# Factors Associated with Biologic Discontinuation in Patients with Inflammatory Bowel Disease in TARGET-IBD

#P027

Edward L. Barnes, MD, MPH[1], Harris Ahmad, MD[2], Joe Zhuo, PhD[2], Antoine G. Sreih, MD[2], James B. Canavan, MD, PhD[2], Joehl Nguyen, MPH[3], Derek Gazis, MS[4], Janet S. Hildebrand, MPH[4], Julie M. Crawford, MD[4], Millie D. Long, MD, MPH[1], John S. Hanson, MD[5]

[1]Division of Gastroenterology and Hepatology, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA; [2]Bristol Myers Squibb, Princeton, NJ, USA; [3]Division of Pharmaceutical Outcomes and Policy, Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA; [4]Target RWE Health Evidence Solutions, Durham, NC, USA; [5]Atrium Health Gastroenterology and Hepatology, Charlotte, NC, USA

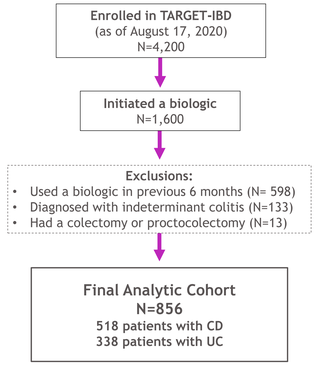
## Background

- A substantial portion of patients who initiate biologic therapy for the treatment of Crohn's disease (CD) and ulcerative colitis (UC) discontinue therapy within 6-12 months of induction.
- To better understand patterns of treatment discontinuation in the real-world management of patients with inflammatory bowel disease (IBD), we identified factors associated with treatment discontinuation among patients enrolled in TARGET-IBD, an observational registry of patients with IBD.

## Methods

- Patients receiving care in 34 community and academic practices in the US were enrolled in TARGET-IBD, a longitudinal cohort study of IBD patients, begun in 2017.
- Participants starting a biologic (anti-TNF, anti-integrin, or anti IL-12/23) who had no biologic use in the previous 6 months were eligible for analysis.
- The primary outcome was biologic treatment discontinuation.
- Kaplan-Meier methods and multivariable Cox proportional hazards regression were used to estimate time (days) to treatment discontinuation.
- Patients who died, had total colectomy or proctocolectomy, or who were lost to follow-up, were censored.

**Figure 1. Flow Diagram of Adult Participants in TARGET-IBD, Who Were Eligible for Analysis of Biologic Treatment Discontinuation**




## Results

**Table 1. Descriptive Characteristics by Disease Type**

| | Crohn's Disease (n=518) | Ulcerative Colitis (n=338) | All participants (N=856) | *P-value*[1] |
|---|---|---|---|---|
| **Drug class**[2], n (%) | | | | |
| anti-TNF (Adalimumab, Infliximab, other) | 357 (69.0%) | 244 (72.2%) | 601 (70.2%) | |
| anti-integrin (Vedolizumab) | 81 (15.6%) | 92 (27.2%) | 173 (20.2%) | *<0.001* |
| anti IL-12/23 (Ustekinumab) | 80 (15.4%) | 2 (0.6%) | 82 (9.6%) | |
| **Site type, n (%)** | | | | |
| Academic | 390 (75.3%) | 224 (66.3%) | 614 (71.7%) | *0.004* |
| Community | 128 (24.7%) | 114 (33.7%) | 242 (28.3%) | |
| **Sex, n (%)** | | | | |
| Female | 294 (56.8%) | 178 (52.7%) | 472 (55.1%) | *0.24* |
| Male | 224 (43.2%) | 160 (47.3%) | 384 (44.9%) | |
| **Race, n (%)** | | | | |
| White | 446 (87.8%) | 284 (88.5%) | 730 (88.1%) | |
| Black | 36 (7.1%) | 25 (7.8%) | 61 (7.4%) | *0.62* |
| Other / Unknown | 36 (5.1%) | 29 (3.7%) | 65 (4.5%) | |
| **Insurance type at enrollment**[3] | | | | |
| Private | 399 (77.0%) | 271 (80.2%) | 670 (78.3%) | |
| Medicare | 71 (13.7%) | 38 (11.2%) | 109 (12.7%) | – |
| Medicaid | 48 (9.3%) | 24 (7.1%) | 72 (8.4%) | |
| Supplemental/Other/Uninsured/Unknown | 38 (0.1%) | 26 (3.0%) | 64 (2.9%) | |
| **Age of onset of disease, n (%)** | | | | |
| <= 30 years | 276 (56.6%) | 165 (52.1%) | 441 (54.8%) | |
| > 30 years | 212 (43.4%) | 152 (47.9%) | 364 (45.2%) | *0.21* |
| Unknown | 30 | 21 | 51 | |
| **BMI (kg/m$^2$)** | | | | |
| Median | 25 | 27 | 26 | |
| Q1 - Q3 (IQR) | 22 - 30 (8) | 23 - 32 (9) | 22 - 30 (8) | *0.003* |
| Min - Max | 15 - 72 | 16 - 60 | 15 - 72 | |
| **Age at therapy start (years)** | | | | |
| Median (n) | 40 (518) | 37 (338) | 39 (856) | |
| Q1 - Q3 (IQR) | 29 - 54 (25) | 28 - 58 (30) | 29 - 55 (27) | *0.75* |
| Min - Max | 18 - 81 | 18 - 82 | 18 - 82 | |
| **Duration of disease at therapy start** | | | | |
| Median years | 5 | 4 | 5 | |
| Q1 - Q3 (IQR) | 1 - 16 (15) | 1 - 11 (10) | 1 - 13 (12) | *0.006* |
| Min - Max | 0 - 57 | 0 - 46 | 0 - 57 | |
| **Previous biologic exposure** | | | | |
| No | 382 (73.7%) | 311 (92.0%) | 693 (81.0%) | *<0.001* |
| Yes | 136 (26.3%) | 27 (8.0%) | 163 (19.0%) | |
| **Concomitant steroid use at therapy start** | 200 (38.6%) | 185 (54.7%) | 385 (45.0%) | *<0.001* |
| **Concomitant methotrexate/thiopurine use** | 121 (23.4%) | 68 (20.1%) | 189 (22.1%) | *0.26* |
| **History of IBD surgery** | 170 (32.8%) | 12 (3.6%) | 182 (21.3%) | *<0.001* |
| **History of fistula** | 83 (16.0%) | 5 (1.5%) | 88 (10.3%) | *<0.001* |
| **C-Reactive Protein, n (%)**[4] | | | | |
| < 5 mg/dL | 77 (57.0%) | 57 (60.6%) | 134 (58.5%) | |
| >= 5 mg/dL | 58 (43.0%) | 37 (39.4%) | 95 (41.5%) | *0.53* |
| Missing | 383 | 244 | 627 | |
| **Anatomical Location (CD)** | | | | |
| Colonic | 97 (19.8%) | | | |
| Ileocolonic | 240 (49.1%) | | | |
| Ileal | 152 (31.1%) | | | |
| Missing | 29 | | | |
| **Type / Stage (CD)** | | | | |
| Inflammatory (B1) | 251 (48.5%) | | | |
| Stricturing (B2) | 126 (24.3%) | | | |
| Penetrating/Fistulizing (B3) | 136 (26.3%) | | | |
| Inactive | 5 (1.0%) | | | |
| **Anatomical Location (UC)** | | | | |
| Extensive | | 189 (60.4%) | | |
| Left-Sided | | 111 (35.5%) | | |
| Proctitis | | 13 (4.2%) | | |
| Missing | | 25 | | |

[1]P-values are from general association tests for differences by disease type.
[2]Based on earliest initiation of biologic therapy with no biologic use in the previous 6 months.
[3]Patients may have >1 insurance policy, therefore categories are not exclusive.
[4]CRP based on most recent value within 1 month prior to therapy start.

**Table 2. Previous Biologic Exposure according to Current Drug Class**

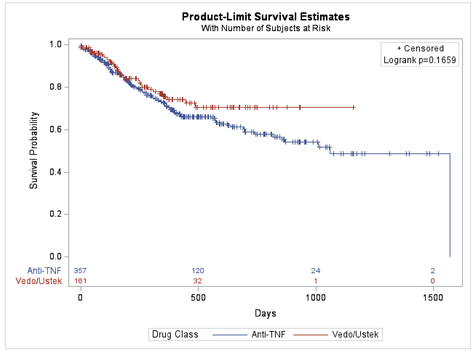
| | Current Biologic | | | | | |
|---|---|---|---|---|---|---|
| | Crohn's Disease | | | Ulcerative Colitis | | |
| | Anti-TNF (n=357) | Anti-Integrin (n=81) | Anti IL-12/23 (n=80) | Anti-TNF (n=244) | Anti-Integrin (n=92) | Anti IL12/23 (n=2) |
| **Previous biologic use, n (%)** | | | | | | |
| No | 300 (84.0%) | 48 (59.3%) | 34 (42.5%) | 231 (94.7%) | 78 (84.8%) | 2 (100.0%) |
| Yes | 57 (16.0%) | 33 (40.7%) | 46 (57.5%) | 13 (5.3%) | 14 (15.2%) | 0 (0.0%) |
| **Previous biologic(s)**[1] | | | | | | |
| n | 57 | 33 | 46 | 13 | 14 | 0 |
| Anti-TNF | 56 (98.2%) | 32 (97.0%) | 45 (97.8%) | 11 (84.6%) | 14 (100.0%) | NA |
| Anti-Integrin | 5 (8.8%) | 8 (24.2%) | 13 (28.3%) | 5 (38.5%) | 1 (7.1%) | NA |
| Anti IL-12/23 | 2 (3.5%) | 3 (9.1%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | NA |

[1]Participants may have been on multiple previous biologics.

## Results Continued

**Figure 2. Kaplan-Meier Survival Curves**

A. Time to Biologic Discontinuation – Crohn's Disease




B. Time to Biologic Discontinuation – Ulcerative Colitis

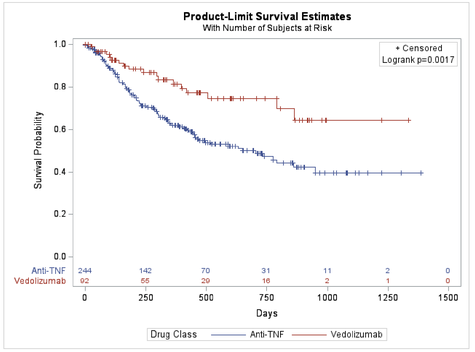
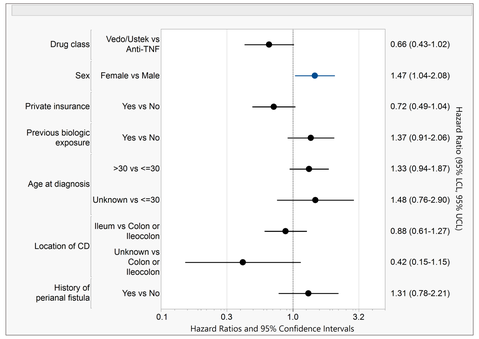
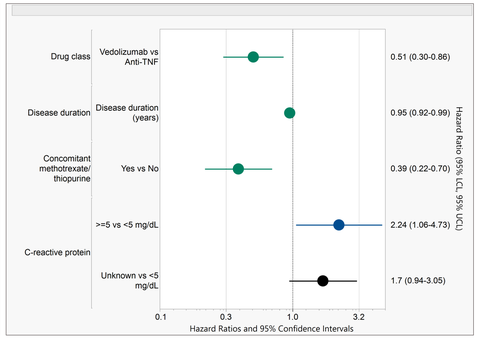



**Figure 3. Multivariable Cox Proportional Hazards Regression Models**

A. Associations[1] of Risk Factors for Biologic Discontinuation – Crohn's Disease




B. Associations[1] of Risk Factors for Biologic Discontinuation – Ulcerative Colitis




[1]Hazard ratios mutually adjusted for all other variables in the model

**Table 3. Reasons for Discontinuation of Biologic Therapy**

| | Crohn's Disease (n=518) | Ulcerative Colitis (n=338) | All Participants (N=856) |
|---|---|---|---|
| **Biologic discontinuation, n (%)** | | | |
| No | 371 (71.6%) | 217 (64.2%) | 588 (68.7%) |
| Yes | 147 (28.4%) | 121 (35.8%) | 268 (31.3%) |
| **Reason(s) for discontinuation**[1] | | | |
| n | 147 | 121 | 268 |
| Antibodies developed | 18 (12.2%) | 9 (7.4%) | 27 (10.1%) |
| Side effects of therapy | 36 (24.5%) | 25 (20.7%) | 61 (22.8%) |
| Primary non-response/lack of efficacy | 29 (19.7%) | 26 (21.5%) | 55 (20.5%) |
| Secondary non-response/lack of efficacy | 32 (21.8%) | 50 (41.3%) | 82 (30.6%) |
| Other | 32 (21.8%) | 20 (16.5%) | 52 (19.4%) |
| Unknown | 15 (10.2%) | 10 (8.3%) | 25 (9.3%) |

[1]Participants may have >1 reason for discontinuing.

## Summary of Main Findings

- In this cohort of IBD patients initiating biologic therapy, nearly 1/3 discontinued that therapy during the course of observation (mean time to discontinuation or censoring = 383 days).
- The most common reasons for treatment discontinuation were: secondary loss of response, side effects, and primary non-response.
- If the number of patients with anti-drug antibodies is added, the magnitude of secondary loss of response is even greater.
- In this study, the durability of vedolizumab/ustekinumab appears to be greater than anti-TNF agents.

## Conclusions

- The durability of biologic treatment remains a significant issue in IBD management.
- Strategies to mitigate both primary non-response and, especially, secondary loss of response need to be explored among patients with IBD.
- Future research should explore potential strategies to improve durability such as therapeutic drug monitoring and genetic variants leading to differential response.
- The durability of vedolizumab or ustekinumab seen in this study may have implications for "sequencing" of biologic therapy.

### Acknowledgments

- TARGET-IBD is a collaboration among academic and community investigators and the pharmaceutical industry. We thank the study staff, nurses, health care providers, and participants at each study center for their contributions to this work. Target RWE is the sponsor of TARGET-IBD and is solely responsible for its content. TARGET-IBD is supported in part by funding from AbbVie, Inc. and Bristol Myers Squibb.
- Author Disclosures:
  - Edward L. Barnes: consultant for AbbVie, Takeda, Gilead, Pfizer, Target RWE
  - John S. Hanson: Pfizer- Speakers' Bureau, AbbVie- Speakers' Bureau, BMS- Advisory Board, Target RWE- Advisor on TARGET-IBD Steering Committee
  - James Canavan: Employee and shareholder of Bristol Myers Squibb
  - Antoine Sreih: Employee and shareholder of Bristol Myers Squibb
  - Joe Zhuo: Employee and shareholder of Bristol Myers Squibb
  - Harris Ahmad: Employee and shareholder of Bristol Myers Squibb
  - Joehl Nguyen: Consultant for Bristol Myers Squibb
  - Derek Gazis, Janet S. Hildebrand, Julie M. Crawford: Employees of Target RWE
  - Millie D. Long: Consulting fees from AbbVie, Pfizer, Janssen, Takeda, Prometheus, Salix, UCB, Target RWE; Research support from Takeda and Pfizer

Presented at the Advances in Inflammatory Bowel Diseases (AIBD) Conference, December 2020, Virtual Event

Email: Edward_Barnes@med.unc.edu