AP&T Alimentary Pharmacology and Therapeutics

Real-world assessment of therapy changes, suboptimal treatment and associated costs in patients with ulcerative colitis or Crohn's disease

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Publication data
Submitted 25 October 2013
First decision 27 November 2013
Resubmitted 4 March 2014
Accepted 5 March 2014
EV Pub Online 3 April 2014

This article was accepted for publication after full peer-review.

SUMMARY

Background
Treatments for Crohn's disease (CD) and ulcerative colitis (UC) are not uniformly effective, thus necessitating dose changes, switching, and augmentation and carry adverse event risk, often requiring discontinuation, which reduces treatment benefits.

Aim
To assess continuity of and changes to initial CD and UC treatments, as well as costs associated with specific parameters defining suboptimal therapy.

Methods
Commercial US insurance claims (2006–2010) were retrospectively analysed. CD and UC patients receiving monotherapy with 5-aminosalicylates (5-ASAs), corticosteroids (CS), immunomodulators (IM) or biologics were included. Continuity of and changes to initial (index) therapy and associated costs (2011 US$) were assessed over 12 months following therapy initiation. Suboptimal therapy included discontinuation or switch (except for CS), dose escalation, augmentation, inadequate loading (biologics only), prolonged CS use (>3 months), surgery or hospitalisation.

Results
The study included 13 005 CD and 19 878 UC patients. Augmentation was a common index therapy change (~20% of 5-ASA initiators, ~40% of CS initiators, ≥40% of IM initiators and 26–55% of biologic initiators) in both CD and UC patients. Approximately 50% of CD and UC 5-ASA initiators discontinued/interrupted treatment. Approximately 80% of CD and UC patients had ≥1 suboptimal therapy marker. Mean all-cause total costs per CD patient were significantly higher in those with vs. without suboptimal therapy ($18 736 vs. $10 878; $P < 0.001$); in UC, the disparity was smaller ($12 679 vs. $9653; $P < 0.001$).

Conclusions
Frequent dose and treatment changes were observed in all classes of initial UC and CD treatments. The economic impact of suboptimal therapy among UC and CD patients is substantial.

Aliment Pharmacol Ther 2014; **39:** 1143–1155

doi:10.1111/apt.12727

INTRODUCTION

The public health burden of ulcerative colitis (UC) and Crohn's disease (CD), collectively comprising inflammatory bowel disease (IBD), is high. The overall prevalence of UC and CD combined in the US was recently estimated at 1.2 million people.[1] UC affects approximately 600 000 individuals in the US, with an annual incidence of 8–12 cases per 100 000 US population.[2–6] CD is slightly less prevalent, affecting approximately 565 000 individuals in the US, with an estimated annual incidence of 5 per 100 000 US population.[1, 7, 8] UC and CD are associated with high morbidity and decreased quality-of-life,[9, 10] as well as a substantial direct and indirect cost burden. One recent study estimated that patients with UC and CD cost managed care payers $5066 and $8265, respectively, in annual disease-attributable costs.[11] Extrapolating to current incidence estimates, the authors of this study estimated that the total annual direct economic burden of UC and CD in the US is at least $6.3 billion ($2.7 billion for UC and $3.6 billion for CD). Other studies have estimated even higher direct costs for UC, at more than $4 billion in annual direct costs, including $960 million in hospital costs and $680 million in drug costs.[12] The indirect costs of UC and CD combined have been estimated at $3.6 billion in lost productivity due to workplace absence.[13]

A broad range of therapies are available for the induction and maintenance of disease control in UC and CD. For mild to moderately severe disease, pharmacological treatment options include oral 5-aminosalicylates (5-ASAs) (e.g. sulfasalazine, mesalazine (mesalamine), balsalazide) and corticosteroids. Therapies for moderate to severe IBD include higher dose oral or intravenous (IV) corticosteroids, immunomodulators (azathioprine, mercaptopurine, methotrexate, ciclosporin) and biological therapies (infliximab, adalimumab, certolizumab pegol, natalizumab). Severe cases lacking or losing response to these therapies may eventually require surgery, typically colectomy with or without ileoanal pouch creation for UC patients, and bowel resection, strictureplasty or drainage of abscesses for CD patients. There are limitations to current medical therapies for UC and CD. They are not uniformly effective or durable, and may therefore require frequent dose escalation or therapy change, and carry adverse event risk often requiring early discontinuation of therapy;[14–16] combined, these factors reduce treatment benefits. Selection of initial therapies, optimisation of such therapies and the timing of interventions is of great interest to UC and CD clinicians.[15, 17]

Limited data exist from real-world practice settings regarding initial treatment selections and therapy changes among patients with UC or CD, as well as the potential cost implications of suboptimal treatment as defined by changes in treatment patterns. Such information, as gathered from outside the highly controlled setting of clinical trials, is increasingly required by payers, providers, regulatory authorities and other health care decision makers in assessments of both existing and novel pharmacotherapies. This study sought to address these knowledge gaps using a retrospective analysis of insurance claims data from a large population of patients enrolled in commercially managed care health plans.

MATERIALS AND METHODS

Data source

Data were obtained from the MarketScan Commercial Claims and Encounters (CCAE) database for the period 2006–2010. The database includes employer- and health plan-sourced data containing medical (in-patient and out-patient) and prescription drug claims for more than 30 million individuals annually distributed across all four US Census regions. Patient demographics, dates of plan enrolment and other patient-level characteristics (e.g. type of health plan, employment status) are included in the database. Average total plan enrolment duration in the database is approximately 5 years; some patients have less and some patients have more, but the aforementioned plan enrolment dates allow selection of patients with precise enrolment durations as required by the study design. Cost information is captured at the claim level and represents amounts paid/reimbursed to providers. All data are linked within patients across time with a unique, encrypted patient identifier.

Patient selection

From the total population captured by the CCAE database, and based on previous claims-based IBD case identification methods,[18, 19] patients with multiple (at least two) diagnoses of either UC [International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9)-CM 556.xx] or CD (ICD-9-CM 555.xx) on at least two different days between July 1, 2006 and December 31, 2009 were selected for study inclusion. To capture incident cases, patients were required to have at least 6 months of continuous health plan enrolment before their first observed UC or CD diagnosis. Further criteria for patient selection included the presence of at least one claim for a disease-related pharmacotherapy on

or after the date of the first observed diagnosis. Eligible disease-related pharmacotherapies included 5-ASAs, corticosteroids, immunomodulators and biologics. The study index date was assigned as the date of the first observed UC or CD therapy claim, and patients were grouped for analyses according to their index therapy. Patients were followed on continuity of index therapy, changes to index therapy and costs for 1 year from the index date. To ensure all patients had at least 1 year of follow-up duration, patients were required to have at least 12 months of continuous health plan enrolment after the index date.

Patients who had diagnosis codes for both UC and CD were initially assigned to one diagnosis category or the other (UC or CD) based on the majority diagnosis across all their UC and CD claims, but if there was more than one claim for the minority diagnosis, patients were excluded. For example, patients with four UC diagnosis claims and one CD diagnosis claim were included and assigned to the UC group; conversely, patients with four UC claims and two CD claims were excluded entirely. Finally, patients on multiple concurrent treatments at the index date were also excluded from the study (less than 10% of the final study sample). Including only patients treated with a single agent at index helped to 'purify' the treatment change measures assessed downstream and thereby simplify interpretation of the results. Consider, for example, a patient who initiated therapy with both a corticosteroid and a 5-ASA at index; this patient was already experiencing treatment augmentation at index as the intended initial therapy. Mixing this patient with another patient who initiated only a 5-ASA and then later added (augmented with) a corticosteroid may confound interpretation of results regarding the extent of treatment augmentation. We therefore excluded patients on multiple treatments at index.

Study measures

Patient characteristics. Patient characteristics assessed at the index date were age, gender and index therapy. Baseline comorbidity burden was assessed during the 6-month pre-index period based on the Charlson Comorbidity Index (CCI).[20]

Index therapy continuity and changes. All index therapy continuity and change assessments were made based on observed events during the 12-month period after the index date. Each type of change to the index therapy was based on criteria defining such changes as being potentially indicative of suboptimal therapy.

Discontinuation or interruption: Discontinuation or interruption of the index therapy was defined as a therapy exposure gap based on observed refills for oral or injectable drugs, and infusion patterns for infused therapies. Exposure gaps qualifying as discontinuation or interruption of therapy were defined according to criteria specific to the index therapy as follows:

(i) For 5-ASAs, most patients are expected to respond quickly (within 45–90 days after initiation). Therefore, if a patient initiating a 5-ASA was no longer on the drug at 3 months post-initiation, this patient was considered as having a primary nonresponse or an adverse treatment effect, and therefore a discontinuation indicative of suboptimal therapy; discontinuations after 3 months may not indicate primary nonresponse and therefore were not considered a reliable marker of suboptimal therapy.

(ii) For patients initiating the biologics infliximab and adalimumab, or any immunomodulator, and who discontinued these drugs before approximately 3 months after initiation, it may be reasonably concluded that the patient has experienced primary nonresponse or an adverse treatment effect. Therefore, any gap of >60 days within 3 months after initiation of these agents was considered to be a discontinuation indicative of suboptimal therapy.

(iii) For patients initiating the biologic natalizumab, any gap >60 days within 6 months after initiation.

Given that corticosteroids are often used as a 'bridge' to another therapy, discontinuation was not measured for patients initiating corticosteroids.

Upward dose titration: Upward dose titration was defined as a subsequent dose increase above the maintenance dose reached after an initial adjustment period. This was measured according to criteria specific to the index therapy as follows:[15]

(i) For patients initiating biologics, after an initial 90-day adjustment period, defined by a doubling of average daily dose based on number of vials, infusions or injections obtained. Titration was not measured among patients initiating natalizumab as titration is not indicated for this drug.

(ii) For patients initiating immunomodulators, after an initial 90-day adjustment period, upward titration was defined by a minimum 10% increase in average daily dose.

(iii) For 5-ASA initiators, after an initial 45-day adjustment period, upward titration was defined by a

minimum 50% increase in average daily dose or moving from an oral 5-ASA (any daily dose) alone to combination therapy with a rectal 5-ASA.

(iv) For corticosteroid initiators, regardless of timing (no initial adjustment period required), upward titration was defined by moving from a low- to medium-dose oral prescription (≤30 mg/day of oral prednisone or equivalent) to a high-dose oral prescription (>30 mg/day of oral prednisone or equivalent), or moving from any oral dose to IV administration.

Switching: Switching from the index therapy was defined by receipt of an alternative therapy within a specific time frame following exhaustion of the drug supply or covered days for the prior therapy. The switching definition was specific to the index therapy as follows:

(i) For patients initiating biologics, switching was defined by initiation of an alternative biologic agent or alternative drug class within a minimum 90-day gap following exhaustion of the supply or days covered for the index biologic prescription, with no other subsequent biologic prescriptions until at least 180 days after supply exhaustion of the index prescription. Moving from a biologic to 5-ASA was not considered to be a switch.

(ii) For patients initiating immunomodulators, switching was defined as above for biologics.

(iii) For patients initiating 5-ASAs, switching was defined as above for biologics, with the exception that switches must occur within 30 days after supply exhaustion of the index 5-ASA prescription, with no other subsequent 5-ASA prescriptions observed until at least 90 days after supply exhaustion of the index 5-ASA.

(iv) For patients initiation corticosteroids, switching was not evaluated because corticosteroids are most often used as a 'bridge' to another therapy.

Augmentation: Augmentation was defined as a new therapy initiated with the index therapy being continued, as defined by at least one additional prescription claim for the original therapy within 30 days after exhaustion of the days' supply or coverage of the previous prescription.

Other therapeutic events. We also assessed rates of other selected therapeutic events, including inadequate biologic induction dosing, disease-related surgery and hospitalisation, and prolonged corticosteroid use. Inadequate biologic induction dosing was defined as less than three infusions within 12 weeks after the index date for patients initiating infliximab, less than six pens within 6 weeks after the index date for patients initiating adalimumab, and less than one infusion per month for the first 3 months after initiation for patients initiating natalizumab. Disease-related surgery was defined by ICD-9-CM and Current Procedural Terminology procedure codes for colectomy, colostomy/ileostomy, fistula/abscess repair or strictureplasty,[21] while disease-related hospitalisation was defined by in-patient stays carrying a primary or nonprimary discharge diagnosis of UC or CD. Prolonged corticosteroid use was defined as any corticosteroid course of more than 3 months at any point in the 12-month post-index period.

Suboptimal treatment. A composite measure of suboptimal initial IBD treatment was defined as having at least one of the following treatment changes or events as described above: discontinuation (except for corticosteroid initiators), dose escalation, switch (except for corticosteroid initiators), augmentation, inadequate loading (biologic initiators only), prolonged corticosteroid use, disease-related surgery or disease-related hospitalisation. Switches from corticosteroids to alternative agents were not included in the composite measure of suboptimal treatment because it is expected that patients initiating corticosteroids would discontinue them after a short period of time, which is considered an optimal therapeutic strategy based on current guidelines.[22, 23]

In the context of this study, the term 'suboptimal treatment' should not be interpreted as a definitive indicator of ineffective or failed treatment, as the various treatment changes previously described may occur for a variety of reasons, including nonresponse or loss of response to therapy (which may, in fact, indicate medically refractory disease rather than treatment failure), or due to adverse treatment effects. For purposes of this study, we use 'suboptimal therapy' only as a convenient term to describe a broad constellation of treatment change events that, based on previous studies and clinical experience among the authors, are indicative of a less-than-ideal treatment pathway for patients with IBD.

Costs. Total all-cause and disease-related costs were aggregated across claims within each patient over the 12-month post-index period. Disease-related costs were defined by claims with a UC or CD diagnosis code or claims for the noted disease-related treatments or procedures. Costs were inflated at the claim level to 2011 US$ using the medical component of the US Consumer Price Index. Cost data were reported in total and by mutually

exclusive setting (in-patient, emergency department, out-patient and other ambulatory, and pharmacy) in which they were incurred.

Statistical analyses

Analyses were descriptive and exploratory. Unadjusted, descriptive statistics were generated for all analysis variables, which included frequency distributions for categorical variables and mean values and standard deviations for continuous variables. All-cause and disease-related costs per patient were descriptively compared between patients with vs. without at least one of the noted markers of suboptimal treatment using univariate *t*-tests. Statistical significance for these comparisons was reported as *P*-values.

RESULTS

A total of 417 134 patients with at least one UC or CD diagnosis claim were identified in the database, of which 32 883 patients met the final study inclusion criteria (19 878 for UC and 13 005 for CD) (Figure 1). 5-ASA was the predominant index therapy in the UC group (69% of patients); 5-ASA was also the most common index therapy in the CD group (47% of patients). Corticosteroids, immunomodulators and biologics were more frequently used as the index therapy (40%, 8% and 5% of patients respectively) in CD patients than in UC patients (27%, 2% and 1% respectively) (Table 1). In both UC and CD patients, baseline comorbidity burden was highest in patients initiating corticosteroids [UC: mean (s.d.) CCI = 0.8 (1.4); CD: mean (s.d.) CCI = 0.8 (1.3)] or biologics [UC: mean (s.d.) CCI = 0.9 (1.4); CD: mean (s.d.) CCI = 0.6 (1.0)], and lowest in patients initiating 5-ASAs [UC: mean (s.d.) CCI = 0.5 (1.0); UC: mean (s.d.) CCI = 0.5 (1.0)].

Table 2 summarises overall rates of various types of changes to the index therapy during the 12-month post-index period.

Discontinuation/interruption: In both UC and CD patients, approximately half (51% and 52% respectively) of 5-ASA initiators discontinued or interrupted the initial treatment. Rates of index biologic discontinuation or interruption were also similar between UC and CD patients initiating infliximab (13% and 15% respectively).

Upward dose titration: With the exception of immunomodulators, upward dose titration was common for all index therapies in UC patients. Among UC patients initiating corticosteroids and 5-ASA, 37% and 20% of

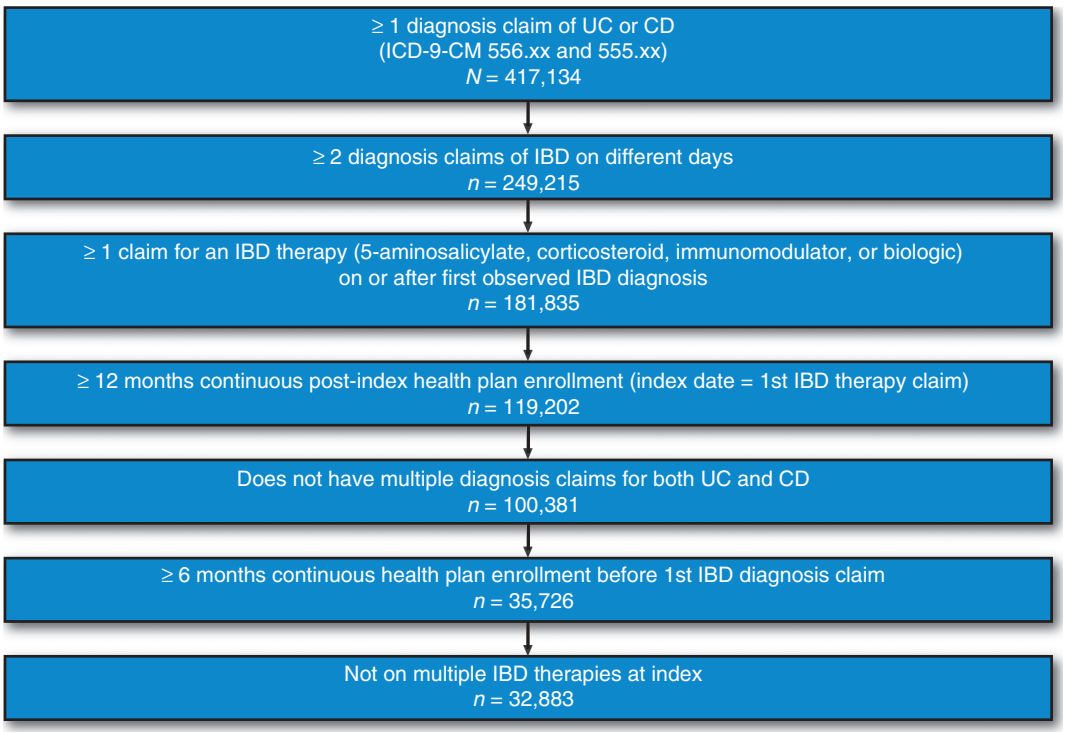

Figure 1 | Sample attrition. UC, ulcerative colitis; CD, Crohn's disease; IBD, inflammatory bowel disease.

Table 1 | Patient characteristics

	Index therapy							
	5-ASA		CS		IM		Biologics	
UC patients (n = 19 878)								
All patients (n, Row%)	13 783	69.3	5455	27.4	473	2.4	167	0.8
Age								
Mean (s.d.)	44.8	(12.7)	46.7	(12.4)	45.0	(13.1)	43.1	(13.7)
Median	47		49		48		47	
Gender (n, Col%)								
Male	6611	48.0	2235	41.0	244	51.6	76	45.5
Female	7172	52.0	3220	59.0	229	48.4	91	54.5
Geographic location (n, Col%)								
Northeast	1880	13.6	498	9.1	65	13.7	17	10.2
South	3800	27.6	1407	25.8	125	26.4	38	22.8
Midwest	5398	39.2	2674	49.0	188	39.8	91	54.5
West	2686	19.5	866	15.9	92	19.5	20	12.0
Other/unknown	19	0.1	10	0.2	3	0.6	1	0.6
Charlson Comorbidity Index								
Mean (s.d.)	0.5	(0.9)	0.8	(1.4)	0.7	(1.1)	0.9	(1.4)
Median	0		0		0		0	
CD patients (n = 13 005)								
All patients (n, Row%)	6136	47.2	5173	39.8	1065	8.2	631	4.9
Age								
Mean (s.d.)	42.9	(14.3)	43.2	(14.4)	40.4	(15.2)	37.5	(14.9)
Median	45		46		43		39	
Gender (n, Col%)								
Male	2791	45.5	2087	40.3	508	47.7	290	46.0
Female	3345	54.5	3086	59.7	557	52.3	341	54.0
Geographic location (n, Col%)								
Northeast	898	14.6	526	10.2	123	11.6	52	8.2
South	1872	30.5	1563	30.2	381	35.8	185	29.3
Midwest	2400	39.1	2401	46.4	375	35.2	305	48.3
West	954	15.6	672	13.0	181	17.0	88	14.0
Other/unknown	12	0.2	11	0.2	5	0.5	1	0.2
Charlson Comorbidity Index								
Mean (s.d.)	0.5 (1.0)		0.8 (1.3)		0.5 (0.9)		0.6 (1.0)	
Median	0		0		0		0	

UC, ulcerative colitis; CD, Crohn's disease; s.d., standard deviation; 5-ASA, 5-aminosalicylate; CS, corticosteroid; IM, immunomodulator; Col, column.

patients, respectively, had an upward titration. Among UC patients initiating a biologic, upward titration was substantially more common for infliximab (29%) than adalimumab (13%). Upward titration rates were similar in CD patients as in UC patients for each index therapy, with the exception of patients initiating 5-ASA for whom upward titration was substantially less frequent (6%) in CD patients. The prevalence of upward titration among all biologic initiators combined was 27% and 28% for UC and CD patients respectively (data not shown).

Switching: Among UC patients, switching occurred in 11% of adalimumab initiators, 9% of infliximab initiators, 9% of immunomodulator initiators and 6% of 5-ASA initiators. Switching was generally more common in CD patients: 11% of 5-ASA initiators, 11% of immunomodulator initiators, and 35%, 18% and 11% of certolizumab pegol, adalimumab and infliximab initiators respectively. Augmentation was common (at least 20%) for all index treatment groups in both UC and CD patients.

Among patients in each index therapy class who switched to an alternative treatment, Figure 2 summarises the distribution of the next agent used after switch. Among all UC and CD patients who switched index treatment, regardless of index therapy, the most common

Table 2 | Summary of changes to the index therapy

	Index therapy											
							Biologics*					
	5-ASA		CS		IM		Adalimumab		Certolizumab		Infliximab	
UC patients (n = 19 876)												
All patients (n, Row%)	13 783	69.3	5455	27.4	473	2.4	38	0.2	0	0.0	128	0.6
Discontinuation/interruption (n, Col%)	6965	50.5	N/A		0	0.0	0	0.0	–	–	17	13.3
Upward dosage titration (n, Col%)	2811	20.4	2008	36.8	37	7.8	5	13.1	–	–	37	28.9
Switch (n, Col%)	801	5.8	N/A		42	8.8	4	10.5	–	–	–	9.4
Augmentation (n, Col%)	2879	20.9	2241	41.1	281	59.4	21	55.3	–	–	43	33.6
CD patients (n = 13 005)												
All patients (n, Row%)	6136	47.2	5173	39.8	1065	8.2	192	1.5	23	0.2	409	3.1
Discontinuation/interruption (n, Col%)	3213	52.4	N/A		1	0.1	13	6.8	5	21.7	63	15.4
Upward dosage titration (n, Col%)	353	5.8	1860	36.0	84	7.9	32	16.7	8	34.8	124	30.3
Switch (n, Col%)	650	10.6	N/A		121	11.3	34	17.7	8	34.8	46	11.3
Augmentation (n, Col%)	1385	22.6	2106	40.7	423	39.7	86	44.8	7	30.4	106	25.9

UC, ulcerative colitis; CD, Crohn's disease; 5-ASA, 5-aminosalicylate; CS, corticosteroid; IM, immunomodulator; Col, column.

* Not assessed for natalizumab among both UC patients (n = 1) and CD patients (n = 7), or for certolizumab among UC patients (n = 0).

next agent after switch was corticosteroids (at least half of patients who switched across all index groups). Regardless of index therapy or IBD subtype, immunomodulators were the next most common agents used in switching.

Augmentation: Table 3 describes the proportion of patients and the agent used for augmenting the index therapy. Among UC and CD patients who initiated 5-ASA, the vast majority of those who augmented their therapy did so with corticosteroids (89% and 76% of patients who augmented respectively). Among patients initiating corticosteroids who augmented, 5-ASAs were the most common agents used in augmentation for both UC (87%) and CD (63%) patients. Among UC and CD patients who initiated infliximab and who later augmented therapy, choice of agent added to the index therapy was distributed more evenly across the available therapy options.

Other therapeutic events: Examining other therapeutic events, inadequate induction dosing for patients initiating biologics occurred in 50% of adalimumab users in the UC group and 46% of adalimumab users in the CD group (data not shown). Among CD patients initiating certolizumab pegol, 13% had inadequate induction dosing. Inadequate induction dosing was not observed for any infliximab initiators in either UC or CD patients. For both UC and CD patients, disease-related surgery and hospitalisation was most common among patients initiating the biologic therapies (except UC patients initiating adalimumab) (Figure 3). Prolonged corticosteroid use was similar across index treatment groups in UC patients (range: 10–11% across all index therapy groups), with the exception of patients initiating immunomodulators, in whom 24% had prolonged use. Prolonged corticosteroid use was also similar across index treatment groups in CD patients (range: 8–14.5% across all index therapy groups), with the exception of patients initiating corticosteroids (33% with prolonged use).

Costs: Results of the cost analysis, stratified by patients with vs. without a measure of suboptimal therapy, are presented in Table 4. In total, 81% and 80% of UC and CD patients, respectively, had at least one of the noted proxy measures for suboptimal therapy. In UC patients, total all-cause costs per patient were significantly higher in those with vs. without suboptimal therapy ($12 679 vs. $9653; $P < 0.001$), as were total IBD-related costs ($3378 vs. $2314; $P < 0.001$). Similarly, total all-cause costs per

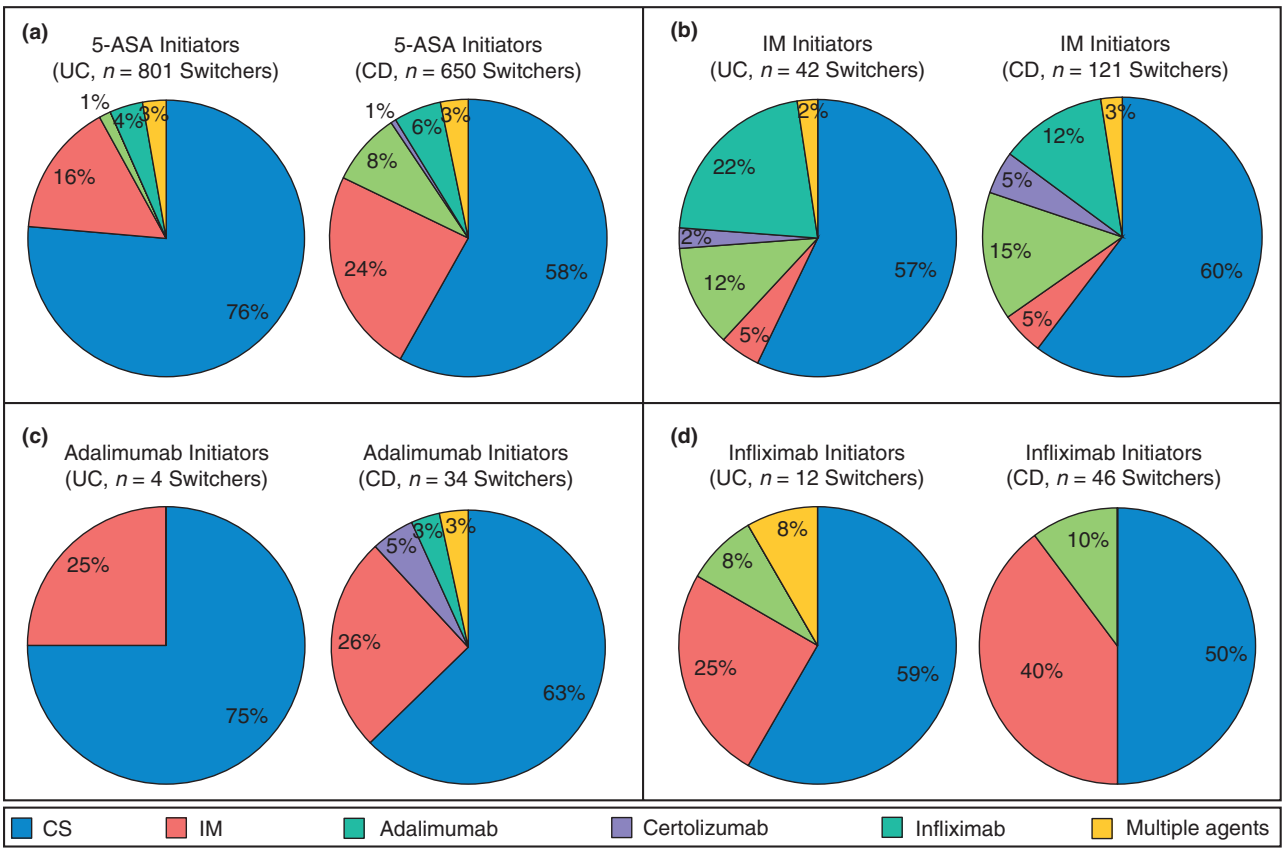

Figure 2 | Distribution of next agent used in switching from index therapy.* UC, ulcerative colitis; CD, Crohn's disease; 5-ASA, 5-aminosalicylate; CS, corticosteroid; IM, immunomodulator. *Not assessed for natalizumab initiators among UC patients (n = 1) or CD patients (n = 7), nor for certolizumab initiators among UC patients (n = 0). Tabular data for certolizumab initiators among CD patients (n = 23) available upon request.

CD patient were significantly higher in those with vs. without suboptimal therapy ($18 736 vs. $10 878; $P < 0.001$), as were total IBD-related costs ($7367 vs. $3213; $P < 0.001$). In both UC and CD patients, costs were driven largely by out-patient and other ambulatory encounters as well as by prescription drugs.

DISCUSSION

This study provides real-world information from a large population on a broad array of measures evaluating therapy continuity, treatment changes, and surgery and hospitalisation among UC and CD patients with newly initiated treatment, as well as the potential cost impact of these changes to payers. Only limited data on these measures were available in previous literature for a large scale, real-world population. Our study demonstrates a high prevalence of 5-ASA use as an index therapy and frequent dose and treatment changes with all classes of therapy. Other indicators of potential unsuccessful or suboptimal therapy in our study were the frequency of surgery and hospitalisation, and prolonged corticosteroid use with some therapy classes. These observations highlight remaining unmet needs in the treatment of UC and CD including inadequate therapy choice, suboptimal loading doses or optimisation, and, as important, the existence of medically refractory disease. These findings support a need for further assessment of optimal therapy selection and additional therapy choices in UC and CD patients. Our findings also suggest that the cost consequences of suboptimal UC and CD therapy are substantial, but appear to be much larger in CD than in UC patients. In CD patients, suboptimal therapy was associated with an approximately 0.7-fold and 1.3-fold increase in all-cause and disease-related costs, respectively, compared with an approximately 0.3-fold and 0.5-fold increase, respectively, in UC patients.

Suboptimal therapy can be defined in a number of ways, and so it may be useful to compare findings from our study with the few available previous reports that have assessed similar measures. One previous study

Table 3 | Augmentation of the index therapy

	Frequency of augmentation (%)	Second agent added (% of augmenters)				
		5-ASA	CS	IM	Biologic	Multiple agents
Index therapy, UC patients						
5-ASA (n = 13 783)	20.9	–	88.8	6.3	0.7	4.2
CS (n = 5455)	41.1	87.0	–	9.0	2.5	1.5
IM (n = 473)	59.4	55.2	35.9	–	2.5	6.4
Biologics*						
Adalimumab (n = 38)	55.3	38.1	28.6	19.1	–	14.2
Infliximab (n = 128)	33.6	23.3	34.9	11.6	–	30.2
Index therapy, CD patients						
5-ASA (n = 6136)	22.57	–	76.1	12.9	4.0	6.9
CS (n = 5173)	40.71	62.8	–	22.8	12.6	1.8
IM (n = 1065)	39.72	37.1	47.0	–	8.5	7.3
Biologics*						
Adalimumab (n = 192)	44.79	16.3	57.0	18.6	–	8.1
Certolizumab (n = 23)	30.43	42.9	42.9	14.3	–	0.0
Infliximab (n = 409)	25.92	14.2	43.4	30.2	–	12.3

UC, ulcerative colitis; CD, Crohn's disease; 5-ASA, 5-aminosalicylate; CS, corticosteroid; IM, immunomodulator; Col, column.

* Not assessed for natalizumab among both UC patients (n = 1) and CD patients (n = 7), or for certolizumab among UC patients (n = 0).

conducted on a small sample of 67 UC and CD patients found that 77% of patients had prolonged corticosteroid use,[24] which is substantially higher than the maximum rate (33%) of prolonged corticosteroid therapy observed across all index treatment groups in our study population. Another previous study examining the extent of biologic dose escalation in patients with CD found overall upward titration rates ranging from 32% to 38%,[15] which was somewhat higher than the overall rate of dose escalation found in our study (28%) for CD patients. This same study also found similar 12-month rates of IBD-related surgery after biologic initiation as reported in the current analysis. Finally, although previous cost studies have not compared costs between patients with and without evidence of suboptimal therapy, our per-patient cost estimates for the year following treatment initiation were consistent with the range found in the previously cited study of Kappelman *et al.*[11]

Although the impact of inadequate or suboptimal therapy on patient-centric clinical outcomes (e.g. quality-of-life) was not directly measured in this study, it may be inferred from our knowledge about the natural history of UC and CD, as well as our understanding about the quality-of-life of patients living with these conditions.[21, 25] Our study showed that under-dosed treatments ('suboptimal' by our definitions) may result in downstream adverse cost and resource use outcomes (e.g. increased hospitalisations and surgeries), which we expect to be correlated with reduced quality-of-life. In addition to the direct measurement of the quality-of-life effects of suboptimal therapy, future studies should also seek to measure the broader societal impact and costs (e.g. caregiver burden, lost workplace productivity) of suboptimal therapy in UC and CD.

Our study was subject to several limitations. First, several clinical (e.g. disease severity and symptoms) and socio-demographic characteristics (e.g. educational and income level) that may affect treatment selection were unavailable in our database and therefore could not be assessed as possible confounders or considered for additional context of our findings. Second, it was not possible to confirm whether patients identified for analysis were true incident UC or CD cases because of the lack of access in the database to medical histories on patients prior to the beginning of their health plan enrolment and prior to database entry. However, the minimum 6-month enrolment criterion helped to ensure that the selected patients at least had a half-year period of relatively quiescent disease before the first diagnosis observed in the database. Third, we only analysed patients receiving single therapies as their initial treatment. This was in keeping with our belief that most patients are started on a single therapy, but furthermore due to the need to simplify the analysis and to avoid

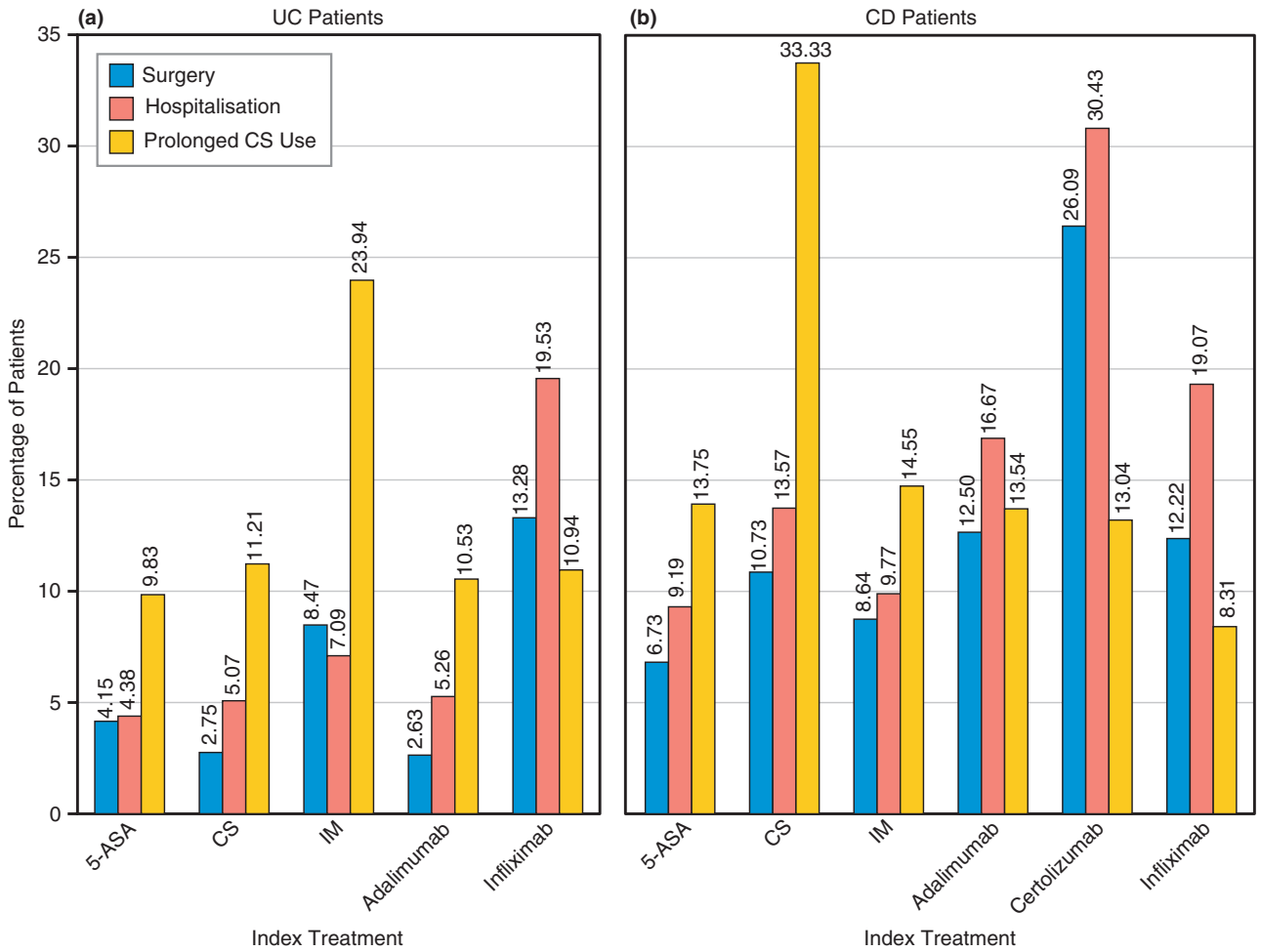

Figure 3 | IBD-related surgery, hospitalisation and prolonged corticosteroid use. IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease; 5-ASA, 5-aminosalicylate; CS, corticosteroid; IM, immunomodulator.

confounding of interpretation of results, particularly regarding treatment augmentation. This approach is supported by the low number of patients excluded due to combination prescriptions at index, but it remains true that our findings do not reflect the prescribing patterns of clinicians who use combination therapies in the initial stage of IBD treatment. Fourth, it is possible that some treatment changes observed in our study sample were due to adverse effects associated with the initial treatment selection. However, it is not possible to attribute adverse effect causality with treatments using administrative data, and so we were unable to assess specific reasons for certain treatment changes even though nonresponse and adverse effects are presumed to be the primary reasons. Nonetheless, we believe that the changes defined for each type of treatment remain indicative of suboptimal therapy, whether such changes were because of nonresponse or adverse effects. Fifth, the findings from this study may not be generalisable to individuals with IBD enrolled in federal health plans (e.g. Medicare, Medicaid) or to uninsured persons with IBD. Recent data presented at the 2013 annual meeting of the American College of Gastroenterology[26] suggest that approximately 26% of all individuals with IBD either have no insurance coverage or reduced coverage from the previous year. Insurance and financial barriers were cited as reasons for frequent patient-initiated delays in treatment, dose skipping and reduced number of doses taken, and delayed physician visits, all of which presumably reduce treatment benefits. As our study includes a well-insured IBD population, the extent of suboptimal therapy estimated in this study may be underestimated relative to the general IBD population. Sixth, if any patient received biologic (or other medication) coverage from other sources outside the health plan(s) captured in the study database, such claims covered by other

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Table 4 | All-cause and IBD-related health care costs per patient, by suboptimal treatment status

	Had suboptimal treatment?		
	No	Yes	*P*-value
UC patients (*n* = 19 876)			
n (Row%)	3759 (18.51)	16 119 (81.49)	
In-patient services			
Mean (s.d.) All-cause costs	$31.99 ($336.27)	$48.35 ($784.41)	0.19
Mean (s.d.) IBD-related costs	$1.00 ($18.68)	$6.64 ($167.89)	0.03
Emergency room visits			
Mean (s.d.) All-cause costs	$195.22 ($1157.07)	$232.55 ($1065.76)	0.05
Mean (s.d.) IBD-related costs	$10.27 ($170.03)	$22.77 ($224.75)	<0.001
Out-patient and other ambulatory encounters			
Mean (s.d.) All-cause costs	$6575.51 ($9385.9)	$8795.15 ($16 671.50)	<0.001
Mean (s.d.) IBD-related costs	$685.17 ($2652.86)	$1157.14 ($3504.25)	<0.001
Pharmacy claims			
Mean (s.d.) All-cause costs	$2850.74 ($3907.38)	$3604.62 ($9301.59)	<0.001
Mean (s.d.) IBD-related costs	$1617.38 ($2573.30)	$2191.64 ($3712.17)	<0.001
Total			
Mean (s.d.) All-cause costs	$9653.42 ($12 123.78)	$12 679.54 ($23 853.80)	<0.001
Mean (s.d.) IBD-related costs	$2313.81 ($4478.38)	$3377.63 ($6247.15)	<0.001
CD patients (*n* = 13 005)			
n (Row%)	2546 (19.58)	10 459 (80.42)	
In-patient services			
Mean (s.d.) All-cause costs	$34.29 ($761.91)	$58.66 ($598.91)	0.07
Mean (s.d.) IBD-related costs	$2.45 ($90.68)	$12.19 ($378.34)	0.18
Emergency room visits			
Mean (s.d.) All-cause costs	$192.70 ($649.56)	$408.91 ($1794.63)	<0.001
Mean (s.d.) IBD-related costs	$26.29 ($202.65)	$100.66 ($816.28)	<0.001
Other medical encounters			
Mean (s.d.) All-cause costs	$7526.69 ($10 652.05)	$12 632.47 ($20 570.87)	<0.001
Mean (s.d.) IBD-related costs	$1375.75 ($5645.59)	$3152.65 ($10 206.31)	<0.001
Pharmacy claims			
Mean (s.d.) All-cause costs	$3124.00 ($5789.77)	$5637.43 ($11 268.26)	<0.001
Mean (s.d.) IBD-related costs	$1808.28 ($4841.58)	$4101.80 ($9484.88)	<0.001
Total			
Mean (s.d.) All-cause costs	$10 877.66 ($15 166.27)	$18 736.49 ($29 335.51)	<0.001
Mean (s.d.) IBD-related costs	$3212.77 ($9975.86)	$7367.05 ($18 307.56)	<0.001

IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease; s.d., standard deviation.

insurance sources would not be captured in our data. However, we believe this scenario to be unlikely for the vast majority of patients in our study sample. Seventh, dosing for some immunomodulators is determined based on body weight. It is possible that some patients may receive higher doses of an immunomodulator as a result of increasing body weight stemming from improved health induced by the treatment. Because information on body weight was unavailable in our study data, we were unable to distinguish planned ('desired') upward immunomodulator titrations due to increasing body weight from those due to a true lack or loss of response to therapy. Finally, we had no access to patient charts and could not confirm IBD case ascertainment nor other comorbid diagnoses, both of which are subject to coding accuracy for the purposes of billing.

Despite these limitations, our study highlights some of the key indicators of potential suboptimal therapy in the treatment of UC and CD. Future research, which cannot be addressed using administrative data, should attempt to address the reasons why suboptimal UC and CD therapy occurs. Some possible reasons include misinformation among providers, concerns about risks of specific therapies, lack of insurance coverage for certain treatment modalities and patient unwillingness to accept therapy when prescribed. Approaches to addressing these issues, including education of physicians, patients and payers, should also be explored.

In summary, our study showed that frequent dose and treatment changes, as well as other suboptimal treatments (e.g. prolonged corticosteroid use), were required with all classes of UC and CD therapy in real-world practice settings. Our findings also suggest that the cost consequences of suboptimal UC and CD therapy are substantial, particularly for patients with CD.

AUTHORSHIP

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Author contributions: Study concept and design: DTR. Data acquisition: KLD. Analysis and interpretation of data: DTR, RM, KLD and CCW. Drafting of the manuscript: DTR and KLD. Critical revision of the manuscript or important intellectual content: DTR, RM, KLD and CCW. Statistical analysis: KLD and CCW. Material support: RM. Study supervision: DTR and RM. All authors approved the final version of the manuscript.

ACKNOWLEDGEMENTS

Declaration of personal interests: Dr Rubin receives grant/research support from AbbVie, Prometheus, Shire and Warner Chilcott. He also serves as a consultant to AbbVie, Janssen Biotech, Inc., Emmi, Given Imaging, Ironwood, Prometheus, Santarus Inc., Takeda, Telsar Pharmaceuticals, UCB Pharma, and Vertex Pharmaceuticals; and holds a management position with Cornerstones Health, Inc. David T. Rubin is an employee at the University of Chicago Medicine. Reema Mody is an employee of Takeda Pharmaceuticals International, Inc. which provided the funding for the conduct of this study. Keith L. Davis has served as an advisory board member for Merck Sharpe & Dohme, Corp. Keith L Davis is an employee of RTI Health Solutions which was contracted by Takeda Pharmaceuticals International, Inc. to conduct this study. Chi-Chuan Wang: at the time this study was conducted, he was an employee of RTI Health Solutions which was contracted by Takeda Pharmaceuticals International, Inc. to conduct this study.

Declaration of funding interests: This study was funded in full by Takeda Pharmaceuticals International, Inc., which is conducting clinical research in IBD. The writing and preparation of this paper was funded in full by Takeda Pharmaceuticals International, Inc.

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