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Treatment sequences, outcomes, healthcare utilization, and costs in patients with inflammatory bowel diseases requiring advanced treatment—real world comparative effectiveness from German claims data

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Abstract

Background There is limited data on inflammatory bowel disease advanced therapy sequences. Therefore, we examined real-world advanced therapy sequences to compare persistence, healthcare use and costs in first-line advanced therapy.

Methods Evaluable patient characteristics, treatments, sequences, and outcomes were extracted from the WIG2 claims benchmark database and observed from 2014 to 2021. Therapeutic effectiveness (persistence without discontinuation or inadequate response), healthcare resource utilization, and associated costs were analyzed. Advanced treatment group differences were adjusted by inverse probability weighting.

Results Two thousand nine hundred forty-eight patients with Crohn's disease or ulcerative colitis initiated at least one of the following advanced therapies during the study period: adalimumab (1,260), golimumab (111), infliximab (1,035), tofacitinib (17), ustekinumab (138) or vedolizumab (387). In patients with ulcerative colitis, vedolizumab as first-line advanced therapy demonstrated superior effectiveness in persistence without inadequate response over three years compared to infliximab ($p < 0.05$). Patients taking infliximab or ustekinumab had higher disease-related costs than those taking adalimumab, golimumab, tofacitinib or vedolizumab. In Crohn's disease patients, first-line treatment with adalimumab ($p < 0.001$), ustekinumab ($p < 0.001$) and vedolizumab ($p < 0.017$), showed superior persistence over 3 years compared to infliximab, and time to inadequate response was longer in patients taking adalimumab and vedolizumab ($p < 0.001$). Disease-specific treatment costs were lower in patients receiving adalimumab or vedolizumab as first-line advanced therapy. Compared to infliximab, patients treated with ustekinumab had significantly higher costs.

Conclusions Anti-TNF agents were most frequently used in first-line advanced therapy; however, vedolizumab appeared to be a preferred choice in terms of persistence and cost measures over three years from the start of treatment.

Keywords Inflammatory bowel disease, Advanced therapy sequencing, Real-world effectiveness

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Background

The prevalence of inflammatory bowel diseases (IBD)—like ulcerative colitis (UC) and Crohn's disease (CD)— is increasing globally; IBD prevalence is upwards of 0.3% in North America, Australia, and various countries across Europe. IBD is also emerging in newly industrialized countries with rapidly increasing incidence, posing a significant challenge for healthcare professionals and policymakers when providing effective and affordable care [1].

The primary therapeutic objectives for IBD patients aim for clinical response and remission, achieving endoscopic healing, normalizing inflammatory markers, reducing disability, and restoring quality of life [2–5]. In Germany, several advanced therapies are approved for UC and/or CD treatment: anti-tumor necrosis factor α (anti-TNF) agents such as adalimumab (ADA, CD approval in 2007, UC approval in 2012), infliximab (IFX, CD approval in 1999, UC approval in 2008), and golimumab (GOL, only approved in UC, 2013); the integrin-inhibitor vedolizumab (VDZ, CD/UC approval in 2014); interleukin-12/23 antagonist ustekinumab (UST, CD/UC approval in 2014/2017); and Janus kinase (JAK) inhibitor tofacitinib (TOF, UC approval in 2018). Other JAK inhibitors such as filgotinib and upadacitinib, S1P modulators ozanimod and estrasimod, and the IL-23 inhibitors risankizumab and mirikizumab, were also recently approved for use in UC and/or CD. UC and CD guidelines [6, 7] recommend systemic steroid therapy as initial treatment to induce remission in moderate to severe UC and CD; however, corticosteroids are not recommended for maintenance of remission. For recurring flare-ups, steroid-dependent or steroid refractory IBD, conventional treatment escalation should be followed by initiating advanced therapy [3, 4].

Although several advanced therapy options are available, recent studies have only reported moderate persistence rates and therapy switches frequently occur in real-world care [8, 9]. Current research also suggests the first advanced therapy may influence the disease phenotype due to differences in the underlying molecular mechanisms —the therapeutic pressure alters the immune response, potentially leading to anti-TNF-resistance [10, 11]. Therefore, decisive optimal sequencing is highly clinically relevant, but data supporting practical guidance is lacking.

To optimize treatment sequencies, Bressler [12] extensively reviewed published data on advanced therapies such as ADA, VDZ, UST, TOF, upadacitinib, ozanimod, and risankizumab, to treat UC and CD. In UC patients, clinical remission rates with ADA and VDZ were lower in patients previously exposed to anti-TNF therapy, indicating reduced effectiveness when used as second-line treatments [13, 14]. In contrast, UST, TOF, and upadacitinib maintained similar effectiveness regardless of prior anti-TNF use [12]. In CD patients, endoscopic remission rates also declined with prior anti-TNF exposure for patients treated with ADA and VDZ [15, 16], while UST and risankizumab showed consistent efficacy in both TNF-naïve and TNF-exposed patients [12].

Conversely, using VDZ as first-line advanced therapy did not appear to reduce the effectiveness of subsequent anti-TNF treatment. Anti-TNF agents demonstrated comparable effectiveness whether used initially or after VDZ failure [8, 9]. The EVOLVE study supported this finding, and also reported longer treatment persistence with VDZ as first-line advanced therapy in UC patients, possibly due to fewer serious infections and adverse events [17].

Several other studies have suggested that the effectiveness of advanced therapies depends on their position in the treatment sequence. Gros et al. [18] showed that prior exposure to advanced therapies increased the risk of VDZ discontinuation in UC patients by 54% (one prior therapy) and 112% (two or more prior therapies) compared to treatment-naïve patients. The LOVE-CD study also indicated that VDZ was more effective in CD patients when used as first-line advanced therapy rather than after anti-TNF exposure [19]. In UC patients who failed first-line anti-TNF therapy with GOL or ADA, the EFFICACY trial reported higher clinical remission rates at 14 weeks with VDZ (59%) than with IFX (50%) as second-line treatment [20]. A 10-year timeframe Markov model supported early use of VDZ or ADA for CD treatment, with VDZ providing the best long-term outcomes in terms of quality of life, disease activity, and surgery rates [21]. In UC, the head-to-head VARSITY trial showed higher clinical remission with VDZ than ADA (31.2% vs. 22.5%), though prior anti-TNF exposure reduced remission rates for both [22]. Real-world data further supported VDZ's superiority, showing higher treatment persistence and lower switch rates when used as first-line advanced therapy compared to anti-TNF agents [23, 24].

In real-world settings, comparisons of anti-TNF, UST, VDZ, and other newer treatment options in advanced therapy-naïve patients are essential to help physicians choose the best initial advanced therapy. However, to the best of our knowledge, no head-to-head studies, or studies on optimal sequencing of advanced IBD treatments, are available.

In this study we describe advanced therapy sequences from real-world data in Germany from 2014 to 2021 and compare therapy persistence, healthcare resource utilization (HCRU), and treatment costs by different first-line advanced therapy agents (ADA, IFX, GOL, UST, VDZ or TOF) for up to six years.

Materials and methods

Database

We analyzed German health claims data from the WIG2 benchmark database (owned by WIG2: Wissenschaftliches Institut für Gesundheitsökonomie und Gesundheitssystemforschung, Leipzig, Germany) using a longitudinal retrospective observational design. This anonymized healthcare claims database of approximately four million patients, insured by one of several different German statutory health insurance (SHI) providers, contains data spanning from 01 January 2014 to 31 December 2021. The database includes core data on the insured, and is representative of the German SHI population in terms of age, gender, and morbidity [25].

Using codes documented for billing purposes, we can identify diagnoses in both the outpatient and inpatient settings (by International Statistical Classification of Diseases and Related Health Problems 10th Revision, German version; ICD-10 GM codes), prescribed medications by Anatomical Therapeutic Chemical (ATC) code, medical aids and operating procedures, the order of these diagnoses/events, and their costs.

Study population and design

We selected adult (≥18 years) advanced therapy-naïve UC and CD patients, with at least one prescription of an advanced IBD therapy (ADA, IFX, TOF, GOL, UST, or VDZ) between 01 January 2015 to 30 June 2021 (see patient attrition flow chart in Supplementary Fig. 1, Additional File 21). The index date was the date of the first prescription with both, prescriptions from outpatient (i.e., ATC codes) and inpatient setting (i.e., OPS codes) considered and with a UC or CD diagnosis documented in the same quarter. We identified patients as having UC or CD if they had a main inpatient discharge ICD-10 GM diagnosis for UC or CD in the baseline year preceding the index date or confirmed outpatient or inpatient secondary diagnoses (for details see Supplementary Table 1, Additional File 1) in at least two quarters (M2Q criterion) within a period of one year following the first diagnosis claim. Thereby, the first confirmed outpatient or inpatient secondary diagnosis was required to be coded during the baseline year preceding the index date and the confirmatory second diagnosis claim was allowed to pass the index date.

The study period spanned from 01 January 2015 to 31 December 2021 (2014 for pre-index period only), allowing one year prior to the index date and at least six months of follow-up after index prescription.

We excluded patients who received an advanced therapy in the 12 months prior to index date to ensure patients were advanced therapy-naïve, as well as patients who did not have at least six months of continuous data following the index date (unless deceased).

We observed advanced treatment-naïve patients from the start of their index therapy—which we will refer to as their first-line advanced therapy (1L) — up to censoring. Censoring events included death, end of data availability (i.e., 31 December 2021), or end of insurance. For the comparative analysis based on 1L therapy, an additional censoring event included the start of the subsequent treatment line (2L, 3L).

Patient demographics, number of comorbidities (for definitions, see Supplementary Table 3, Additional File 3), and information on medical history, were assessed from the pre-index year (baseline). Outcomes of interest for each advanced therapy line include effectiveness endpoints (time to next treatment, TTNT, time to inadequate response, TTIR), as well as health economic parameters (UC/CD-related HCRU such as hospitalizations, surgical procedures, or sick leave), and SHI treatment costs. All outcomes were assessed per line of advanced IBD therapy, indication group (CD or UC), and advanced treatment subgroup.

Study endpoints and analyses

Advanced therapy lines and sequences

We describe the order of advanced therapy prescriptions as a sequence; the individual therapy lines are described by the temporal order (1L, 2L, or 3L) of the advanced therapy agents. Furthermore, the order is determined by the first appearance of each agent. We identified a new treatment pathway by recognizing switches from one agent to another; a switch is defined as a prescription of another advanced therapy without a concomitant refill prescription of the previous index therapy within a 180-day period after Defined Daily Dose (DDD) supply consumption. We observed the different therapy lines from the start to the end of each, so from the start of 1L to the start of 2L treatment, 2L to 3L treatment and so on. Patients were followed and included in the analyses for the respective treatment lines, and were removed from the analysis of that treatment line once a different advanced therapy was prescribed, starting the next line.

Time to next treatment (TTNT) and Time to inadequate response (TTIR)

TTNT is defined as the number of days from index date (start of 1L treatment) to start of 2L treatment. We adapted and modified Bokemeyer et al.'s [26] TTIR and defined it as the number of days to first inadequate response event per patient, within the period after the index date, until starting 2L treatment or the censoring date. Patients were categorized as inadequate responders if: they discontinued their 1L index treatment (>60 days prescription gap following end of supply from previous prescription), switched to another advanced therapy,

had continued corticosteroids prescriptions (prolonged use of corticosteroids with ≥ 2 outpatient corticosteroid prescriptions during cohort's follow-up period with high dosing (> 840mg/6 week time span threshold), underwent an IBD-related surgical procedure (for details see Additional File 12, Supplementary Table 12), had an IBD-related hospitalization (hospital admission with a primary diagnosis of UC/CD or IBD-related complications (see Additional File 13, Supplementary Table 13), or if their 1L advanced treatment dose was escalated (for any reason). Detailed definitions of the individual outcomes that make up the composite endpoint TTIR are described in Supplementary Table 2, Additional File 2.

Health economic outcomes

Healthcare resource utilization for patients with 1L advanced treatment is defined by the total number of IBD-related events and their respective duration per patient year (hospitalizations, length of hospital stays, number of surgeries, number of IBD-related sick leave absences, number of IBD-related sick leave days). IBD-related treatment costs included direct costs for IBD-specific hospitalizations, IBD-specific medications, and IBD-specific outpatient treatment. IBD-related SHI sick leave payments are reported for eligible insured patients (direct SHI sick leave payments are only paid for eligible insured patients, such as employees, and for sick leaves of ≥ 6 weeks in duration).

In addition, total all-cause SHI costs for each observed subgroup are reported, including direct costs for all-cause hospitalizations, medications, and outpatient treatment. Sick leave payments (all-cause) were also reported separately. Costs are accumulated over the entire post-index follow-up period until a censoring date or the start of 2L advanced treatment. HCRU and cost measures will be reported per patient year for the UC/CD indication groups and advanced treatment subgroups.

When calculating medication costs for advanced therapies, we adjusted prices per product as of June 2022 (identified by pharmaceutical central number, PCN, including biosimilars available on the market for ADA and IFX). A detailed overview of the included outcome variables and their definitions is in Supplementary Table 2, Additional File 2.

Statistical methods

We conducted analyses by disease type and treatment subgroup. Baseline characteristics, HCRU, and cost outcome variables are described as a mean and standard deviation (SD), per indication and treatment group. Treatment lines and sequences are reported by the number and proportion of patients per group. We used Sankey diagrams to visualize sequences including up to four treatment lines and show absolute numbers and proportions. Information on therapy prescriptions, sequences, and any endpoints are only generated for clusters with a minimum size of $n = 5$ patients.

Cumulative rates for the time-dependent outcomes are derived from Kaplan–Meier analyses, which calculate the probability of the event of interest (next treatment, inadequate response) at a given point in time. For the comparative outcome assessment, we focused on the 36-month time horizon. We calculated the final Kaplan–Meier estimates by multiplying the successive probabilities of all those previously calculated [27]. TTNT and TTIR (displayed as Kaplan–Meier curves), display the population at risk over time, which decreases in number compared to the total number of patients at the start. This is because the number at risk only includes patients who are still in the 1L advanced treatment. Censored survival times are also marked in the Kaplan–Meier curves. Patients who did not reach the time-dependent endpoint at the end of the observation period remain at risk. The median time to event (horizontal line at 0.5) is the earliest time the survival probability of not starting a next line of treatment/not reaching inadequate response drops to 0.5 or below [28]. The mean survival time is represented by the area under the survival curve in the interval from zero to the maximum observed or the maximum censored survival time. Kaplan–Meier-based mean, standard error, and median time to event per indication group and advanced treatment subgroup are reported, including its 95% confidence intervals (CI).

Since IFX has been approved for the treatment of CD since 1999, we compared treatment subgroup outcomes of IFX with the later approved ADA/UST/GOL/TOF for UC, and ADA/UST/ VDZ for CD [29]. To account for potential observational study bias, we conducted comparative analyses using inverse probability weighting. This method adjusts for baseline differences between treatment and control cohorts by assigning weights to individuals based on the probability of receiving treatment given a set of observed characteristics at baseline. We applied logistic regression to estimate propensity scores, in which the exposure status was regressed on observed baseline characteristics. The estimated propensity score is the predicted probability of treatment with VDZ/ADA/IFX/TOF/GOL/UST derived from the fitted regression model. Using a higher weighting of individuals whose characteristics resemble the comparative group most closely, we formed weighted groups that were more similar to compensate for the lack of randomization [30, 31]. Matching characteristics and negative control outcomes were adapted from Wilke et al. [32]. We used sex, age, comorbidities documented during baseline, the Charlson comorbidity index (CCI) score (see

Supplementary Table 14, Additional File 14), the number of IBD-related hospitalizations, and the number of systemic corticosteroid prescriptions (ATC code H02) for matching (see Supplementary Table 3, Additional File 3 for definitions).

Results are reported for unadjusted and adjusted comparisons. We used the standardized mean difference (SMD) between groups to evaluate the balance before and after inverse probability weighting. A value of SMD > 0.1 is generally deemed as a significant indicator of imbalance [33].

For adjusted comparison of TTNT and TTIR, we calculated hazard ratios based on Cox regression with 95% CI and reported p-values. HCRU and mean cost differences of index treatment when compared with index IFX are estimated by least-squares and reported including their 95% CI. P-values below 0.05 were considered statistically significant. All analyses were implemented using Microsoft structured query language (SQL) Server 2016 and R Version 4.1.

Due to the quality control measures of the legally regulated billing processes, missing data is unlikely from a technical perspective. Missing data for covariates will occur when an existing comorbidity or medication is not recorded in the database. In such a case, we assumed that the patient did not suffer from the respective comorbidity/was not prescribed the respective medication.

Ethical statement

The study uses claims data that is anonymized to protect the privacy of subjects and healthcare providers. No identifying personal data was collected. Since all data is anonymized according to German data protection regulations, use for scientific purposes is in conformity with German law, and no additional permissions are needed from an institutional review board (IRB) or an independent ethics committee (IEC).

Results

Patient population and advanced treatment lines

Thirteen thousand six hundred thirty-one patients received an advanced therapy during the index period. Among those, 9,488 had no documented prescription of an advanced IBD therapy agent in the pre-index year and were selected as advanced therapy-naïve. 475 patients were excluded from the cohort because of their age (< 18 years). Of the remaining 9,013 patients, 3,254 met further inclusion criteria. Patients with both UC and CD diagnoses (306) could not be clearly classified and were excluded from further analysis. After we applied all inclusion/exclusion criteria, 2,948 patients formed the sample for the analyses (Supplementary Fig. 1, Additional File 21). In 2,125 patients (CD 1,374; UC 751), we observed only one line of advanced treatment. There were 564 patients with a second line (CD 312; UC 252) and 259 (CD 105; UC 154) with a third line.

Overall, 2,295 patients (UC 756, CD 1,539) received an anti-TNF agent as 1L, 387 patients (UC 248, CD 139) received VDZ, and 138 patients received UST. In the UC cohort, IFX was the most common 1L treatment prescribed (419; 36.2%) followed by ADA (337; 29.1%), and VDZ (248; 21.4%) and GOL (111; 9.6%). UST was 1L therapy in 25 cases (2.2%) followed by TOF with 17 patients (1.5%). In patients with CD, ADA was the preferred 1L agent (923; 51.5%), while the second most prescribed 1L treatment in CD patients was IFX (616; 34.4%); VDZ was a distant third most prescribed (139; 7.8%) followed by UST (113; 6.3%).

Among those who received 2L treatment, VDZ was most common in UC patients (154; 37.9%), while UST was most common in CD patients (141; 33.8%). Figure 1 summarizes treatment choices and sequences in UC and CD patients.

The following sections present the results for the unadjusted and adjusted comparisons of therapy persistence and health economic outcomes for the 1L treatment. Additional results can be found in the appendix; comparisons of the second advanced treatment lines (HCRU/cost outcomes in Supplementary Tables 6 and 7, Additional Files 6 and 7; KM curves in Supplementary Figs. 2 and 3, Additional Files 22 and 23) and for the entire period from 1L until censoring (regardless of additional lines, see Supplementary Tables 4 and 5, Additional Files 4 and 5 and Additional Files 15 and 16, Supplementary Tables 15 and 16).

Time to next treatment (TTNT) and Time to inadequate response (TTIR) in advanced 1L treatment; unadjusted and adjusted populations

Baseline and clinical characteristics

We analyzed a total of 2,948 patients (UC 1,157; CD 1,791) who received a 1L treatment; baseline characteristics are summarized in Supplementary Table 9, Additional File 9. In adjusted comparisons, none of the covariates in the inverse probability weighted model differed between the subgroups (SMD between the groups ≤ 0.1). Goodness of fit statistics of the adjustment can be found in Supplementary Tables 10 and 11, Additional Files 10 and 11 for 1L comparisons and in Supplementary Tables 18 and 19, Additional Files 18 and 19 for the 2L.

The vast majority of patients could be followed through both the induction and maintenance phases for the 1L of advanced therapies in 1,550 CD patients (ADA 824, 89.3%; UST 100, 88.5%; IFX 513, 83.3%; VDZ 113, 81.3%) and in 960 UC patients (VDZ 216, 87.1%; GOL 96, 86.5%;

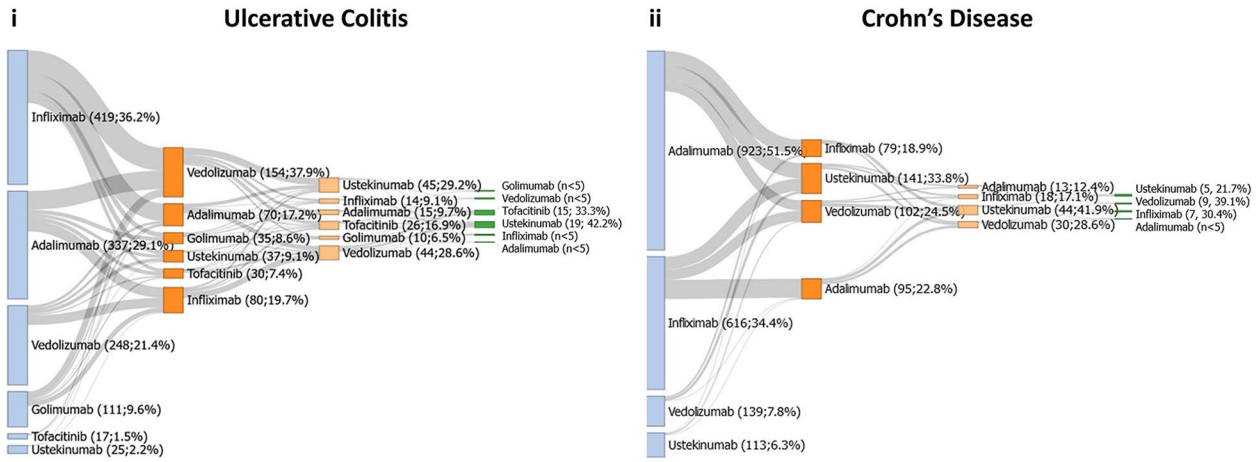

Fig. 1 Advanced treatment sequences and frequencies in UC (**a**) and CD (**b**) shown in Sankey diagrams

UST 23, 92.0%; ADA 287, 85.2%). Slightly lower proportions were observed for IFX and TOF in UC (326, 77.8% and 12, 70.6%). The remaining patients include those who switched to another treatment, were censored due to death, end of data availability, insurance discontinuation, or transition to a subsequent treatment line as per our censoring definition.

Ulcerative colitis

The probability of starting next treatment (TTNT) and inadequate response (TTIR) differed among treatment subgroups. In unadjusted comparison, UST and VDZ had comparably high rates of therapy persistence at three years, while GOL persistence was lowest. Of the patients initially treated with GOL, 51.2% did not switch to a new treatment during the follow-up period, compared to 53.8% treated with IFX, 52.1% treated with ADA, 68.6% treated with TOF, 72.0% treated with UST and 69.3% treated with VDZ. Most (83.6%) patients treated with UST did not have an inadequate response after three years, followed by patients treated with VDZ (45.5%). UC patients taking GOL were most likely to have an inadequate response (17.3%) while patients taking ADA, IFX, and TOF fell somewhere in the middle (26.1%, 23.8%, 38.5%, respectively) (Fig. 2).

In adjusted pairwise comparisons with IFX as the reference group, the Cox regression model yielded hazard ratios (HRs) and 95% CIs of starting a next treatment of 1.07 (0.85–1.35) in patients taking ADA, 1.01 (0.69–1.46) in patients taking GOL, 0.36 (0.10–1.27) in patients taking UST and 0.63 (0.47–0.84) in patients taking VDZ; however, of these, only the comparison between IFX and VDZ reached statistical significance ($p < 0.05$) (Fig. 2a). In a pairwise comparison with IFX, UC patients taking both VDZ and UST had a lower risk of inadequate response (TTIR), with a HR of 0.53 (0.42–0.66; $p < 0.001$) in patients taking VDZ and a HR of 0.22 (0.08–0.64; $p < 0.05$) in patients taking UST. In the comparison of GOL with IFX, the risk of starting next treatment was significantly higher (HRs of 1.54, 1.19–2.00; $p = 0.001$) and the comparison with ADA did not reach significance (Fig. 2b).

Compared to IFX, there was a significantly lower risk of dose escalation (HR 0.07; $p < 0.001$) (Fig. 2c) and IBD-related hospitalizations (HR 0.47; $p = 0.001$) (Fig. 2d) in patients treated with VDZ compared to IFX. With a HR of 3.36 ($p < 0.001$), the risk of dose escalation was significantly higher in patients treated with GOL (compared to IFX). Compared to IFX, the lower probability of IBD-related hospitalizations in patients taking ADA (HR 0.66) also reached statistical significance ($p = 0.032$).

Crohn's disease

There were notable differences in the likelihood of next treatment initiation and inadequate response in patients with CD when comparing advanced 1L treatment subgroups. In unadjusted analyses, the UST and VDZ subgroups had the highest rates of therapy persistence at three years, while the IFX subgroup had the lowest. Among patients initially treated with IFX, 60.6% did not switch to a new treatment, compared to 71.6% taking ADA, 74.4% taking VDZ, and 86.6% taking UST. Patients taking VDZ showed the highest rate of patients without an inadequate response event after three years, at 48.8%. This was followed by UST with a rate of 39.0%. IFX had the lowest rate at 19.1% (Fig. 3). The probability of a next treatment and inadequate response in adjusted pairwise comparisons was lower for each of the advanced therapies that were compared to IFX. In a pairwise comparison, CD patients had a

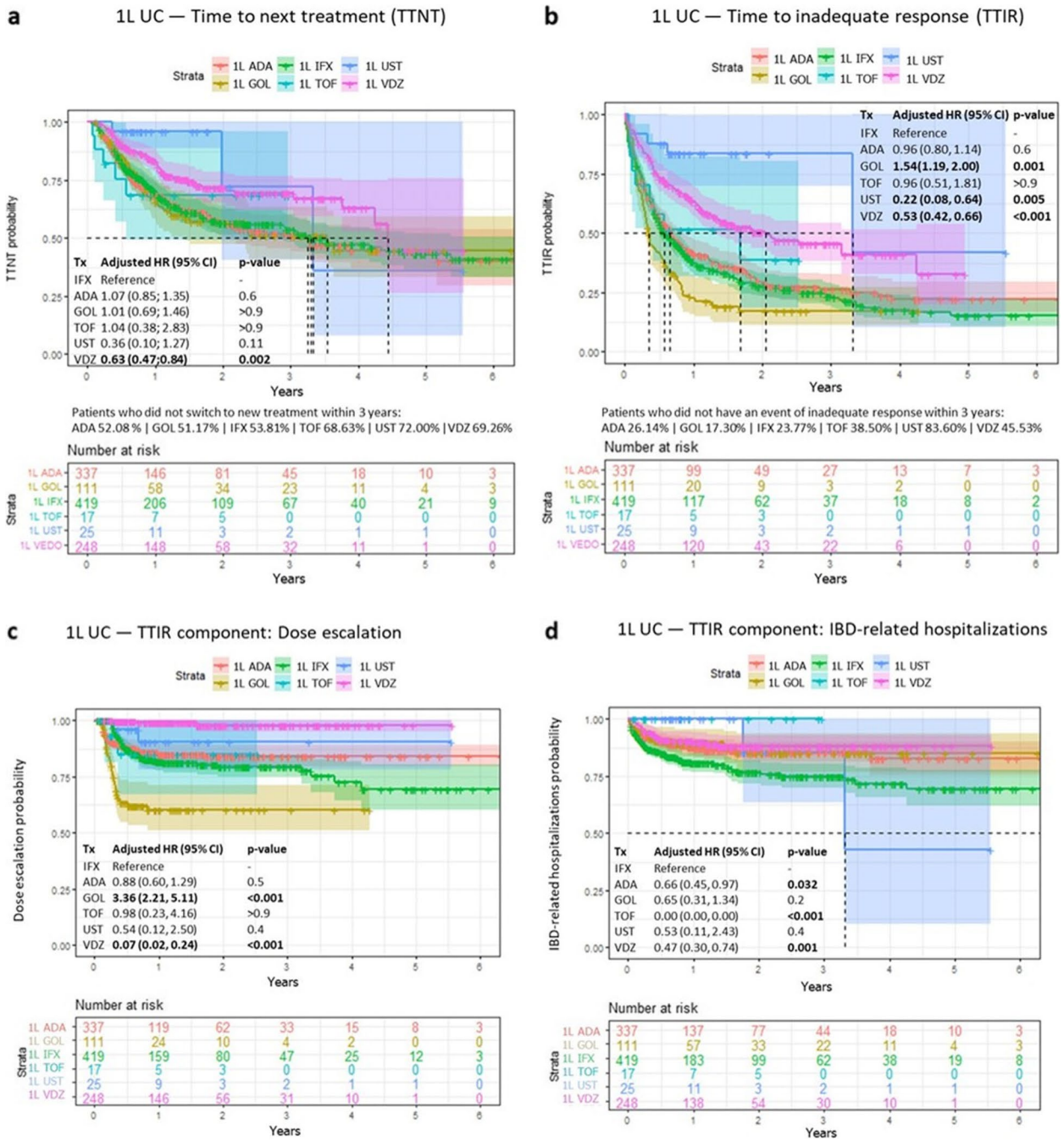

Fig. 2 1L advanced treatment effectiveness in Ulcerative Colitis (UC) population up to six years of follow-up unadjusted (**a**) Time to next treatment (TTNT) start, (**b**) Time to inadequate response (TTIR), (**c**) Time to dose escalation (TTIR component) and (**d**) Time to Inflammatory Bowel Disease (IBD)-related hospitalizations (TTIR component) plotted in Kaplan–Meier curves with 3-year outcome assessments; Hazard Ratios (HR) from Cox models with 95% Confidence Interval (CI) and p-values from adjusted pairwise comparison of advanced agents with Infliximab (IFX) as reference group. ADA: Adalimumab, GOL: Golimumab, TOF: Tofacitinib, UST: Ustekinumab, VDZ: Vedolizumab

lower risk of starting a next treatment for any advanced agent—when compared to IFX as reference—with HRs (95% CIs) of 0.27 (0.14–0.52) for UST, 0.68 (0.55–0.83) for ADA and 0.57 (0.36–0.90) for VDZ (with $p < 0.001$ for UST/ADA and $p < 0.05$ for VDZ; Fig. 3a). In TTIR adjusted pairwise comparison (with IFX as reference), VDZ had the lowest risk of inadequate response with an HR of 0.59 (0.44–0.79; $p < 0.001$). In patients taking

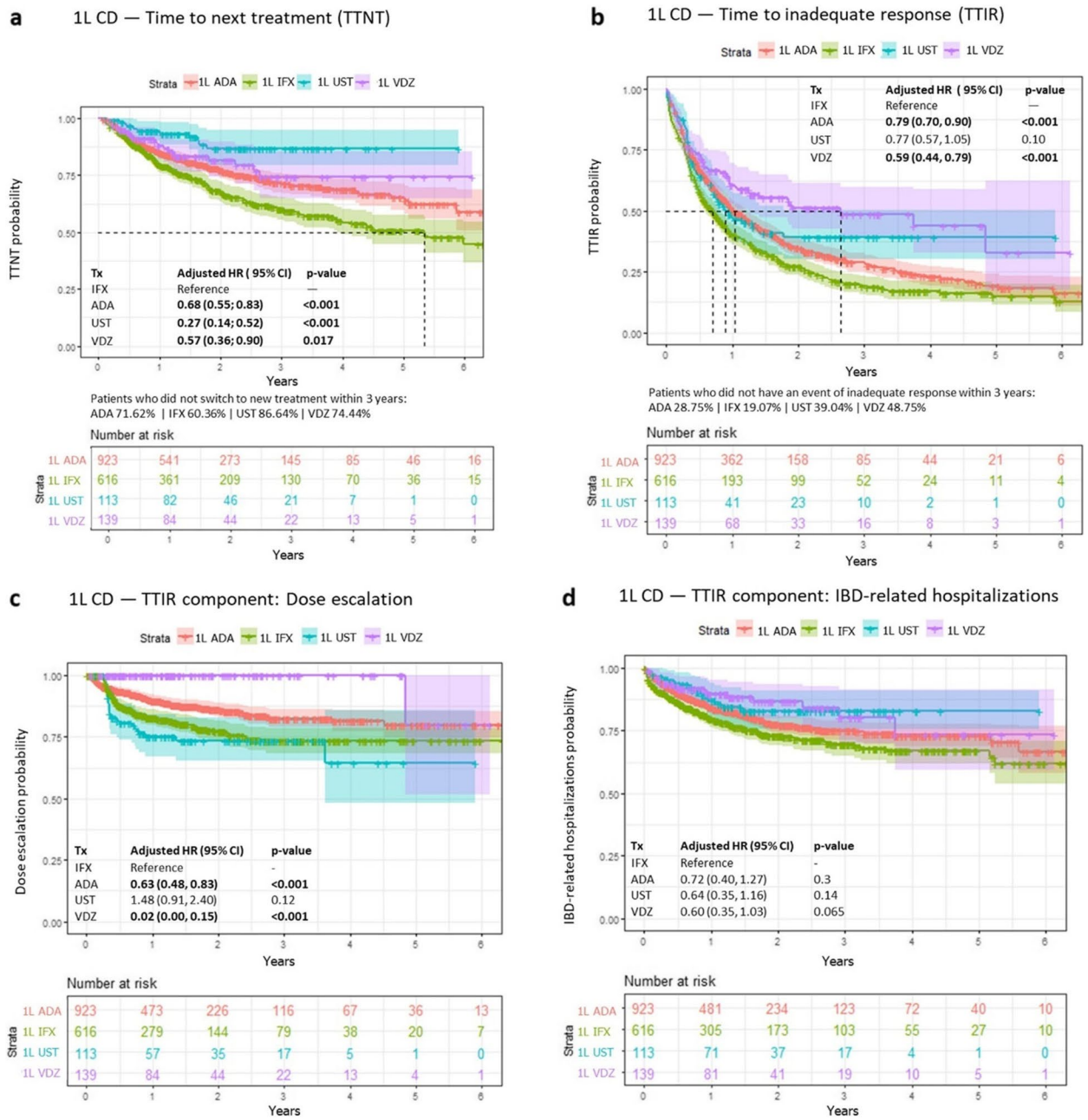

Fig. 3 1L advanced treatment effectiveness in Crohn's Disease (CD) population up to six years of follow-up unadjusted (**a**) Time to next treatment (TTNT) start, (**b**) Time to inadequate response (TTIR), (**c**) Time to dose escalation (TTIR component) and (**d**) Time to Inflammatory Bowel Disease (IBD)-related hospitalizations (TTIR component) plotted in Kaplan–Meier curves with 3-year outcome assessments; Hazard Ratios (HR) from Cox models with 95% Confidence Interval (CI) and p-values from adjusted pairwise comparison of advanced agents with Infliximab (IFX) as reference group. ADA: Adalimumab, UST: Ustekinumab, VDZ: Vedolizumab

ADA, the HR was 0.79 (0.70–0.90; $p < 0.001$) while no significant differences resulted from the comparison of TTIR between IFX and UST. There was a significantly lower dose escalation likelihood in patients treated with VDZ (HR 0.02; $p < 0.001$) and patients treated with ADA (HR 0.63; $p < 0.001$) when compared to IFX (Fig. 3c). We observed no significant differences in the probability of IBD-related hospitalizations in any of the adjusted comparisons (Fig. 3c).

Health economic outcomes

Ulcerative colitis

Compared to 1L IFX, patients with UC who were prescribed VDZ, ADA, or UST in 1L had fewer mean IBD-related hospitalizations (– 0.21 admissions in patients taking VDZ and – 0.19 admissions in those taking ADA, both $p < 0.001$; – 0.24 admissions in patients taking UST, $p < 0.05$,) and shorter duration of hospital stays (– 1.5 days in patients taking VDZ and – 1.2 days in those taking ADA, with both $p < 0.05$; and – 2.3 in patients taking UST with $p < 0.001$) per patient year (Table 1). We saw the highest IBD-related treatment costs per patient year in patients treated with UST as 1L, with an average of EUR 42,814. This is significantly higher than the other subgroups, where total IBD-related costs ranged from EUR 18,270 in patients that received TOF to EUR 22,685 in those treated with GOL. The costs for the IFX group were about EUR 25,000 (with some variation due to inverse probability weighting). Total IBD-related treatment costs were significantly lower in patients who were prescribed ADA (difference between the means was EUR – 6,616, $p < 0.001$), VDZ (EUR -2,428, $p < 0.001$) TOF (EUR – 6,730, $p < 0.05$) or GOL (EUR – 2,257, $p < 0.05$) in 1L. In contrast, total IBD-related treatment costs were significantly higher in patients treated with UST with a mean difference of EUR 17,879 ($p < 0.05$).

Crohn's disease

In CD patients with 1L, only VDZ had both fewer IBD-related hospitalizations (– 0.23 events; $p \leq 0.001$) and shorter duration of hospital stays (– 1.9 days; $p \leq 0.05$) compared to IFX (Table 2); only one of these differences was significant for each of GOL and ADA. Total IBD-specific treatment costs were significantly lower for 1L patients that received VDZ (EUR -2,786; $p \leq 0.001$) or ADA (EUR – 6,396; $p \leq 0.001$). Compared to IFX in 1L, patients prescribed UST had more IBD-related SHI costs per patient year (EUR + 13,031, $p \leq 0.001$).

Discussion

The increasing number of available UC and CD treatment options prompt advanced therapy effectiveness research; this study addresses this evidence gap. Data derived from 2,948 IBD patients revealed that anti-TNF agents ADA and IFX were the primary 1L therapy choices in the study period. Recent real-world data support our findings. Kapizioni et al.'s analysis of real-world data from the UK IBD BioResource [9] revealed that IFX was the most used 1L therapy among a cohort of 13,222 patients enrolled between January 2017 and January 2020 (4,185 UC; 9,037 CD), with about 59% of UC and 61% of CD patients with IFX as initial treatment. Overall, 3,506 (84%) UC patients and 8,689 (96%) CD patients were treated with a 1L anti-TNF therapy [9, 34]. A retrospective study reviewing physician-administered charts from 2014 to 2019 in France, Germany, and the United Kingdom, revealed that 95.7% of physicians preferred anti-TNF treatments as 1L advanced therapy for UC, specifically IFX or ADA and their biosimilars. Anti-TNF preference in CD was similar (92.3%) [34]. However, these studies also show that VDZ and UST have become a common choice for 1L as well as 2L treatment choice in UC and/or CD, respectively. In UC patients not responding to anti-TNF treatments, 80.7% of physicians favored VDZ as 2L therapy. Following anti-TNF failure in CD patients, preferences for 2L treatment were evenly split between VDZ and UST, each chosen by about half of physicians [34]. In the UK IBD BioResource study, VDZ emerged as the most commonly used medication following TNF inhibitors for 1L treatment, with 16.0% of UC patients and 3.1% of CD patients receiving it [9, 34]. Compared to these studies, our results show a further shift in rates towards 1L therapies other than anti-TNF (with 21.4% VDZ/9.6% GOL for UC patients and 7.8% VDZ/6.3% UST for CD patients). This observation is probably due to a progressive trend in the use of other advanced therapy options, which is evident in our more recent observation period.

Next to UST, 1L VDZ had the highest three-year persistence rates; 69.3% of VDZ and 72.0% of UST patients remained on their original 1L therapy, indicating that VDZ and UST might be superior to IFX for UC treatment. We analyzed HRs of next treatment initiation for the different agents compared to IFX in 1L with a Cox model, whereby only the VDZ comparison reached statistical significance. Two recent studies examined VDZ persistence as a 1L treatment option compared to anti-TNF agents in advanced therapy-naïve patients with retrospective, controlled designs. In line with our findings, these studies found longer persistence and superior clinical remission rates of VDZ compared to anti-TNF agents and lower likelihood of therapy discontinuation at 24 months compared to IFX as reference [24, 35].

UC patients taking VDZ and UST had a significantly lower inadequate response risk compared to UC patients taking IFX, whereas patients taking ADA did not show a statistically significant difference compared to patients taking IFX. Patients treated with VDZ had a lower risk of dose escalation and IBD-related hospital admissions in the long-term observation. Our findings align with other real-world studies analyzing 1L advanced treatment in UC patients. Using inverse probability weighted comparison, Bokemeyer et al. [24] also found that a lower percentage of VDZ-treated bio-naïve patients switched to other advanced therapies (29% VDZ vs. 54% anti-TNF) within two years. A multicentre retrospective medical chart review defined inadequate response by therapy

Table 1 IBD-related HCRU/costs in UC patients with 1L advanced treatment, up to six years of follow-up

Health economic outcome parameters PPY	ADA ($n=419$) vs. IFX[1]	p-value[2]	GOL ($n=424$) vs. IFX[1]	p-value[2]	TOF ($n=399$) vs. IFX[1]	p-value[2]	VDZ ($n=419$) vs. IFX[1]	p-value[2]	UST ($n=443$) vs. IFX[1]	p-value[2]
Number of IBD-related hospitalizations (events)	0.15 (0.69) vs 0.34 (1.15)	**<0.001**	0.18 (1.37) vs 0.34 (1.15)	0.061	0.00 (0.00) vs. 0.35 (1.17)	**<0.001**	0.13 (0.56) vs 0.34 (1.16)	**<0.001**	0.11 (0.26) vs. 0.35 (1.18)	**0.002**
Duration of IBD-related hospital-stays (days)	1.5 (10.2) vs. 2.7 (10.0)	**0.014**	1.60 (14.17) vs. 2.70 (10.09)	0.2	0.00 (0.00) vs. 2.83 (10.35)	**<0.001**	1.18 (9.83) vs 2.68 (10.03)	**0.010**	0.50 (1.02) vs. 2.84 (10.36)	**<0.001**
Number of IBD-related surgeries (events)	0.09 (0.64) vs 0.16 (0.68)	0.053	0.11 (0.51) vs 0.15 (0.66)	0.3	0.04 (0.11) vs. 0.16 (0.67)	**0.008**	0.10 (0.64) vs. 0.16 (0.66)	0.2	0.12 (0.50) vs. 0.16 (0.67)	0.6
Duration of IBD-related sick-leave (days)	22 (56) vs. 23 (56)	0.8	17 (43) vs. 23 (55)	0.4	3 (5) vs. 24 (56)	**<0.001**	18 (50) vs. 23 (56)	0.3	12 (19) vs. 24 (56)	0.15
Number of IBD-related sick-leave (events)	0.77 (1.28) vs. 1.50 (2.20)	**<0.001**	0.90 (1.22) vs. 1.48 (2.19)	**0.003**	0.59 (0.76) vs. 1.47 (2.16)	**0.018**	1.37 (2.02) vs. 1.46 (2.17)	0.7	0.42 (0.51) vs. 1.46 (2.15)	**<0.001**
Costs for IBD-specific hospitalizations (EUR)	659 (4,352) vs. 1,305 (5,108)	**0.003**	932 (7,563) vs. 1,302 (5,099)	0.4	0 (0) vs. 1,350 (5,186)	**<0.001**	511 (2,885) vs. 1,308 (5,109)	**<0.001**	236 (518) vs. 1,346 (5,175)	**<0.001**
Costs for IBD-specific medication (EUR)	17,066 (7,663) vs. 22,672 (10,177)	**<0.001**	21,044 (7,104) vs. 22,608 (10,092)	**0.044**	17,754 (8,319) vs. 22,616 (10,100)	**0.038**	20,883 (6,298) vs. 22,465 (10,014)	**0.015**	41,860 (18,724) vs. 22,555 (10,087)	**0.003**
Costs for IBD-specific outpatient treatment (EUR)	650 (432) vs. 989 (552)	**<0.001**	692 (482) vs. 986 (551)	**<0.001**	516 (550) vs. 988 (556)	**<0.001**	960 (491) vs. 989 (550)	0.5	718 (517) vs. 988 (555)	0.094
Total costs for IBD-specific treatment (EUR)	18,400 (9,100) vs. 25,016 (11,178)	**<0.001**	22,685 (11,664) vs. 24,942 (11,092)	**0.016**	18,270 (8,465) vs. 25,000 (11,120)	**0.004**	22,380 (6,910) vs. 24,808 (11,029)	**<0.001**	42,814 (19,366) vs. 24,935 (11,106)	**0.008**
Total costs for all-cause treatment (EUR)	30,576 (17,807) vs. 32,794 (24,357)	0.2	34,968 (16,246) vs. 32,571 (24,136)	0.2	22,327 (9,528) vs. 32,760 (24,287)	**<0.001**	27,910 (14,735) vs. 32,461 (23,956)	**0.002**	114,646 (146,095) vs. 32,659 (24,187)	0.12

Abbreviations: PPY Per patient year, *SD* Standard deviation, *IFX* Infliximab, *ADA* Adalimumab, *GOL* Golimumab, *TOF* Tofacitinib, *VDZ* Vedolizumab, *UST* Ustekinumab, *IBD* Inflammatory Bowel Disease, *UC* Ulcerative Colitis

Bold font highlights statistical significance

[1] Mean (SD), pairwise comparison with IFX as reference after adjustment; 1L ADA/GOL/TOF/VDZ/UST vs. 1L IFX in UC patients

[2] Regression least-squares mean differences

Table 2 IBD-related HCRU/costs in CD patients with 1L advanced treatment, up to six years of follow-up

Health economic outcome parameters PPY	ADA ($n=615$) vs. IFX[1]	p-value[2]	VDZ ($n=615$) vs. IFX[1]	p-value[2]	UST ($n=620$) vs. IFX[1]	p-value[2]
Number of IBD-related hospitalizations (events)	0.21 (0.60) vs. 0.36 (0.99)	**0.001**	0.16 (0.51) vs. 0.39 (1.04)	**< 0.001**	0.25 (0.53) vs. 0.38 (1.03)	0.12
Duration of IBD-related hospital-stays (days)	3.0 (18.5) vs. 3.1 (11.6)	> 0.9	1.5 (9.7) vs. 3.4 (12.1)	**0.008**	1.61 (5.51) vs. 3.30 (12.04)	**0.012**
Number of IBD-related surgeries (events)	0.27 (0.82) vs. 0.29 (0.90)	0.6	0.34 (1.10) vs. 0.30 (0.96)	0.7	0.29 (0.99) vs. 0.30 (0.94)	> 0.9
Duration of IBD-related sick-leave (days)	21 (51) vs. 18 (40)	0.3	24 (64) vs. 18 (41)	0.4	20 (47) vs. 18 (41)	0.7
Number of IBD-related sick-leave (events)	0.71 (1.15) vs. 1.42 (2.18)	**< 0.001**	1.40 (1.91) vs. 1.42 (2.15)	> 0.9	0.85 (1.25) vs. 1.43 (2.17)	**0.002**
Costs for IBD-specific hospitalizations (EUR)	866 (3,635) vs. 1,451 (5,561)	**0.013**	605 (3,032) vs. 1,670 (6,141)	**< 0.001**	1,074 (3,225) vs. 1,601 (6,014)	0.14
Costs for IBD-specific medication (EUR)	16,041 (6,843) vs. 21,534 (9,978)	**< 0.001**	19,638 (6,051) vs. 21,510 (10,193)	**0.004**	35,231 (11,742) vs. 21,565 (10,155)	**< 0.001**
Costs for IBD-specific outpatient treatment (EUR)	684 (429) vs. 958 (517)	**< 0.001**	1,082 (586) vs. 966 (521)	**0.048**	745 (479) vs. 961 (517)	**< 0.001**
Total costs for IBD-specific treatment (EUR)	17,702 (7,850) vs. 24,098 (10,438)	**< 0.001**	21,520 (6,556) vs. 24,306 (10,726)	**< 0.001**	37,312 (11,763) vs. 24,281 (10,655)	**< 0.001**
Total costs for all-cause treatment (EUR)	30,037 (49,336) vs. 34,080 (32,610)	**0.026**	43,778 (223,662) vs. 34,906 (34,441)	0.5	60,661 (42,306) vs. 34,735 (34,182)	**< 0.001**

Abbreviations: PPY Per patient year, *SD* Standard deviation, *IFX* Infliximab, *ADA* Adalimumab, *VDZ* Vedolizumab, UST Ustekinumab, *IBD* Inflammatory Bowel Disease, *CD* Crohn's Disease

Bold font highlights statistical significance

[1] Mean (SD), pairwise comparison with IFX as reference after adjustment; ADA/VDZ/UST vs. 1L IFX in CD patients

[2] Regression least-squares mean differences

discontinuation, therapeutic adjustment, hospitalization or emergency treatment and found that 44% of patients in their sample had an inadequate response within one year after index treatment. The adjusted model found that VDZ as index therapy was associated with a 53% lower risk of inadequate response compared to anti-TNF agents [36]. UC patients taking 1L VDZ also showed greater effectiveness in terms of treatment discontinuation or failure compared to patients taking anti-TNF agents over a 5-year period [9]. Overall, our results on therapy persistence confirm earlier findings; the variation in inadequate response estimates may be due to the somewhat different definitions and indicators used by previous studies.

In comparative analyses of advanced therapies in UC, few studies considered health economic parameters of HCRU or costs in addition to the clinical endpoints. In our analysis, compared to IFX, mean total IBD-related treatments costs per patient year were lower in patients with 1L GOL and VDZ (in similar absolute numbers), lowest in those who received ADA, and considerably higher in patients treated with UST.

Bokemeyer et al. [26] reported costs of EUR 39,149, with most expenses caused by UC-related outpatient medications (EUR 28,885 per patient year). Our results are consistent with these findings, with some price effects that may be attributed to more recent data. However, no direct comparison is possible because their cost assessments were not stratified by the different advanced agents. However, the study found that patients with escalated index treatment had higher total all-cause costs per patient year compared to those without dose escalation (EUR 42,949 vs. EUR 35,805, $p < 0.001$). The same was true for total UC-specific costs (EUR 40,173 vs. EUR 31,488, $p < 0.001$), due to the high costs of UC medications.

In patients with Crohn's disease, therapy persistence and inadequate response results show similar —albeit less clear—patterns than in the patients with UC. Compared to 1L IFX, treatment with ADA, UST and VDZ seems superior in terms of TTNT. UST and VDZ demonstrated the highest 3-year therapy persistence rates in unadjusted analyses (with 86.6% and 74.4% respectively), significantly outperforming IFX (60.6%).

VDZ presented the lowest risk of inadequate response among the 1L treatments we analyzed. In addition, our study also showed that the use of ADA and VDZ in 1L was associated with lower IBD-specific treatment costs per patient year compared to IFX. In terms of SHI costs

for IBD-specific treatment, the use of UST was found to be more expensive compared to IFX.

The retrospective multicentre EVOLVE study [17] assessed 1,095 advanced therapy-naïve UC and CD patients for clinical effectiveness, safety, and treatment persistence of VDZ and anti-TNF agents over 24 months. Primary non-response included treatment discontinuation, disease flare-up, IBD-related surgery or hospitalization, or dose escalation. Clinical effectiveness was similar between VDZ and anti-TNF, but VDZ was associated with significantly lower rates of serious adverse events and infections (HR 0.42 and 0.40, respectively). In UC, VDZ showed higher treatment persistence (76.3% vs. 52.4%) and less dose escalation than anti-TNF agents. These differences were not observed in CD patients. Our findings align with EVOLVE for UC, but in CD, we observed advantages for both ADA and VDZ over IFX. Since we include the anti-TNF agents individually (rather than pooled) in the comparisons, and have longer observation periods, our results examine comparative effectiveness of anti-TNF and VDZ in CD patients in more detail.

Our results should be considered while acknowledging some limitations. It should be noted that concomitant use of immunomodulators such as azathioprine (AZA), 6-mercaptopurine (6-MP) or methotrexate (see Additional File 8, Supplementary Table 8) may affect anti-TNF persistence, however an assessment of this impact was beyond the scope of our study. Combination therapy with IFX and azathioprine has been shown to improve corticosteroid-free remission and mucosal healing compared to either drug alone in both UC and CD patients [37, 38]. However, data on the effectiveness of combining other advanced therapies with immunomodulators remain limited or no clear benefit has been found to date [39]. In our study population, 25.1% of UC patients and 22.7% of CD patients treated with IFX also received AZA or 6-MP during first-line advanced treatment. Thiopurines were also used in combination with ADA, GOL, UST and VDZ, although less frequently. Methotrexate was used in combination with advanced therapies in only a few cases, primarily in patients receiving ADA (UC: 3.3%; CD: 3.0%) (see Supplementary Table 20, Additional File 20). As a result, treatment outcomes may have been influenced by whether or not patients received additional immunomodulator therapy. This could have influenced the observed TTNT and TTIR of advanced therapies in our cohort and should be considered when interpreting the results.

Other limitations arise from the database used and the structure of SHI data. The use of algorithms to categorize patients' outcomes, diseases, or prescribed medications based on health claims data depends on the quality of the documentation; the absence of a claim does not necessarily mean the absence of the comorbidity or drug exposure. Other limitations include the risk of coding misclassification— especially of diagnoses. In addition, outpatient billing is only available by quarter; this means we could not identify data documented in the outpatient sector by an exact date, nor could we determine the order of diagnoses documented exactly within the quarter. Moreover, drug prescriptions are not linked to ICD 10-GM diagnoses. Therefore, we could not rule out the possibility that UC and CD patients in our sample were prescribed drugs analyzed here for another indication. We designed the study using strict inclusion and exclusion criteria with this limitation in mind, which stipulated that both a reliable and clear (without overlap of UC and CD) diagnosis and an advanced therapy prescription had to be present in the same quarter of a calendar year. For any comparative results, we cannot rule out bias since randomization is not possible in retrospective claims data analyses. To address any potential bias, we employed a widely recognized statistical method to account for differing baseline characteristics among the patient groups. However, adjustment is limited to known confounders, therefore bias cannot be ruled out.

The availability of data on oral small molecules such as tofacitinib and upadacitinib was limited, as these therapies were only approved relatively late during the study period. Additionally, adoption into clinical practice and delays in claims data processing further reduced the number of observable cases. Likewise, UST has only been approved for use in UC since 2019, so the number of patients with 1L UST treatment was too low to draw reliable conclusions. Data on other biologics and small molecule drugs, like new classes of S1P modulators, additional JAKis and IL-23 inhibitors, are also not available, as all of these drugs were not approved during the study period. Therefore, future analyses with longer follow-up periods will be necessary.

Moreover, comparative analyses based on small patient subgroups may be subject to increased variability and limited robustness, even when statistical adjustment methods such as inverse probability weighting are applied. This is particularly relevant for cost estimates, which inherently show considerable dispersion. As an example, the comparison of all-cause costs between treatment groups in UC first-line advanced therapy, especially for patients treated with UST, was based on a limited number of cases and did not reach statistical significance. Thus, these results should be interpreted cautiously and viewed as exploratory.

Given the large number of statistical comparisons performed, no formal correction for multiple testing was applied, in line with the exploratory nature of the study. Although this approach avoids overly conservative

adjustments [40], it may increase the likelihood of type I errors. Therefore, results should be interpreted cautiously, especially when isolated significant differences are observed.

Prescribing practices during the study period may have been influenced by the availability and approval timelines of newer advanced therapies, although no regulatory requirements mandated specific first-line choices in Germany. Although biosimilar quotas for anti-TNF agents were introduced during the middle of the study period, they primarily addressed the exchange between originators and biosimilars, not the initiation of specific drug classes. Therefore, we do not believe that these quotas substantially influenced first-line biologic prescribing during the core study phase. Nonetheless, it should be acknowledged that current or evolving policies (e.g., biosimilar quotas) may affect future prescribing practices. Additionally, there are limitations regarding the evaluation of medication costs, as further biosimilar approvals after the study period have likely led to additional price reductions beyond the adjustments already applied in this study. Finally, a potential limitation of the study is that the SHI data do not cover people who have private health insurance (PHI) and therefore may not be representative of the total population. However, in Germany, health insurance is compulsory for all residents and around 90% of the population is covered by SHI. The remainder are mainly covered by PHI, typically higher-income individuals, civil servants, or the self-employed [41]. These sub-groups may be slightly under-represented in our study. However, as the PHI population represents only a small proportion (~ 10%) of the total German population, the impact on the overall representativeness in terms of age, gender, and morbidity is considered low for most research questions [42].

Conclusions

Our observational study with real-world conditions indicates that anti-TNF agents were mostly used as 1L advanced therapy in IBD patients. However, in line with other recent research, our results challenge the justification for anti-TNFs as the first-line advanced therapy for IBD. We found evidence that 1L long-term VDZ appears to be a favorable treatment choice from both effectiveness and cost perspective.

Abbreviations

ADA	Adalimumab
ATC	Anatomical Therapeutic Chemical
anti-TNF	Anti-tumor necrosis factor α
AZA	Azathioprine
CCI	Charlson Comorbidity Index
CD	Crohn's disease
CI	Confidence interval
DDD	Defined Daily Dose
GOL	Golimumab
HRs	Hazard ratios
HCRU	Healthcare resource utilization
IBD	Inflammatory Bowel Disease
IFX	Infliximab
JAK	Janus kinase
6-MP	6-Mercaptopurine
PCN	Pharmaceutical central number
PHI	Private health insurance
QALYs	Quality-Adjusted Life Years
SD	Standard deviation
SMD	Standardized mean difference
SHI	Statutory health insurance
TTIR	Time to inadequate response
TTNT	Time to next treatment
TOF	Tofacitinib
UC	Ulcerative colitis
UST	Ustekinumab
VDZ	Vedolizumab

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12876-025-04022-7.

Additional file 1. Supplementary Table 1: Crohn's disease and ulcerative colitis patient identification (ICD-10 GM codes). Table of all ICD-10 Codes and their description that were used to identify patients with CD and/or UC.

Additional file 2. Supplementary Table 2: Outcome variables and definitions. Detailed overview of the included outcome variables and their definitions.

Additional file 3. Supplementary Table 3: Baseline confounders for balancing via IPW. Definitions for patient demographics, number of comorbidities and other baseline confounders.

Additional file 4. Supplementary Table 4: IBD-related HCRU and costs in CD patients based on their first advanced therapy from 1L until censoring; pairwise comparison with IFX as reference after IPW adjustment. Additional results for the entire period from 1L until censoring (regardless of additional lines): CD patients.

Additional file 5. Supplementary Table 5: IBD-related HCRU and costs in UC patients based on their first advanced therapy from 1L until censoring; pairwise comparison with IFX as reference after IPW adjustment. Additional results for the entire period from 1L until censoring (regardless of additional lines): UC patients.

Additional file 6. Supplementary Table 6: IBD-related HCRU and costs in CD patients with 2L advanced treatment, up to 6 years of follow-up, pairwise comparison with IFX as reference after IPW adjustment. Additional information for HCRU and cost: CD patients.

Additional file 7. Supplementary Table 7: IBD-related HCRU and costs in UC patients with 2L advanced treatment, up to 6 years of follow-up, pairwise comparison with IFX as reference after IPW adjustment. Additional information for HCRU and cost: UC patients.

Additional file 8. Supplementary Table 8: Concomitant treatments. Shows therapy classification incl. mechanism of action, Generic Name and ATC codes.

Additional file 9. Supplementary Table 9: Baseline characteristics of patients. Detailed overview of baseline characteristics (sex, age at index) für UC and CD patients stratified by advanced index drug.

Additional file 10. Supplementary Table 10: Goodness of fit statistics for IPW comparison of 1L UC patients. Detailed overview of goodness of fit statistics: 1L UC patients.

Additional file 11. Supplementary Table 11: Goodness of fit statistics for IPW comparison of 1L CD patients. Detailed overview of goodness of fit statistics: 1L CD patients.

Additional file 12. Supplementary Table 12: IBD-related surgeries. Table of IBD-related surgical procedure codes and their description.

Additional file 13. Supplementary Table 13: IBD- related complications. Table of IBD-related complications: ICD-10-Codes and their description.

Additional file 14. Supplementary Table 14: Charlson Comorbidity Index (CCI). Shows conditions with their respective ICD-10-GM Diagnosis Codes.

Additional file 15. Supplementary Table 15: Goodness of fit statistics for IPW comparison of CD patients from start 1L to censoring. Detailed overview of goodness of fit statistics: CD patients from start 1L to censoring.

Additional file 16. Supplementary Table 16: Goodness of fit statistics for IPW comparison of UC patients from start 1L to censoring. Detailed overview of goodness of fit statistics: UC patients from start 1L to censoring.

Additional file 17. Supplementary Table 17: Medications used in conventional CD/UC therapy. Shows medications used in conventional CD/UC therapy with generic name and ATC codes.

Additional file 18. Supplementary Table 18: Goodness of fit statistics for IPW comparison of 2L UC patients. Detailed overview of goodness of fit statistics: 2L UC patients.

Additional file 19. Supplementary Table 19: Goodness of fit statistics for IPW comparison of 2L CD patients. Detailed overview of goodness of fit statistics: 2L CD patients.

Additional file 20. Supplementary Table 20: Concomitant treatment of CD and UC patients with immunomodulators in 1L. Shows number and proportion of patients receiving azathioprine, 6-mercaptopurine or methotrexate.

Additional file 21. Supplementary Figure 1: Patient attrition. Figure shows flow chart illustrating patient attrition in the study population.

Additional file 22. Supplementary Figure 2: TTNT and TTIR in UC 2L patients. Figure Shows Kaplan Meier curves for TTNT and TTIR in UC 2L patients with TTIR components dose escalation and IBD-related hospitalizations.

Additional file 23. Supplementary Figure 3: TTNT and TTIR in CD 2L patients. Figure Shows Kaplan Meier curves for TTNT and TTIR in CD 2L patients with TTIR components dose escalation and IBD-related hospitalizations.

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Authors' contributions
RK, SK, JS, CD, AD, NT, IW, and JB designed the study. JB performed data analysis with data interpretation led by RK, AD, NT, and IW, and contributions from all authors. IW wrote the initial draft of the manuscript and all authors provided critical feedback. CD and JS provided references for discussion of the data. All authors have approved the manuscript's findings and conclusions and have agreed to the final version.

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Data availability
The datasets generated during and/or analyzed during the current study are not publicly available due to data protection aspects. The data underlying this article will be shared at aggregate/population level upon reasonable request to the corresponding author.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
Niels Teich reports personal fees from AbbVie, Falk, Fering, Pfizer, Galapagos and Takeda outside the submitted work. Axel Dignass reports fees for participation in clinical trials, review activities such as data monitoring boards, statistical analysis and end point committees from Abivax, AbbVie, Arena Pharmaceuticals, Bristol Myers Squibb/Celgene, Dr Falk Foundation, Galapagos, Gilead, Janssen, and Pfizer; consultancy fees from AbbVie, Amgen, Arena Pharmaceuticals, Biogen, Boehringer Ingelheim, Bristol Myers Squibb/Celgene, Celltrion, Dr Falk Foundation, Ferring Pharmaceuticals, Fresenius Kabi, Galapagos, Janssen, Lilly, MSD, Pfizer, Pharmacosmos, Roche/Genentech, Sandoz/Hexal, Takeda, Tillotts, and Vifor Pharma; payment from lectures including service on speakers bureaus from AbbVie, Biogen, CED Service GmbH, Celltrion, Falk Foundation, Ferring, Galapagos, Gilead, High5MD, Janssen, Materia Prima, MedToday, MSD, Pfizer, Streamed-Up, Takeda, Tillotts, and Vifor Pharma; payment for manuscript prep-aration from Falk Foundation, Takeda, Thieme, and UniMed Verlag. Ines Weinhold and Julia Borchert declare that there are no conflicts of interest with regard to the research, authorship and/or publication of this abstract. Both are employees of WIG2 GmbH. WIG2 GmbH received funding from Takeda Pharma Vertrieb GmbH & Co. KG for the conduct of the study. Juliane Sünwoldt, Christina Dünweber, Robert Kudernatsch and Stephan Kaiser are employees of Takeda Pharma Vertrieb GmbH & Co.KG. They hold no Takeda stock or stock options. This study was funded by Takeda Pharma Vertrieb GmbH & Co.KG.

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