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REVIEW

A Systematic Review of the Economic and Health-Related Quality of Life Impact of Advanced Therapies Used to Treat Moderate-to-Severe Ulcerative Colitis

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ABSTRACT

Introduction: The clinical benefits of advanced therapies (i.e., biologics and small-molecule drugs) in the treatment of moderate-to-severe ulcerative colitis (UC) have been demonstrated; however, there is less clarity regarding the economic and health-related quality of life (HRQoL) impact of these treatments. We conducted a systematic literature review to synthesize data on cost, healthcare resource utilization (HCRU), and HRQoL for patients who received approved advanced therapies for moderate-to-severe UC in the United States and Europe.

Methods: Databases including MEDLINE, Embase, the Database of Abstracts of Reviews of Effects (DARE), the National Health Service Economic Evaluation Database (NHS EED), and EconLit were searched systematically to identify observational studies published between January 1, 2010 and October 14, 2021 that assessed the impact of advanced therapies on cost, HCRU, and/or HRQoL in adults with moderate-to-severe UC. Supplementary gray literature searches of conference proceedings from the past 4 years (January 2018 to October 2021) were also performed.

Results: 47 publications of 40 unique cost/HCRU studies and 13 publications of nine unique HRQoL studies were included. Findings demonstrated that biologics have a positive impact on indirect costs (i.e., productivity, presenteeism, and absenteeism) and HRQoL. High costs of biologics were not always fully offset by reductions in cost and HCRU associated with disease management. For many patients, treatment switching and dose escalations were required, thus increasing drug costs, particularly when switching across treatment classes.

Conclusion: These findings highlight a high unmet need for therapies for moderate-to-severe UC that can reduce the healthcare burden and impact on society. Further research is warranted, as the reported evidence was limited by the small sample sizes of some treatment groups within a study.

PLAIN LANGUAGE SUMMARY

Although advanced therapies, such as biologics and small-molecule drugs, have shown clinical

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benefit in treating moderate-to-severe ulcerative colitis, their economic impact and effect on patients' quality of life is less clear. This study comprehensively reviewed the cost and use of healthcare resources associated with starting treatment with advanced therapies for ulcerative colitis, as well as the impact of these treatments on quality of life. We found that while biologics have a benefit on work productivity, work attendance, work absence, and quality of life, the high costs of biologics were not always fully met by reductions in disease management costs and healthcare resources. Many patients needed to switch treatments or required dose increases, which were expensive. There is a high unmet need for therapies for moderate-to-severe ulcerative colitis that can reduce healthcare costs, use of healthcare resources, and effect on society.

Keywords: Ulcerative colitis; Biologic therapy; Systematic literature review; Direct costs; Indirect costs; Healthcare resource utilization; Health-related quality of life

Key Summary Points

Why carry out this study?

Advanced therapies (i.e., biologics and small-molecule drugs) have demonstrated clear clinical benefits for the treatment of moderate-to-severe ulcerative colitis; however, the economic and health-related quality of life impact of these treatments are less well understood.

We conducted a systematic literature review to synthesize data on cost and healthcare resource utilization and assess health-related quality of life for patients treated with approved advanced therapies for moderate-to-severe ulcerative colitis.

What was learned from the study?

This study demonstrates the positive impact that biologic therapies have had on indirect costs (i.e., productivity, presenteeism, and absenteeism) as well as health-related quality of life, but highlights that the high costs of biologics are not always fully offset by reductions in cost and resource use associated with disease.

For many patients, treatment switching and dose escalation were required, albeit at considerable expense, especially when switching between treatment classes and to less convenient routes of administration (e.g., subcutaneous to intravenous).

This systematic review highlights a high unmet need for therapies for moderate-to-severe ulcerative colitis that reduce the healthcare burden and impact on society.

INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory bowel disease that primarily affects the colon and rectum [1] and is most often diagnosed between the ages of 30 and 40 years [2]. The prevalence of UC varies worldwide and is most often diagnosed in developed regions, such as Europe and the USA, where approximately one in every 200–747 and 350 people, respectively, are affected [3]. Although most patients with UC experience mild disease activity, 20% of patients with UC experience at least one severe exacerbation over the course of their disease [4]. On the basis of the Truelove and Witts criteria and Mayo Clinic score, patients with moderate-to-severe disease experience frequent daily (four or more) bloody

stools [5], and have severe endoscopic disease activity (presence of ulcers), are dependent on or refractory to corticosteroids, and/or are at high risk of colectomy [6–8]. Patients typically experience periods of remission between symptomatic flares, which can lead to abdominal pain, vomiting, diarrhea, fever, rectal bleeding, weight loss, and even gastrointestinal bleeding [1, 9].

The goal of treatment is to induce and maintain remission, as well as to prevent and manage complications, improve health-related quality of life (HRQoL), and achieve mucosal healing [8, 10–12]. Patients living with UC can have a variable disease course; therefore, treatment choice largely depends on disease activity (active or remission), severity, and steroid dependence [8, 10, 11]. Most patients with moderate-to-severe disease in the USA and Europe typically receive conventional therapies, including aminosalicylates (5-ASAs), corticosteroids, and/or immunomodulators (i.e., azathioprine and 6-mercaptopurine) as first-line therapy, but these therapies are often insufficient to induce or maintain adequate response [4, 13].

Over the past 20 years, the development and approval of biologic agents has provided additional treatment options for patients with moderate-to-severe UC. The first biologics to receive regulatory approval in the USA and Europe were the tumor necrosis factor-α antagonists (anti-TNFs) infliximab, adalimumab, and golimumab, followed by the anti-integrin agent vedolizumab, and the interleukin-12/23 antagonist ustekinumab. For many patients, biologic agents successfully induce and maintain remission, in turn reducing the need for hospitalization and colectomy [12]. However, the effectiveness of biologics often diminishes over time, leading to the need for dose escalation or treatment switching [14]. As such, new biologics as well as small-molecule drugs that target intracellular transduction pathways are being developed for the treatment of moderate-to-severe UC [15–21]. The US Food and Drug Administration and European Medicines Agency recently approved two Janus kinase (JAK) inhibitors, tofacitinib and upadacitinib, and a sphingosine 1-phosphate receptor modulator, ozanimod, for the treatment of moderate-to-severe UC [15, 22–27].

With the emergence of additional treatments for patients with moderate-to-severe UC, an up-to-date indirect treatment comparison has established that these treatments vary with respect to comparative efficacy and safety [12]. Although the clinical benefits of biologics and small-molecule drugs in the treatment of moderate-to-severe UC are well understood, there is less clarity regarding the economic and humanistic impact of these treatments. Some studies have reported the high cost of biologic therapies, and some have suggested costs may be reduced from decreased hospitalizations, emergency department visits, surgeries, and improvements in indirect costs and HRQoL [28–32]. However, there is an important need to collect and comprehensively synthesize these data.

These considerations invite questions about economic and HRQoL outcomes related to treatment with biologics in patients with moderate-to-severe UC. Given that anti-TNFs have been available for more than 20 years [33], real-world evidence (including long-term follow-up data and data on treatment switching) is now available for assessment. Therefore, we conducted a systematic literature review to quantify the cost and healthcare resource utilization (HCRU) and assess HRQoL for patients treated with approved biologic therapy and small-molecule drugs for moderate-to-severe UC.

METHODS

This study was conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines [34–36], International Society for Pharmacoepidemiology guidelines for good pharmacoepidemiology practice [37], methodology outlined by the Cochrane Collaboration, and applicable regulatory requirements [38]. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors. The study protocol was not registered but is available upon request.

Systematic Literature Review

Systematic searches were conducted via OvidSP in MEDLINE, Embase, the Database of Abstracts of Reviews of Effects (DARE), National Health Service Economic Evaluation Database (NHS EED), and EconLit to identify relevant observational studies (including prospective and retrospective cohort studies and cross-sectional analyses) published between January 1, 2010 and October 14, 2021, involving adult patients (18 years or older) with moderate-to-severe UC treated with approved biologic and small-molecule therapies. Two search strategies (one on economic outcomes and another on HRQoL outcomes) were developed in accordance with the pre-specified population, intervention, comparison, outcome, and study design (PICOS) framework (Supplementary Material Tables 1 and 2). Supplementary gray literature searches of conference proceedings from the past 4 years (January 1, 2018 to October 14, 2021) were also performed.

Study inclusion criteria are described in Table 1. The overall objective was to summarize evidence on cost and HCRU and assess HRQoL for patients treated with approved advanced therapies (biologics and small-molecule drugs) for moderate-to-severe UC. Geography was limited to the USA and Europe because of the high prevalence of UC in those regions [3].

All abstracts and subsequent full texts were screened by two independent investigators, with disagreements resolved through discussion and consensus or by a third investigator. Study and patients' characteristics, methodology, results, and conclusions from the accepted studies were extracted into a prespecified data extraction form by a single investigator and validated by a second investigator. Study findings were summarized in a descriptive synthesis.

Outcomes are presented as reported in each respective study with costs (total, direct, and indirect) reported as US dollars, euros, or British pound sterling at the time of each study. Findings were qualitatively synthesized.

RESULTS

Summary of Included Studies

The literature searches identified 3006 unique publications, of which 56 reporting on 47 unique studies met the inclusion criteria. Of the 47 unique studies, 40 reported on cost/HCRU and nine reported on HRQoL including two cost/HCRU studies that also reported HRQoL. The PRISMA diagram in Fig. 1 [39–42] illustrates the flow of references through the review.

Of the 56 publications that met the inclusion criteria, the evidence base was reported primarily as full-text articles (33 [58.9%]), with 23 (41.1%) conference abstracts. Across the 47 unique studies identified, 21 (44.7%) focused on the USA, 25 (53.2%) on Europe, and one (2.1%) reported data for both regions. Figure 2 presents the distribution of outcomes by country [43, 44]. Most studies were retrospective cohorts (34 [72.3%]), followed by prospective cohorts (10 [21.3%]) and cross-sectional (3 [6.4%]). For the cohort studies, follow-up duration ranged from 2 months to 12 years. Data collection ranged from January 1991 to September 2019, with most studies (40 [85.1%]) within the 2010–2017 timeframe when only adalimumab, golimumab, infliximab, and vedolizumab were approved for UC (Supplementary Material, Fig. 1). Table 2 provides additional details on the included studies [28–32, 39–41, 43–89].

Details of patient characteristics were limited, mainly because the biologic-treated populations were reported as subgroups of broader inflammatory bowel disease or UC study populations. Approximately half of the included studies reported separate outcomes of interest for subsets of patients with UC treated with biologics. Sample sizes for biologic-treated patients ranged from 11 (the subset of patients with UC in a small study from Spain) to 7705 (a US claims study). European studies generally had smaller patient populations, particularly across treatment groups.

Regarding specific treatments, 22 (46.8%) of the 47 studies assessed a mix of advanced therapies, while others assessed specific drugs or reported outcomes separately by biologic agent

Table 1 PICOS framework

Domain	Inclusion criteria	Exclusion criteria
Population	Adults (≥ 18 years) with moderate-to-severe UC	Pediatric patients (< 18 years)
		Patients with mild UC
		Mixed populations without results reported separately for adults with moderate-to-severe UC
		Patients with UC who were entirely comorbid
Interventions/comparators	Approved biologic and small-molecule agents including, but not limited to, adalimumab, golimumab, infliximab, tofacitinib, ustekinumab, or vedolizumab, or biosimilar versions of these therapies	No interventions or comparators of interest
Outcomes	**Economic outcomes**	**Economic outcomes**
	Total costs (direct + indirect)	Hospitalizations reported as a risk factor for another outcome such as colectomies or postoperative complications
	Direct costs and individual cost components (i.e., healthcare visits, ED visits, hospitalizations)	Studies examining/reporting:
	Indirect costs (i.e., productivity losses; absenteeism, presenteeism, WPAI score)	Only readmission rates following surgical procedures for UC
	HCRU (i.e., healthcare visits, ED visits, hospitalizations, LOS)	Primarily on clinical outcomes
	Patient-reported outcomes (HRQoL and utilities)	Only on postoperative resource use (e.g., hospitalizations, readmission rates)
	Change from baseline in the following disease-specific and generic HRQoL measures:	**Patient-reported outcomes (HRQoL and utilities)**
	SF-36	Outcomes based on different surgical approaches
	EQ-5D	Outcomes of interest for only a select group of patients with specific surgical-related adverse events
	IBDQ	
	SIBDQ	
	Utilities/disutilities	
Study design	Observational studies, including prospective and retrospective cohort studies and cross-sectional analyses	Case reports or case series, letters to the editor, editorials, comments, notes, narrative reviews, clinical trials, systematic literature reviews, or meta-analyses
		Studies focusing solely on comparisons between UC and Crohn's disease

Table 1 continued

Domain	Inclusion criteria	Exclusion criteria
Timeframe	Full-text articles: January 1, 2010 to October 14, 2021	Full-text articles published prior to January 1, 2010
	Conference abstracts: January 1, 2018 to October 14, 2021	Conference abstracts presented prior to January 1, 2018

CUCQ Crohn's and Ulcerative Colitis Questionnaire, *ED* emergency department, *EQ-5D* EuroQol-5D, *HCRU* healthcare resource utilization, *HRQoL* health-related quality of life, *IBDQ* Inflammatory Bowel Disease Questionnaire, *LOS* length of stay, *RFIPC* Rating Form of Inflammatory Bowel Disease Patient Concerns, *SF-36* 36-item Short Form questionnaire, *SIBDQ* Short Inflammatory Bowel Disease Questionnaire, *UC* ulcerative colitis, *WPAI* Work Productivity and Activity Impairment

(Fig. 3). Infliximab was the most frequently referenced treatment in 15 (31.9%) studies, followed by adalimumab in 11 (23.4%), golimumab in 10 (21.3%), and vedolizumab in 10 (21.3%) studies. One study assessed ustekinumab, but alongside other biologics and for a very limited sample of patients ($n = 3$). The off-label data on certolizumab pegol and natalizumab are not summarized in this review because of the lack of availability of data and small sample sizes when data were reported.

Cost Outcomes

Of the 40 studies, 25 (62.5%) reported cost outcomes (12, USA; 13, Europe); details are provided in Supplementary Material Tables 3 and 4. Twenty-two (55.0%) of the 40 studies reported direct costs (11, USA; 11, Europe) either as total direct costs (medical and pharmacy) and/or individual components of medical costs (e.g., outpatient visits, hospitalization, surgical procedures, etc.). Irrespective of geography, total direct costs were driven by pharmacy expenses, given the high costs associated with biologic therapy, with similar trends observed in Germany (adalimumab, €24,151; golimumab, €27,791; infliximab, €24,462; vedolizumab, €26,621) and the USA (adalimumab, $56,366; golimumab, $61,500; infliximab, $60,234; vedolizumab, $72,274) for individual biologic agents (Fig. 4). Hospitalizations were associated with the highest medical costs, followed by outpatient visits and emergency services. This trend was evident in all studies except for Perera et al., which reported higher outpatient costs than hospital-related expenses for all biologics except adalimumab [58].

Direct Costs Associated with Initiation of and Switching Between Biologics

Of the 40 studies, four (10.0% [two, USA; two, Europe]) assessed the direct costs associated with initiating biologic therapy (Fig. 5; Supplementary Material Table 3). Trends were consistent across studies in biologic-naïve patients and those who had previously received anti-TNFs and were starting a new biologic.

Among two USA studies, initiation of biologics was associated with reductions in mean costs of outpatient visits, hospitalizations, and emergency department visits over both 6 months and 1 year except for the initiation of vedolizumab, which was associated with increased outpatient visits [50, 58]. There were no data reported for the USA with regard to changes in medication use or surgical procedures after biologic initiation.

In contrast to the USA studies, two German studies demonstrated increased mean annual costs of outpatient visits, hospitalizations, emergency services, in addition to prescriptions

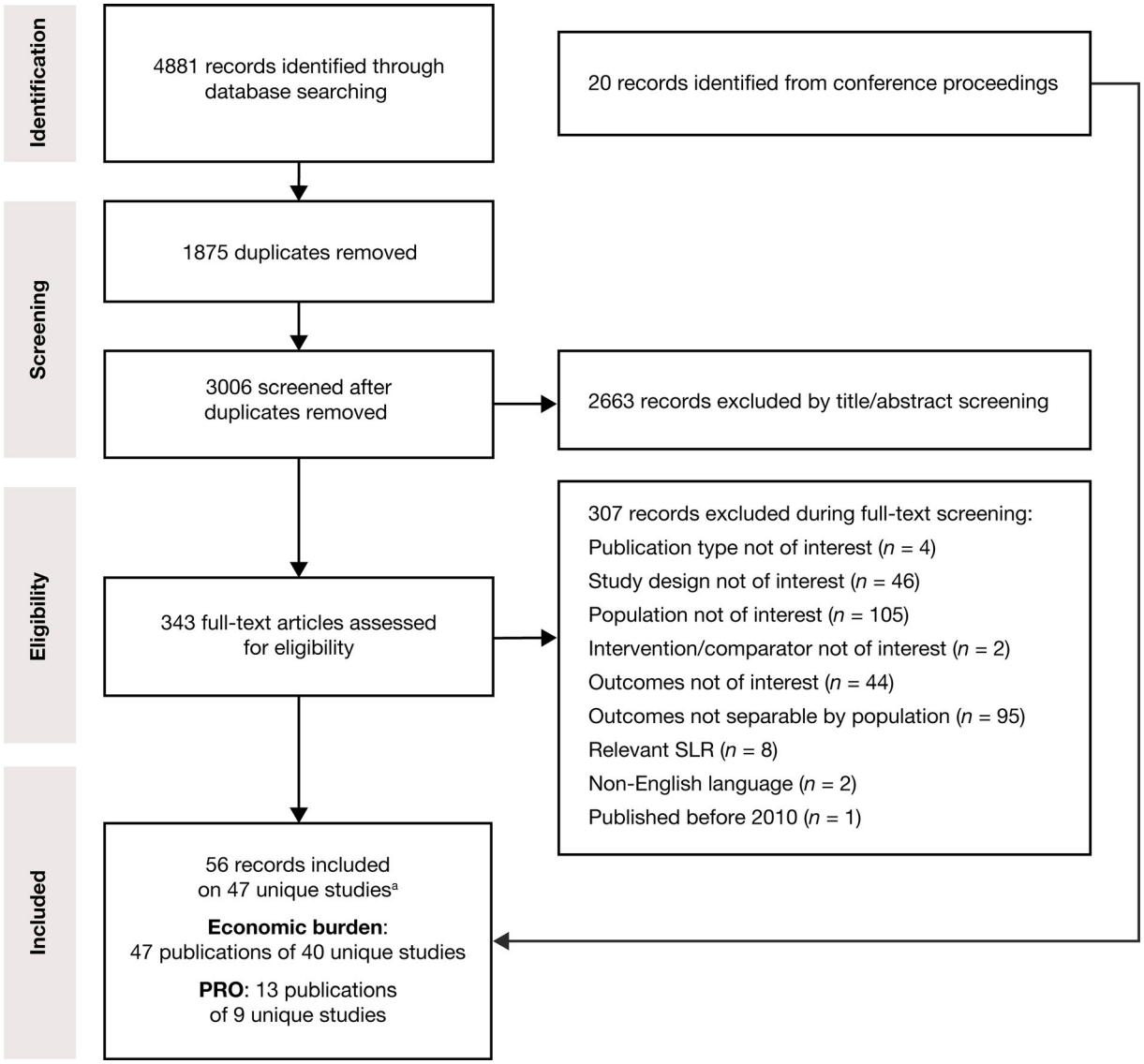

Fig. 1 PRISMA diagram of study attrition. [a]Two studies reported across four publications on both the economic burden of UC and associated HRQoL [39–42]. *HRQoL* health-related quality of life, *PRISMA* Preferred Reporting Items for Systematic reviews and Meta-Analyses, *PRO* patient-reported outcome, *SLR* systematic literature review, *UC* ulcerative colitis

and surgical procedures over the first year of biologic treatment [31, 69], with Dignass et al. reporting subsequent reductions in medical and pharmacy costs over the second year of treatment below those observed before biologic initiation. These findings suggest that the highest burden associated with biologic use is observed in the first year of treatment [69].

Of the 40 studies, two USA studies (5.0%) assessed cost outcomes associated with biologic switching and found that changing therapies can be expensive, particularly if a different drug class is involved. Chiorean et al. compared costs (2017 US$) associated with switching from one anti-TNF to another anti-TNF or vedolizumab, and found that switching to vedolizumab incurred significantly higher healthcare costs within the first 6 months after the switch versus switching to adalimumab or infliximab ($54,528 vs. $43,118–47,861, $P < 0.05$), but not when switching to golimumab ($54,528 vs. $49,677) [50]. These differences were driven by

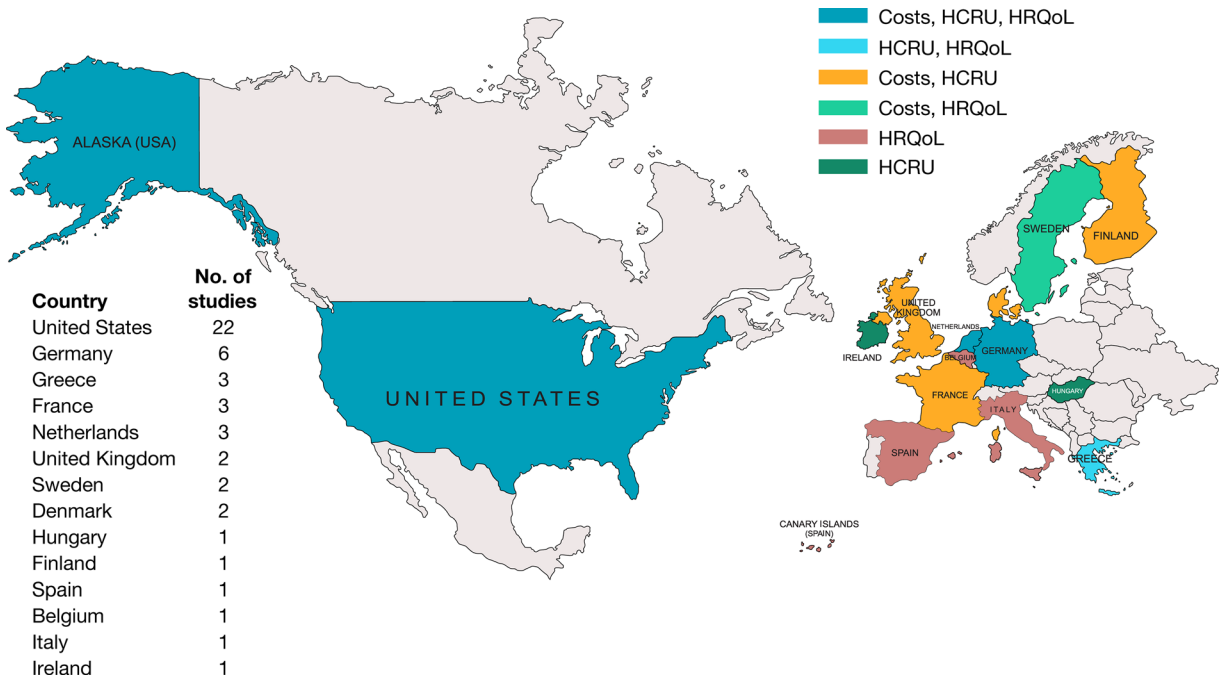

Fig. 2 Geographic distribution of reported outcomes. Two studies reported data from multiple regions: one study from the Netherlands and Belgium [43] and one from the USA and France [44]. *HCRU* healthcare resource utilization, *HRQoL* health-related quality of life

higher medical expenses (outpatient costs; \$7768 vs. \$5216, $P < 0.05$) and drug costs (\$36,689 vs. \$29,573, $P < 0.05$) for vedolizumab compared with adalimumab and by higher non-index drug-related pharmacy costs (\$3825 vs. \$2914, $P < 0.05$) compared with infliximab [50]. Among patients switching anti-TNFs, Null et al. found that patients treated with infliximab or adalimumab who remained on their initial anti-TNF (irrespective of dose stability) had lower mean quarterly total healthcare costs (2014 US\$) versus patients who switched to the other anti-TNF (\$9632–10,113 vs. \$15,004) [56]. The biggest driver of higher costs related to treatment switching aside from costs related to anti-TNFs was inpatient medical costs (\$3559 vs. \$540–749) [56].

Indirect Costs

Six (15.0%) of the 40 studies (two, USA; four, Europe) reported indirect costs (Supplementary Material Table 4). Pilon et al. reported total indirect costs as \$11,898 per person per year, representing 13.0% of the total cost burden of patients with UC who received biologics in the USA, which was primarily attributable to costs associated with work absences due to disability costs (Supplementary Material Table 4) [59]. In Germany, Teich et al. found that initiation of golimumab was associated with significant improvements ($P < 0.0001$) in work productivity and the capacity for daily activities starting as early as month 3, with these improvements maintained up to 24 months (end of study follow-up) [39]. Picker et al. also found that patients receiving anti-TNFs, vedolizumab, or tofacitinib who were previously treated with advanced therapies had fewer sick days from work than treatment-naïve patients (12.2 vs. 13.2) per year and lower costs associated with UC-related sick leave (€2909 vs. €3404 per patient-year) [81, 82]. Cross et al. found that patients in the USA who were treated with biologics or JAK inhibitors were burdened most by impaired daily activities due to UC, followed by

Table 2 Characteristics of included studies

Study; publication type	Study design	Country	Data source	Study years	Study population	Sample size	Advanced therapy	Follow-up duration, months	Outcomes reported
USA									
Bornheimer 2019 [45]; abstract	Retrospective cohort	USA	IQVIA RWD Adjudicated Claims Database	01/2011 to 12/2017	Patients with UC receiving ≥ 1 IBD-related biologic	4832	Not specified	60	Costs
Borren 2020 [46]; article	Prospective cohort	USA	Prospective Registry for IBD Study	12/2014 to 06/2018	Patients with moderate-to-severe UC initiating biologic therapy	308	ADA, IFX, UST, or VDZ	12.4	HRQoL
Cai 2020 [47]; abstract	Retrospective cohort	USA	IBM MarketScan Commercial Claims Database	01/2017 to 12/2017	Adults with UC and ≥ 1 medical or pharmacy claim for a biologic	6414	Not specified	12	Costs, HCRU
Carter 2011 [30]; article	Retrospective cohort	USA	IMS LifeLink database	09/2004 to 03/2009	Patients with UC newly initiating IFX	420	IFX	12–14	Costs, HCRU
Chapman 2019 [48]; abstract	Retrospective cohort	USA	PharMetrics Plus claims data	01/2013 to 10/2017	Patients with UC newly initiating biologic therapy	3595	ADA, GOL, IFX, or VDZ	12	HCRU
Chen 2021 [49]; abstract	Retrospective cohort	USA	Optum Research Database	2016 to 2019	Patients with UC treated with biologic therapy	NR	Anti-TNF or VDZ	NR	HCRU

Table 2 continued

Study; publication type	Study design	Country	Data source	Study years	Study population	Sample size	Advanced therapy	Follow-up duration, months	Outcomes reported
Chiorean 2020 [50]; article	Retrospective cohort	USA	IBM MarketScan databases	01/2000 to 09/2017	Patients with UC who switched from an initial anti-TNF to another anti-TNF or VDZ	1348	ADA, GOL, IFX, or VDZ	6	Costs, HCRU
Cross 2020 [51]; abstract	Retrospective cohort	USA	Corrona IBD registry	5/2017 to 9/2019	Patients with UC on biologics/JAK inhibitors	315	Not specified	NR	Costs
Hunter 2019 [52]; abstract	Cross-sectional	USA	Truven Health MarketScan Commercial and Medicare Supplemental Databases	01/2007 to 12/2017	Patients with UC currently receiving biologics	NR	Not specified	NA	HCRU
Kirchgesner 2021 [44]; article	Retrospective cohort	USA	IBM MarketScan and Optum's Clinformatics Data Mart Database	MarketScan (2004 to 2018); Optum (2005 to 2019)	Anti-TNF-naïve patients with moderate-to-severe UC initiating biologic therapy	878	IFX	9.3	HCRU
Kochar 2018 [53]; abstract	Retrospective cohort	USA	Truven Health MarketScan database	05/2014 to 12/2015	Patients with UC who are new users of VDZ	249	VDZ	6	HCRU

Table 2 continued

Study; publication type	Study design	Country	Data source	Study years	Study population	Sample size	Advanced therapy	Follow-up duration, months	Outcomes reported
Long 2019 [28]; article	Retrospective cohort	USA	IQVIA RWD Adjudicated Claims Database	07/2011 to 07/2014	Patients with UC who were new and chronic users (≥ 60 days) of anti-TNFs	2851	ADA, CZP, GOL, or IFX	2	Costs, HCRU
Long 2020 [29]; article	Retrospective cohort	USA	IBM MarketScan Research Databases	01/2012 to 03/2017	Patients with UC initiating biologic therapy	2331	ADA, GOL, IFX, or VDZ	12	Costs, HCRU
Naegeli 2019 [54]; abstract	Cross-sectional	USA	IBM MarketScan Commercial, Medicaid, and Medicare Supplemental Claims database	01/2017 to 12/2017	Patients with UC receiving biologics	7705	Not specified	NA	HCRU
Nguyen 2020 [55]; abstract	Cross-sectional	USA	IBM Watson Health MarketScan database	2010 to 2017	Patients with UC initiating biologic therapy	7331	Not specified	NA	HCRU
Null 2017 [56]; article	Retrospective cohort	USA	Humana Research Database	01/2007 to 12/2014	Patients with UC initiating biologic therapy	295	ADA or IFX	12	Costs, HCRU

Table 2 continued

Study; publication type	Study design	Country	Data source	Study years	Study population	Sample size	Advanced therapy	Follow-up duration, months	Outcomes reported
Patel 2018 [57]; abstract	Retrospective cohort	USA	Explorys Universe database	05/2014 to 10/2017	Biologic-naïve patients with UC initiating treatment with IFX or VDZ	150	IFX or VDZ	12	HCRU
Perera 2018 [58]; article	Retrospective cohort	USA	Truven Health MarketScan Commercial and Medicare Supplemental Databases	04/2010 to 03/2015	Patients with UC initiating biologics	2195	ADA, CZP, GOL, IFX, NAT, UST, or VDZ	12	Costs, HCRU
Pilon 2020 [59]; article	Retrospective cohort	USA	Optum Healthcare Solutions, Inc employer claims database	01/1999 to 03/2017	Patients with moderate-to-severe UC receiving biologics	889	ADA, CZP, GOL, IFX, NAT, or VDZ	58.8	Costs
Rubin 2020 [60]; article	Retrospective cohort	USA	IBM MarketScan Commercial Claims & Encounters and Medicare Supplemental & Coordination of Benefits databases	01/2001 to 12/2014	Patients with UC and $\geq$ 1 anti-TNF drug claim	4451	Anti-TNF (not specified)	12	Costs

Table 2 continued

Study; publication type	Study design	Country	Data source	Study years	Study population	Sample size	Advanced therapy	Follow-up duration, months	Outcomes reported
Stewart 2021 [61]; article	Retrospective cohort	USA	Optimum Clinformatics Data Mart	01/2013 to 12/2018	Patients with UC initiating an anti-TNF agent	492	ADA or GOL	12	HCRU
Wolf 2021 [62]; abstract	Retrospective cohort	USA	MarketScan Commercial Claims data	01/2012 to 12/2016	Patients with UC initiating biologic therapy	2972	ADA, IFX, GOL, or VDZ	24	Costs, HCRU
Europe									
Armuzzi 2021 [63]; abstract	Prospective cohort	Italy	GO-CARE study	NR	Patients with UC treated with GOL	83	GOL	12.4	HRQoL
Armuzzi 2018 [32]; article									
Bamias 2021 [64]; article	Prospective cohort	Greece	Greek tertiary GI-IBD centers	11/2015 to 05/2019	Patients with UC initiating therapy with VDZ	96	VDZ	12.4	HRQoL
Bamias 2019 [65]; abstract									

Table 2 continued

Study; publication type	Study design	Country	Data source	Study years	Study population	Sample size	Advanced therapy	Follow-up duration, months	Outcomes reported
Black 2016 [66]; article	Retrospective cohort	UK	Hospital Treatment Insights database (IMS Health Ltd, UK)	01/2010 to 03/2014	Patients with UC treated with ADA	191	ADA	12	Costs
Campbell-Hill 2018 [31]; abstract	Retrospective cohort	Germany	Patient charts from 15 German centers	07/2014 to 10/2015	Patients with UC initiating VDZ or an anti-TNF agent	140	ADA, GOL, IFX, or IFX biosimilar	12	Costs
Casellas 2012 [67]; article	Retrospective cohort	Spain	Crohn-Colitis Care Unit (UACC) at Hospital Universitario Valle de Hebrón	NR	Patients with UC treated with anti-TNFs	11	ADA or IFX	12	HRQoL
Desmond 2012 [68]; article	Prospective cohort	Ireland	IBD database of a tertiary referral center, Cork University Hospital	01/1991 to 01/2009	Patients with UC admitted to the Cork University Hospital	25	ADA or IFX	Median: 14.2	HCRU
Dignass 2020 [69]; article	Retrospective cohort	Germany	German statutory health insurance database	01/2013 to 12/2015	Patients with UC newly initiating biologic therapy	304	ADA, GOL, IFX, or VDZ	24	Costs, HCRU
Dignass 2019 [70, 71]; abstracts									

Table 2 continued

Study; publication type	Study design	Country	Data source	Study years	Study population	Sample size	Advanced therapy	Follow-up duration, months	Outcomes reported
Eriksson 2021 [72]; article	Prospective cohort	Sweden	Swedish National Quality Register for IBD (SWIBREG); SVEAH Study	06/2015 to 11/2018	Patients with active UC at the onset of biologic treatment	117	VDZ	12	HRQoL
Gatopoulou 2021 [73]; article	Prospective cohort	Greece	GO-LIFE study	2015 to 2018	Anti-TNF-naïve patients with moderately to severely active UC and inadequate response, intolerability, or contraindication to conventional therapies	81	GOL	12	HRQoL
Khalili 2020 [74]; article	Retrospective cohort	Sweden	Swedish National Patient Register	2014	Patients with UC on anti-TNF therapy	862	Anti-TNF (not specified)	12	Costs
Kirchgesner 2021 [44]; article	Retrospective cohort	France	SNDS	2009 to 2018	Anti-TNF-naïve patients with moderate-to-severe UC initiating biologic therapy	620	IFX	9.3	HCRU

Table 2 continued

Study; publication type	Study design	Country	Data source	Study years	Study population	Sample size	Advanced therapy	Follow-up duration, months	Outcomes reported
Lawton 2019 [75]; article	Retrospective cohort	France	Outpatient clinic at the Nancy University hospital	11/2016 to 02/2017	Patients with UC treated with ADA or IFX	25	ADA, IFX, or IFX biosimilar	12	Costs
Lo 2020 [76]; article	Prospective cohort	Denmark	Danish national registries	01/2003 to 12/2004	Patients with UC receiving biologics	28	Not specified	144	Costs
Lowenberg 2014 [77]; article	Retrospective cohort	Netherlands	Local hospital database	11/2003 to 08/2012	Patients hospitalized for severe corticosteroid-refractory UC and treated with IFX	16	IFX	Median: 34.5	Costs, HCRU
Mandel 2014 [78]; article	Retrospective cohort	Hungary	Patients' medical charts	01/2008 to NR	Patients with steroid-refractory UC receiving at least one maintenance anti-TNF therapy	42	ADA or IFX	Median: 102	HCRU
Mantzaris 2019 [79]; abstract	Prospective cohort	Greece	GO-LIFE study	NR	Anti-TNF-naïve patients with moderate-to-severe UC and inadequate response to conventional therapies	50	GOL	6	HCRU

Table 2 continued

Study; publication type	Study design	Country	Data source	Study years	Study population	Sample size	Advanced therapy	Follow-up duration, months	Outcomes reported
Oussalah 2010 [80]; article	Retrospective cohort	France	Medical records of patients from five academic centers in France	12/2007 to 12/2014	Patients with UC initiating first-line anti-TNF therapy	191	ADA or IFX	Median: 18	HCRU
Picker 2021 [81] Picker 2021 [82] Bokemeyer 2021[83]; abstracts	Retrospective cohort	Germany	AOK PLUS	01/2015 to 06/2019	Patients with UC undergoing advanced therapies	574	Anti-TNFs (not specified), TOF, or VDZ	48	Costs, HCRU
Pöllinger 2019 [84]; article	Retrospective cohort	Germany	Arvato Health Analytics GmbH database in cooperation with Gesundheitsforen Leipzig GmbH	2007 to 2015	Patients with moderate-to-severe UC treated with biologics	154	ADA	12	Costs
Sebastian 2019 [85]; article	Retrospective cohort	UK	11 acute hospitals	05/2016 to 05/2018	Hospitalized, steroid-refractory patients with ASUC	131	IFX	12	HCRU
Singh 2017 [86]; article	Retrospective cohort	Denmark	Danish National Patient Registry	2005 to 2014	Biologic-naïve patients with UC	275	ADA or IFX	Median: ADA 15.6 Median: IFX 27.6	HCRU

Table 2 continued

Study; publication type	Study design	Country	Data source	Study years	Study population	Sample size	Advanced therapy	Follow-up duration, months	Outcomes reported
Teich 2021 [39]; article Teich 2020 [40]; article Teich 2019 [42]; abstract	Prospective cohort	Germany	GO CUTE study	03/2014 to 08/2019	Patients with UC who were suitable for GOL therapy	282	GOL	24	Costs, HCRU, HRQoL
van der Valk 2015 [41]; article	Prospective cohort	Netherlands	COIN study	10/2010 to 10/2011	Patients with UC on anti-TNF therapy	34	ADA or IFX	24	Costs, HRQoL
van Gennep 2017 [43]; article	Retrospective cohort	Netherlands, Belgium	Academic Medical Center in Amsterdam, the Netherlands, and the University Hospitals in Leuven, Belgium	2010 to 01/2015	Patients with moderate-to-severe UC starting treatment with an anti-TNF agent	59	ADA, GOL, or IFX	Median: 29	HRQoL
Wilke 2020 [87]; article	Retrospective cohort	Germany	Regional German Sickness Fund	01/2011 to 12/2015	Patients newly diagnosed with UC initiating anti-TNF therapies	131	ADA, CZP, IFX, or GOL	Median: 51	Costs

Table 2 continued

Study; publication type	Study design	Country	Data source	Study years	Study population	Sample size	Advanced therapy	Follow-up duration, months	Outcomes reported
Ylisaukko-Oja 2019 [88]; article Torvinen 2018 [89]; abstract	Retrospective cohort	Finland	The Hospital District of Southwest Finland	2014 to 2016	Anti-TNF-naïve patients with UC initiating treatment with IFX	110	IFX	12	Costs, HCRU

ADA adalimumab, *CZP* certolizumab pegol, *GI* gastrointestinal, *GOL* golimumab, *HCRU* healthcare resource utilization, *HRQoL* health-related quality of life, *IBD* inflammatory bowel disease, *IFX* infliximab, *JAK* Janus kinase, *NA* not applicable, *NAT* natalizumab, *NR* not reported, *RWD* real-world data, *SNDS* Système National des Données de Santé (French nationwide health insurance database), *TNF* tumor necrosis factor, *UC* ulcerative colitis, *UST* ustekinumab, *VDZ* vedolizumab

loss of work productivity, work impairments, and work time missed. In comparison with patients treated with 5-ASAs, patients treated with biologics or JAK inhibitors were more likely to be employed, and experienced more frequent work and activity impairments across all four WPAI domains [51].

HCRU Outcomes

Thirty-one (77.5%) of the 40 studies reported HCRU outcomes (18, USA; 13, Europe; Supplementary Material Table 5). HCRU was driven primarily by use of outpatient services in the USA and Europe. After outpatient visits, the emergency department was the next most commonly used resource in the USA [50, 54, 56], while hospital services were used more frequently in Europe [39, 69, 88]. Reporting of surgical procedures alongside other services was limited to six studies, but consistently was the least-used service among patients treated with advanced therapies.

HCRU Outcomes Based on Initiation of and Switching Between Biologics

Ten (25.0%) of the 40 studies (five, USA; four, Europe; one from both the USA and France) assessed the impact of biologic initiation on healthcare services utilization (Fig. 3). Trends were generally consistent across studies whether patients were biologic therapy-naïve and initiating biologic treatment or had previously received an anti-TNF and were starting a new biologic therapy. However, three USA studies assessing golimumab (two on patients naïve to biologic therapy [58, 61] and one on patients switching biologics [50]) reported increased inpatient admissions and emergency department visits after initiation of a second biologic compared with the decreases observed upon initiation of first biologic agent.

Among the USA studies, initiation of biologic therapy was generally associated with reduced hospitalization rates and emergency department visits, but more frequent outpatient visits (consistent with our findings on costs). Patients initiating adalimumab had fewer

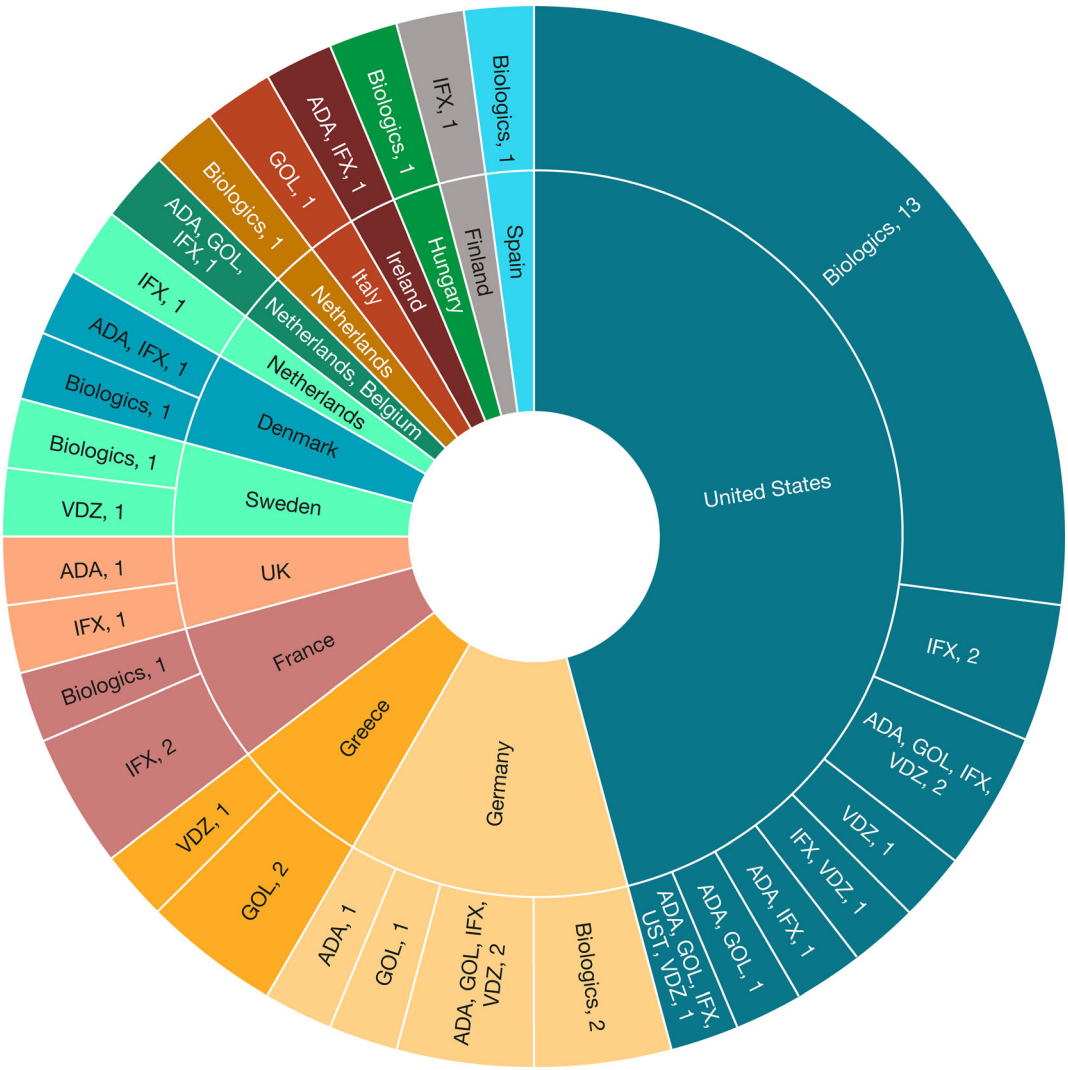

Fig. 3 Biologic treatments evaluated by country. *ADA* adalimumab, *BEL* Belgium, *DNK* Denmark, *GOL* golimumab, *UK* United Kingdom, *UST* ustekinumab, *VDZ* vedolizumab

outpatient visits after 6 and 12 months of treatment compared with baseline [50, 58, 61]. HCRU associated with initiation of golimumab was reported by the same three studies reporting data for adalimumab [50, 58, 61], but results were inconsistent across and within these studies regarding increased or decreased use of individual services.

The European (n = 4) and USA studies (n = 5) were largely consistent in reporting increased outpatient visits and decreased emergency services use over the first year of biologic initiation, while mixed results were observed across two studies that reported hospitalization rates. Similar to findings on costs, Dignass et al. noted overall increased HCRU associated with the first year of biologic initiation, with subsequent reductions below those observed before biologic initiation over the second year of treatment [69].

Consistent with findings on costs, USA patients switching from one anti-TNF to another anti-TNF were more likely to utilize healthcare services (emergency department, hospital, and outpatient) [56]. Chen et al. also suggested that the timing of anti-TNF switching

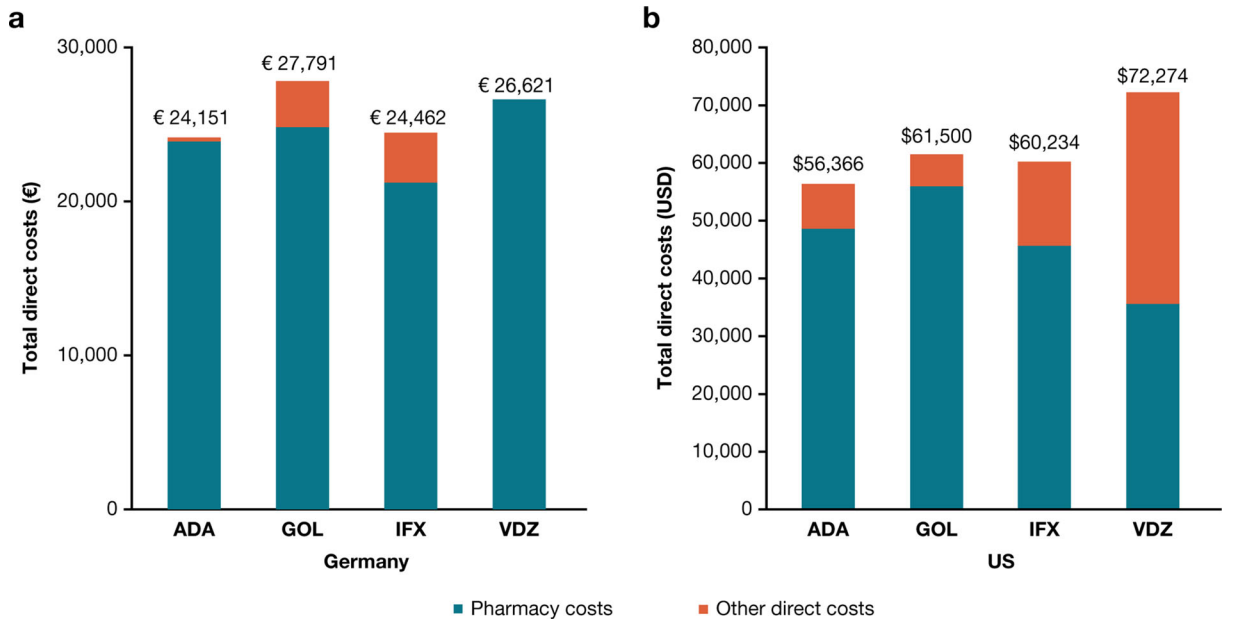

Fig. 4 Direct costs in **a** euros and **b** US dollars associated with the first year of biologic therapy for patients with moderate-to-severe UC in the USA and Germany. Data on direct costs of moderate-to-severe UC were reported by two studies; one in the USA [58] and one in Germany [69]. *ADA* adalimumab, *GOL* golimumab, *IFX* infliximab, *UC* ulcerative colitis, *USD* United States dollar, *VDZ* vedolizumab

may affect utilization of healthcare services wherein patients treated with an anti-TNF agent before switching to vedolizumab (irrespective of receipt of immunomodulators) experienced more hospitalizations, colectomies, and UC-related laboratory tests (Supplementary Material Table 5) [49]. Also consistent with findings on costs, Chiorean et al. demonstrated higher HCRU burden, driven by more frequent outpatient visits when patients switched from anti-TNF therapy to vedolizumab versus patients switching to adalimumab or golimumab [50]. However, use of outpatient services was similar to patients switching to infliximab, possibly because both drugs are administered intravenously rather than subcutaneously, as with adalimumab and golimumab.

HCRU Outcomes Associated with Dose Changes and Treatment Combinations

Four studies (two, USA; two, Europe) assessed the HCRU outcomes associated with dose changes. In a USA study by Null et al., escalation or reduction of adalimumab or infliximab doses was associated with slightly more frequent use of outpatient services (57.2% vs. 55.3%) and increased medication claims (average 3.83 vs. 3.75 claims) over 1 year compared with patients on a stable dose [56]. Meanwhile, a German study by Picker et al. suggested that dose escalation of infliximab in the first year of treatment was associated with slightly fewer hospitalizations (average per patient 0.3 vs. 0.4) or gastroenterologist visits (average per patient 2.1 vs. 2.3) versus patients who did not undergo dose escalation [82]. Other findings related to infliximab that were consistent across USA and European studies showed that the timing and dose of induction and maintenance therapy have an impact on HCRU. Sebastian et al. found that an accelerated regimen (two 5-mg/kg doses at week 0 and one 5-mg/kg dose on or before week 1 and/or before week 2) was associated with longer hospital stays and higher rates of colectomy than the standard regimen (5 mg/kg at weeks 0 and 2), although the between-group differences were not significant ($P > 0.05$) [85]. Similarly,

a

Outcome	Geographic Region	Direct costs: ADA (*n* = 3)	GOL (*n* = 3)	IFX (*n* = 3)	UST (*n* = 1)	VDZ (*n* = 4)	Biologics (*n* = 4)
Outpatient visits	US (*n* = 2)	↓	↓	↓	↓	↑	-
	Europe (*n* = 1)	-	-	-	-	-	↑
Hospital stays	US (*n* = 2)	↓	↓	↓	↑	↓	-
	Europe (*n* = 1)	-	-	-	-	-	↑
ED visits	US (*n* = 2)	↓	↓	↓	↑	↓	-
	Europe (*n* = 1)	-	-	-	-	-	↑
Prescriptions (biologics)	US (*n* = 2)	↑	↑	↑	↑	↑	↑
	Europe (*n* = 2)	↑	↑	↑	↑	↑	↑
Prescriptions (non-biologics)	US (*n* = 0)	-	-	-	-	-	-
	Europe (*n* = 1)	-	-	-	-	-	↓
Surgical procedures	US (*n* = 0)	-	-	-	-	-	-
	Europe (*n* = 1)	-	-	-	-	-	↑

b

Outcome	Geographic Region	Resource use: ADA (*n* = 3)	GOL (*n* = 5)	IFX (*n* = 3)	UST (*n* = 1)	VDZ (*n* = 4)	Biologics (*n* = 4)
Outpatient visits	US (*n* = 3)	↓	↔	↑	↑	↑	-
	Europe (*n* = 3)	-	↓	-	-	-	↑
Hospital stays	US (*n* = 5)	↓	↔	↓	↑	↓	↓
	Europe (*n* = 5)	-	↓	↓	-	-	↔
ED visits	US (*n* = 4)	↓	↔	↓	↑	↓	↑
	Europe (*n* = 2)	-	↓	-	-	-	↓
Prescriptions (non-biologics)	US (*n* = 4)	↓	↓	↑	-	-	↓
	Europe (*n* = 2)	-	-	↑			↓
Surgical procedures	US (*n* = 2)	-	-	-	-	-	↓
	Europe (*n* = 1)	-	-	-	-	-	↓

Fig. 5 Changes in direct healthcare costs (**a**)[a] and HCRU (**b**)[b] associated with initiation of biologic therapy (pre vs. post biologic use) in patients with moderate-to-severe UC. Green arrows indicate a positive outcome after initiation of biologic therapy (pre vs. post biologic use). Red arrows indicate a negative outcome after initiation of biologic therapy (pre vs. post biologic use). Gray horizontal arrows indicate conflicting data regarding changes in the outcome after initiation of biologic therapy (pre vs. post biologic use). [a]Data on direct healthcare costs were reported by four publications [31, 50, 58, 69]. [b]Data on HCRU were reported by 10 publications [39, 44, 50, 52, 55, 58, 61, 69, 78, 79]. *ADA* adalimumab, *ED* emergency department, *GOL* golimumab, *HCRU* healthcare resource utilization, *IFX* infliximab, *UST* ustekinumab, *VDZ* vedolizumab, *UC* ulcerative colitis, *US* United States

patients who received the maintenance regimen of infliximab exhibited fewer hospitalizations in the first year of treatment versus those who received only induction therapy (10.6% vs. 16.4%). Some of these findings suggest that deviations from the approved labeling in a real-world setting may counteract some of the benefit associated with biologic therapy [30].

Long et al. demonstrated that receipt of biologics in combination with immunosuppressants and/or corticosteroids was associated with higher annual rates of all-cause and UC-related hospitalizations and emergency department visits in the USA (Supplementary Material Table 5) [28]. By contrast, infliximab plus thiopurines was associated with lower rates of UC- or colectomy-related hospitalizations within 16 weeks of treatment initiation in the USA (6.3–7.9% vs. 11.1–11.3%) and in France (10.5% vs. 6.1%) compared with patients receiving infliximab monotherapy [44].

HRQoL

Evidence of the impact of biologic therapy on HRQoL in the USA and Europe was limited. Only one USA study and eight European studies from Germany, Greece, Italy, the Netherlands, and Sweden assessed HRQoL in biologic-treated patients (Supplementary Material Table 6). All studies, irrespective of biologic agent or geographic region, demonstrated improved Inflammatory Bowel Disease Questionnaire (IBDQ), Short IBDQ (SIBDQ), EuroQol-5D (EQ-5D), and Short Form-12 (SF-12) scores after initiation of biologic treatment. Significant improvements in HRQoL were observed as early as 3 months in three studies [42, 46, 65] and were maintained up to 1 year [46, 65, 67, 72, 73] and 2 years [39, 42], respectively.

DISCUSSION

To our knowledge, this is the first systematic literature review focused on the impact of advanced therapies on economic and HRQoL outcomes in patients with moderate-to-severe UC. Forty studies included across the USA and Europe demonstrated that the economic burden in patients with moderate-to-severe UC starting treatment with biologics or small-molecule drugs was high in these regions, driven primarily by the cost of these treatments and outpatient visits associated with administration and monitoring. However, biologic initiation was shown to reduce the indirect cost burden to these patients and improve quality of life.

Aside from prescription costs increasing the total healthcare costs associated with biologic treatments, hospitalization-related expenses were the main drivers of medical costs, followed by outpatient visit and emergency services costs. Among healthcare services, outpatient visits were the most common, followed by emergency department visits within the USA studies, while hospital services were used more frequently than the emergency services in Europe. Initiation of biologic therapy was generally associated with reduced medical costs (outpatient, hospital, emergency) and visits (hospital and emergency), increased outpatient visits, and significant improvements in work and activity impairments and quality of life over a range of follow-up from 3 months to 2 years. Despite some reductions in costs and HCRU, the high cost of advanced therapies may not be fully offset. Dignass et al. demonstrated that first year of biologic treatment (1–12 months) was often associated with increased medical and pharmacy costs and HCRU, with subsequent cost reductions below those observed before biologic initiation over the second year of treatment (13–24 months) [69]. These findings suggest that the highest burden associated with biologic use is observed in the first year of treatment.

In general, our findings are consistent with a recently published systematic literature review that assessed cost-of-illness of inflammatory bowel disease, and concluded that since the introduction of biologic treatments, the cost of medications has increased, but the costs associated with inpatient visits, hospitalizations, and surgery have not declined enough to offset increases in treatment costs [90]. Similarly, a recent systematic review on the economic burden of Crohn's disease in Europe found the cost of biologics to be the main driver, over and above the cost of surgery and hospitalizations.

Similar trends have also been observed in moderate-to-severe psoriasis, another chronic inflammatory condition that is commonly treated with similar biologic therapies, such as adalimumab and infliximab [91, 92].

Although the use of biologics adds a substantial cost to patient care, further consideration is required regarding how treatment patterns and switching impact overall cost and HCRU trends in real-world settings. A recent publication by Huynh et al. noted that physicians in Europe reported lack of treatment effectiveness as the primary reason for treatment switching in patients with UC [93]. Bokemeyer et al. found that loss of response can occur within 5 months of treatment (median time to inadequate response 4.8 months), with as many as 75% of patients exhibiting signs of inadequate response, defined as augmentation, corticosteroid dependence, discontinuation, escalation, hospitalization, surgery, or switching after the first year on biologics and increasing to 85% over 2 years [94]. Patients who switched treatments were more likely to incur higher healthcare costs, use more healthcare services, and require hospitalization, often due to adverse events.

Findings from our review suggest that switching to more convenient routes of administration (e.g., intravenous to subcutaneous) is associated with lower healthcare costs and HCRU, specifically intravenous administration of infliximab compared with subcutaneous administration of adalimumab [56]. This finding is further substantiated by a recent study by Bergqvist et al., which examined patients switching from intravenously administered vedolizumab to subcutaneous administration, and found a 15% reduction in costs associated with the subcutaneous autoinjector, along with increased patient satisfaction and comparable efficacy and safety [95]. On the contrary, a study by Causey et al. found that self-administered subcutaneous injections were associated with reduced compliance, and in turn increased use of emergency or hospital services [96]. For most patients and physicians, ease of administration is an important factor in managing UC; nearly half of patients treated with biologic therapies (47%) prefer oral treatment over injectable [97].

Given the current unmet need in UC for more cost-effective treatments resulting in greater medication adherence with better long-term efficacy without dose escalation or concomitant therapies, several oral treatments have been recently approved. These therapies include the small-molecule drugs tofacitinib (2018), ozanimod (2021), and upadacitinib (2022). On the basis of indirect comparisons, these new treatments have demonstrated significant superiority over adalimumab in terms of endoscopic improvements and similar efficacy compared with the other biologics in their ability to induce remission [12, 98–101]. The approval of oral treatments options shows great promise with their ability to mitigate the increased costs and HCRU associated with other routes of administration. However, assessing the economic impact of these treatments within the context of their clinical efficacy is beyond the framework of this review. Additionally, the emergence of biosimilars also offers additional, less expensive treatment options to help manage the cost of treating UC. Biosimilars are also preferred by 30% of physicians in Europe as first-line therapy because they are more affordable to patients [93].

Furthermore, costs and HCRU associated with administration of treatment are important to consider in the context of the evolving treatment landscape with the emergence of oral therapies. However, administration and monitoring costs associated with biologics were rarely reported, representing a substantial gap in the literature, with only one USA study reporting costs for infliximab and adalimumab [56]. As adalimumab can be self-administered subcutaneously, administration costs were not reported. However, infliximab, which is administered intravenously—most often at outpatient clinics [30]—had a reported annual administration cost of $1634 per patient, on average [56]. Costs associated with patient monitoring after biologic administration (i.e., through blood panels and assays) were similar between adalimumab and infliximab ($21 vs. $42, respectively) [56].

STUDY LIMITATIONS

While one of the primary benefits of conducting a systematic literature review is to capture all available evidence, the searches performed for this review relied on accurate database indexing and clear descriptions of the study populations in the titles and abstracts of manuscripts. The searches were conducted in October 2021, and therefore did not capture recent, relevant studies, including the full manuscript of Bokemeyer et al. [94], which was published after completion of our review. Despite this limitation, more recently published evidence on the economic burden and HRQoL for patients with moderate-to-severe UC in the USA and Europe has been sparse, and is not anticipated to impact the overall conclusions of this review.

Overall, the outcomes reported were quite heterogeneous across studies, with a small subset of studies providing the most recent, robust, and comprehensive data on the cost and HCRU impact of biologics for the USA and Germany [50, 58, 69]. These studies were the main contributors to the descriptive trends, depicting the impact of initiation of biologic therapy. In general, data from other studies reporting a smaller set of outcomes were consistent with the findings of these studies. Whether the changes observed in medical and pharmacy costs and services after initiation of advanced therapies are statistically significant remains to be seen as no statistical comparisons were performed by the study authors.

Substantial variability was also observed in how outcomes were reported with respect to units, costing years, and/or follow-up duration, thus limiting our ability to synthesize the evidence in its entirety. Most studies reported annual costs or annualized rates of HCRU while others captured 3-month or 6-month data or costs and/or HCRU over the entire study period (i.e., up to 4 years). Furthermore, HCRU was often captured as a proportion of patients or a mean number of visits, but studies rarely reported both.

Most studies collected data from large claims databases, which do not fully characterize whether patients are truly naïve to biologics or if previous biologics of a different class have been received. Therefore, an assumption based on the enrollment criteria reported by the study was required, which typically was defined on the basis of the absence or presence of prescriptions for biologic agents within a particular timeframe (i.e., 6 to 12 months) before the index date. Moreover, the studies included here focused on the USA and Europe, which have advanced healthcare systems; hence, these findings may not be representative of other countries.

The reported evidence was also limited by small sample sizes for some studies or particular treatment groups within a study in which findings should be interpreted carefully. One-third of the studies reported results for fewer than 50 patients (range 3–48). More than half of these studies reported on biologic-treated patients as a subset of a larger study and one included groups of patients receiving more newly approved treatments (e.g., ustekinumab) or unapproved treatments (e.g., certolizumab and natalizumab). Thus, data specifically for certolizumab and natalizumab were omitted because of concerns around interpretability of findings based on their off-label use. Additionally, many (41.1%) studies were captured as conference abstracts with limited or inadequate information, so the results should be interpreted with caution.

Other limitations include the retrospective and observational nature of the studies included. Given the inconsistencies across studies, additional data on analyses by age, sex, cultural background, socioeconomic status, treatment access, detailed profiling of different therapies, and in-depth analyses on initiation, switching, and dose escalation of therapies are needed.

CONCLUSIONS

The introduction of advanced therapies has provided new and effective treatment options for patients with moderate-to-severe UC, but the impact of these treatments on economic burden and HRQoL is less understood. Findings from this systematic review suggest that the

economic burden in patients with moderate-to-severe UC initiating treatment with biologics or small-molecule drugs was high and primarily driven by treatment costs and costs associated with outpatient visits. It also demonstrates the positive impact that biologic therapies have had on indirect costs (i.e., productivity, presenteeism, and absenteeism) as well as quality of life. However, this review also highlights that the high costs of biologics are not always fully offset by reductions in cost and HCRU associated with disease. Many patients require treatment switching and dose escalations, which are costly, in particular when switching across treatment classes or for patients initiating biologics. It is unclear whether reduced indirect costs and improved HRQoL would offset the high costs of biologics, especially in the long term. Moreover, the advantages of small-molecule drugs over biologics need to be further substantiated in terms of economic, social, and personal impact. Thus, there remains a high unmet need for therapies for moderate-to-severe UC that reduce healthcare burden and impact on society. As use of newer biologic therapies expands globally, high-quality, prospective real-world studies that evaluate short- and long-term economic burden and HRQoL are required.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies

and does not contain any new studies with human participants or animals performed by any of the authors.

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