PERSISTENCE AMONG PATIENTS WITH CROHN'S DISEASE PREVIOUSLY TREATED WITH AN ANTI-TUMOR NECROSIS FACTOR INHIBITOR AND SWITCHING OR CYCLING TO ANOTHER BIOLOGIC AGENT

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BACKGROUND

Persistence on a biologic in Crohn's disease (CD) could be interpreted as an indicator of treatment effectiveness, tolerability, and safety in a real-world setting[1,2]

About a third of patients do not respond to a first-line anti-TNF treatment,[3,4] and may either cycle to another anti-TNF (i.e., adalimumab, infliximab, certolizumab) or switch to biologics with a different mechanism of action (i.e., ustekinumab, vedolizumab)

There is limited real-world information on biologic persistence and other treatment patterns of patients with CD who switch or cycle following the discontinuation of a first-line anti-TNF

OBJECTIVE

To describe and compare treatment persistence of patients with CD previously treated with anti-TNF who cycled to another anti-TNF vs switched to another class of biologics

METHODS

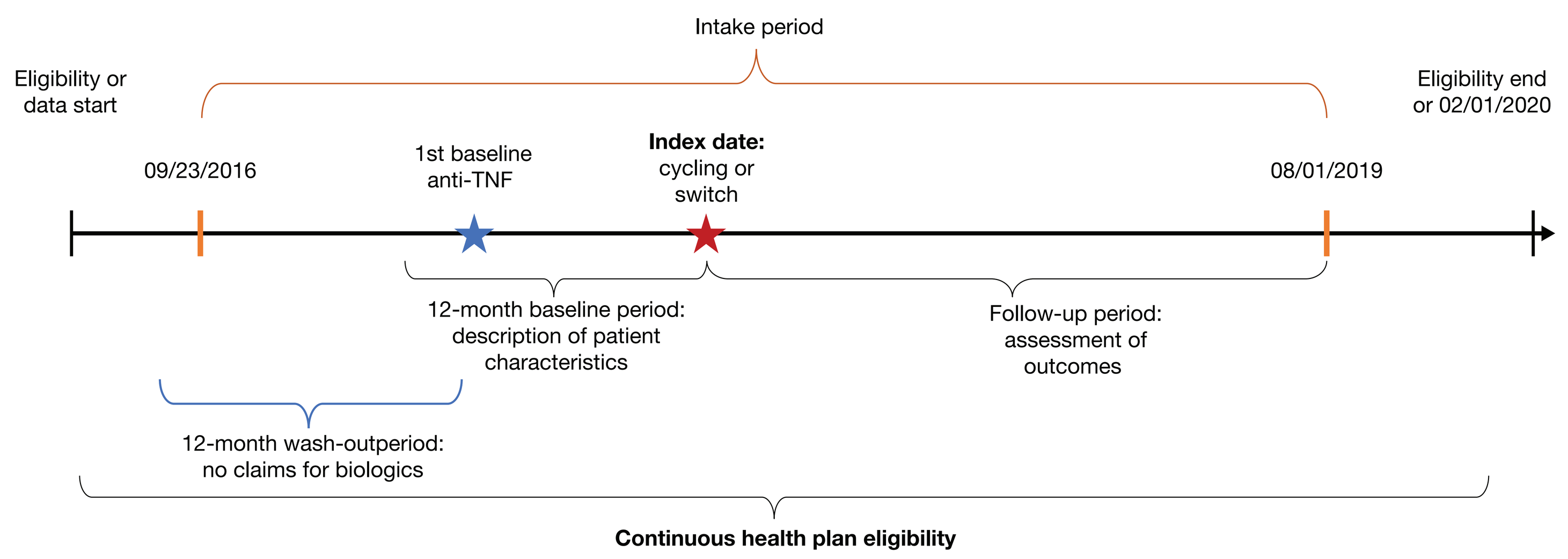
Data Source

- IBM MarketScan Commercial Database was used
- Data includes demographics, health plan enrollment, and fully adjudicated claims for inpatient and outpatient services and outpatient prescription drugs
- Data complies with the patient confidentiality requirements of the Health Insurance Portability and Accountability Act

Study Design

- A retrospective longitudinal cohort design was used (**Figure 1**)
- Patients cycling to another anti-TNF (i.e., adalimumab, infliximab, certolizumab) or switching to a biologic in a different class (i.e., ustekinumab, vedolizumab) after first-line anti-TNF were selected based on the first claim of their second-line biologic (i.e., the *index date* and *index biologic*) during the intake period (09/23/2016 – 08/01/2019)
- The study period spanned from 09/23/2015 to 02/01/2020 (i.e., the beginning of the Coronavirus Disease 2019 pandemic in the US)
- The 12 months before the index date was defined as the baseline period; the follow-up period spanned the index date until the end of the continuous insurance eligibility or the end of the study period, whichever came first

Figure 1. Study Design


Intake period
Eligibility or data start
Eligibility end or 02/01/2020
09/23/2016
1st baseline anti-TNF
Index date: cycling or switch
08/01/2019
12-month baseline period: description of patient characteristics
Follow-up period: assessment of outcomes
12-month wash-outperiod: no claims for biologics
Continuous health plan eligibility

Study Sample

- Inclusion criteria:
  - ≥1 claim for an anti-TNF; the first claim defined the baseline anti-TNF
  - ≥12 months of continuous health plan eligibility before the baseline anti-TNF initiation (wash-out)
  - Discontinuation of the baseline anti-TNF (i.e., exposure gap >120 days for infliximab and >60 days for adalimumab or certolizumab pegol)
  - ≥1 claim indicating cycling to another anti-TNF or switching to a biologic from another class during the intake period
  - ≥18 years old as of index date with ≥12 months of continuous insurance eligibility prior to this date
  - ≥1 diagnosis for CD (International Classification of Diseases, Ninth/Tenth Revision, Clinical Modification [ICD-9/10-CM]: 555.x; K50.x) during the baseline period
- Exclusion criteria:
  - ≥1 medical claim for rheumatoid arthritis, psoriatic arthritis, plaque psoriasis, ankylosing spondylitis, relapsing polychondritis, juvenile idiopathic arthritis, hidradenitis suppurativa or uveitis during the baseline period
  - >1 medical or pharmacy claim for biologic agents indicated for CD on the index date
  - Algorithm-based ulcerative colitis or IBD that could not be precisely identified during the baseline period[5]

CONCLUSIONS

- **Following the discontinuation of the first-line anti-TNF agent, patients with CD who switched to a different class of biologic were significantly more persistent than patients who cycled to another anti-TNF agent**
- **Moreover, patients who switched to a different class of biologic were significantly more persistent and on monotherapy compared to patients who cycled to another anti-TNF agent**
- **The patients who switched to a different class of biologic were also less likely to switch again compared to the patients who cycled to another anti-TNF agent**
- **These results may inform choice of next treatment for bio-experienced patients with CD who experience loss of response to the first-line anti-TNF therapy**

METHODS (CONT'D)

Imputation of Days of Supply

- Missing days of supply in medical claims or out of bound days of supply in pharmacy claims were imputed based on the United States (US) label frequency of administration,[6,7] the mode of days of supply, and distribution of time to the next claim observed in the data

Outcome Measures

- Persistence on index biologic, defined as an absence of an index biologic exposure gap between the end of supply and the date of the following claim or end of the follow-up period. The last day of supply preceding the gap defined the discontinuation date. The following gap definition was used:
  - >120 days for infliximab, ustekinumab, and vedolizumab, based on twice the duration of the maintenance cycle of 8 weeks (~60 days)
  - >60 days for adalimumab, and certolizumab pegol based on twice the duration of the maintenance cycle of 4 weeks (~30 days) for certolizumab pegol; adalimumab has per-label maintenance cycle of 2 weeks (~15 days), but each dispensing typically contains two doses covering 4 weeks
- Persistence on index biologic and corticosteroid-free, a composite outcome defined as the absence of both an index biologic exposure gap and any corticosteroid use for ≥14 consecutive days of supply after a 90-day grace period from the index date to allow for corticosteroid tapering following initiation of a biologic
- Persistence on index biologic and being on monotherapy, a composite outcome defined as the absence of both an index biologic exposure gap and any use of immunomodulators (i.e., azathioprine, cyclosporine, mercaptopurine, methotrexate, tacrolimus) or non-index biologics
- All persistence outcomes were assessed from the index date until the event date (for composite outcomes, the earliest among the discontinuation date or corticosteroid/immunomodulator/new biologic use); patients without the outcome were censored at the last day of the index biologic supply during follow-up
- Switch to a non-index biologic defined among all patients as a claim for a non-index biologic with the days of supply ending after the index biologic discontinuation. Time to switch spanned the index date to the first claim of a non-index biologic; if switch was not observed, patients were censored at the end of the follow-up
- Restart among discontinuers defined as a new claim for the index biologic after the end of the minimum therapy exposure gap (i.e., 120 days for infliximab, ustekinumab, and vedolizumab, 60 days for adalimumab, and certolizumab pegol); time to restart spanned the end of the minimum gap to the first new claim of the index biologic; if restart was not observed, patients were censored at the end of the follow-up

Statistical Analysis

- Inverse probability of treatment weights-average treatment effect (IPTW-ATE) was used to balance baseline characteristics including demographics, comorbidities, IBD-related surgery, medication use, healthcare resource use and costs; standardized differences <10% indicated balance[8]
- Weighted Kaplan-Meier and univariate Cox proportional hazards models were used to describe and compare outcomes at 12 months of follow-up (or, for restart, at 12 months since the end of the minimum exposure gap); the subset of patients who discontinued were not re-weighted for the restart analysis

Sensitivity Analyses

- Persistence was evaluated using the following exposure gap sensitivity definitions:
  - Sensitivity 1, twice the per-label maintenance cycle for each agent:
    - >120 days for infliximab, ustekinumab, and vedolizumab
    - >60 days for certolizumab pegol
    - >30 days for adalimumab
  - Sensitivity 2, fixed gap >120 days for all biologics (a conservative analysis)

RESULTS

Study population and weighted baseline characteristics

- After weighting, the switching cohort included 444 patients and the cycling cohort 441 patients; based on standardized differences, cohorts were well balanced (**Table 1**)

Table 1. Selected baseline characteristics in weighted switching and cycling cohorts[1]

Mean ± SD or n (%)	Switching N=444	Cycling N=441	Standardized difference
Age	40.4 ± 14.2	39.5 ± 13.9	6.3
Female	250 (56.3%)	257 (58.4%)	4.3
Index biologic			
Switching			
Ustekinumab	228 (51.4%)		-
Vedolizumab	216 (48.6%)		-
Cycling			
Infliximab		231 (52.3%)	-
Adalimumab		150 (34.1%)	-
Certolizumab pegol		60 (13.6%)	-
Immunomodulator or corticosteroid use,[2] or CD-related hospitalizations, or surgeries	263 (59.1%)	266 (60.5%)	2.7
CD-related surgery	38 (8.6%)	37 (8.4%)	0.9
Charlson Comorbidity Index	0.54 ± 0.9	0.52 ± 0.9	1.4
Medication			
Corticosteroids	343 (77.1%)	331 (75.0%)	4.8
≥60 days of continuous corticosteroid use	137 (30.9%)	144 (32.7%)	3.9
5-ASA	150 (33.7%)	138 (31.3%)	5.1
Immunomodulators	149 (33.5%)	154 (34.9%)	2.9
Antidiarrheals	26 (5.8%)	27 (6.0%)	0.9
Baseline anti-TNF			
Adalimumab	288 (64.9%)	278 (63.1%)	3.7
Infliximab	140 (31.4%)	148 (33.5%)	4.4
Certolizumab pegol	16 (3.7%)	15 (3.4%)	1.6
Year of index date, n (%)			
2016	27 (6.0%)	28 (6.4%)	1.6
2017	143 (32.2%)	144 (32.6%)	1.0
2018	165 (37.2%)	158 (35.8%)	3.0
2019	110 (24.6%)	111 (25.2%)	1.4
All-cause costs (US$ 2021)	72,594 ± 52,331	71,643 ± 53,192	1.8
Prescription drug costs	35,134 ± 29,132	34,340 ± 30,674	2.7
Total medical costs	37,459 ± 51,598	37,303 ± 52,046	0.3
Duration of follow-up, months	17.4 ± 9.6	18.1 ± 9.6	-

CD: Crohn's disease; SD: standard deviation; TNF: tumor necrosis factor; 5-ASA: 5-aminosalicylic acid
Notes:
1. Cohorts were weighted on baseline characteristics using inverse probability of treatment weights; characteristics considered well balanced if standardized difference is <10%
2. At least one episode of ≥90 days of continuous use of corticosteroids

Persistence at 12 months of follow-up

- The probability of persistence was significantly higher in the switching cohort compared to the cycling cohort (75.7% vs 67.5%; **Figure 2**)
- The switching cohort had a statistically significant 44% higher rate of persistence on index biologic (**Figure 3**)
- The probability of being persistent and corticosteroid-free was numerically higher in the switching cohort compared to the cycling cohort (52.9% vs 49.9%, respectively)
- The probability of being persistent and on monotherapy was significantly higher in the switching cohort compared to the cycling cohort (58.2% vs 44.2%, respectively)
- The switching cohort had a statistically significant 56% higher rate of being persistent and on monotherapy

Figure 2. Kaplan-Meier curves for weighted cohorts for being a) persistent to index biologic, b) persistent and corticosteroid-free, c) persistent while on monotherapy

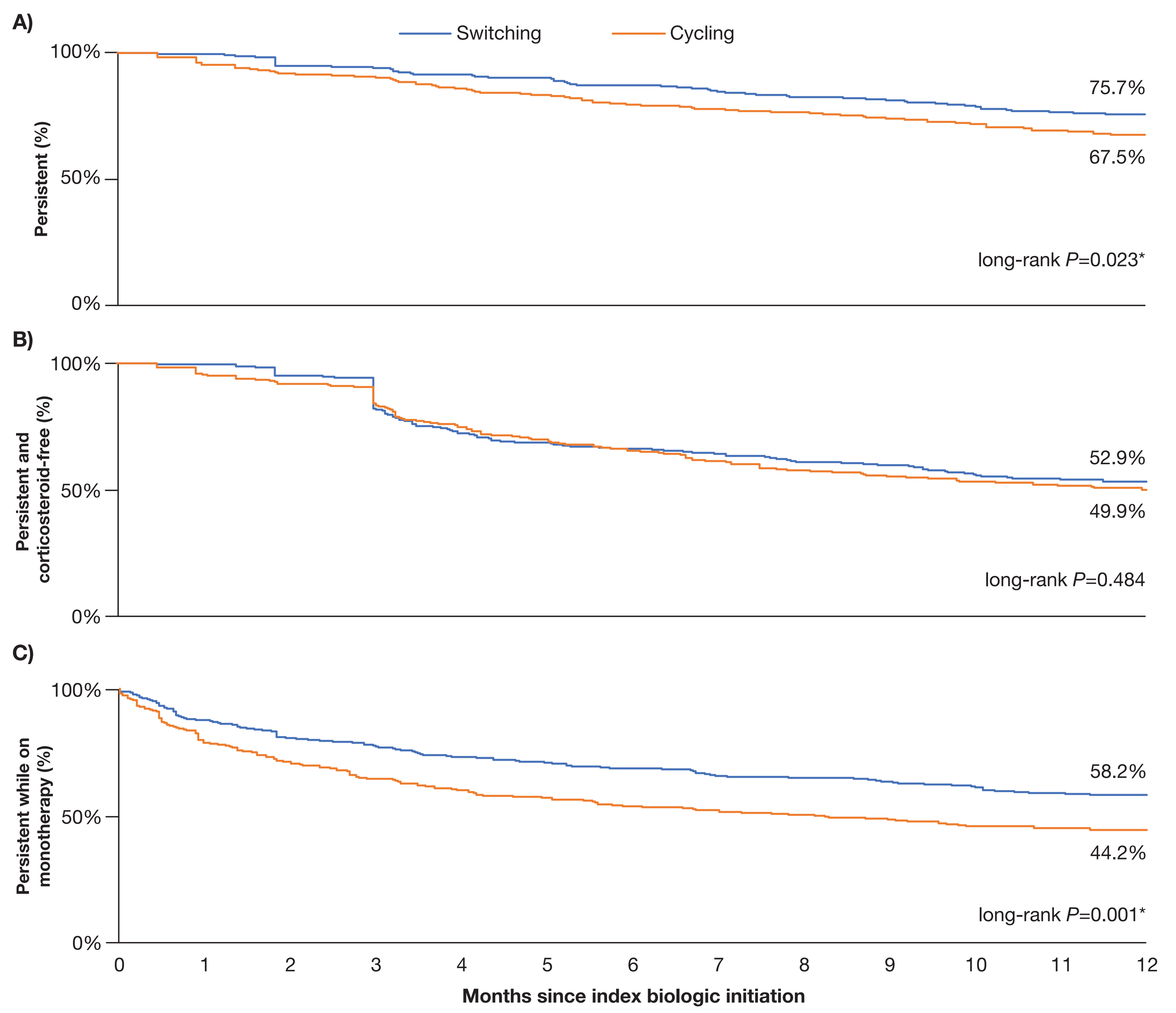
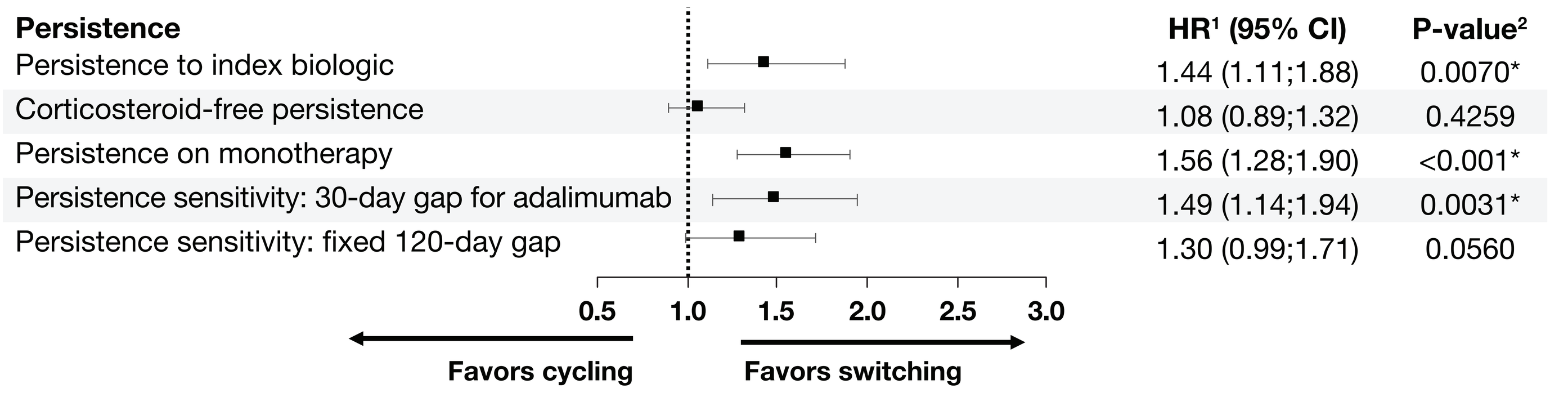

Switching
Cycling
A)
Persistent (%)
100%
50%
0%
75.7%
67.5%
long-rank P=0.023*
B)
Persistent and corticosteroid-free (%)
52.9%
49.9%
long-rank P=0.484
C)
Persistent while on monotherapy (%)
58.2%
44.2%
long-rank P=0.001*
0 1 2 3 4 5 6 7 8 9 10 11 12
Months since index biologic initiation

Figure 3. Hazard ratios for persistence in switching vs. cycling cohorts

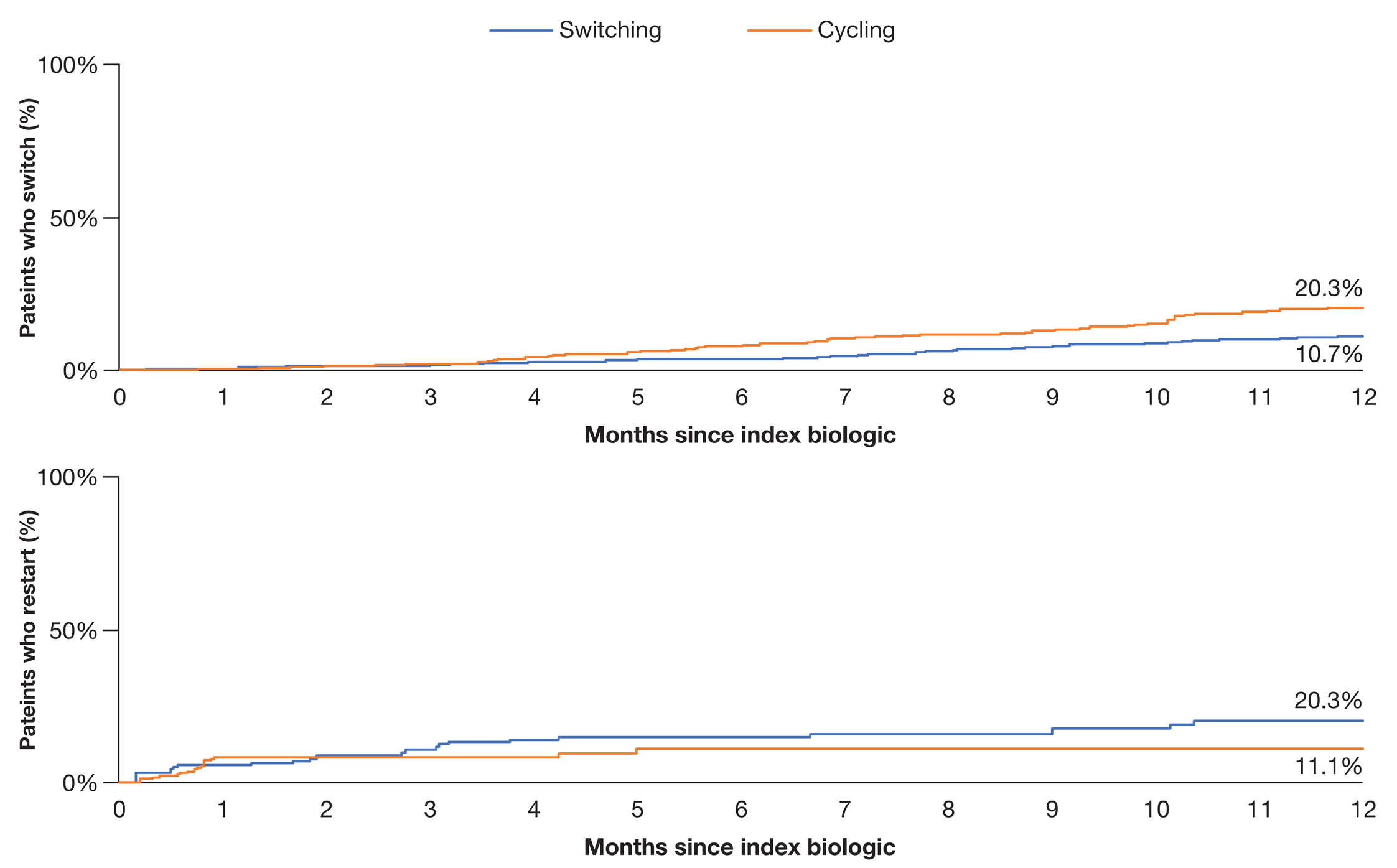

Persistence
Persistence to index biologic
Corticosteroid-free persistence
Persistence on monotherapy
Persistence sensitivity: 30-day gap for adalimumab
Persistence sensitivity: fixed 120-day gap
HR[1] (95% CI)
1.44 (1.11;1.88)
1.08 (0.89;1.32)
1.56 (1.28;1.90)
1.49 (1.14;1.94)
1.30 (0.99;1.71)
P-value[2]
0.0070*
0.4259
<0.001*
0.0031*
0.0560
0.5 1.0 1.5 2.0 2.5 3.0
Favors cycling
Favors switching

**: significant at the 0.05 level*
CI: confidence interval; HR: hazard ratio
Notes:
1. Weighted univariate Cox proportional hazard models were used to compare the 12-month persistence rates between the weighted cohorts
*2. P-values < 0.05 were considered statistically significant and were indicated with **

Restart at 12 months since discontinuation and switch at 12 months of follow-up

- The probability of restart after discontinuation was 20.3% in the switching cohort and 11.1% in the cycling cohort (**Figure 4**)
- The probability of a new switch was 10.7% in the switching cohort and 20.3% in the cycling cohort

Figure 4. Kaplan-Meier curves for weighted cohort for a) new switch to non-index biologic b) restarting of index biologic after discontinuation[1]



Note:
1. Subset of patients who discontinued were not re-weighted for the restart analysis

Sensitivity Analysis

Sensitivity 1 - 120/60/30-day exposure gap sensitivity

- The probability of persistence was significantly higher in the switching compared to the cycling cohort (75.7% and 66.7%, log-rank P-value=0.0129)
- Patients in the switching cohort had a statistically significant 49% higher rate of being persistent (hazard ratio [HR]: 1.49; P-value = 0.0031)

Sensitivity 2 - fixed 120-day exposure gap sensitivity

- The probability of persistence was numerically higher in the switching compared to the cycling cohort (75.7% vs 69.9%; log-rank P-value = 0.1067)
- The rate of being persistent was numerically 30% higher in the switching versus the cycling cohort (HR: 1.30 [95% confidence interval: 0.99 – 1.71]; P-value = 0.0560)

Limitations

- Results may not be generalizable to patients without health insurance, or with insurance other than commercial
- Prescription fills do not account for whether the medication dispensed was taken as prescribed
- The imputation of days of supply for certain agents assumes that the time to next claim is a proxy for the time between doses
- There may be residual confounding due to unmeasured confounders

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Disclosure

Funded by Janssen Scientific Affairs, LLC

Presented at American College of Gastroenterology (ACG) 2022; October 21-26, 2022; Charlotte, NC, USA, and Virtual.