Real-world utilization of top-down and step-up therapy and initial costs in Crohn disease

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Plain language summary

The number of biologics approved for Crohn disease (CD) is increasing. This has spurred interest in how immune-modulating treatments are used during the course of disease. Our results showed use of early immune-modulating treatment increased from 2010 to 2018. Patients with this treatment pattern also had higher nondrug medical costs in the first year compared with people initially prescribed typical agents. Future research should look at long-term costs and outcomes in a real-world setting.

Implications for managed care pharmacy

Our retrospective cohort study using administrative claims data found an increasing trend in the use of top-down (TD) or early biologic/immunomodulator therapies and an associated higher nondrug-related medical cost for the TD strategy in patients initiating medication therapy for CD. These findings align with the strategy of initiating TD therapy in patients with a high disease burden and can inform payers and policymakers of increasing early use of biologic therapies for patients with CD.

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ABSTRACT

BACKGROUND: Medication treatment strategies for Crohn disease (CD) include step-up (SU) therapy, beginning with oral anti-inflammatory agents, and top-down (TD) therapy, beginning with biologics or immunomodulators. The real-world utilization and short-term medical costs associated with these treatment strategies are not well described.

OBJECTIVE: To examine the prevalence of TD therapy use over time and compare the first-year direct medical expenditures among patients initiating CD medication treatment with SU and TD therapy in a real-world setting.

METHODS: We conducted a retrospective cohort study of Optum Clinformatics Data Mart examining adult patients with CD newly initiated on medication therapy from 2010 to 2018. Included patients had a CD-indicated medication dispensed within 60 days after their initial CD diagnosis, were continuously enrolled in the health plan throughout the study period, and did not have comorbidities treated with a biologic also indicated for CD. A generalized linear model was used to quantify the differences in adjusted mean first-year CD-specific, direct nonpharmacy medical costs between users of TD and SU therapy.

RESULTS: We identified 3,157 patients newly initiating medication therapy for CD (2,392 [75.8%] patients treated with SU therapy and 765 [24.2%] treated with TD therapy). The use of TD therapy over the study period increased from 17% in 2011 to 31% in 2017. TD therapy was also associated with a 149.8% ($1,230) higher adjusted average per-patient first-year CD-direct nonpharmacy medical cost compared with SU therapy (adjusted ratio of cost for TD compared with SU [2.498, 95% CI = 2.12-2.95]).

CONCLUSIONS: In patients newly initiating medication therapy for CD, TD therapy use increased between 2010 and 2017 and was associated with higher first-year nonpharmacy medical expenditure. These findings align with the strategy of initiating TD therapy in patients with a higher disease burden. Further research is needed to determine long-term overall health care costs and clinical outcomes associated with SU and TD strategies in a real-world setting.

Crohn disease (CD) is an inflammatory bowel disease (IBD) characterized by relapsing intestinal inflammation and gastrointestinal (GI) tissue damage. Medication therapy options for CD include aminosalicylates, corticosteroids, antimicrobials, immunomodulators, and biologics. Treatment sequencing for CD that begins with anti-inflammatory agents (aminosalicylates, corticosteroids, and/or antimicrobials) and progresses to immunomodulatory agents and/or biologics has been termed *step-up* (SU) therapy.[1,2] Conversely, early biologic, or *top-down* (TD) therapy, sequences use biologics and/or immunomodulators as the initially prescribed therapies and anti-inflammatory agents (aminosalicylates, corticosteroids, and/or antimicrobials) as secondary therapy, if needed.[1,2]

The use of TD therapy in CD has been debated for more than a decade.[3] Mixed evidence of an association between TD therapy and disease control, reduced relapses, and symptom improvements exists but suggests patients with moderate to severe CD may benefit most from early biologic TD treatment strategies.[4-6] However, clinical experts have hesitated to embrace widespread use of TD therapy because of the adverse risks and costs associated with the TD therapy medications.[6,7] The potential adverse consequences of the immunomodulators indicated for CD include increased risk of infection, hepatitis, bone marrow suppression, pancreatitis, and lymphoma.[8] The biologics indicated for CD are associated with an increased risk of opportunistic infection, malignancy, demyelinating disorders, autoimmunity, and congestive heart failure.[9] Conversely, anti-inflammatory agents (aminosalicylates, corticosteroids, and antimicrobials) have less severe adverse reactions compared with TD therapies. Furthermore, the prices of TD therapies, especially those in the market exclusivity period, can have substantial budget implications for payers, whereas many SU therapies have generic options and are considered less costly.[10]

Although economic models of patients initiating medication therapy for CD suggest that TD or early biologic therapy is cost-saving/cost-effective in time horizons 5 years or greater for patients with moderate to severe CD, compared with SU or late biologic therapy, the real-world short-term costs associated with initiating therapy for CD with SU or TD therapy have not been reported.[11-15] The objectives of this research were to examine patient and clinical characteristics associated with use of SU and TD treatment sequencing and to quantify the differences in medical costs among patients newly initiating medication therapy for CD with TD therapy compared with SU therapy in a real-world setting. This research ascertained how the proportion of patients initiating medication treatment for CD with either SU or TD therapy changed over time. Furthermore, this research examined the differences in average per-patient medical expenditure accrued in the first year between initiating CD medication therapy with either SU or TD strategies, adjusting for demographic and clinical factors.

Methods

We conducted a retrospective, cohort study of patients newly diagnosed and initiated on medication therapy for CD between 2010 and 2018 using the Optum Clinformatics Data Mart.[16] Optum Clinformatics Data Mart is an administrative claims data repository with detailed, deidentified, longitudinal pharmacy, medical, laboratory, and inpatient data.

INCLUSION CRITERIA

Patients were included in the study population if they had at least 2 *International Classification of Diseases, Tenth Edition, Clinical Modification* (ICD-10-CM) and *International Classification of Diseases, Ninth Edition, Clinical Modification* (ICD-9-CM) codes for CD (ICD-10-CM/ICD-9-CM: K50.x/555.x), (see Supplementary Table 1, available in online article) in any setting at least 30 days apart within the follow-up period.[17-22] The index diagnosis date was defined as the first diagnosis code appearing in the available claims data (spanning from 2010 to 2018). Patients were required to have a 1-year period prior to the index diagnosis without either a CD-indicated therapy dispensed or a documented CD-specific ICD code.

The medication exposure period was the 60-day period following index diagnosis. Patients with a CD-indicated medication dispensed during the medication exposure period without any CD-indicated medication dispensed in the 1-year prediagnosis period were considered newly initiated on medication therapy for CD. Each patient was followed for 365 days after the 60-day medication exposure period to determine cost and health care utilization outcomes (see Supplementary Figure 1 for a study schematic diagram).

EXCLUSION CRITERIA

Patients were excluded if they were younger than 18 years on the index diagnosis date. Furthermore, patients without full enrollment in the health care plan for the duration of the pre-index and follow-up period or whose pre-index or follow-up periods fell outside the 2010-2018 study period were excluded. Lastly, we excluded patients who had at least 2 ICD codes on different dates for any comorbidity treated with a biologic also indicated for CD (ankylosing spondylitis, Behçet disease, hidradenitis, Kawasaki disease, multiple sclerosis, nonradiographic axial spondyloarthritis, psoriasis, rheumatoid arthritis, ulcerative colitis, and

uveitis; see Supplementary Table 2 for excluded comorbidities and ICD codes).[23]

SU AND TD GROUP DEFINITION

Among the population of patients newly initiated on medication therapy for CD, patients were further classified into the SU or TD groups based on the therapies prescribed during the 60-day exposure period following the index diagnosis date. If a patient was dispensed an anti-inflammatory medication (aminosalicylate, corticosteroid, or antimicrobial) in the 60 days following initial diagnosis without an immunomodulator/biologic agent, the patient was assigned to the SU therapy group. For corticosteroid and CD-indicated antibiotic medications dispensed in the 60-day exposure period, we required the days supplied to be greater than or equal to 15 days to exclude short-term use of these medications for other indications, such as acute illness. Patients who received an immunomodulator and/or biologic during the 60-day follow-up period were included in the TD therapy group. Lastly, if a patient had both an immunomodulator/biologic and long-term anti-inflammatory medication dispensed in the exposure period, we included them in the TD therapy group. See Supplementary Table 3 for medications used to categorize the SU and TD groups.

INDEPENDENT VARIABLES

Baseline demographic variables of interest included patient age at index diagnosis, sex, geographic location, payer type, and diagnosis year. Geographic location of residence was categorized into 9 US regions: East North Central, East South Central, Middle Atlantic, Mountain, New England, Pacific, South Atlantic, West North Central, and West South Central. Payer type was subdivided into commercial, Medicare for patients younger than 65 years, and Medicare for patients aged 65 years or older. The diagnosis year variable was derived from the date of index diagnosis and was used to identify the percentage of SU and TD utilization by year.

Clinical variables of interest included disease location in the GI tract, comorbidities, GI-related hospitalizations prior to diagnosis, and CD-related surgical procedures performed in the 60 days following the first documented diagnosis code for CD. In other research, these disease-related variables, among others, are related to severity of IBD and frequency of hospitalizations and surgeries.[24] Disease location was determined based on the CD ICD codes, which are subdivided into disease of the small intestine (ICD-9/ICD-10: 555.0/K50.0), large intestine (ICD-9/ICD-10: 555.1/K50.1), small and large intestine (ICD-9/ICD-10: 555.2/K50.8), and unspecified (ICD-9/ICD-10: 555.9/K50.9). If the index diagnosis indicated a location in the GI tract of "unspecified," we then looked at the diagnoses during the 60-day exposure period to determine if a disease location was specified by the subsequent ICD-10 codes. Comorbidity burden was quantified using the Elixhauser index, a diagnosis-derived score generated by weighting a patient's comorbidities, which performs well for health care utilization and expenditure outcomes.[25,26] The Elixhauser index was calculated using diagnosis codes present in the prediagnosis period. Prior GI-related hospitalization was coded as a binary variable representing at least 1 inpatient stay during the 1-year prediagnosis period. GI-related hospitalizations were defined as having a discharge diagnosis of colonic conditions, including indeterminate colitis (ICD-9/ICD-10: 558.9/K52.3), noninfective gastroenteritis (ICD-9/ICD-10: 558.9/K52.9), diverticular disease of the colon (ICD-9/ICD-10: 562.12/K57.3), enterocolitis due to *Clostridioides* (*Clostridium*) *difficile* (ICD-9/ICD-10: 008.45/A04.7), and unspecified origin of gastroenteritis and colitis (ICD-9/ICD-10: 009.1/A09.9).[27] We also included hospitalizations for complications of CD, including stricture/obstruction (ICD-9/ICD-10: 560.9/K56.6), fistulas (ICD-9/ICD-10: 569.81/K63.2), abscesses (ICD-9/ICD-10: 569.5/K63.0), and ulcers (ICD-9/ICD-10: 569.82/K63.3) in the GI-related hospitalization definition.[1] Lastly, we examined CD-related surgical procedures performed within the 60 days following the index diagnosis as a binary variable. CD-related surgical procedures were identified using ICD procedure codes for enterostomy (including colostomy and ileostomy), small bowel resection, colorectal resection, local excision of large intestine lesion, and other bowel surgeries.[23]

COST AND UTILIZATION ANALYSIS

The cost and utilization variables were calculated in the 1-year follow-up period after the 60-day medication exposure period. Both all-cause and CD-related costs were calculated. All-cause costs included health care expenditures of any type, encompassing all pharmacy, outpatient health care, laboratory testing, imaging, and hospitalization/emergency department (ED) utilization costs for any indication. CD-related costs were calculated as the sum of prescriptions dispensed for CD-indicated therapies as well as medical visits and hospitalizations with a primary diagnosis of CD in the follow-up period. CD-related costs were further split into pharmacy and medical costs, with pharmacy including only prescription medication costs, and medical costs including outpatient health care visits, laboratory tests, imaging, and hospitalization/ED utilization in the follow-up period. Costs were adjusted for inflation to the 2017 US dollar value using the Personal Health Care Expenditure deflator.[28]

CD-specific medical utilization was calculated as a sum of health care visits, including outpatient appointments, laboratory tests, imaging, and hospitalization/ED use with CD as the primary diagnosis in the follow-up period. CD-specific prescription medication utilization represented the number of total prescriptions dispensed for any CD-indicated therapy in the follow-up period.

The generalized linear model quantified the differences in medical costs in patients using TD therapy compared with SU therapy while controlling for confounding by sex, age group, disease location, geographic location, payer type, Elixhauser index, GI-related hospitalizations prior to diagnosis, CD-related surgical procedures performed within the 60 days following the index diagnosis, and diagnosis year. The primary independent variable was treatment sequence (SU or TD), and the dependent variable was direct first-year CD-specific medical costs, which represented the overall CD-specific cost without including the costs of CD prescription medications. We did not include CD prescription medication costs in the dependent variable because TD therapy is associated with higher-priced medication therapies, and the objective of our analysis was to examine medical expenditure.

STATISTICAL ANALYSIS

A descriptive analysis at the patient-level categorized by treatment sequence (SU or TD) was conducted for all independent variables. Results were reported using descriptive statistics, and significance was tested using t-tests for continuous variables and chi-square tests for categorical variables. The significance of the trend in the use of TD over time was assessed with a joinpoint regression analysis.

A generalized linear model with a gamma distribution and log link function was used to estimate the differences in per-patient average adjusted CD-specific medical costs for covariates of influence. Skewness and kurtosis were assessed for the CD-specific medical cost distribution, and the modified Park test was used to determine that a gamma distribution was an appropriate choice for modeling the CD-specific medical cost data. The generalized linear model was optimized with manual backward elimination, and significance was assessed by the difference in Akaike information criterion. Nonsignificant variables were removed from the model to enhance fit. The model was considered optimized when all included variables either had at least 1 statistically significant strata or were considered clinically relevant irrespective of significance (eg, sex), and removing additional variables did not result in a statistically significant decrease in Akaike information criterion. B coefficients were exponentiated to derive adjusted odds ratios, standard errors, and 95% CIs. The estimates presented represent the percentage difference in cost for a particular level of a variable when other independent variables are at their reference level. Results with a *P* value less than or equal to 0.05 were discussed. All statistical analyses were performed using SAS version 9.4 statistical analysis software. This study was deemed exempt by the Institutional Review Board at the University of Rhode Island.

Results

POPULATION AND GROUP RESULTS

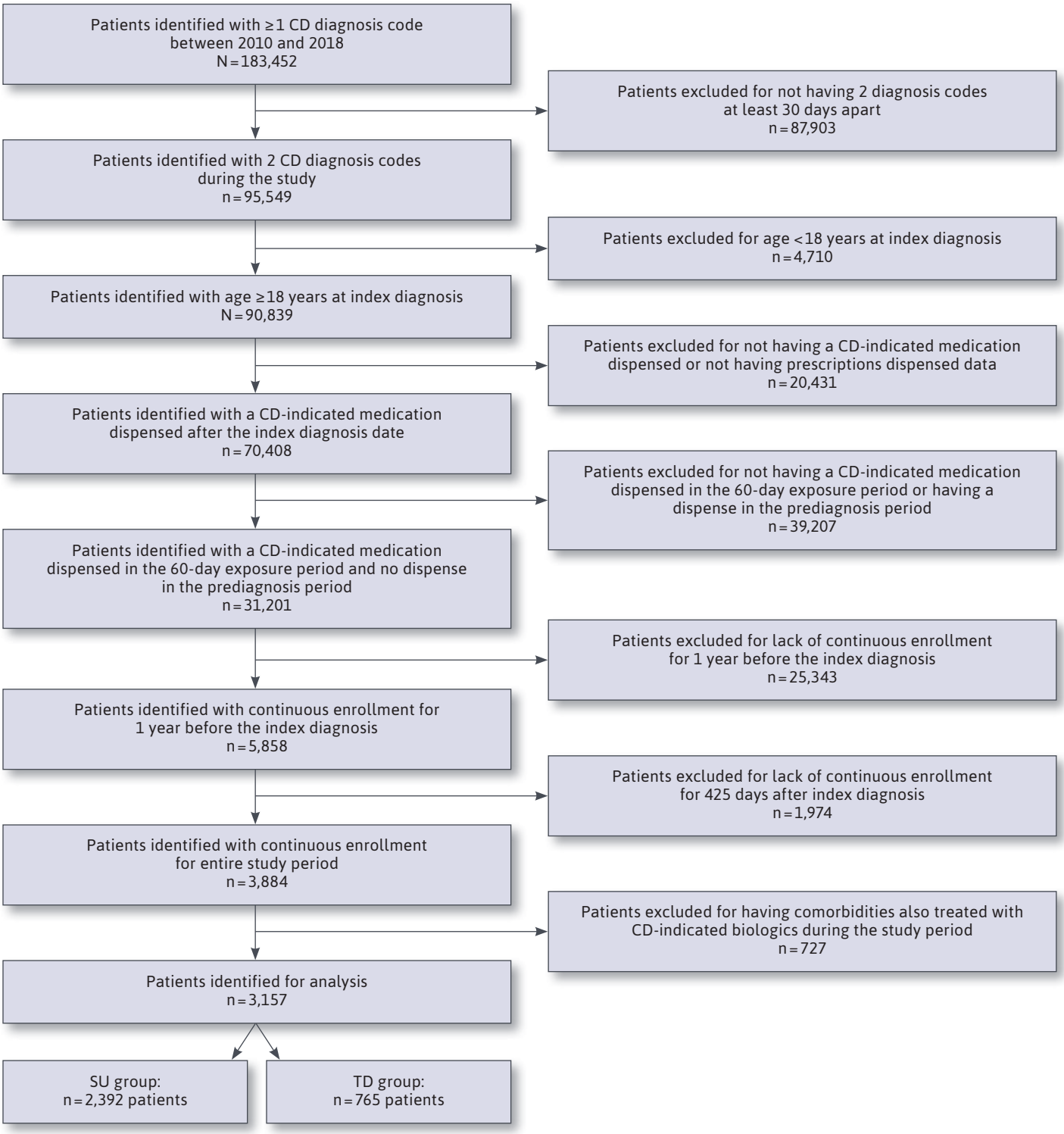
We identified 3,157 adult patients with 2 ICD diagnosis codes for CD at least 30 days apart, who were newly initiated on medication therapy, had continuous enrollment, and lacked exclusion comorbidities. The SU group consisted of 2,392 patients and the TD group consisted of 765 patients. See Figure 1 for a population flow diagram. Of the 765 patients in the TD group, 564 (73.7%) patients also received a SU medication in the 60-day exposure period after the index diagnosis date. SU therapy was the dominant treatment sequencing strategy used in our study period, but over time, the frequency of TD utilization increased significantly (joinpoint regression $P=0.007$; see Figure 2 for a visual of SU and TD utilization over time).

DESCRIPTIVE CHARACTERISTICS

Baseline descriptive characteristics are presented in Table 1. The study population was 53.7% female, and the mean age was 46.7 years (SD: 18.9 years). The SU group consisted of a slightly larger proportion of female patients than the TD group (SU: 55.0%; TD: 49.7%; $P=0.01$). The mean age in the SU group was 48.9 years (SD: 18.9), which was higher than the mean age of 39.7 years (16.7) in the TD group ($P<0.001$). The SU group had a larger percentage of patients with disease in the small intestine, the large intestine, and an unspecified location (SU: 34.8%, 24.5%, 15.6%; TD: 33.1%, 17.5%, 10.1%, respectively), and the TD group had a larger percentage of patients with disease located in both the small and large intestine (SU: 25.1%; TD: 39.4%, respectively; chi-square $P<0.001$). More patients in the TD group had commercial insurance (SU: 74.0%, TD: 88.1%), and more patients in the SU group had Medicare (for patients aged both <65 and ≥ 65 years [SU: 3.8%, 22.2%; TD: 2.8%, 9.2%, respectively; chi-square $P<0.001$]). The mean Elixhauser index was higher in the SU group compared with the TD group (SU: 2.2 [SD = 2.5], TD: 1.7 [2.1]; $P<0.001$).

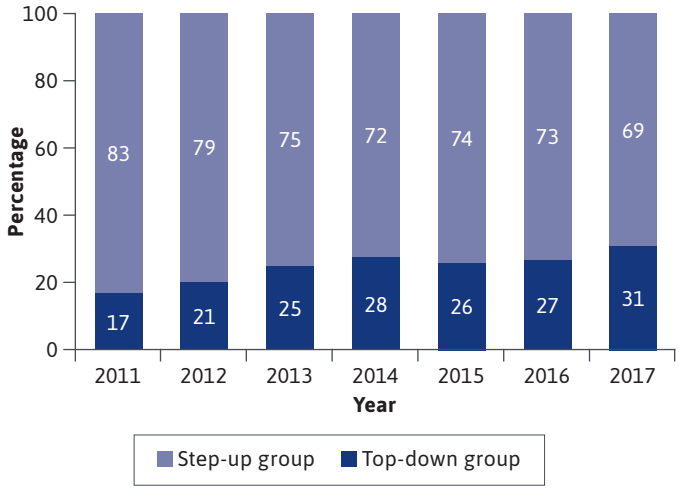
The average all-cause and CD-specific costs were higher in the TD group compared with the SU group (TD: $51,359, $32,664; SU: $34,989, $11,765, respectively). The average CD-specific medical cost, encompassing hospitalization,

FIGURE 1 Population Flow Diagram



CD = Crohn disease; SU = step-up; TD = top-down.

FIGURE 2 Percentage of Step-Up and Top-Down Therapy Initiated by Year



outpatient visits, laboratory tests, and procedures for CD in the year following medication therapy initiation, was higher in the TD group (TD: $11,653; SU: $4,616). Additionally, the average CD-specific medication cost was also higher in the TD group (TD: $21,011; SU: $7,025). The average per-patient out-of-pocket cost was higher for patients with Medicare (aged > 65 years), compared with commercial, in both the SU and TD groups (SU: $382, $244 [$P < 0.001$]; TD: $468, $356 [$P = 0.46$], respectively). Similarly, the mean CD-specific medical utilization, including all health care visits and procedures, was more than twice as high in the TD group compared with the SU group (TD: 15.4 visits; SU: 6.4 visits). On average, 11.5 prescriptions were dispensed to patients in the TD group during the 1-year follow-up period after treatment initiation, compared with 7.0 prescriptions in the SU group.

LINEAR REGRESSION FINDINGS

The generalized linear model was optimized by removing the statistically nonsignificant geographic location variable. The sex, Elixhauser index, and CD-related surgical procedure variables were also nonsignificant variables in the model but were retained for clinical relevance because eliminating these variables from the model did not produce a better fitting model. The results of the fitted model are presented in Table 2. Patients who initiated CD medication therapy with TD therapy had a 149.8% ($1,230.3) greater first-year adjusted average per-patient CD-specific direct medical cost than those who initiated with SU therapy while controlling for factors associated with both treatment sequence and higher first-year medical costs.

Discussion

Among patients initiating medication therapy for CD, we found a trend of increasing TD therapy utilization over time and a higher first-year adjusted average per-patient CD-specific direct medical cost among patients using TD therapy, controlling for patient demographic and clinical factors. Limited real-world data exist describing the utilization and medical expenditure associated with initial medication therapy sequences for the treatment of CD. We found higher medical cost among patients initiating therapy for CD with TD as compared with SU therapy, while controlling for factors associated with both treatment sequence and higher first-year medical costs, including younger age, prior hospitalization for CD, and having disease in both the small and large intestine.

Although SU therapy was more commonly used overall (SU: 75.8%, TD: 24.2%), our analysis revealed that the utilization of TD treatment as initial medication therapy for CD increased over time, from 17% in 2011 to 31% in 2018. Previous real-world analyses published in 2020, 2018, and 2014 also showed that SU treatments were the dominant option for induction and maintenance medication therapy in CD.[29-31] Our results add to this finding by describing the trend of increasing use of TD as initial therapy over time. This trend may be attributed to increased availability of and growing familiarity with biologic and immunomodulating therapies, as well as changes in guideline recommendations. Over the course of our study period, the number of biologic treatment options for CD increased with the approval of vedolizumab (2014), the label expansion of ustekinumab to include CD (2016), and the approval of infliximab biosimilars Inflectra (2016), Renflexis (2017), and Ixifi (2017).[32] The clinical research accompanying these regulatory actions provided an enhanced understanding of the role of biologic therapy in CD.

Additionally, guideline recommendations for the use of medication for CD have been revised to address the earlier use of biologics and immunomodulating therapies. The 2006 American Gastroenterological Association (AGA) and 2009 American College of Gastroenterology guidelines recommended infliximab/biologic therapy in patients with moderate to severe CD when mesalamine, corticosteroid, and/or immunosuppressive therapy (ie, SU therapy) do not achieve an adequate response.[33-35] The 2013 AGA guidelines were revised to recommend anti–tumor

TABLE 1 Baseline Characteristics of Patients With CD According to Step-Up or Top-Down Treatment Initiation Strategy

	SU group	TD group	Significance
Total, N	2,392	765	
Sex, n (%)			
Female	1,316 (55.0)	380 (49.7)	$P=0.0099$
Male	1,076 (45.0)	385 (50.3)	
Age at diagnosis (in years), n (%)			
18-29	460 (19.2)	277 (36.2)	$P<0.0001$
30-44	585 (24.5)	212 (27.7)	
45-64	755 (31.6)	193 (25.2)	
≥65	592 (24.8)	83 (10.9)	
Overall age, mean (SD), years	48.9 (18.9)	39.7 (17.0)	
Disease location (ICD-9/ICD-10 code), n (%)			
Small intestine (555.0, K50.0)	832 (34.8)	253 (33.1)	$P<0.0001$
Large intestine (555.1, K50.1)	585 (24.5)	134 (17.5)	
Small and large intestine (555.2, K50.8)	601 (25.1)	301 (39.4)	
Unspecified (555.9, K50.9)	374 (15.6)	77 (10.1)	
Geographic location, n (%)			
East North Central	403 (16.9)	164 (21.4)	$P<0.0001$
East South Central	72 (3.0)	24 (3.1)	
Middle Atlantic	173 (7.2)	45 (5.9)	
Mountain	227 (9.5)	60 (7.8)	
New England	114 (4.8)	31 (4.1)	
Pacific	266 (11.1)	73 (9.5)	
South Atlantic	624 (26.1)	158 (20.7)	
West North Central	231 (9.7)	121 (15.8)	
West South Central	282 (11.8)	89 (11.6)	

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necrosis factor (TNF) therapy with or without an immunosuppressant/thiopurine as initial treatment in patients with moderate or high-risk CD.[36-38] The American College of Gastroenterology guidelines for moderate to severe CD recommended anti-TNF therapy in patients with disease resistant to corticosteroids and refractory to thiopurines or methotrexate. Furthermore, anti-integrin therapy (vedolizumab) and natalizumab therapy were suggested for initial induction therapy; whereas ustekinumab was recommended only after a trial of corticosteroids, thiopurines, methotrexate, or anti-TNF inhibitors.[39] Therefore, the updated CD medication treatment guidelines endorsed the early use of biologics and could signal continuing growth of TD therapy.

In our baseline analysis, the mean age of the patients in the TD group was less than that of the SU group. Similar results were found in a study conducted in patients hospitalized for IBD in Canada; younger patients had a higher adjusted odds of immunomodulator or biologic use prior to hospitalization (odds ratio of young compared with age 65 years or older: 2.5 [95% CI=1.2-5.1]).[27] In our analysis, factors influencing the increased use of TD therapy in younger adults may include higher disease severity at diagnosis, increased life expectancy, and differing coverage policies/cost sharing between employer-sponsored and Medicare insurance. Moreover, aging is associated with multimorbidity, which may lead to polypharmacy, increased risk of drug interactions, and complicated medication

TABLE 1 Baseline Characteristics of Patients With CD According to Step-Up or Top-Down Treatment Initiation Strategy *(continued)*

	SU group	TD group	Significance
Payer type, n (%)			
Commercial	1,770 (74.0)	674 (88.1)	*P*<0.0001
Medicare (age <65 years)	91 (3.8)	21 (2.8)	
Medicare (age ≥65 years)	531 (22.2)	70 (9.2)	
Elixhauser index, n (%)			
0	666 (27.8)	250 (32.7)	*P*<0.0001
1-2	924 (38.6)	349 (45.6)	
≥3	802 (33.5)	166 (21.7)	
Elixhauser score, mean (SD)	2.24 (2.5)	1.65 (2.1)	
GI-related hospitalization prior to diagnosis			
Prior hospitalization, n (%)	216 (9.0)	62 (8.1)	*P*=0.4317
CD-related surgical procedures performed within 60 days following index diagnosis			
Procedure performed, n (%)	1,388 (58.0)	470 (61.4)	*P*=0.0951
First-year costs, mean (SD)			
All-cause cost	34,898 (88,168)	51,359 (66,988)	*P*<0.0001
CD-specific direct cost	11,765 (24,752)	32,664 (32,570)	
CD-specific medical costs	4,616 (16,731)	11,653 (26,031)	
CD-specific medication costs	7,025 (12,560)	21,011 (21,074)	
First-year utilization			
CD-specific medical utilization, mean (SD)	6.42 (9.9)	14.35 (13.0)	*P*<0.0001
CD-specific prescription medication utilization, mean (SD)	6.97 (6.3)	11.53 (7.2)	

Costs were standardized to the 2017 US dollar using the Personal Health Care Expenditure.

All-cause cost refers to health care expenditures for any indication, encompassing all pharmacy, outpatient health care, laboratory testing, imaging, and hospitalization/emergency department costs. CD-specific direct cost refers to sum of cost prescriptions dispensed for CD-indicated therapies and medical visits and hospitalizations with a primary diagnosis of CD in the follow-up period. CD-specific medical cost/utilization refers to cost relating to number of health care visits, including outpatient appointments, laboratory tests, imaging, hospitalization/emergency department use, with CD as the primary diagnosis. CD-Specific Medication Cost/Utilization is the cost relating to number of prescriptions dispensed for CD-indicated medications.

CD=Crohn disease; GI=gastrointestinal; ICD=International Classification of Diseases; SU=step-up; TD=top-down.

regimens. Furthermore, prescribers may deem the risks of TD therapies in older adults to exceed the potential clinical benefits, especially when life expectancy does not compel a need for longer-term disease control.[40]

In this analysis, the TD group had a larger proportion of patients using commercial insurance and a smaller proportion of patients with Medicare than the SU group. Differences in patient out-of-pocket costs and coverage policies between commercial insurance and Medicare may have been influential in this finding. Medicare Part D typically has a 25% cost-sharing requirement for most branded medications, and during the period of our study, the coverage gap (ie, doughnut hole) required even higher cost sharing. In both the SU and TD groups of our study, out-of-pocket spending for prescriptions was higher for patients with Medicare compared with commercial insurance. Therefore, for high-cost therapies, such as biologics, larger cost-sharing percentages can impact the affordability and sustainability of using TD therapy, and SU therapy provides a less costly option. Furthermore, coverage policies may require patients to step through lower-costing agents prior to obtaining biologics.

The univariable analysis indicated disease-specific expenditure and utilization during the first treatment year were higher in the TD group. Although higher CD-specific medication costs can be expected in the TD group, given the prices of biologic therapies, the utilization of CD medications in the 1-year follow-up period was significantly

TABLE 2 Results of Optimized General Linear Model Predicting Factors Associated With CD-Specific Medical Expenditure

	Adjusted odds ratio[a]	SE[b]	Adjusted odds ratio 95% CI[b]	Adjusted costs, US $[b]	Percentage difference in cost[c]
Therapy strategy					
TD	2.5	1.1	(2.1-3.0)	2,052	149.8
SU	Reference				
Sex					
Female	1.2	1.1	(1.0-1.32)	944	14.9
Male	Reference				
Age group (in years)					
18-29	3.7	1.3	(2.2-5.8)	3,038	269.9
30-44	2.4	1.3	(1.4-3.7)	1,953	137.8
45-64	1.9	1.3	(1.1-2.9)	1,525	85.6
≥65	Reference				
Disease location (ICD-9/ICD-10 code)					
Small intestine (555.0, K50.0)	2.0	1.1	(1.7-2.4)	1,638	99.4
Large intestine (555.1, K50.1)	Reference				
Small and large intestine (555.2, K50.8)	3.1	1.1	(2.5-3.7)	2,522	207.0
Unspecified (555.9, K50.9)	0.4	1.1	(0.3-0.5)	350	–57.4
Payer type					
Commercial	Reference				
Medicare (age <65 years)	0.4	1.2	(0.3-0.6)	337	–59.0
Medicare (age ≥65 years)	1.5	1.3	(0.9-2.3)	1,191	45.0
Elixhauser index					
0	Reference				
1-2	1.0	1.1	(0.8-1.2)	818	–0.5
≥3	1.1	1.1	(0.9-1.3)	869	5.8

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higher in the TD group (TD: 11.5 prescriptions dispensed, SU: 7 prescriptions dispensed). Although the days supplied varied for each prescription, this finding may suggest an increased adherence rate, a more regular use of prescribed therapies, and/or a higher proportion of days covered by a CD-indicated therapy in the TD group. Over half of the TD group also had a SU therapy dispensed in the follow-up period, which may suggest patients using TD therapy also use SU therapy for breakthrough symptom control. Alternatively, in the SU group, patients may have used their medications on an as-needed basis for symptom control.

In the multivariate model predicting first-year disease-specific costs, TD therapy was associated with a higher cost (149.78% higher) compared with SU therapy. Because medication costs were not included in the predictive model, this finding indicates that the use of TD therapy was associated with higher costs for outpatient visits, inpatient care, ED use, laboratory testing, imaging, and/or procedures in the first year after CD diagnosis. The higher first-year medical cost observed in the TD group could be suggestive of an increased cost of care for initiating TD therapy. TD therapy is associated with decreased immune system functioning and injection site reactions not observed with SU therapy. The AGA guidelines for therapeutic drug monitoring in IBD do not recommend proactive monitoring for patients with IBD treated with anti-TNF inhibitors but do recommend routine thiopurine methyltransferase and complete blood count testing to guide thiopurine dosing.[41]

TABLE 2 Results of Optimized General Linear Model Predicting Factors Associated With CD-Specific Medical Expenditure *(continued)*

	Adjusted odds ratio[a]	SE[b]	Adjusted odds ratio 95% CI[b]	Adjusted costs, US $[b]	Percentage difference in cost[c]
GI-related hospitalization prior to diagnosis					
Prior hospitalization	2.8	1.1	(2.2-3.6)	2,297	179.7
No prior hospitalization	Reference				
CD-related surgical procedures performed within 60 days following index diagnosis					
Procedure performed	0.9	1.1	(0.8-1.1)	748	–8.9
No procedure performed	Reference				
Diagnosis year					
2011	Reference				
2012	0.9	1.1	(0.7-1.1)	740	–10.0
2013	1.4	1.1	(1.1-1.7)	1,121	36.5
2014	1.7	1.1	(1.3-2.3)	1,429	73.9
2015	1.1	1.1	(0.9-1.4)	901	9.7
2016	1.4	1.1	(1.1-1.8)	1,132	37.9
2017	0.8	1.1	(0.7-1.1)	692	–15.7

Dependent variable: CD-specific medical costs, which represents all health care costs, without medication costs.
[a]*Adjusted exponentiated β coefficient.*
[b]*Adjusted exponentiated values.*
[c]*Percentage change in cost when all other independent variables are at the reference level.*
CD = Crohn disease; GI = gastrointestinal; ICD = International Classification of Diseases; SU = step-up; TD = top-down.

Although a microlevel cost analysis was outside the scope of our study, posttherapy monitoring may influence the higher follow-up cost observed in the TD group. Furthermore, some TD therapies have higher costs because of administration by a health care professional or training patients to self-administer. These therapy-related costs, beyond the price of the medication, may have contributed to the higher overall medical costs among the TD group observed in our analysis. The higher health care costs among the TD group may also suggest that these patients had more severe CD. Patients with moderate to severe CD would be expected to have higher first-year medical utilization consequent to increased symptomology and the need for more intensified medical follow-up.

LIMITATIONS

The design and nature of the data used for this study introduced limitations that are important to acknowledge. Ascertaining CD disease severity from claims data is challenging because of limited patient-specific symptom and pathophysiology data captured in billing codes. Yet we attempted to address disease severity in our model by defining the diagnosis location in the GI tract, the occurrence of GI-related hospitalizations prior to diagnosis, and CD-related surgical procedures performed within the 60 days following the index diagnosis. These variables were identified as risk factors of increased rates of hospitalizations and surgeries for CD as well as a higher CD severity index previously in a study using claims data.[24] Although our model included variables that indicate disease severity by proxy, residual confounding may be present because of the lack of pathophysiologic and patient-reported data about CD symptoms.

Additional limitations of this study include only addressing short-term costs among newly treated patients with CD, and therefore, the results are not generalizable to longer-term therapy or to patients with prevalent CD. Furthermore, although pharmacy claims data provide detailed information on medication names, doses, and dispense dates, only medications charged to the health plan are captured. We also only assessed initial therapy dispensed in the 60 days after index diagnosis and did not account for therapy switching or adherence with medication during the follow-up period. Prescriber bias may be present in this study, as

regional or institutional prescribing norms, clinical expertise, expected cost of medications, and prescriber experience may influence preference of TD or SU therapy. Lastly, because of the chronic and cyclical nature of CD, the identified incident diagnosis date may represent an initiation of therapy after an extended period of disease remission.

Conclusions

We identified patient/clinical characteristics and first-year medical expenditures associated with SU and TD utilization in patients newly initiating medication therapy for CD. These findings, along with the increasing development and approval of biologic/specialty therapies for CD, align with the strategy of initiating TD therapy in patients with a higher disease burden. Therefore, understanding prescription medication utilization trends and associated costs is imperative. Further research is needed to determine the long-term overall health care costs and use of medical and surgical services associated with SU and TD treatment strategies in a real-world setting.

DISCLOSURES

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