TREATMENT PATTERNS OF ANTI-TUMOR NECROSIS FACTOR AND ANTI-INTEGRIN THERAPIES IN INFLAMMATORY BOWEL DISEASE (IBD): ANALYSIS OF U.S. INSURANCE CLAIMS

Wayne Pan, MD, PhD, MBA[1]; Jennie H. Best, PhD[1]; Sheila R. Reddy, PhD, RPh[2]; Eunice Chang, PhD[2]; Marian H. Tarbox, MPP[2]; Michael S. Broder, MD, MSHS[2]

[1] US Medical Affairs, Genentech, South San Francisco, CA, United States; [2] Partnership for Health Analytic Research (PHAR), LLC, Beverly Hills, CA, United States

BACKGROUND

- IBD, a chronic disease comprised of Crohn's disease (CD) and ulcerative colitis (UC), affects approximately 1.3% of adults in the U.S.[1]
- Anti-tumor necrosis factor (aTNF) and anti-integrin (al) agents have been effective for some patients with moderate-to-severe symptoms not alleviated by initial therapy[2,3]
- This study objective was to examine real-world treatment patterns of aTNF and al therapies in IBD in the U.S. to identify indications of treatment failures and potential areas for improving treatment outcomes

METHODS

Study design and data source

- Retrospective study using the IQVIA™ Real-World Data Adjudicated Claims – U.S. database from 7/1/11-6/30/16

Patient identification

- Patients (≥18 years) with ≥2 medical claims (inpatient or non-diagnostic outpatient) for UC (ICD-9-CM: 556.x; ICD-10-CM: K51.x) or CD (555.x; K50.x) ≥7 days apart and who initiated aTNF (adalimumab, infliximab, certolizumab, golimumab) or al (vedolizumab) during the identification period (1/1/12-6/30/15)
- Start date of either an aTNF or al in claims was the index date
- Patients followed ≥3 months after index until enrollment or study end, whichever came first (mean follow-up time: 702.3 days (CD) and 679.3 days (UC))
- Additional identification requirements
  - ≥1 qualifying diagnosis of CD or UC occurred within 6 months prior to (baseline period) or on the index date
  - Continuous health plan enrollment during baseline and ≥3 months post-index
  - For CD patients, having <2 claims for UC (or <2 claims for CD for UC patients) during study period
  - No baseline use of index therapy
- Index monotherapy defined by absence of "other" IBD therapies (i.e. aminosalicylates [AS], oral corticosteroids [chronic OCS, i.e., continuous use ≥60 days], or immunosuppressants [IS]) within 30 days after index, while their presence indicated index combination therapy
  - No patients used an aTNF and al agent together at index

Study measures

- Baseline demographic, medication use, and clinical characteristics
- Treatment pattern variables
  - Persistence (continuation) versus discontinuation of index therapy (discontinuation defined by gap in use of ≥60 days)
  - Restart of index therapy after discontinuing treatment
  - Add-on of new therapy to index therapy
  - Switching from index therapy to different IBD treatment
  - UC or CD surgical procedures (e.g., colostomy, ileostomy, enterostomy, small bowel or colorectal resection, lower/other GI therapeutic procedures)

Statistical analysis

- Descriptive statistics were reported for each aTNF or al index therapy
- GRAPHx, a visual tool, was used to examine patterns of medication use for individual patients over time. Colored segments denoted index therapy duration, restarts, add-on/switches (mono) or other changes (combo), and IBD-related surgery
- CD and UC patients were analyzed separately

RESULTS

Baseline characteristics

- We identified 9,805 CD and 4,853 UC patients **(Table 1; Tables 2A/B)**
  - CD patients had mean (SD) age of 39.3 (13.9) years and were 55.2% female vs 41.3 (13.8) years and 46.9% female in UC
  - Comorbid conditions were common, as CD and UC patients in all treatment groups had >2 chronic conditions on average
  - Immunosuppressants, OCS, and aminosalicylates were the most commonly used medications at baseline for CD and UC patients

Treatment patterns

Highlighted treatment patterns, below, focus on adalimumab and infliximab due to their large sample sizes relative to other index treatments

- Monotherapy adalimumab or infliximab was most commonly initiated at index, followed by combinations of these aTNFs with other agents **(Tables 2A/B)**
  - CD: 42.4% patients on adalimumab, 26.0% on infliximab, 15.8% on adalimumab + other, and 8.6% on infliximab + other
  - UC: 29.2% patients on adalimumab, 31.8% on infliximab, 18.4% on adalimumab + other, and 16.5% on infliximab + other
  - Significantly fewer CD and UC patients (0.1% to 5.1%) initiated certolizumab, golimumab, or vedolizumab monotherapy or combination therapy
- Median duration of use was about 8-9 months for CD patients who initiated adalimumab and infliximab, compared to 4-5 months for UC patients who initiated adalimumab or infliximab **(Figure 1)**

Table 1. Patient Identification

Step/Definition	No. of Patients CD	UC
A. No. of patients who had 2+ CD or 2+ UC claims (inpatient or non-diagnostic outpatient claims) ≥7 days apart in the study period (7/1/2011 – 6/30/2016)	154,897 (2+ CD dx)	153,289 (2+ UC dx)
B. Of A, no. of patients without concomitant CD and UC diagnoses in the study period[a]	136,686	135,075
C. Of B, no. of patients who received aTNF (adalimumab, infliximab, certolizumab, golimumab) or al (vedolizumab) in the study period	45,878	16,731
D. Of C, no. of patients who newly start aTNF (adalimumab, infliximab, certolizumab, golimumab) or al (vedolizumab) in ID period (1/1/2012 – 6/30/2015)[b]	24,510	9,379
E. Of D, no. of patients who had qualified diagnosis prior to or on the index date (first aTNF or al in ID period)	21,193	8,466
F. Of E, with age ≥18 years at index date	19,148	8,200
G. Of F, with continuous enrollment 6 months year prior to the index date and first 3 months of follow-up	**9,805**	**4,853**

aTNF: anti-tumor necrosis factor; al: anti-integrin; CD: Crohn's disease; dx: diagnosis; ID: identification; UC: ulcerative colitis.
[a] Concomitant diagnosis = CD patients with 2 or more claims of UC or vice versa.
[b] Patients did not receive aTNF or al during 6 months prior to the index date (6-month wash-out period).

RESULTS (continued)

Table 2A. Patients with CD: Baseline Demographic and Clinical Characteristics, among Initiators of aTNF or al Therapy at Index

	Adalimumab n = 4,159; 42.4%	Adalimumab + 'Other' n = 1,549; 15.8%	Infliximab n = 2,553; 26.0%	Infliximab + 'Other' n = 847; 8.6%	Certolizumab n = 502; 5.1%	Certolizumab + 'Other' n = 164; 1.7%	Golimumab n = 15; 0.2%	Golimumab + 'Other' n = 7; 0.1%	Vedolizumab n = 9; 0.1%	All n = 9,805; 100%
Age, year, mean (SD)	39.6 (13.6)	40.9 (13.7)	37.7 (14.4)	38.7 (14.7)	40.4 (12.9)	42.5 (13.2)	48.1 (12.6)	50.9 (12.9)	34.3 (11.7)	39.3 (13.9)
Female, %	56.0	53.5	53.1	51.1	67.1	61.6	73.3	71.4	77.8	55.2
CCI, mean (SD)	0.9 (1.4)	1.0 (1.5)	0.9 (1.5)	1.0 (1.6)	0.8 (1.4)	1.1 (1.5)	1.4 (1.5)	1.4 (2.0)	1.0 (2.0)	0.9 (1.5)
No. of chronic conditions, mean (SD)	2.8 (1.7)	2.9 (1.8)	2.6 (1.8)	2.7 (1.7)	2.9 (1.8)	3.1 (1.8)	3.7 (1.1)	3.7 (2.1)	2.9 (1.9)	2.7 (1.7)
Baseline Medication Use, %										
Immunosuppressants	27.1	52.9	21.2	58.1	25.7	56.1	40.0	42.9	55.6	32.8
Chronic OCS	26.2	37.6	19.0	39.9	22.5	37.8	26.7	28.6	22.2	27.3
Aminosalicylates	30.7	50.5	23.2	46.4	21.5	36.6	33.3	42.9	0.0	32.8
Antidiarrheal agents	6.1	7.2	4.4	6.7	9.6	7.3	6.7	0.0	0.0	6.1
Antispasmodics	9.1	9.6	6.7	10.6	7.2	6.1	6.7	0.0	11.1	8.5
NSAIDS	9.5	10.3	6.9	8.6	7.4	9.1	40.0	14.3	0.0	8.8
Proton pump inhibitor/H2 blockers	24.0	28.1	21.0	31.3	25.7	29.3	26.7	14.3	33.3	24.7

aTNF: anti-tumor necrosis factor; al: anti-integrin; CCI: Charlson Comorbidity Index; CD: Crohn's disease; 'Other': aminosalicylates (AS), chronic oral corticosteroids (chronic OCS, with chronic defined as continuous use ≥ 60 days), or immunosuppressants (IMS).

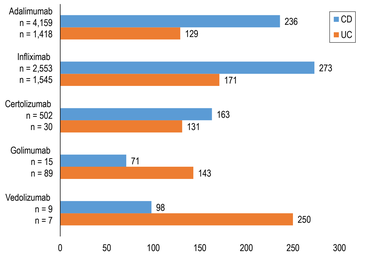
Table 2B. Patients with UC: Baseline Demographic and Clinical Characteristics, among Initiators of aTNF or al Therapy at Index

	Adalimumab n = 1,418; 29.2%	Adalimumab + 'Other' n = 892; 18.4%	Infliximab n = 1,545; 31.8%	Infliximab + 'Other' n = 803; 16.5%	Certolizumab n = 30; 0.6%	Certolizumab + 'Other' n = 18; 0.4%	Golimumab n = 89; 1.8%	Golimumab + 'Other' n = 51; 1.1%	Vedolizumab n = 7; 0.1%	All n = 4,853; 100.0%
Age, year, mean (SD)	41.3 (13.2)	42.6 (13.2)	40.4 (14.3)	41.3 (14.1)	45.8 (13.1)	38.8 (13.7)	41.1 (14.7)	40.0 (15.1)	39.7 (17.8)	41.3 (13.8)
Female, %	49.6	43.5	48.3	43.6	60.0	72.2	40.4	33.3	71.4	46.9
CCI, mean (SD)	1.2 (1.5)	1.3 (1.7)	1.5 (1.7)	1.6 (1.7)	1.2 (1.3)	1.1 (1.5)	1.3 (1.7)	1.3 (1.8)	1.9 (1.5)	1.4 (1.7)
No. of chronic conditions, mean (SD)	2.6 (1.6)	2.7 (1.7)	2.6 (1.7)	2.7 (1.7)	3.4 (1.9)	2.5 (1.6)	2.7 (1.7)	2.7 (1.8)	4.3 (1.8)	2.7 (1.7)
Baseline Medication Use, %										
Immunosuppressants	31.7	43.7	27.9	49.6	30.0	50.0	32.6	43.1	28.6	35.9
Chronic OCS	39.3	47.4	36.6	51.8	33.3	66.7	46.1	60.8	42.9	42.4
Aminosalicylates	66.8	84.1	57.4	81.3	43.3	55.6	66.3	86.3	42.9	69.4
Antidiarrheal agents	6.2	7.4	5.2	6.6	10.0	11.1	6.7	7.8	14.3	6.2
Antispasmodics	9.7	10.7	10.4	12.6	3.3	5.6	4.5	5.9	0.0	10.4
NSAIDS	11.1	10.7	5.8	7.3	23.3	11.1	4.5	5.9	28.6	8.6
Proton pump inhibitor/H2 blockers	19.6	23.5	18.7	26.0	13.3	33.3	22.5	15.7	28.6	21.1

aTNF: anti-tumor necrosis factor; al: anti-integrin; CCI: Charlson Comorbidity Index; 'Other': aminosalicylates (AS), chronic oral corticosteroids (chronic OCS, with chronic defined as continuous use ≥ 60 days), or immunosuppressants (IMS); UC: ulcerative colitis.

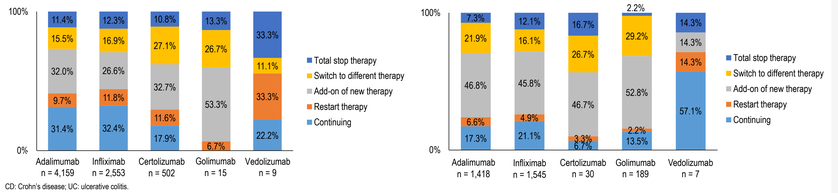
- Approximately 30% of CD patients and 20% of UC patients continued their index monotherapy with an aTNF **(Figures 2 and 3)**
- More than 40% of CD patients initiating aTNF monotherapy added new therapy or switched to a different therapy (i.e., signs of treatment failure; **Figure 2)**
  - 32.0% of adalimumab users added new therapy; 15.5% switched to different therapy
  - 26.6% of infliximab added new therapy; 16.9% switched to different therapy
- More than 60% of UC patients initiating aTNF monotherapy added new therapy or switched to a different therapy, again, signaling unsuccessful treatment **(Figure 2)**
  - 46.8% of adalimumab users added new therapy; 21.9% switched to different therapy
  - 45.8% of infliximab users added new therapy; 16.1% switched to different therapy
- In nearly all cases (98-100%), the add-on therapy was an AS, chronic OCS, or IS; the next-line agents following a switch presented in **Figure 3**

Figure 1. Median Days on Index Treatment during Follow-Up, among Initiators of aTNF or al Monotherapy at Index



CD: Crohn's disease; UC: ulcerative colitis.

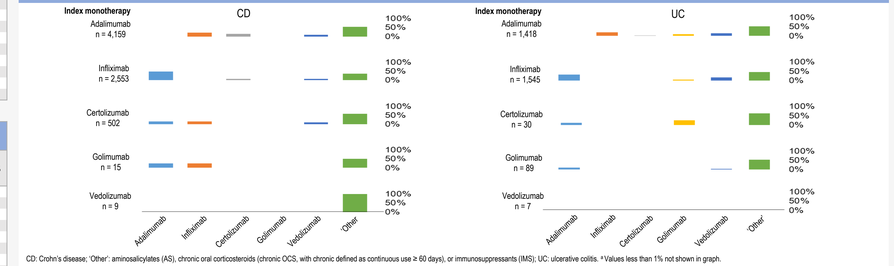
Figure 2. Treatment Changes, among Initiators of aTNF or al Monotherapy at Index



CD: Crohn's disease; UC: ulcerative colitis.

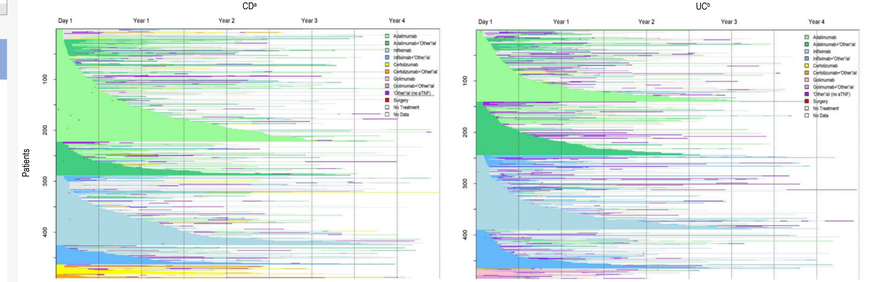
- Restarts of index therapy after a gap occurred in 10-12% of CD and 5-7% of UC patients initiating adalimumab or infliximab monotherapy **(Figure 2)**
- About 11-12% of CD and 7-12% of UC patients stopped adalimumab or infliximab monotherapy and remained off therapy until the end of follow-up **(Figure 2)**
- IBD-related surgery occurred in <8% of patients, mainly during index treatment among CD patients and after in UC patients (tabular result not shown)
- Graphical analysis (**Figures 4A/B**) showed patterns consistent with those described above

Figure 3. Next Line of Treatment following a Switch, among Initiators of aTNF or al Monotherapy at Index[a]



CD: Crohn's disease; 'Other': aminosalicylates (AS), chronic oral corticosteroids (chronic OCS, with chronic defined as continuous use ≥ 60 days), or immunosuppressants (IMS); UC: ulcerative colitis. [a] Values less than 1% not shown in graph.

Figure 4. Treatment and Surgery Patterns, among Initiators of aTNF Therapy at Index[a]



aTNF: anti-tumor necrosis factor; al: anti-integrin (i.e., vedolizumab); CD: Crohn's disease; UC: ulcerative colitis; 'Other'al indicates the presence of an AS, chronic OCS, IS, or al.
Note: no patients used an aTNF and al together at index, although we observed a few examples (≤2%) of this combined use as an add-on therapy. [a] Initiators of al therapy at index not shown due to small sizes. [b] N = 490; 5% of overall sample. [c] N = 485; 10% of overall sample.

LIMITATIONS

- Our study findings on aTNF and al treatment patterns in the US and may not be generalizable to uninsured individuals with CD or UC, to those with other types of insurance, or to patients in other countries

CONCLUSIONS

- Treatment patterns varied by therapy type and IBD group
- Adalimumab and infliximab monotherapies, followed by their combination therapies, were most frequently used to treat CD and UC
  - Vedolizumab was rarely used, likely due to its late approval date
- Surgery occurred at similar rates, albeit different timing, among CD and UC patients
- Many patients who initiated aTNF therapy had a relatively short duration of this treatment due to the need for switching or adding new therapies, either of which signals treatment failure; this was observed for 46.9% and 65.6% of patients with CD and UC, respectively, underscoring the continued unmet medical need in the moderate-to-severe IBD population

REFERENCES

1. Dahlhamer JM et al. MMWR Morb Mortal Wkly Rep. 2016;65:1166-69. Doi: http://dx.doi.org/10.15585/mmwr.mm6542a3. 2. McAuliffe ME et al. Curr Med Res Opin. 2015.31(9):1655-64. 3. Lichtenstein GR et al. Am J Gastroenterol. 2009;104(2):465-83.

Disclosure statement: W. Pan was and J. Best is an employee of Genentech. S. R. Reddy, E. Chang, M. H. Tarbox, and M. S. Broder are employees of Partnership for Health Analytic Research, LLC.

This study was sponsored by Genentech, Inc. Research was conducted by Partnership for Health Analytic Research, LLC.