LONG-TERM PERSISTENCE ON USTEKINUMAB OR ADALIMUMAB AMONG BIO-NAÏVE PATIENTS WITH CROHN'S DISEASE

D0369

M. Zhdanava,[1] Z. Ding,[2] A.M. Manceur,[1] S. Kachroo,[2] C. Holiday,[1] R. Zhao,[2] J. Izanec,[2] D. Pilon[1]

[1]Analysis Group, Inc. Montreal, QC, Canada; [2]Janssen Scientific Affairs, LLC, Horsham, PA, USA

BACKGROUND

In the real-world, persistence on biologics in Crohn's disease (CD) has been shown to be an important indicator of treatment effectiveness and safety, among other factors[1,2]

Real-world evidence has previously demonstrated superior one-year persistence of ustekinumab relative to adalimumab.[3] However, an understanding of persistence beyond one year is lacking

OBJECTIVE

To compare long term treatment persistence, persistence while corticosteroid-free, and being persistent while on monotherapy among bio-naïve patients with CD initiated on ustekinumab or adalimumab

METHODS

Data source

- IBM MarketScan Commercial Database (01/01/2015-02/01/2020) was used
- The database includes demographic variables, information on health plan enrollment, and fully adjudicated claims for inpatient and outpatient services as well as outpatient prescription drugs
- This database complies with the patient confidentiality requirements of the Health Insurance Portability and Accountability Act

Study design

- A retrospective longitudinal cohort design was used
- 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)
- Bio-naïve patients with CD were classified into either the ustekinumab (approved for CD on 09/23/2016 in the US) or adalimumab (approved for CD on 02/27/2007 in the US) cohort based on the agent first initiated during the intake period (09/23/2016 - 08/01/2019)
- The index date was the date of ustekinumab or adalimumab initiation
- The 12 months before the index date were defined as the baseline period; the follow-up period spanned the index date until the earliest among continuous insurance eligibility or study period end

Study sample

- Inclusion criteria:
  - ≥1 claim for ustekinumab or adalimumab with the first claim for each agent during the intake period
  - ≥1 diagnosis for CD (International Classification of Diseases, Ninth/Tenth Revision, Clinical Modification (ICD-9/10-CM): 555.x; K50.x) in the baseline period
  - Bio-naïve patients (i.e., no medical or pharmacy claims for biologics indicated for CD including ustekinumab, adalimumab, infliximab, vedolizumab, certolizumab pegol, or natalizumab during the baseline period) in the baseline period
  - ≥18 years old as of index date with ≥12 months of continuous insurance eligibility prior to this date
- Exclusion criteria:
  - >1 biologic initiated on the index date
  - Algorithm-based ulcerative colitis or IBD (inflammatory bowel disease) that could not be precisely identified during the baseline period[4]
  - ≥1 medical claim for ankylosing spondylitis, hidradenitis suppurativa, juvenile idiopathic arthritis, plaque psoriasis, psoriatic arthritis, relapsing polychondritis, rheumatoid arthritis, and uveitis during the baseline period

Imputation of days of supply

- Days of supply where imputed were missing (e.g., in medical claims) or if out of bound in pharmacy claims based on the US label frequency of administration,[5,6] the mode of days of supply observed in the data, and distribution of time to the next claim

Outcome measures

- Persistence on index agent, defined as an absence of an index agent exposure gap (ustekinumab: >120 days; adalimumab: >60 days) 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 exposure gap was the discontinuation date
  - 120 days represents approximately twice the US label stated frequency of administration for a maintenance dose of ustekinumab[5] and approximately twice the mode of the days of supply in pharmacy claims (56 days)
  - 60 days represents approximately four times the US label stated frequency of administration for maintenance dose of adalimumab (14 days)[6] and approximately twice the mode of the days of supply in pharmacy claims (28 days; patients typically receive two maintenance doses per claim)
- Persistence on index agent and being corticosteroid-free, a composite outcome defined as the absence of an index agent exposure gap and absence of corticosteroid use for > 14 consecutive days of supply after a 90-day grace period from the index date to allow for corticosteroid tapering following biologic initiation[7]
- Persistence on index agent and being on monotherapy, a composite outcome defined as the absence of an index agent exposure gap and absence of use of immunomodulators (i.e., azathioprine, cyclosporine, mercaptopurine, methotrexate, tacrolimus) or non-index biologics
- Time to all persistence outcomes was assessed from the index date until the discontinuation 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 supply of the index agent during follow-up

Statistical analysis

- Inverse probability of treatment weights-average treatment effect on treated (IPTW-ATT) 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 Cox proportional hazards models were used to describe and compare outcomes at 24 months of follow-up

Sensitivity analyses

- Sensitivity analysis for exposure gap defining discontinuation of ustekinumab and adalimumab included:
  - Non-conservative analysis for ustekinumab vs adalimumab with the gap approximately twice the US label stated frequency of administration during maintenance phase (i.e., >120 and >30 days, respectively)
  - Conservative analysis for ustekinumab vs adalimumab with the gap >120 days for both biologics

CONCLUSIONS

- **Bio-naïve patients with CD initiated on ustekinumab were significantly more persistent than those initiated on adalimumab at 24 months of follow-up**
- **Bio-naïve patients with CD initiated on ustekinumab also had a significantly higher rate of being persistent and corticosteroid-free, and of being persistent and on monotherapy than those initiated on adalimumab at 24 months of follow-up**
- **These results were robust in sensitivity analyses that included a definition of persistence that was more conservative for ustekinumab relative to adalimumab**

RESULTS

Study population and weighted baseline characteristics

- A total of 3,646 bio-naïve patients with CD met eligibility criteria, with 671 initiating ustekinumab and 2,975 initiating adalimumab
- Based on the standardized differences, the IPTW cohorts were well balanced (**Table 1**)

Table 1. Selected baseline characteristics in weighted ustekinumab and adalimumab cohorts

Mean ± standard deviation or n (%)	Ustekinumab N=671		Adalimumab N=2,975		Standardized difference
Age	41.7	± 13.3	41.6	± 13.8	0.8
Female	371	(55.3%)	1,642	(55.2%)	0.2
Year of index date					
2016	21	(3.1%)	99	(3.3%)	1.1
2017	193	(28.8%)	837	(28.1%)	1.4
2018	259	(38.6%)	1,165	(39.1%)	1.1
2019	198	(29.5%)	875	(29.4%)	0.3
All-cause healthcare costs (US$ 2020)	35,258	± 57,472	30,104	± 52,884	9.3
Prescription drug costs	5,095	± 11,691	5,029	± 18,564	0.4
Total medical costs	30,163	± 55,485	25,075	± 47,187	9.9
Abdominal pain	372	(55.4%)	1,775	(59.7%)	8.5
Anemia	218	(32.5%)	872	(29.3%)	6.9
Diarrhea	233	(34.7%)	1,064	(35.8%)	2.2
Cardiovascular disease	215	(32.0%)	944	(31.7%)	0.7
Nausea and vomiting	169	(25.2%)	775	(26.1%)	2.0
Fatigue	125	(18.6%)	492	(16.5%)	5.5
Quan-Charlson comorbidity index	0.60	± 1.2	0.61	± 1.1	0.8
CD-related surgery Medication	57	(8.5%)	221	(7.4%)	4.0
Corticosteroids[1]	440	(65.6%)	2,068	(69.5%)	8.4
≥ 90 days of continuous use	103	(15.4%)	445	(14.9%)	1.1
Immunomodulators	177	(26.4%)	797	(26.8%)	1.0
5- aminosalicylic acid	177	(26.4%)	795	(26.7%)	0.8
Antidiarrheals	51	(7.6%)	204	(6.9%)	2.8
Duration of follow-up, months	15.1	± 9.2	17.4	± 10.7	-

CD: Crohn's disease
Note:
1. Corticosteroids included prednisone, prednisolone, budesonide, hydrocortisone, and dexamethasone in oral modes of administration. Episodes of continuous use were defined allowing 14 days gaps without corticosteroids use.

Persistence at 24 months of follow-up

- At 24 months of follow-up, a significantly higher proportion of patients in the ustekinumab compared to the adalimumab cohort remained persistent (66.4% vs 48.5%; **Figure 1**)
- Patients in the ustekinumab cohort had a statistically significant 66% higher rate of persistence on index biologic (**Figure 2**)
- A significantly higher proportion of patients in the ustekinumab compared to the adalimumab cohort were persistent on index agent and corticosteroid-free (43.1% vs 35.7%)
- Patients in the ustekinumab cohort had a statistically significant 15% higher rate of being persistent and corticosteroid-free versus the adalimumab cohort
- Significantly higher proportion in the ustekinumab cohort were persistent and on monotherapy compared to the adalimumab cohort (48.7% vs 36.2%)
- Patients in the ustekinumab cohort had a statistically significant 44% higher rate of being persistent and on monotherapy

Figure 1. Kaplan-Meier curves of being: a) persistent on index biologic, b) persistent and corticosteroid-free, c) persistent and on monotherapy in weighted ustekinumab and adalimumab

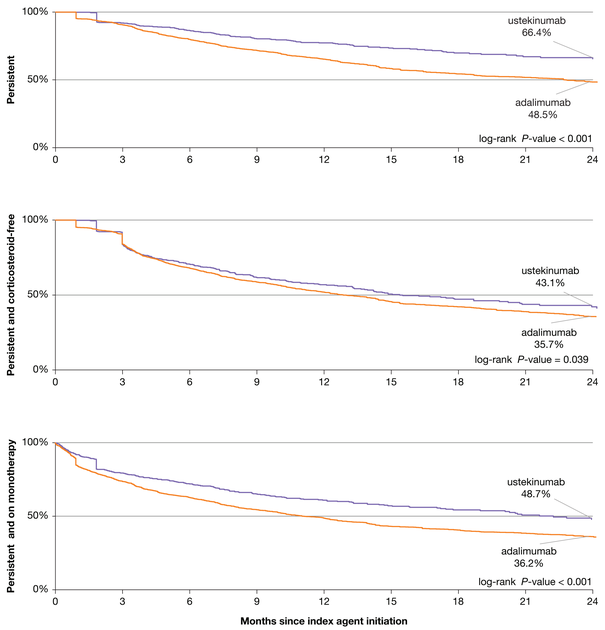
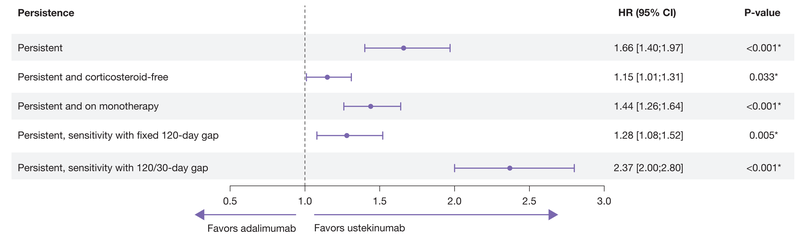


Figure 2. Persistence on ustekinumab compared to adalimumab at 24 months of follow-up[1]



** P-value < 0.05; CI: confidence interval; HR: hazard ratio;*
Note:
1.Weighted univariate Cox proportional hazard models were used to compare the 12-month persistence rates between the weighted cohorts

Sensitivity Analyses

120/30-day exposure gap sensitivity

- A significantly higher proportion of patients in the ustekinumab cohort compared the adalimumab cohort remained persistent at 24 months (66.4% and 33.8%, respectively; log-rank *P*-value<0.001)
- Patients in the ustekinumab cohort were over two times more persistent compared to patients in the adalimumab cohort (**Figure 2**)

Fixed exposure gap sensitivity

- A significantly higher proportion of patients in the ustekinumab cohort compared to the adalimumab cohort remained persistent at 24 months (66.4% vs 57.3%; log-rank *P*-value=0.009)
- Patients in the ustekinumab cohort had a statistically significant 24% higher rate of persistence compared to patients in the adalimumab cohort in this sensitivity (**Figure 2**)

Limitations

- Results may not be generalizable to patients without health insurance or with insurance other than commercial
- Analyses of administrative claims depend on correct diagnosis, procedure, and drug codes, and misclassification may have occurred
- Prescription fills do not account for whether the medication dispensed was taken as prescribed
- There may be residual confounding due to unmeasured confounders

References

1. Patel H, et al. *PLoS One.* 2017;12(4):e0175099.
2. Chen C, et al. *Inflammatory Bowel Diseases.* 2019;25(8):1417-1427.
3. Pilon D, et al. *Official journal of the American College of Gastroenterology | ACG.* 2021;116:S328-S329.
4. Manceur AM, et al. *Journal of Medical Economics.* 2020;23(10):1092-1101.
5. US Food and Drug Administration. STELARA® (Ustekinumab) Injection, for Subcutaneous or Intravenous Use: Highlights of Prescribing Information. 2020
6. US Food and Drug Administration. HUMIRA® (Adalimumab) Injection, for Subcutaneous Use: Highlights of Prescribing Information. 2021
7. Lichtenstein GR, et al. *Official journal of the American College of Gastroenterology | ACG.* 2018;113(4):481-517.
8. Austin PC. *Communications in Statistics - Simulation and Computation.* 2009;38(6):1228-1234

Disclosure

Funded by Janssen Scientific Affairs, LLC