# EVALUATION OF TREATMENT PATTERNS AMONG CROHN'S DISEASE PATIENTS INITIATING BIOLOGICS WITH THREE YEARS OF FOLLOW-UP

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## BACKGROUND

Crohn's disease (CD) is a chronic inflammatory disease of the gastrointestinal tract, which is associated with high healthcare resource utilization, and high healthcare costs resulting in estimated direct medical costs of $3.48 billion in the United States in 2016.[1,2]

Many new biologic therapies have been recently approved for CD. However, there is limited real-world evidence on treatment patterns, and dose titration among CD patients using biologics with 3 years of follow-up post-initiation of index biologics.

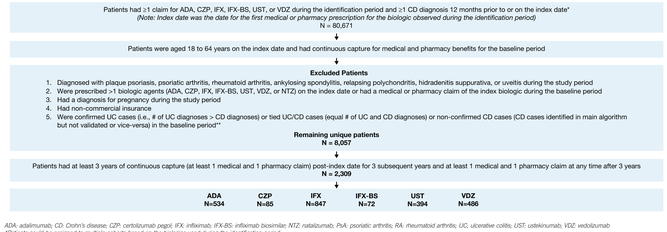
## OBJECTIVE

**This descriptive study examined biologic treatment patterns among Crohn's Disease (CD) patients initiating biologics with 3 years of follow-up. We examined the CD patients treated with adalimumab (ADA), certolizumab pegol (CZP), infliximab (IFX) and its biosimilar products (IFX-BS), ustekinumab (UST), and vedolizumab (VDZ).**

## METHODS

- Databases: The study used an all-payer claims database (APCD), which provides insight to approximately 80% of the US healthcare system.
- Study Period: SEP 26, 2015 - OCT 31, 2021
- Identification Period: SEP 26, 2016 – OCT 31, 2018
- Index Date: Index date was defined as the first claim date for ADA, CZP, IFX, IFX-biosimilar, UST, or VDZ among adult patients with ≥1 CD medical claim and ≥1 medical/pharmacy claim for the study biologic agents during the identification period.
- Study Cohorts: Using a claims-based algorithm, confirmed CD patients (number of CD diagnoses claims > number of ulcerative colitis (UC) diagnoses claims) were included in the final cohorts. Patients could be assigned to multiple cohorts if they used more than one biologic during the identification period, so study cohorts were not mutually exclusive. CZP was excluded from further analysis due to small sample size.
- Baseline Period: 1-year prior to the index date
- Follow-up Period: 3-year post the index date
- Only commercially enrolled adult CD patients who had continuous capture during the baseline and at least 3 years of follow-up period were included. The 3-year of continuous capture during the follow-up period was defined as having ≥1 medical and ≥1 pharmacy claims for every year for 3 years post-index and at any time post the 3-year period.

**Figure 1. Patient Selection Criteria**




*ADA: adalimumab; CD: Crohn's disease, CZP: certolizumab pegol; IFX: infliximab; IFX-BS: infliximab biosimilar, NTZ: natalizumab; PsA: psoriatic arthritis; RA: rheumatoid arthritis; UC: ulcerative colitis; UST: ustekinumab; VDZ: vedolizumab*
**Patients could be assigned to multiple cohorts based on the biologics used during the identification period*
***A modified algorithm based on the Manitoba study by Bernstein et al. was used to define confirmed UC, tied UC/CD cases or non-confirmed CD case.[3,4]*

### Baseline and outcome variables

- Baseline variables: age, sex, US geographic region, Charlson comorbidity index (CCI) score, and baseline comorbidities.
- Outcome variables: The following outcomes were examined during the follow-up period.
  1. **Persistence:** Proportion of patients who remained on the index biologic without a gap of >60 days for ADA and >120 days for IFX, UST, and VDZ (gapped days were approximately two times of the United States Food and Drug Administration [FDA] labeled maintenance dosing interval) between the run-out date of two consecutive biologic claims were considered persistent to their index biologic.
  2. **Switch:** Patients who were administered a non-index biologic during follow-up.
  3. **Restart:** Patients who restarted their index biologic (after the gap of >60 days for ADA and >120 days for IFX, UST, and VDZ) during follow-up.
  4. **Discontinuation:** Patients who were not persistent to their index biologic were classified as discontinuers.
     - **Discontinuation without restart/switch**: Patients who were not administered/prescribed any biologics after the discontinuation date (defined as the run-out date of the last index medication claim or the switch date, whichever occurred first) without any restart or switch until the end of follow-up.
  5. **Dose titration:** Titration of maintenance dose was assessed among patients with ≥2 maintenance doses of same benefit type. The first instance of unit change in dose with respect to initial dose is defined as the dose titration. A decrease of ≤50%, or >50% from the starting average dose was defined as dose reduction. An increase of ≤50%, 51-100%, or of >100% from the starting average dose was defined as dose escalation.

### Statistical Analysis

- Descriptive analyses were conducted for the eligible CD patient population. Means and standard deviations were computed for continuous variables, and frequency and percentages were generated for categorical variables. CZP and IFX-BS patients were not included in the analyses because of small sample size. Treatment patterns including persistence and dose titration were summarized using descriptive statistics across cohort groups. No comparative analyses were done between the products.

## CONCLUSION

**During the 3 years of follow-up, unadjusted persistence was highest in the UST cohort. In addition, the UST cohort had the numerically lowest proportion of patients with dose titration but the numerically highest proportion of patients with dose-reduction. The IFX cohort had the numerically highest proportion of patients with >100% dose escalation and UST had the lowest.**

## RESULTS

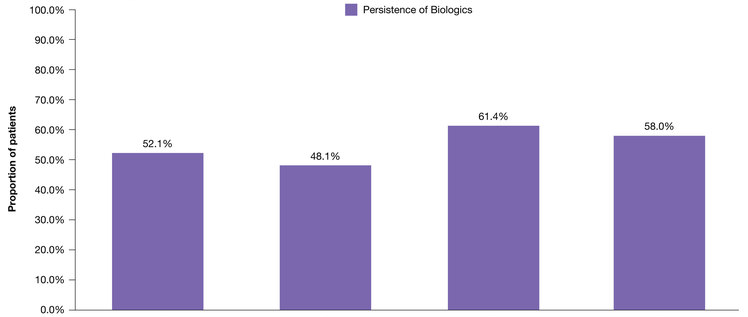
- A total of 2,309 CD patients were identified for the study, of which 534 [23.1%] were treated with ADA, 85 [3.7%] with CZP, 847 [36.7%] with IFX, 72 [3.1%] with IFX-BS, 394 [17.1%] with UST, and 486 [21.1%] with VDZ.
- Patients on UST and VDZ were slightly older and had slightly higher CCI score (**Table 1**).
- Common comorbidities among CD patients included anemia, hypertension, anxiety, depression, fatigue, obesity, and hyperlipidemia (**Table 1**).

**Table 1. Descriptive Baseline Characteristics Among Crohn's Disease Patients**

| Characteristics | ADA (N=534) | IFX (N=847) | UST (N=394) | VDZ (N=486) |
|---|---|---|---|---|
| **Age in years, mean** | 43.5 | 43.7 | 44.0 | 45.3 |
| **Age group, years** | | | | |
| 18-34 | 24.0% | 26.4% | 25.6% | 20.0% |
| 35-54 | 52.4% | 47.2% | 48.5% | 52.3% |
| 55-64 | 23.6% | 26.3% | 25.9% | 27.8% |
| **Sex** | | | | |
| Male | 45.7% | 42.0% | 46.7% | 43.6% |
| Female | 54.3% | 58.0% | 53.3% | 56.4% |
| **US geographic region** | | | | |
| Northeast | 14.0% | 19.0% | 17.5% | 19.5% |
| North Central | 33.1% | 33.1% | 37.3% | 35.2% |
| South | 37.6% | 30.7% | 30.5% | 31.5% |
| West | 15.2% | 17.2% | 14.7% | 13.8% |
| **Index Year** | | | | |
| 2016 | 14.2% | 13.2% | 7.9% | 13.4% |
| 2017 | 56.7% | 55.1% | 53.0% | 51.4% |
| 2018 | 29.0% | 31.6% | 39.1% | 35.2% |
| **Charlson Comorbidity Index Score** | 0.5 | 0.5 | 0.7 | 0.6 |
| **Comorbidities** | | | | |
| Anemia | 17.4% | 16.9% | 30.2% | 21.0% |
| Anxiety | 14.0% | 12.8% | 19.8% | 17.5% |
| Atherosclerosis | 0.2% | 0.5% | 0.5% | 0.0% |
| Celiac Disease | 1.1% | 2.1% | 6.1% | 2.9% |
| Cholelithiasis | 0.6% | 0.0% | 0.3% | 0.2% |
| Chronic pain | 5.8% | 4.7% | 8.9% | 8.2% |
| Depression | 14.2% | 12.4% | 18.3% | 17.3% |
| Diabetes | 6.2% | 6.3% | 7.4% | 7.2% |
| Fatigue | 7.7% | 8.6% | 14.2% | 11.3% |
| Fistula | 3.4% | 6.7% | 6.3% | 6.0% |
| Hyperlipidemia | 9.2% | 9.3% | 9.6% | 10.7% |
| Hypertension | 18.9% | 15.7% | 20.3% | 17.5% |
| Obesity | 10.1% | 9.4% | 11.7% | 9.9% |
| Venous Thromboembolism | 0.7% | 1.5% | 2.8% | 1.6% |

*Due to rounding of the percentages, some of the categorical variables might not add up to a 100%*
*ADA: adalimumab; IFX: infliximab; UST: ustekinumab; VDZ: vedolizumab*

**Figure 2. Persistence among Crohn's Disease Patients using Biologics with 3 Years of Follow-Up**




| | ADA | IFX | UST | VDZ |
|---|---|---|---|---|
| **Sample Size** | **534** | **847** | **394** | **486** |
| **Switchers** | 142 (26.6%) | 279 (32.9%) | 74 (18.8%) | 119 (24.5%) |
| **Restarters** | 130 (24.3%) | 206 (24.3%) | 89 (22.6%) | 105 (21.6%) |
| **Overall Discontinuation** | 256 (47.9%) | 440 (52%) | 152 (38.6%) | 204 (42%) |
| **Discontinuation without restart/switch** | 199 (37.3%) | 238 (28.1%) | 121 (30.7%) | 123 (25.3%) |

*A variable discontinuation gap of > 60 days for ADA and >120 days for IFX, UST, and VDZ between the run-out date of two consecutive biologic claims (gap approximately two times the maintenance dosing interval) was used to define the discontinuation*
*ADA: adalimumab; IFX: infliximab; UST: ustekinumab; VDZ: vedolizumab*
*Note:*
**For NDC codes, day-supply is the equivalent of day of supply. For HCPCS codes, it is the 'expected injection coverage' as recommended by FDA. It is 14 days for ADA, 28 days for CZP, and 56 days for IFX, IFX biosimilar, UST, and VDZ.*
**The presented % are based on the sample size of each index biologic.*

- Persistence over 3 years follow up was highest numerically for UST [61.4%] patients, followed by VDZ [58.0%], ADA [52.1%], and IFX [48.1%] (**Figure 2**).
- The unadjusted overall discontinuation rate was highest numerically for IFX [52.0%] followed by ADA [47.9%], VDZ [42.0%] and UST [38.6%] (**Figure 2**).
- The discontinuation rate without switch or restart was highest numerically for ADA [37.3%], followed by UST [30.7%], IFX [28.1%], and VDZ [25.3%] (**Figure 2**).

**Table 2. Dose Titration among Crohn's Disease Patients using Biologics with 3 Years of Follow-Up**

| Biologics | % |
|---|---|
| **ADA Sample Size (N=534)** | |
| **Eligible Cases** | **68.7*** |
| Dose Reduction | 5.2 |
| ≤50% Dose Reduction | 3.8 |
| >50% Dose Reduction | 1.4 |
| Dose Escalation | 47.4 |
| ≤50% Dose Escalation | 3.0 |
| 51-100% Dose Escalation | 32.2 |
| >100% Dose Escalation | 12.3 |
| **IFX Sample Size (N=847)** | |
| **Eligible Cases** | **76.5*** |
| Dose Reduction | 11.4 |
| ≤50% Dose Reduction | 6.6 |
| >50% Dose Reduction | 4.8 |
| Dose Escalation | 65.9 |
| ≤50% Dose Escalation | 8.3 |
| 51-100% Dose Escalation | 16.5 |
| >100% Dose Escalation | 41.1 |
| **UST Sample Size (N=394)** | |
| **Eligible Cases** | **50.8*** |
| Dose Reduction | 16.5 |
| ≤50% Dose Reduction | 16.0 |
| >50% Dose Reduction | 0.5 |
| Dose Escalation | 35.5 |
| ≤50% Dose Escalation | 13.0 |
| 51-100% Dose Escalation | 14.0 |
| >100% Dose Escalation | 8.5 |
| **VDZ Sample Size (N=486)** | |
| **Eligible Cases** | **74.5*** |
| Dose Reduction | 14.6 |
| ≤50% Dose Reduction | 8.8 |
| >50% Dose Reduction | 5.8 |
| Dose Escalation | 53.3 |
| ≤50% Dose Escalation | 3.9 |
| 51-100% Dose Escalation | 23.2 |
| >100% Dose Escalation | 26.2 |

*ADA: adalimumab; IFX: infliximab; UST: ustekinumab; VDZ: vedolizumab*
**Provided % are of eligible cases with respect to biologic sample size. Other provided % are with respect to eligible cases*

- Over the 3 years of follow-up, the proportion of patients with dose titration was highest for IFX (76.5%) and VDZ (74.5%) and lowest for UST (50.8%) (**Table 2**).
- The highest cases of dose reduction were observed in patients with UST (16.5%) (**Table 2**).
- The highest cases of dose escalation were observed in patients with IFX (65.9%) followed by VDZ (53.3%) (**Table 2**).
- The highest cases of >100% of dose escalation were observed in patients with IFX (41.1%) and lowest in patients with UST (8.5%) (**Table 2**).

### Limitations

- Due to small sample size for the bio-experienced group, the study could not stratify the results across bio-naïve and bio-experienced patients. This stratification is important to understand the inherent variability between patients in each group. Compared to the bio-naïve group, the bio-experienced patients have an inherent bias introduced from prior biologic treatment exposure and potential non-response or failure that leads to initiation of a new biologic therapy. This needs to be explored in future studies using larger data on these patients, especially in the bio-experienced group.
- Analysis of claims data depends on correct diagnosis, procedure, and drug codes. Coding errors can result in misclassification.
- There are limitations about the operational definitions of various variables. 1) Dose escalation is based on change in units between claims from the same beneficiaries and does not look at exact formulation type. However, it avoids the process of making assumptions regarding doses for HCPCS codes 2) Discontinuation and treatment switch could be due to other reasons such as: insurance coverage, adverse events, or other reasons not related to loss of response.
- There would be potential under-capture of biologics use with claims data, which is primarily used for billing and not research purposes. Furthermore, medications received over the counter or provided as samples by the physician are not observed in claims data.

### References

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### Disclosures

Ruizhi Zhao, Zhijie Ding, and Sumesh Kachroo are employees of Janssen Scientific Affairs, LLC, and Johnson & Johnson. Parul Gupta, Laurence Gozalo, Robert Bruette, Victor M Johnson, and Keshia Maughn are employees of STATinMED, LLC and supported this study as a paid consultant to Janssen Scientific Affairs.
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