Incidence of Inflammatory Bowel Disease Events in Adalimumab Clinical Trials Across Indications

Jeffrey R Curtis[1], Dirk Elewaut[2], Su Chen[3], Maja Hojnik[4], Navit Naveh[5], Jaclyn K Anderson[3]

[1]Division of Clinical Immunology and Rheumatology, University of Alabama at Birmingham, Birmingham, Alabama, United States; [2]VIB Inflammation Research Center, University of Gent, Gent, Belgium; [3]AbbVie Inc., North Chicago, Illinois, United States; [4]AbbVie, Ljubljana, Slovenia; [5]AbbVie, Hod HaSharon, Israel

BACKGROUND

- Adalimumab (ADA) is approved for the treatment of Crohn's disease (CD) and ulcerative colitis (UC); therefore, it is postulated that new onset or flare of inflammatory bowel disease (IBD) is a rare occurrence in ADA clinical trials for non-IBD indications

OBJECTIVE

- The purpose of this analysis was to determine the rates of IBD adverse events (AEs) in ADA clinical trials, particularly in spondyloarthritis (SpA) patients who are at a higher risk of IBD as a feature of SpA

METHODS

CLINICAL TRIALS

- The rates of IBD AEs in 73 phase 2–4 interventional ADA clinical trials in rheumatoid arthritis (RA), polyarticular juvenile idiopathic arthritis (pJIA), pediatric enthesitis-related arthritis (peds ERA), uveitis (non-infectious intermediate, posterior, or pan-uveitis), hidradenitis suppurativa (HS), adult and pediatric psoriasis (Ps), psoriatic arthritis (PsA), non-PsA peripheral SpA (pSpA), non-radiographic axial spondyloarthritis (nr-axSpA), and ankylosing spondylitis (AS) were analyzed **(Table 1)**
- Trials in UC, CD, and intestinal Behcet's disease (BD) were excluded from this analysis; however, patients with UC, CD, and BD were not excluded from the trials included in this analysis

Table 1. List of Indications and Clinical Trials

Indication	No. of Trials	No. of Patients
All ADA trials[a]	73	23 735
Psoriatic arthritis (PsA)	4	837
Non-PsA peripheral spondyloarthritis (pSpA)	1	165
Non-radiographic axial spondyloarthritis (nr-axSpA)	1	190
Ankylosing spondylitis (AS)	5	2026
Rheumatoid arthritis	35	15 152
Uveitis	2	387
Hidradenitis suppurativa (HS)	4	733
Adult psoriasis	16	3500
Pediatric psoriasis	1	111
All juvenile idiopathic arthritis[b]	4	274

[a]All ADA adult and pediatric patients in all interventional studies excluding Crohn's disease, ulcerative colitis, and intestinal Behcet's disease.
[b]All ADA patients in all interventional studies of pJIA, and peds ERA.
pJIA = polyarticular juvenile idiopathic arthritis; peds ERA = pediatric enthesitis-related arthritis.

ASSESSMENT FOR INFLAMMATORY BOWEL DISEASE (IBD)

- The search criteria for IBD events included the following standardized MedDRA queries preferred terms and did not distinguish between new onset IBD and flare of pre-existing disease:
  - Inflammatory bowel disease (IBD)
  - Ulcerative colitis (UC)
  - Crohn's disease (CD)
  - IBD-not otherwise specified (NOS)
  - Ulcerative proctitis
- In addition to the MedDRA queries, manual assessment to distinguish new-onset IBD and flare of pre-existing disease was performed for events occurring in patients with axial SpA (nr-axSpA and AS)

STATISTICAL ANALYSES

- IBD events were defined as an IBD flare in patients with pre-existing IBD, or new onset IBD among those without pre-existing IBD
- Incidence rates of IBD events (combined new onset and flare) were calculated separately for placebo (PBO)- and ADA-treated patients during the PBO-controlled periods of interventional clinical trials of ADA
- Overall incidence rates of IBD events were determined in patients treated with ADA during the PBO-controlled periods and open-label extensions of all interventional clinical trials of ADA
- The risk of an IBD event over a 1-year period of ADA treatment was also calculated
  - Due to variable follow-up duration in the studies included in this analysis the time period included was limited to 1 year to improve comparability between studies
- Incidence rates of IBD events are reported as events per 100 patient-years (PYs)
- 95% confidence intervals (CI) were based on exact Poisson confidence limits

ACKNOWLEDGMENTS

AbbVie funded the studies, contributed to their design, and participated in data collection, analysis and interpretation of the data, and in writing, review, and approval of the publication. Medical writing support was provided by Deepa Venkitaramani, PhD, of AbbVie.

RESULTS

- ADA was administered to 23 735 patients, representing 36 404.6 PYs of exposure
- Incidence rates for IBD events during the PBO-controlled period of ADA interventional trials were <0.1/100 PYs for both ADA- and PBO-treated patients **(Table 2)**
- In axSpA, the IBD rates in ADA- and PBO-treated patients during PBO-controlled period were 0.6/100 PYs and 1.1/100 PYs, respectively **(Table 2)**
  - There was only 1 IBD event reported in a patient on ADA treatment (in an AS patient) and 1 IBD event reported in patients treated with PBO (in a nr-axSpA patient)
- During the PBO-controlled period, there were no reports of IBD events in PsA, non-PsA pSpA, RA, uveitis, HS, adult and pediatric Ps, pJIA, and peds ERA trials **(Table 2)**

Table 2. Incidence of IBD Events in Patients From PBO-controlled Period of ADA Clinical Trials

	Adalimumab (ADA)			Placebo (PBO)		
Indication	N (PYs)	All IBD AEs, n	IR/100 PYs (95% CI)	N (PYs)	All IBD AEs, n	IR/100 PYs (95% CI)
All ADA trials[a]	5774 (2065.6)	1	<0.1 (0.0–0.3)	3102 (1041.8)	1	0.1 (0.0–0.5)
All SpA[b]	856 (261.5)	1	0.4 (0.0–2.1)	655 (192.9)	1	0.5 (0–2.9)
PsA	202 (77.8)	0	0.0	211 (81.1)	0	0.0
Non-PsA pSpA	84 (19.1)	0	0.0	81 (18.8)	0	0.0
All axSpA[c]	570 (164.6)	1	0.6 (0.0–3.4)	363 (93.0)	1	1.1 (0.0–6.0)
nr-axSpA	95 (21.5)	0	0.0	97 (22.2)	1	4.5 (0.1–25.1)
AS	475 (143.1)	1	0.7 (0.0–3.9)	266 (70.8)	0	0.0
Rheumatoid Arthritis	2687 (1136.5)	0	0.0	1154 (481.1)	0	0.0
Uveitis	119 (64.4)	0	0.0	120 (47.4)	0	0.0
Hidradenitis suppurativa	419 (103.1)	0	0.0	366 (85.8)	0	0.0
Adult psoriasis	1594 (461.2)	0	0.0	727 (206.0)	0	0.0
All JIA[d]	99 (38.7)	0	0.0	80 (28.6)	0	0.0

[a]All ADA- and PBO-treated adult and pediatric patients in all interventional studies excluding Crohn's disease and ulcerative colitis.
[b]All ADA- and PBO-treated patients in all interventional studies of PsA, non-PsA pSpA, nr-axSpA, and AS.
[c]All ADA- and PBO-treated patients in all interventional studies of nr-axSpA and AS.
[d]All ADA- patients in all interventional studies of pJIA and peds ERA.
IBD = inflammatory bowel disease; PBO = placebo; ADA = adalimumab; PYs = patient years; AEs = adverse events; IR = incidence rates; CI = confidence interval; SpA = spondyloarthritis; PsA = psoriatic arthritis; pSpA = non-PsA peripheral spondyloarthritis; axSpA = axial spondyloarthritis; nr-axSpA = non-radiographic axSpA; AS = ankylosing spondylitis; pJIA = polyarticular juvenile idiopathic arthritis; peds ERA = pediatric enthesitis-related arthritis.

- Overall, the incidence rate for IBD events in ADA-treated patients during PBO-controlled periods and open-label extensions across all interventional trials included in this analysis was 0.1/100 PYs **(Table 3)**
- The rates of IBD events varied across therapeutic indications from <0.1 to 0.8/100 PYs
- In SpA, the overall rate of IBD was 0.5/100 PYs, while the rates were 0, 0.8, 0.5, and 0.7/100 PYs in PsA, non-PsA pSpA, nr-axSpA, and AS, respectively **(Table 3)**
  - 2216 patients with axSpA (AS: 2026, nr-axSpA: 190) were exposed to ADA; in AS, 14 IBD events (7 new onset and 7 flares) were reported in 12 patients (7 new onset and 5 flares), while in nr-axSpA, 2 IBD events were reported in 1 patient (2 flares)
- There were no reports of IBD events in pediatric patients

Table 3. Incidence of IBD Events in Patients From All Non-registry ADA Clinical Trials

Indication	N (PYs)	All IBD AEs, n	IR/100 PYs (95% CI)
All ADA trials[a]	23 735 (36 404.6)	40	0.1 (0.1–0.2)
All SpA[b]	3218 (3919.9)	19	0.5 (0.3–0.8)
PsA	837 (997.5)	0	0.0
Non-PsA pSpA	165 (390.7)	3	0.8 (0.2–2.2)
All axSpA[c]	2216 (2531.7)	16	0.6 (0.4–1.0)
nr-axSpA	190 (412.2)	2	0.5 (0.1–1.8)
AS	2026 (2119.5)	14	0.7 (0.4–1.1)
Rheumatoid Arthritis	15 152 (24 813.0)	16	<0.1 (0.0–0.1)
Uveitis	387 (538.8)	1	0.2 (0.0–1.0)
Hidradenitis suppurativa	733 (836.3)	3	0.4 (0.1–1.1)
Adult psoriasis	3500 (5268.7)	1	<0.1 (0.0–0.1)
Pediatric psoriasis	111 (121.5)	0	0.0
All JIA[d]	274 (797.4)	0	0.0

[a]All ADA adult and pediatric patients during PBO-controlled periods and open-label extensions across all interventional studies excluding Crohn's disease, ulcerative colitis, and intestinal Behcet's disease.
[b]All ADA patients in all interventional studies of PsA, non-PsA pSpA, nr-axSpA, and AS.
[c]All ADA patients in all interventional studies of nr-axSpA and AS.
[d]All ADA patients in all interventional studies of JIA, pJIA, and peds ERA.
IBD = inflammatory bowel disease; ADA = adalimumab; PYs = patient years; AEs = adverse events; IR = incidence rates; CI = confidence interval; SpA = spondyloarthritis; PsA = psoriatic arthritis; pSpA = non-PsA peripheral spondyloarthritis; axSpA = axial spondyloarthritis; nr-axSpA = non-radiographic axSpA; AS = ankylosing spondylitis; JIA = juvenile idiopathic arthritis; pJIA = polyarticular juvenile idiopathic arthritis; peds ERA = pediatric enthesitis-related arthritis.

- The risk of an IBD event occurring over a 1-year period in all interventional ADA trials was 0.1/100 PYs **(Table 4)**
- The 1-year risk of an IBD event was <0.1/100 PYs in both RA and Ps trials
- The 1-year risk of an IBD event was 0.0 in PsA, uveitis, HS, pediatric Ps, pJIA, and peds ERA trials, since no IBD event was reported through 1 year of ADA treatment

Table 4. Risk of IBD Event Over 1-year in Patients From All Non-registry ADA Clinical Trials

Indication	N (PYs)	All IBD AEs, n	IR/100 PYs (95% CI)
All ADA trials[a]	23 735 (15 366.7)	15	0.1 (0.1–0.2)
All SpA[b]	3218 (1711.4)	8	0.5 (0.2–0.9)
PsA	837 (491.6)	0	0.0
Non-PsA pSpA	165 (154.1)	1	0.6 (0.0–3.6)
All axSpA[c]	2216 (1065.7)	7	0.7 (0.3–1.4)
nr-axSpA	190 (166.0)	1	0.6 (0.0–3.4)
AS	2026 (899.6)	6	0.7 (0.2–1.5)
Rheumatoid Arthritis	15 152 (10 072.3)	6	<0.1 (0.0–0.1)
Uveitis	387 (306.3)	0	0.0
Hidradenitis suppurativa	733 (591.0)	0	0.0
Adult psoriasis	3500 (2245.9)	1	<0.1 (0.0–0.2)
Pediatric psoriasis	111 (96.6)	0	0.0
All JIA[d]	274 (234.4)	0	0.0

[a]All ADA adult and pediatric patients in all interventional studies excluding Crohn's disease, ulcerative colitis, and intestinal Behcet's disease.
[b]All ADA patients in all interventional studies of PsA, non-PsA pSpA, nr-axSpA, and AS.
[c]All ADA patients in all interventional studies of nr-axSpA and AS.
[d]All ADA patients in all interventional studies of JIA, pJIA, and peds ERA.
IBD = inflammatory bowel disease; ADA = adalimumab; PYs = patient years; AEs = adverse events; IR = incidence rates; CI = confidence interval; SpA = spondyloarthritis; PsA = psoriatic arthritis; pSpA = non-PsA peripheral spondyloarthritis; axSpA = axial spondyloarthritis; nr-axSpA = non-radiographic axSpA; AS = ankylosing spondylitis; JIA = juvenile idiopathic arthritis; pJIA = polyarticular juvenile idiopathic arthritis; peds ERA = pediatric enthesitis-related arthritis.

CONCLUSIONS

- The rates of IBD AEs in ADA clinical trials were generally low across all indications, with all events occurring in adult patients
- Axial SpA patients are generally at higher risk of manifesting IBD
  - In the combined group of axSpA patients (AS and nr-axSpA), the rates of IBD for ADA-treated patients were numerically lower than for PBO-treated patients
  - In AS patients, the rates of IBD for ADA- and PBO-treated patients were low (0.7/100 PYs [95% CI, 0.4–1.1] and 0.0, respectively) and were similar to published PBO rates pooled across multiple AS clinical trials with TNF inhibitors (1.3/100 PYs [95% CI, 0.2–4.8])[1]
- In patients at risk for IBD who require biologic therapy, ADA is a reasonable therapeutic option based on the observed low IBD event rates in ADA clinical trials and its demonstrated efficacy in treating UC and CD patients

REFERENCES

1. Braun, J. et al. *Arthritis & Rheum.* 2007;57:639–47.

DISCLOSURES

JR Curtis has received research grants and/or consulting fees from Amgen, BMS, Corrona, Crescendo, Janssen, Pfizer, and UCB.

D Elewaut has received research grants, consulting fees, and/or speaker's fees from AbbVie.

S Chen, M Hojnik, N Naveh, and JK Anderson are employees of AbbVie and may own stock/options.

abbvie