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Background: Vedolizumab effectiveness estimates immediately after Food and Drug Administration (FDA) approval for ulcerative colitis (UC) and Crohn's disease (CD) are limited by use in refractory populations. We aimed to compare treatment patterns and outcomes of vedolizumab in 2 time frames after FDA approval.

Methods: We used 2 data sets for time trend analysis, an academic multicenter vedolizumab consortium (VICTORY) and the Truven MarketScan database, and 2 time periods, May 2014–June 2015 (Era 1) and July 2015–June 2017 (Era 2). VICTORY cumulative 12-month clinical remission, corticosteroid-free remission, and mucosal healing rates, and Truven 12-month hospitalization and surgery rates, were compared between Eras 1 and 2 using time-to-event analyses.

Results: A total of 3661 vedolizumab-treated patients were included (n = 1087 VICTORY, n = 2574 Truven). In both cohorts, CD and UC patients treated during Era 2 were more likely to be biologic naïve. Compared with Era 1, Era 2 CD patients in the VICTORY consortium had higher rates of clinical remission (31% vs 40%, $P = 0.03$) and mucosal healing (42% vs 58%, $P < 0.01$). These trends were not observed for UC. In the Truven database, UC patients treated during Era 2 had lower rates of inflammatory bowel disease–related hospitalization (22.4% vs 9.6%, $P < 0.001$) and surgery (17.2% vs 9.4%, $P = 0.008$), which was not observed for CD.

Conclusion: Since FDA approval, remission and mucosal healing rates have increased for vedolizumab-treated CD patients, and vedolizumab-treated UC patients have had fewer hospitalizations and surgeries. This is likely due to differences between patient populations treated immediately after drug approval and those treated later.

Key Words: vedolizumab, trends utilization, hospitalization, surgery

INTRODUCTION

Vedolizumab (VDZ) is now widely available for treatment of Crohn's disease (CD) and ulcerative colitis (UC). Phase III clinical trials demonstrated a significant benefit compared with placebo for achieving clinical remission and steroid-free remission in both diseases.[1, 2] As the drug has been integrated into practice over the past 4 years, attention has shifted to real-world outcomes and expectations given the variation in populations between clinical trials and clinical practice.[3]

In a systematic review of real-world evidence, Engel et al. quantified week 52 clinical response and remission to be 45% and 32% in CD and 48% and 39% in UC, respectively.[4] Predictors of response to VDZ have similarly been studied, and patients with more severe disease or prior tumor necrosis factor (TNF) antagonist exposure have consistently been shown to be less likely to respond to VDZ across multiple cohorts in both CD and UC.[5] Although these data help clarify the optimal positioning of the drug, they are partially limited by the fact that cohort studies to date have predominantly reported on initial experiences with VDZ right after launch. Because VDZ is the first biologic to be approved with an alternative mechanism of action to TNF antagonists, a significant proportion of the early use is likely to have been among patients who were not responding or were experiencing a suboptimal response to current therapy. Patients and providers were waiting for US Food and Drug Administration (FDA) approval of VDZ to see whether this drug with a new mechanism of action would help. This "warehouse effect" of a new drug waiting in storage for FDA approval could have significant implications for early response rates in this first cohort of patients receiving the drug. Generating real-world evidence stratified by time since commercial drug launch could help support the hypothesis that the first patients receiving newly approved drugs have lower response rates than those receiving it later, after the sickest patients waiting the longest to get the drug have been treated.

Our study reports on 3-year data from 2 complementary cohorts—a large multicenter academic consortium (VICTORY) and a more nationally representative cohort from the Truven MarketScan database—to understand if outcomes varied over time and how these variations in outcomes correlated with shifting patient characteristics and treatment utilization. These data are essential to determine the evidence needed to characterize expectations in routine practice with novel therapeutic agents as they come to market.

METHODS

Data Sets

The VICTORY consortium is a collaborative research group where outcomes are pooled for inflammatory bowel disease (IBD) patients treated with biologic agents.[6–10] Institutional review board approval was obtained from each site for ongoing data collection and transfer. Data were collected individually by sites using a standardized data collection form and transferred (after de-identification) to the coordinating site (University of California, San Diego) for data compilation and analysis. The current analysis represents data collected between May 2014 and June 2017.

Truven Health Analytics MarketScan is a nationally representative US commercial claims and Medicare supplemental database consisting of medical and pharmacy claims of more than 150 employers, including 100 health plans (payers), and representing approximately 170 million covered lives. The current analysis is based on available data from January 1, 2010, to October 31, 2017.

The results of this study are reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for cohort studies.[11]

Variables

Data on variables of interest collected from the consortium registry included the following: patient characteristics (age at diagnosis, age at VDZ initiation, sex, smoking status, body mass index), disease characteristics (prior hospitalizations,

prior surgeries, disease-related complications or extraintestinal manifestations, and phenotype classified according to Montreal subclassifications), and treatment history (steroids, immunomodulators, and TNF antagonists; duration of use; indication for discontinuation; and complications). Variables of interest specific to VDZ use were baseline disease severity (endoscopic, radiographic, or clinical assessments), concomitant treatments (steroids and/or immunomodulators), infusions (dates, intervals, premedications), prescribing site and provider, and follow-up assessments (endoscopic, radiographic, or clinical assessments). Consortium registry data represent a patient's entire documented IBD medical history.

Data on variables of interest were collected for the period of individual patient observation within the Truven MarketScan database, including patient characteristics (age at VDZ initiation, sex, history of fistulizing disease, fistula during the 12 months before VDZ initiation, and stricture during the 12 months before VDZ initiation), disease characteristics (disease duration, prior hospitalizations, and prior surgeries), and treatment history or concomitant therapies (steroids, immunomodulators, and TNF antagonists) (Supplementary Data). Truven MarketScan data represent a patient's documented claims data from periods of observation within Truven and therefore are unable to capture events or historic information before entry into the Truven MarketScan database.

Participants

Patients from the VICTORY consortium were included in the current analysis if they had (a) a confirmed diagnosis of UC or CD based on clinical, endoscopic, and/or histologic data; (b) active clinical symptoms attributed to UC or CD before VDZ therapy; and (c) at least 1 clinical or endoscopic follow-up after VDZ initiation irrespective of response status after induction.

Patients from the Truven claims database were included in the current analysis if they (a) had VDZ treatment during the identification period of May 1, 2014, to June 30, 2017; (b) were 18 years of age or older on the VDZ initiation date; (c) had 2 separate UC or CD diagnoses 30 days apart after January 1, 2001, and before the date of VDZ initiation; and (d) had at least 6 months of pre- and postindex continuous enrollment (Supplementary Data). If a patient was diagnosed with both UC and CD, the diagnosis closer to the index date was used to categorize the patient into the UC or CD group. If both UC and CD were diagnosed on the same day, the patient was excluded, as his or her disease phenotype could not be accurately captured. Any UC patient with a prior IBD-related surgery and/or fistula or stricture diagnosis before or after VDZ initiation was also excluded because of uncertainty in disease phenotype and classification.

Outcomes

We compared treatment outcomes within the first 12 months of VDZ launch (Era 1; May 2014–June 2015) and the subsequent 24 months (Era 2; July 2015–June 2017) to assess temporal trends in outcomes associated with shifting treatment patterns and utilization. Treatment effectiveness was assessed using the VICTORY consortium, and clinical outcomes of interest were 12-month cumulative rates for clinical remission (CREM), corticosteroid-free remission (CSFREM), and mucosal healing (MH). Disease-related complications were assessed using the Truven MarketScan database, and clinical outcomes of interest were 12-month rates and proportions for IBD-related hospitalization and surgery.

Definitions

CREM was defined based on the physician global assessment (PGA) as complete resolution of disease-related symptoms. CSFREM was reported only in patients on either prednisone or budesonide at the initiation of VDZ and was defined as achievement of CREM, tapering off of steroids, and the absence of a subsequent steroid prescription within 1 month. MH was defined as the absence of ulcers and/or erosions in CD and a Mayo endoscopic subscore of 0 or 1 for UC. The coordinating site investigator (P.S.D.) used de-identified endoscopy reports to confirm endoscopic scores, and any discrepancies were resolved through consensus between the study sites and the coordinating site. IBD-related hospitalization and surgery were identified in the Truven MarketScan database using prespecified coding criteria (Supplementary Data).

Statistical Analysis

Our a priori hypothesis was that over time VDZ has been increasingly utilized in less refractory, immunosuppressive- (azathioprine, 6-mercaptopurine, methotrexate) and/or biologic-naïve patients and that this shift to earlier prescribing has resulted in improved outcomes. A step-wise analysis was used to assess associations between temporal trends in patient characteristics, VDZ positioning, and outcomes (Fig. 1).

Statistical analyses were performed using SPSS and SAS. Continuous variables were presented as means (and SDs), or as medians (and interquartile ranges [IQRs]) if the distribution was skewed, and categorical or binary variables were presented as proportions or percentages. The comparison of baseline continuous variables used the independent-samples *t* test (2 group comparisons) or 1-way analysis of variance (ANOVA) with Bonferroni correction (3 or more group comparisons), and the comparison of baseline binary variables used the Pearson chi-square or Fisher exact test. Effectiveness outcomes in the consortium were described quantitatively as cumulative rates using Kaplan-Meier survival and time-to-event analyses and were compared using log-rank analyses. IBD-related hospitalization and surgery were analyzed as the proportion of patients developing these events by 12 months of observation using the chi-square or Fisher exact test.

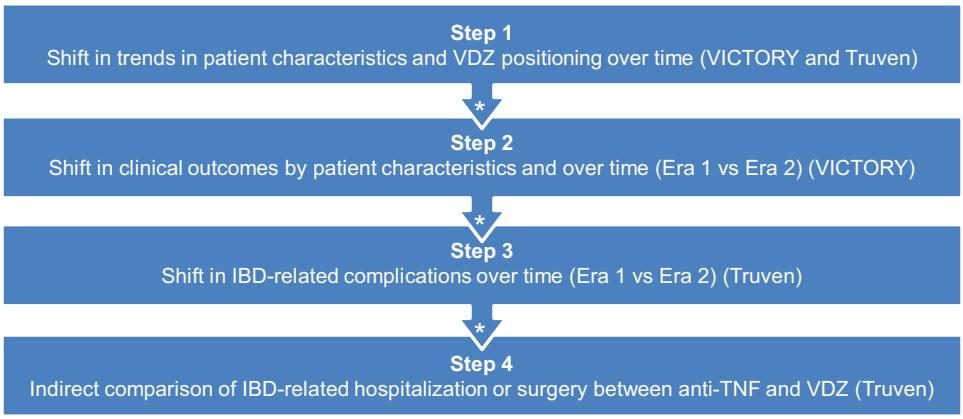

FIGURE 1. Stepwise approach to vedolizumab utilization trends over time. Step 1: First, an assessment was performed for shifts in positioning over time within the VICTORY consortium and Truven MarketScan database cohorts. Step 2: If significant differences or consistent trends in differences were observed, we then assessed differences in effectiveness within the VICTORY consortium stratified by factors known to influence treatment outcomes (prior immunosuppressive or TNF antagonist exposure, history of disease-related complications). Step 3: Once shifts in positioning toward use in more responsive subpopulations were confirmed, only then were assessments of shifts in outcomes over time in both cohorts assessed. Step 4: If significant shifts in outcomes over time were observed for IBD-related hospitalization or surgery, then a comparison was made to rates of IBD-related hospitalization or surgery with TNF antagonist therapy in the Truven MarketScan database to understand if rates for these events with VDZ had regressed to expected outcomes with other biologics. *Significant differences or consistent trends were observed.

RESULTS

Temporal Trends in Patient Characteristics and Treatment Positioning

A total of 1087 VDZ-treated patients from the VICTORY consortium cohort and 2574 VDZ-treated patients from the Truven MarketScan database cohort were included in the current analysis (Tables 1 and 2). In both cohorts, UC and CD patients treated during Era 2 were more often biologic naïve. For UC, there was a significant shift in both cohorts for use of VDZ in immunosuppressive- and biologic-naïve patients. For CD, this shift in utilization among immunosuppressive- and biologic-naïve patients was only observed in the VICTORY consortium cohort.

In the VICTORY consortium, baseline C-reactive protein values tended to be lower in Era 2 for both CD (Era 1 vs Era 2, 5 vs 4.1 g/dL; $P = 0.09$) and UC (Era 1 vs Era 2, 3.2 vs 1.5 g/dL; $P < 0.01$) patients, and the proportion of patients starting VDZ who were steroid refractory or dependent at the time of initiation was also lower in Era 2 for CD (Era 1 vs Era 2, 41% vs 34%; $P = 0.08$) and UC (Era 1 vs Era 2, 57% vs 41%; $P < 0.01$). Crohn's disease patients in Era 2 were also noted to less often have a history of fistulizing disease (32% vs 41%, $P = 0.03$).

Impact of Treatment Positioning and Temporal Trends in Outcomes

VICTORY Consortium

A total of 660 patients (n = 408 CD, n = 252 UC) were assessed for MH, and cumulative rates for MH were higher in Era 2 for CD and UC, with similar trends observed for CREM (Fig. 2A). Positioning relative to prior immunosuppressive and/or TNF antagonist exposure significantly influenced treatment effectiveness (Fig. 2B). Among CD patients previously exposed to TNF antagonists, those without a history of stricturing or penetrating disease complication had higher 12-month cumulative rates for CREM (42% vs 29%, $P < 0.01$). Similar trends were seen in CD patients previously exposed to TNF antagonists who had no prior history of fistulizing disease complication (CREM, 35% vs 29%; $P = 0.01$; CSFREM, 25% vs 19%; $P = 0.12$; MH, 46% vs 43%; $P = 0.08$).

Truven MarketScan Database

The proportions of patients requiring hospitalization or surgery within 12 months of VDZ initiation were significantly lower in Era 2 than in Era 1 for UC but not CD patients (Fig. 3A). This trend remained consistent in patients stratified by TNF antagonist exposure (Fig. 3B). Rates of IBD-related hospitalization and surgery with VDZ therapy in biologic-naïve UC patients during Era 2 (hospitalization, 4.7%; surgery, 6.0%) were found to be comparable to those seen with TNF antagonist therapy in biologic-naïve UC patients during the same time period (hospitalization, 5.2%; surgery, 7.8%).

DISCUSSION

Real-world evidence is important for several reasons: It helps establish expectations for treatment effectiveness and identifies patients who are more or less likely to respond to a therapeutic intervention in routine practice. Given the heterogeneity among patient populations and treatment utilization, it is important to understand how real-world evidence

TABLE 1. VICTORY Consortium Cohort Baseline Demographics and Characteristics

	Crohn's Disease			Ulcerative Colitis		
	Era 1 (n = 325)	Era 2 (n = 325)	*P*	Era 1 (n = 182)	Era 2 (n = 255)	*P*
Male, No. (%)	130 (40)	142 (44)	0.38	97 (53)	121 (48)	0.25
Age, median (IQR), y	35 (26–50)	38 (28–55)	0.13	37 (26–54)	39 (27–57)	0.26
Disease duration, median (IQR), y	12 (6–21)	11 (6–17)	0.23	6 (3–12)	6 (2–13)	0.31
Current or previous smoker, No. (%)	90 (28)	90 (28)	1.00	41 (23)	80 (31)	0.07
Hospitalized in prior year, No. (%)	122 (38)	113 (35)	0.51	42 (23)	68 (27)	0.44
Severe endoscopic disease, No. (%)	81/207 (39)	87/242 (36)	0.50	50 (39)	84 (41)	0.73
Crohn's disease phenotype, No. (%)						
Stricturing/penetrating disease	229 (71)	209 (65)	0.13	NA	NA	NA
Fistulizing disease	132 (41)	104 (32)	**0.03**	NA	NA	NA
Extensive disease, No. (%)	NA	NA	NA	101 (56)	158 (62)	0.40
Steroid refractory or dependent, No. (%)	134 (41)	111 (34)	0.08	103 (57)	105 (41)	**<0.01**
Baseline CRP, median (IQR), g/dL	5 (1–19)	4.1 (1–15)	0.09	3.2 (0.7–8.7)	1.5 (0.6–5.6)	**<0.01**
Baseline albumin, median (IQR), g/dL	3.9 (3.6–4.3)	3.9 (3.6–4.2)	0.54	4 (3.7–4.3)	4 (3.6–4.2)	0.12
Baseline BMI, median (IQR), kg/m^2	24 (21–28)	24 (21–29)	0.99	24 (22–29)	24 (21–28)	0.11
No prior IS[a] or TNF antagonist exposure, No. (%)	7 (2)	23 (7)	**<0.01**	22 (12)	58 (23)	**<0.01**
TNF antagonist exposure, No. (%)			**<0.01**			0.37
TNF antagonist naïve	20 (6)	40 (12)		52 (29)	91 (36)	
1 prior TNF antagonist	64 (20)	91 (28)		87 (48)	108 (42)	
2 or more prior TNF antagonists	241 (74)	194 (60)		43 (24)	56 (22)	
Concomitant steroids, No. (%)	176 (54)	121 (37)	**<0.01**	112 (62)	127 (50)	**0.02**
Concomitant IS,[a] No. (%)	150 (46)	120 (37)	**0.02**	62 (34)	85 (33)	0.92

Bold text indicates a statistically significant difference with a *P* value of ≤0.05.
[a]Azathioprine, methotrexate, 6-mercaptopurine.

TABLE 2. Truven MarketScan Database Cohort Baseline Demographics and Characteristics

	Crohn's Disease			Ulcerative Colitis		
	Era 1 (n = 213)	Era 2 (n = 1232)	*P*	Era 1 (n = 116)	Era 2 (n = 1013)	*P*
Male, No. (%)	91 (43)	527 (43)	0.99	56 (48)	501 (50)	0.81
Age, median (IQR), y	41 (33–54)	43 (32–55)	0.78	41.5 (33–52.5)	44 (31–55)	0.91
Disease duration, median (IQR), y	2.4 (1.2–5.6)	2.9 (1.3–5.1)	0.38	2 (1.3–3.5)	2.4 (1–4)	0.42
Hospitalized in prior year, No. (%)	48 (23)	228 (19)	0.17	19 (16)	122 (11)	0.19
No prior IS[a] or TNF antagonist exposure, No. (%)	43 (20)	223 (18)	0.47	20 (17)	257 (25)	**0.05**
TNF antagonist exposure, No. (%)			**0.04**			**<0.01**
TNF antagonist naïve	61 (29)	339 (28)		28 (24)	382 (38)	
1 prior TNF antagonist	89 (42)	617 (50)		50 (43)	471 (47)	
2 or more prior TNF antagonists	63 (30)	276 (22)		38 (33)	160 (16)	

Bold text indicates a statistically significant difference with a *P* value of ≤0.05.
[a]Azathioprine, methotrexate, 6-mercaptopurine.

is generated and how well it can be extrapolated to expectations over time as a drug is integrated into and repositioned within treatment algorithms. Analysis of temporal trends in VDZ utilization, treatment effectiveness, and disease outcomes in a 3-year academic multicenter cohort study and a more nationally representative claims data set produced several important observations. First, patients treated within the first year of VDZ launch were overall a sicker group of patients than those currently being treated in clinical practice with regard to disease-related complications, severity, and prior

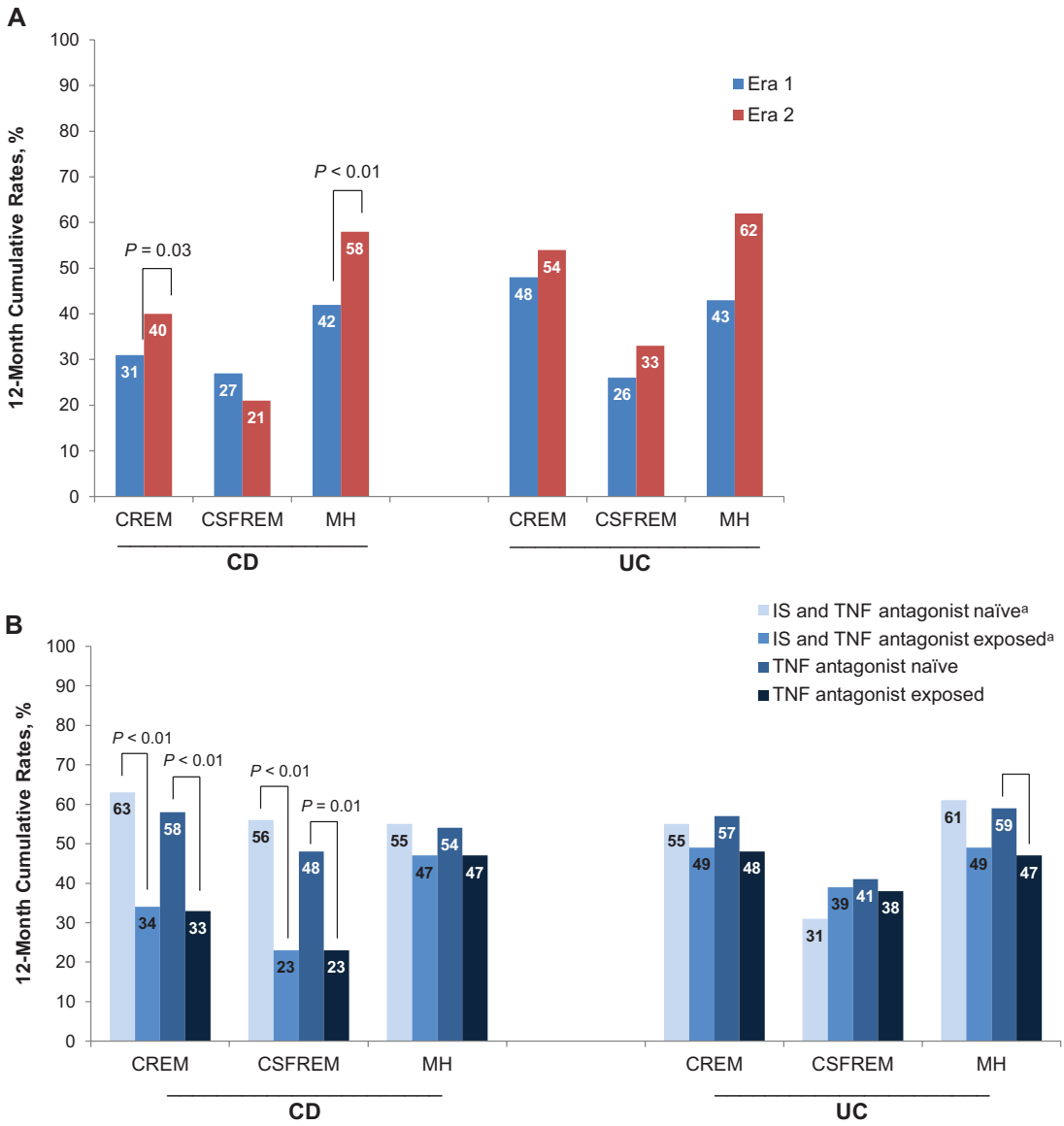

FIGURE 2. Cumulative 12-month rates of treatment effectiveness for vedolizumab in the VICTORY consortium. A, Overall cumulative rates for CD and UC. B, Cumulative rates stratified by prior treatment exposures.

immunosuppressive or TNF antagonist use. Second, over time VDZ has been used more often in patients who are immunosuppressive and/or TNF antagonist naïve with less refractory disease. This shift in positioning is associated with improved outcomes, predominantly in UC, where rates of IBD-related hospitalization or surgery are now comparable to those seen with TNF antagonist therapy in biologic-naïve patients.

Patients with CD were noted to have improvements over time in MH and CREM within the VICTORY consortium; however, there was no significant trend toward improvement in rates of CSFREM or IBD-related hospitalization or surgery within the Truven MarketScan database. The natural history of CD is characterized by episodic flares in disease activity, leading to progressive and irreversible bowel damage.[12] The cumulative destruction is unlikely to be repaired by current medications, and therefore a subset of high-risk CD patients may inevitably require repeated steroid prescriptions, hospitalizations, and surgery, and positioning of therapy within the disease course is likely more important than positioning relative to other therapies. The Truven MarketScan database carries the limitation of not being able to adequately capture the entire disease course of an individual patient before enrollment into Truven, and therefore it is possible that the lack of shift in disease outcomes over time is more a function of how VDZ is positioned according to disease duration and not purely how it is positioned relative to other therapies such as

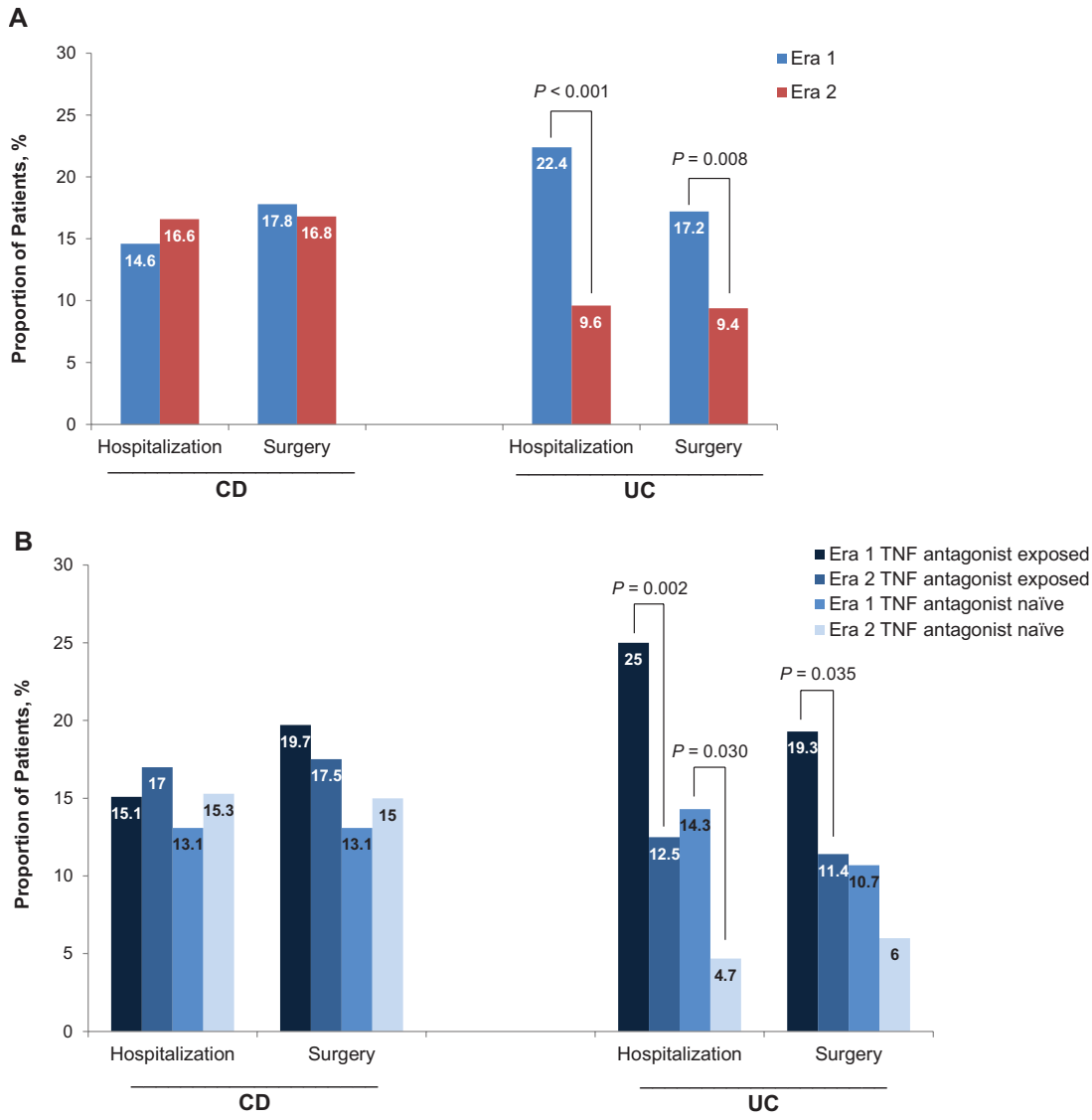

FIGURE 3. Proportion of patients with disease-related complications after 12 months of vedolizumab therapy in the Truven MarketScan database. A, Overall proportions for CD and UC. B, Proportion developing disease-related complications stratified by prior treatment exposures.

immunosuppressive and/or TNF antagonist agents. The shift in effectiveness for a valid surrogate outcome (MH) suggests that future benefit may be achieved in reducing disease-related complications for CD; however, a very small absolute number of immunosuppressive and biologic-naïve CD patients were treated with VDZ overall, and the lack of significance for CSFREM suggests that this requires further assessment in a well-defined cohort, preferably early in the disease course.

Patients with UC, in contrast, were noted to have significantly lower rates of IBD-related hospitalization and surgery within the Truven MarketScan database, despite a lack of significant shift over time in effectiveness within the consortium. Subanalyses of the consortium and Truven revealed an association between positioning of VDZ relative to other therapies and both effectiveness and disease-related outcomes. Furthermore, rates of UC-related hospitalization and surgery while on VDZ have now regressed to rates comparable to TNF antagonist therapy in biologic-naïve patients. The majority of UC patients have a mild to moderate disease course, with only 10%–15% experiencing an aggressive course.[13] Utilizing VDZ early in the disease course before immunosuppressive and/or TNF antagonist agents may therefore be optimal given its favorable safety profile,[10] with more aggressive strategies such as combined immunosuppressive with rapid TNF antagonist dose escalation being reserved for the subset of patients with a more aggressive disease course.

Our study has strengths that allow for an enhanced understanding of the real-world clinical data about use of VDZ

over time since FDA approval, particularly with the use of 2 complementary data sets. The VICTORY consortium cohort allows for a granular and complete assessment of patient characteristics that might influence treatment patterns and outcomes, whereas the Truven MarketScan database cohort is a much broader and real-world assessment of how drugs are being used in routine, including community, practice. The main limitation of Truven is the inability to capture longer-term historic data before enrollment and the inability to capture clinical outcomes of importance (clinical remission and mucosal healing), and the main limitation of the VICTORY consortium is the inability to assess community practice trends (tertiary referral bias) and IBD-related hospitalizations or surgery. Thus, the strengths of each cohort help overcome some of the limitations of the other in the current analysis. Limitations remain, nonetheless, with the retrospective nature of data collection in the consortium and natural limitations inherent to claims-based analyses. Furthermore, although applying this concept to new therapies will be important, it does not necessarily inform the relative positioning of therapies alone and should be taken into consideration alongside other lines of evidence, postmarketing safety, and financial positioning in various markets.

CONCLUSIONS

In summary, since VDZ received FDA approval, over time it has been used earlier in the treatment algorithm for CD and UC. The change in positioning of the drug to be used for patients with less refractory disease was associated with a decrease in IBD-related hospitalizations and surgeries for patients with UC. These changes have not been observed in patients with CD to date, but additional research is needed to understand whether this divergence is a true phenomenon. Taken together, this highlights what we have termed the "warehouse effect": that patients treated within the first year of a drug's approval are likely representative of a select group of high-risk patients who are refractory to currently available therapies and are being warehoused on ineffective and undesirable therapies (ie, chronic steroids) to bridge them through until a promising agent is approved by the FDA and available in routine practice. This effect will need to be considered going forward as newer agents come to market and understanding evolves of the relative positioning of therapies and the optimal use of real-world evidence being generated.

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