgene, MSD, Roche, Sandoz/Hexal, Pfizer Inc, Takeda, Janssen, Vifor; received payment for development of educational presentations from Ferring, Falk Foundation, Tillotts, Takeda; received speaker fees from Falk Foundation; served as consultant for and received manuscript fees from Takeda; served as consultant for and received speaker fees from AbbVie, Ferring, Janssen, MSD, Pfizer Inc, Vifor, Celgene, Tillotts, and Takeda; received payment for development of educational presentations and speaker fees from Tillotts; received manuscript fees from Thieme and Wiley; received research grants from Institut für Gemeinwohl and Stiftung Leben mit Krebs; and received speaker fees from Med Update GmbH.

Joseph C. Cappelleri, Irene Modesto, Agnes Kissler, Lena Dietz, and Marco DiBonaventura are employed by Pfizer Inc (who funded this study). Danielle Bargo was an employee of Pfizer Inc at the time of the study and during manuscript development. Melanie May and Berit Libutzki are employed by HGC Healthcare Consultants GmbH.

JME peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Author contributions

All authors contributed to conception and design; have been involved in drafting the manuscript and revising it for critically important intellectual content; have given final approval of the version to be published and agree to be accountable for all aspects of the work.

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