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Comparative effectiveness of infliximab and adalimumab in Crohn's disease and ulcerative colitis

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Abstract

Introduction—The availability of monoclonal antibodies to tumor necrosis factor α (anti-TNF) has revolutionized management of Crohn's disease (CD) and ulcerative colitis (UC). However, limited data exists regarding comparative effectiveness of these agents to inform clinical practice.

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Methods—This study consisted of patients with CD or UC initiation either infliximab (IFX) or adalimumab (ADA) between 1998 and 2010. A validated likelihood of non-response classification score utilizing frequency of narrative mentions of relevant symptoms in the electronic health record (EHR) was applied to assess comparative effectiveness at 1 year. IBD-related surgery, hospitalization, and use of steroids was determined during this period.

Results—Our final cohort included 1,060 new initiations of IFX (68% for CD) and 391 of ADA (79% for CD). In CD, the likelihood of non-response was higher in ADA than IFX (OR 1.62, 95% CI 1.21 – 2.17). Similar differences favoring efficacy of IFX was observed for the individual symptoms of diarrhea, pain, bleeding, and fatigue. However, there was no difference in IBD-related surgery, hospitalizations or prednisone use within 1 year after initiation of IFX or ADA in CD. There was no difference in narrative or codified outcomes between the two agents in UC.

Conclusion—We identified a modestly higher likelihood of symptomatic non-response at 1 year for ADA compared to IFX in patients with CD. However, there were no differences in IBD-related surgery or hospitalizations suggesting these treatments are broadly comparable in effectiveness in routine clinical practice.

Keywords

Crohn’s disease; ulcerative colitis; treatment response; biologic; infliximab

INTRODUCTION

The availability of monoclonal antibodies to tumor necrosis factor-α (anti-TNF) has revolutionized the management of inflammatory bowel diseases (IBD; Crohn’s disease (CD), ulcerative colitis (UC)). Pivotal clinical trials established efficacy of three anti-TNF agents each for CD (infliximab (IFX)[1], adalimumab (ADA)[2, 3], certolizumab pegol (CZP))[4] and UC (IFX[5], ADA[6], golimumab (GLM)[7]). They reduced the need for corticosteroids, increased rates of remission and reduced disease-related surgery and hospitalizations[1–12]. Observational studies confirmed their effectiveness and durability in clinical practice[11]. Yet, few studies compare the effectiveness of these different agents for IBD[13–18]. Consequently choice of treatment is often influenced by factors other than comparative performance. When compared to placebo, each of the anti-TNFs demonstrates a similar improvement in outcomes[1–12, 19]. However, the differences between the study populations preclude determining comparative efficacy from such comparisons. With the emergence of therapies with distinct mechanisms of action such as integrin inhibitors, there is growing recognition of the need for studies of comparative effectiveness of therapies to accurately inform clinical practice. Randomized controlled trials to determine comparative effectiveness, the gold standard, may be impractical due to the large numbers of patients required to demonstrate subtle differences in efficacy. Observational studies utilizing administrative claims data are limited by lack of clinical information to ascertain symptomatic, laboratory and endoscopic response to treatment. Prospective cohorts also require large numbers of patients and are resource intensive.

It is conceivable that within the next decade, virtually every clinical practice in the United States will utilize an electronic health record (EHR)[20–22]. By automatically and

comprehensively capturing every aspect of a patient's care, the EHR is a powerful, yet under-tapped data source to compare outcomes of IBD patients, in part due to variability in the quantity and quality of content. However, the availability of increasingly sophisticated tools to extract and refine narrative data from clinical text and ascertain context of use allows for the application of such data-mining methods to define meaningful and valid clinical outcomes from the EHR. In this study, we used a large multi-institutional EHR-cohort of IBD patients and validated algorithms using narrative text to classify non-response to biologic therapy[23] to achieve the following aims: (i) To compare the rates of non-response to IFX and ADA in CD and UC using a validated narrative symptom score; and (ii) To compare the rates of IBD-related surgery and hospitalization within 365 days of initiation of IFX or ADA.

METHODS

Study Population

This study examined IBD patients receiving care at either of two tertiary referral academic centers serving over 4 million patients in the Greater Boston metropolitan area. The development of our cohort has been described previously[24]. In brief, from an eligible population of all patients with at least one International Classification of Diseases, 9th edition, clinical modification (ICD-9-CM) codes for CD (555.x) or UC (556.x), we extracted informative data on disease phenotype, complications, medical and surgical treatments using codified and narrative text data identified through natural language processing (NLP) using the Clinical Text Analysis and Knowledge Extraction System (cTAKES) software[25]. Narrative terms were identified using the relevant concept unique identifiers (CUI) from the Unified Medical Language System (UMLS). A classification algorithm using codified and narrative data yielded a final cohort of 5,506 CD and 5,522 UC patients with a positive predictive value of ≥ 97%[24].

This study included patients initiating IFX or ADA between 12/4/1998 and 6/10/2010. We applied our validated algorithm to identify true users and start dates of biologic therapy in the EHR[23]. In brief, from among all patients with at least one codified or narrative mention of IFX or ADA, we excluded those with no codified mentions, fewer than 3 narrative mentions, or an interval of 0 days between the first and last narrative mention. This captured 97% of true users and had a false positive rate (classifying non-users as users) of only 4%. The date of the first codified mention was within 60 days of the actual start date of medication in over 75% of the patients; and fewer than 5% of starts were 61 days or later. Neither CZP nor GLM had distinct codes at the time of this study and could not be included.

Ascertainment of Endpoints

We had two end-points for our study. The first used narrative data to classify probability of being a non-responder to treatment 1 year after initiation. We previously validated a 'likelihood of non-response score' comprising a weighted sum of the number of narrative mentions for the concepts of diarrhea and fatigue within 365 days after initiation of biologic therapy[23]. The cTAKES software differentiates positive mentions ("has diarrhea") from negative mentions ("does NOT have diarrhea") and thus, for each patient, we are able to

calculate a net number of positive mentions. The number of net positive mentions is a reflection of both the frequency and severity of symptoms. This definition was validated against manual chart review by an IBD-specialist using two randomly selected cohorts for derivation and validation. Additionally, cross-validation was performed by comparing this non-response score with requirement for hospitalizations and surgery – this comparison demonstrated strong correlation between the two, supporting the use of our score as an endpoint. The validated likelihood of non-response score accurately differentiated symptomatic non-response from responders ($p < 0.0001$, AUROC 0.84) and correlated with needing IBD-related surgery and hospitalization ($p < 0.0001$). A higher score indicated a greater likelihood of being classified a non-responder at one year. For this study, we used as an outcome a non-response score higher than the median for our cohort. In our previous validation study, a narrative non-response score above the median was associated with an 8-fold increase in probability of symptomatic non-response at 1 year. As secondary narrative endpoints, we examined the cumulative number of mentions of abdominal pain, diarrhea, bleeding, and fatigue individually.

A co-primary hard endpoint was need for IBD-related surgery, hospitalization, or a prescription for prednisone within 365 days of anti-TNF initiation. We also compared each of these outcomes as distinct endpoints and examined the proportion of patients with an elevated CRP who achieved a normal C-reactive protein level (≤ 8mg/dL).

Other variables

Information was obtained on age at first ICD-9-CM code for CD or UC, gender, race, and non-IBD comorbidity using the Charlson comorbidity index[26]. Stricturing or fistulizing complications as well as perianal involvement was determined in CD using the relevant ICD-9-CM codes. The interval between the first ICD-9-CM code for CD or UC and the first codified mention for IFX or ADA was used as a proxy for duration of disease. We also determined if the patient had previously been exposed to another anti-TNF agent which was defined as at least one code for IFX or ADA at any point in their care within our medical system prior to the index anti-TNF initiation. Use of combination therapy was defined as a prescription for azathioprine, 6-mercaptopurine, or methotrexate within 365 days after initiation of the anti-TNF therapy. To account for temporal differences in use of these medications (use of episodic infusions early on with infliximab, trend towards combination therapy later on in the study period), the year of initiation was included as a covariate in the multivariable model.

Statistical Analysis

All analysis was performed using Stata 13.1 (StataCorp, College station, TX). Continuous variables were summarized using means and standard deviations and compared using the t-test while categorical variables were expressed as proportions and compared using the chi-square test. Multivariable logistic regression adjusting for potential confounders was used to compare the probability of being a non-responder at 1 year between those initiating IFX and ADA, separately for UC and CD. Variables were selected for inclusion in this model *a priori* based on literature demonstrating their predictive value for response to therapy or $p < 0.10$ in univariate analysis. Exploratory analyses examined individual narrative mentions of

abdominal pain, diarrhea, bleeding, and fatigue. Similarly, multivariable regression was used to compare the overall composite codified outcome as well as IBD-related hospitalization, surgery, prednisone use, and CRP normalization individually.

To account for non-random assignment to IFX or ADA, we developed a propensity score adjusting for likelihood of receiving IFX or ADA incorporating prior IBD history (age at first code, type of IBD, fistulizing or stricturing complications in CD, duration of IBD), past treatments including immunomodulator use, and number of encounters in the year prior to anti-TNF initiation. The propensity score accurately distinguished between IFX and ADA users ($p < 0.0001$) and was included as a covariate in the multivariable model. A two sided p-value < 0.05 indicated independent statistical significance.

We performed a number of sensitivity analyses. To account for the intensity of healthcare utilization in the year prior to biologic initiation, we adjusted for the total number of distinct clinical notes in the year prior to first codified mention for IFX or ADA. To minimize the potential for ascertainment bias, we repeated our multivariable model in patients with at least 5 clinical notes after the first codified mention for IFX or ADA. Additionally, though our initial algorithm resulted in misclassification of only few (< 5%) prevalent users as incident users, we repeated the analysis in those who had at least 180 days between the first code for IBD and anti-TNF initiation. The study was approved by the Institutional Review Board of Partners Healthcare.

RESULTS

Study population

Our study included 1,060 new initiations of IFX and 391 of ADA (Table 1). The majority of users of either anti-TNF had CD. Those initiating ADA also had a longer interval between their first diagnosis code for IBD and therapy start date and more likely to have had prior anti-TNF exposure (49% vs. 18%, $p < 0.001$), IBD-related surgery or hospitalization. IFX users had a higher mean C-reactive protein within 60 days prior to initiation of therapy (32.0 mg/dl vs. 22.6 mg/dl, p=0.03). The mean number of distinct clinical notes in the year prior (20 vs. 16) or after biologic initiation (24 vs. 20) were higher among ADA users compared to IFX.

Comparative effectiveness in Crohn's disease

A total of 723 and 309 initiations of IFX and ADA respectively were included. On unadjusted analysis, ADA users were more likely to be non-responders (defined as a narrative non-response score above the median) than IFX (Odds ratio (OR) 1.79, 95% confidence interval (CI) 1.37 – 2.34) (Table 2). Patients initiating ADA also had more narrative mentions of diarrhea (5.8 vs. 3.5), abdominal pain (39.4 vs. 21.9), bleeding (11.2 vs. 8.5) and fatigue (2.0 vs. 1.2) compared to IFX users in the first year after therapy ($p < 0.001$ for all). However, there was no difference between the two groups for the composite codified outcome of prednisone prescription, IBD-related surgery or hospitalization (36% vs. 41%, p=0.11). For each of the individual codified outcomes, we found no difference between IFX and ADA (Table 2). Among patients who had C-reactive protein levels

measured following therapy initiation, a similar proportion of IFX and ADA users (76% each) achieved normalization.

In propensity score adjusted analyses, ADA initiation remained associated with a higher adjusted likelihood of being a non-responder at 1 year (OR 1.62, 95% confidence interval (CI) 1.21 – 2.17) compared to IFX (Table 3). As well, similar statistically significant results favoring IFX were observed for each of the narrative endpoints of diarrhea, abdominal pain, bleeding, and fatigue (data not shown). In contrast, there was no difference between IFX and ADA for the composite codified outcome (Odds ratio (OR) 1.17, 95% CI 0.86 – 1.60) or individually for surgery, hospitalization, prednisone use, or normalization of C-reactive protein (Table 3).

The higher likelihood of non-response at 1 year with ADA compared to IFX was noted in both previously anti-TNF exposed (OR 1.67, 95% CI 0.98 – 2.82) or anti-TNF naive (OR 1.65, 95% CI 1.16 – 2.36) populations. There was a greater difference between ADA and IFX in the probability of being a non-responder in those who were not on combination therapy (OR 1.81, 95% CI 1.26 – 2.58) compared to those on combined immunomodulator-anti-TNF therapy (OR 1.46, 95% CI 0.88 – 2.45). Neither prior anti-TNF exposure nor use of combination therapy influenced relative efficacy of IFX and ADA with regards to the codified endpoints.

Comparative effectiveness in ulcerative colitis

A total of 337 IFX initiations and 82 ADA initiations were included in this analysis. There was a trend towards higher likelihood of being a non-responder with ADA compared to IFX (OR 1.64, 95% CI 0.99 – 2.72) (Table 2). However, there was no difference in the codified outcomes between the two groups with similar frequency of occurrence of the composite outcome (53% with IFX compared to 50% with ADA), surgery (13% each), hospitalization (25% vs. 30%) or prednisone use (48% vs. 43%). The comparability of effectiveness of both was confirmed on multivariable analysis where a similar likelihood of being a non-responder at one year (OR 1.53, 95% CI 0.86 – 2.73) or the occurrence of the composite outcome (OR 0.72, 95% CI 0.40 – 1.29) was seen for ADA compared to IFX. Analysis of individual symptoms suggested a borderline greater number of mentions of abdominal pain after ADA initiation when compared to IFX (18.1, 95% CI 0.07 – 36.1) but not for diarrhea, rectal bleeding or fatigue.

Sensitivity Analyses

The higher rates of non-response among ADA users compared to IFX in CD patients persisted in an analysis including patients with at least 5 distinct clinical notes in the year following therapy initiation (n=892, OR 1.47, 95% CI 1.08 – 2.00) or after adjustment for number of clinical notes the year prior (OR 1.46, 95% CI 1.09 – 1.97). An analysis restricted to those with ≥ 180 days between first code for IBD and anti-TNF initiation yielded similar results favoring IFX. No differences were noted in the composite codified outcome in the sensitivity analyses.

DISCUSSION

There is a need for studies of comparative effectiveness of therapies for IBD. However, the expense of prospective cohorts and lack of clinical detail in administrative claims data necessitates novel approaches for such comparative effectiveness research. Using a validated index for classification of likelihood of non-response derived from narrative data extracted from the EHR, we demonstrate a modestly higher likelihood of symptomatic non-response at 1 year for ADA compared to IFX in CD. However, we found no difference in coded endpoints of surgery, hospitalization or prednisone use between the two agents in CD, and no difference in either narrative or codified endpoints in UC.

Few prior studies have compared the effectiveness of IFX and ADA[13–18]. Using Medicare administrative data, Osterman *et al*. showed that over a short follow-up of 26 weeks, both IFX and ADA had similar rates of persistence on therapy, IBD-related surgery or hospitalization[18]. Also using administrative data, Sussman *et al*. showed that while ADA users had lower health-care costs 26 weeks after therapy start compared to IFX, primarily from reduced office-visit related costs as there was no difference in CD-related hospitalizations or emergency room visits[27]. Network meta-analyses inferred comparative effectiveness by pooling data from placebo-controlled RCTs[13–17]. Both Singh *et al*. and Hazelwood *et al*. reported superiority of IFX over ADA for inducing remission in CD with ADA demonstrating a more modest advantage for maintenance of remission[14, 28]. Observational series suggesting similar or small differences in effectiveness between IFX and ADA[29, 30] are also consistent with our study suggesting a modestly lower likelihood of symptomatic non-response with IFX when compared to ADA when used for CD.

Two network meta-analyses in UC suggested superiority of IFX over ADA for both inducing and maintaining remission[13, 15] differ from our findings but may have a few explanations. First, our UC cohort was small and may be underpowered to demonstrate a difference. Second, while in our previous study, the narrative likelihood of non-response score performed equally well in CD and UC in classifying non-responders[23], the reliance on diarrhea and fatigue which may be more specific to CD than UC may have reduced our ability to demonstrate a difference in symptomatic non-response between the two groups. It is also possible that patients initiated on IFX for UC may have more severe disease than those with ADA and our EHR-data is unable to fully capture this difference.

There are several implications to our findings. First, we demonstrate the feasibility and utility of applying NLP to extract narrative text from the EHR for comparative effectiveness studies, allowing for more detailed examination of symptomatic non-response in comparison to administrative claims data. While less rigorous than prospective disease activity measures, it can efficiently and cost-effectively analyze large amount of data generated during routine clinical care. This method may allow pooling together of heterogeneous EHR data from different institutions, achieving large sample sizes for comparisons. In addition, careful validation against chart review and expert annotation reduces the effect of heterogeneity in notes between different clinical providers and provides generalizability to our findings. Additionally, clinical classifiers of non-response may be superior to outcomes such as persistence of therapy used previously, as the latter may represent lack of options for

transitioning to in refractory disease despite persistent disease activity. It is also conceivable that similar methods can be used to identify radiologic, endoscopic, or histologic non-response.

We readily acknowledge several limitations to our study. Our cohort consisting of patients from referral centers may have greater severity of disease than a population-based IBD cohort. Secondly, though ours is one of the largest cohorts thus far examining comparative effectiveness of biologic therapies in IBD, some subgroups were small, reducing our statistical power. Third, while a large number of patients had C-reactive protein levels available before and after initiation of therapy, this may not have been obtained systematically and may be more frequently obtained in those with persistent symptoms indicative of therapy failure. Fourth, detailed information on disease characteristics including duration of disease, extent of involvement in UC, or endoscopic findings before and after initiation of therapy were not routinely available in all patients. Fifth, it is possible that some differences may be due to lower adherence with self-injectable therapies than those delivered in the office rather than a true difference between the drugs. Sixth, more ADA users when compared to IFX users had prior anti-TNF exposure, thereby introducing a potential bias with a lower likelihood of response. However, our multivariable model adjusted for prior anti-TNF use and our findings remained significant in a population with no prior anti-TNF use noted in our healthcare system. However, we acknowledge the possibility of potentially missing data on anti-TNF use prior to establish care within our network. We also did not have information on antibody formation as this was not yet widely available, practiced, or reimbursed during much of the study period.

The strengths of our study include the large sample size, and use of a validated measure of non-response using narrative text in addition to endpoints of IBD-related surgery or hospitalization that allowed for a more comprehensive assessment of comparative effectiveness than either outcome alone or persistence of therapy. We were able to adjust for a number of relevant confounders and our findings were robust on sensitivity analyses accounting for pre-initiation severity of disease as well as frequency of healthcare utilization.

In conclusion, from a large, multi-institutional cohort of patients with IBD, we demonstrate a modestly higher likelihood of non-response at 1 year for ADA compared to IFX in patients with CD. There was no difference in the rate of IBD-related surgery, hospitalizations, or need for prednisone between the two groups. We also identified no difference in outcomes between the two medications in UC. There is a need for robust studies of comparative effectiveness of available therapies in real-world clinical practice. As well, it is important for future studies to examine differences in long-term maintenance beyond 1 year to accurately inform decision making of both patients and providers.

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Table 1

Characteristics of the study population

Characteristic	Infliximab (n = 1,060)	Adalimumab (n = 391)	p-value
Age [Mean(SD)] (in years)	34.1 (0.5)	35.2 (0.7)	0.21
Female (%)	53	56	0.31
Charlson score [Mean(SD)]	2.9	2.8	0.43
Disease duration*[Mean(SD)] (in years)	2.9 (0.1)	4.8 (0.2)	< 0.001
Type of IBD (%)			< 0.001
Crohn's disease	68	79	
Ulcerative colitis	32	21	
Prior anti-TNF exposure (%)	18	49	< 0.001
Prior IBD hospitalization (%)	45	50	0.08
Prior IBD surgery (%)	7	17	< 0.001
Highest C-reactive protein [Mean(SD)] (mg/dL)+	32.0 (2.6)	22.6 (3.3)	0.03

IBD – inflammatory bowel diseases

* Disease duration was defined as the interval between the first ICD-9 code for Crohn's disease or ulcerative colitis and date of first codified mention of infliximab or adalimumab

+ available within 60 days prior to initiation of biologics for 340 patients on infliximab and 144 on adalimumab (Values < 8mg/dL are considered normal)

Table 2

Comparison of outcomes with infliximab and adalimumab users in inflammatory bowel disease

	Infliximab	Adalimumab	p-value
Crohn's disease	(n = 723)	(n = 309)	
Narrative outcomes			
Likelihood of non-response score	0.45 (0.03)	0.73 (0.07)	< 0.0001
Diarrhea[+]	3.5 (0.3)	5.8 (0.6)	0.0001
Abdominal pain[+]	21.9 (1.7)	39.4 (4.6)	< 0.001
Bleeding[+]	8.5 (0.5)	11.2 (0.8)	0.003
Fatigue[+]	1.2 (0.1)	2.0 (0.2)	0.0009
Codified outcomes (%)			
Composite outcome	36	41	0.11
Surgery	7	7	0.89
Hospitalization	27	28	0.75
Prednisone	24	29	0.08
Normal CRP (< 8mg/dL)[†]	76	76	0.96
Ulcerative colitis			
Narrative outcomes	(n = 337)	(n = 82)	
Likelihood of non-response score	0.66 (0.1)	0.80 (0.2)	0.43
Diarrhea[+]	5.1 (0.7)	6.4 (1.4)	0.44
Abdominal pain[+]	26.7 (3.3)	48.0 (9.6)	0.01
Bleeding[+]	14.5 (1.1)	13.5 (1.7)	0.68
Fatigue[+]	1.9 (0.3)	2.2 (0.5)	0.62
Codified outcomes (%)			
Composite outcome	53	50	0.61
Surgery	13	13	0.99
Hospitalization	25	30	0.33
Prednisone	48	43	0.36
Normal CRP (< 8mg/dL)[†]	82	79	0.64

CRP – C-reactive protein

[+] number of narrative mentions in 365 days after initiation of infliximab or adalimumab

[†] available for 309 CD patients with IFX; 212 CD patients with ADA; 195 UC patients with IFX, 53 UC patients on ADA

Table 3

Multivariable analysis[//] of comparative effectiveness of infliximab and adalimumab in inflammatory bowel disease

	Odds Ratio [(for ADA vs. IFX(ref)]	95% confidence interval (CI)
Crohn's disease		
Narrative outcomes		
Symptomatic non-response score at 1 year	1.62	1.21 – 2.17
Codified outcomes		
Composite outcome	1.17	0.86 – 1.60
Surgery	1.28	0.73 – 2.24
Hospitalization	1.01	0.72 – 1.42
Prednisone prescription	1.29	0.92 – 1.81
Normalization of CRP	1.13	0.72 – 1.78
Ulcerative colitis	**Odds Ratio [(for ADA vs. IFX(ref)]**	**95% CI**
Narrative outcomes		
Symptomatic non-response score at 1 year	1.53	0.86 – 2.73
Codified outcomes		
Composite outcome	0.72	0.40 – 1.29
Surgery	0.99	0.43 – 2.25
Hospitalization	1.32	0.70 – 2.47
Prednisone prescription	0.66	0.36 – 1.20
Normalization of CRP	1.13	0.72 – 1.78

CRP – C-reactive protein

[†]available for 309 CD patients with IFX; 212 CD patients with ADA; 195 UC patients with IFX, 53 UC patients with ADA

[//]Adjusted for interval between first IBD diagnosis code and anti-TNF start date, gender, prior surgery or hospitalization, prior anti-TNF use, and combination immunomodulator therapy. Additionally adjusted for perianal involvement and penetrating phenotype in CD