Adverse Reactions After Intravenous Iron Infusion Among Inflammatory Bowel Disease Patients in the United States, 2010–2014

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Background: Anemia is a frequent complication of Crohn's disease (CD) and ulcerative colitis (UC), collectively known as inflammatory bowel disease (IBD). Intravenous (IV) iron is recommended as the initial therapy for patients with clinically active IBD, severe anemia, and intolerance to oral iron. IV iron is associated with serious adverse effects including a black box warning for anaphylaxis with iron dextran and ferumoxytol. We aimed to examine the occurrence of adverse reactions including anaphylaxis after IV iron infusions in a large database of US IBD patients.

Methods: We performed a retrospective analysis for encounters occurring between 2010 and 2014 in MarketScan, a US commercial claims database. We assessed the following adverse events: anaphylactic shock, bronchospasm, and hypotension among IBD patients receiving ferumoxytol, iron dextran, ferric gluconate, iron sucrose, and ferric carboxymaltose. We calculated the adverse event rate per 1000 infusions within 7 days of IV iron infusion.

Results: In our study cohort of 6151 IBD patients (38.4% UC), 37 168 IV iron infusions were given (median, 3 infusions). There were very few adverse events; only 1.3% of IBD patients experienced any adverse reaction. The incident rate per 1000 infusions for any adverse event among IBD patients was highest among those receiving ferumoxytol (2.54, 95% confidence interval [CI], 1.26–5.11), ferric gluconate (1.85; 95% CI, 1.03–3.35), iron sucrose (1.74; 95% CI, 1.09–2.78), and iron dextran (0.96; 95% CI, 0.43–2.13). There were 0.24 anaphylactic shock events per 1000 IV iron infusions.

Conclusions: About 1.3 of 100 IBD patients ever developed any adverse event. Because adverse reactions are rare, physicians should be encouraged to adhere to recommended guidelines for iron replacement among anemic IBD patients.

Key Words: anemia, inflammatory bowel diseases, Crohn's disease, ulcerative colitis, adverse effects

INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC) are inflammatory diseases of the gastrointestinal tract, collectively known as inflammatory bowel disease (IBD). IBD affects between 1.2–1.6 million adults in America, and its prevalence has risen in recent years.[1–4] Most recent prevalence estimates for CD and UC were 241 and 263 per 100 000, respectively,[1] compared with 2007 estimates of 201 and 238 per 100 000 for CD and UC, respectively.[5]

IBD is associated with several extraintestinal manifestations; the most frequently occurring is anemia.[6–18] The prevalence of anemia depends on the hospital setting. Inpatient prevalence estimates range from 32% to 74%, whereas in the outpatient setting anemia occurs in 9%–73% of patients.[6, 9, 10, 12, 14, 18, 19] Patients with anemia in IBD experience poor quality of life, decreased cognitive function, increased morbidity, and increased health care utilization, leading to higher health costs.[10, 14, 15, 17, 20–24] Although the etiology of anemia is multifactorial, iron deficiency is the principal cause of anemia in IBD.[9, 16, 19] Iron deficiency occurs due to iron malabsorption from the small bowel, gastrointestinal blood loss from intestinal inflammation, or reduced dietary intake.[7, 8, 12, 18, 22, 24–26]

Oral iron is the conventional, inexpensive method for treatment of iron deficiency, but it is known to be less effective

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than intravenous (IV) iron due to poor absorption and side effects like nausea, flatulence, abdominal cramps, diarrhea, and constipation, which culminates in intolerance and poor adherence.[13, 16, 17, 25, 27–32] Furthermore, oral iron may worsen IBD activity due to formation of oxygen-free radicals, which leads to gastrointestinal inflammation.[8, 13, 20, 28]

Intravenous iron is the preferred treatment for anemia in IBD patients.[7, 8, 15, 16, 28, 33] According to the European Crohn's and Colitis Organization (ECCO), IV iron is recommended as the initial therapy in patients intolerant to oral iron, patients with clinically active disease or severe anemia (hemoglobin < 10 g/dl), and in patients who need erythropoiesis-stimulating agents.[8, 15] IV iron is fast acting, well-tolerated, improves quality of life, and is less likely to be discontinued compared with oral iron.[7, 9, 13, 17, 25, 28, 34] Despite the available guidelines, there is a lack of evidence to support the safe use of IV iron for treatment of anemia in IBD.[23, 24, 35] This may be due to long-held notions associating earlier formulations of high–molecular weight IV iron dextran with serious adverse effects including anaphylaxis.[20, 30, 36, 37]

We aimed to examine the prevalence of IV iron infusions in IBD patients and the rates of adverse reactions using the Truven Health MarketScan Commercial Claims and Encounters database 2010–2014.

METHODS

Study Design

We performed a retrospective analysis using the MarketScan commercial claims database between January 2010 and December 2014. This database is nationally representative of the United States and contains longitudinal, individual-level health encounters obtained from large employers and health plans across the United States.[38]

Inclusion Criteria

Our study cohort included adults (18–64 years) with at least 2 inpatient or outpatient encounters for IBD using the *International Classification of Diseases*, Ninth Revision, Clinical Modification (ICD-9-CM) codes of 555 for CD and 556 for UC. We required that our cohort include patients who had received any form of IV iron after their first encounter for CD or UC. We simulated new users of IV iron by excluding individuals with less than 6 months from their enrollment date in MarketScan before their first IV iron infusion because we did not want to include individuals who had previously had a side effect to IV iron. We also excluded individuals with the following characteristics; younger than age 18 years at first IBD encounter, inconclusive IBD (n = 1), and fewer than 7 days of follow-up in study. We defined inconclusive IBD as the occurrence of an equal number of encounters for both CD and UC; however, patients with predominant encounters for either CD or UC were classified as conclusive CD or UC, respectively. We assigned the first date of receiving any type of IV iron as our study start date, and the study end date was the last date of encounter in the MarketScan database.

Exposure Assessment

The use of IV iron was determined using encounters associated with an IV iron infusion or a pharmacy record. Five formulations of IV iron were evaluated in our study: ferric carboxymaltose (Healthcare Common Procedure Coding System [HCPCS] code, J1439), ferric gluconate (J2916), ferumoxytol (Q0138, Q0139), iron dextran (J1750), and iron sucrose (J1756). From the outpatient pharmaceutical claims data set, we also examined the National Drug Code (NDC) number of the respective iron formulations (Appendix 1).

Outcome Assessment

Patients who developed anaphylactic shock (ICD-9-CM 995.0), bronchospasm (ICD-9-CM 591.11), or hypotension (ICD-9-CM 458.20) within 1 week of an IV iron infusion were identified.

Statistical Analyses

Data were summarized by CD and UC separately. Descriptive analyses for demographic and clinical characteristics included mean age at first IBD encounter, sex distribution, median length of follow-up during study, median number of IV iron infusions, and frequency distributions of IV iron and biologic medication.

Prevalence of Adverse Events

We evaluated the prevalence per 1000 IV iron infusions for each adverse event by dividing the total number of adverse events by the total number of IV iron infusions and then multiplying by 1000.

Infusion-Level Analysis

The rate of any adverse reactions within 7 days of any IV iron administration was calculated per 1000 infusions using Poisson regression after adjusting for type of IBD, type of IV iron, sex, age at first IBD encounter, and receiving a biologic infusion on the same day as IV iron. We assessed goodness of fit for our models using the chi-square test. Any adverse event was defined as the presence of either anaphylactic shock, hypotension, or bronchospasm. Separate models were fit for developing anaphylactic shock using the same specifications as the any adverse event models, except that we did not adjust for sex or receiving biologics on same day as IV iron.

Person-Level Analysis

We calculated the proportion of individuals who ever had any adverse effect by dividing the number of individuals who ever had any adverse event by the total number of individuals

in our study cohort. Similarly, we calculated the proportion of individuals reporting anaphylactic shock by dividing the total number of individuals who reported anaphylactic shock by the total number of individuals in our study cohort.

All analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA). All reported *P* values are 2-sided, and significance was set at $P < 0.05$.

Ethical Consideration

The Johns Hopkins Institutional Review Board approved this study.

RESULTS

Demographics

During 2010–2014, we identified 380 386 IBD patients with at least 2 inpatient or outpatient encounters in the MarketScan database. The eligible cohort who received IV iron and met our inclusion criteria was comprised of 6151 individuals (3791 CD and 2360 UC) (Fig. 1). The total number of IV iron infusions received during the study period was 37 168 infusions. The median age at first IBD encounter was 43 years in CD patients and 44 years in UC patients. More than two-thirds of our cohort was female; 69% were CD and 66% UC, and the median lengths of study follow-up were 1.13 years and 1.08 years in CD and UC, respectively. Iron sucrose was the most predominant type of IV iron received by CD (57.8%) and UC (57.6%) patients, whereas biologic use was higher among CD (46.6%) compared with UC (28.6%) patients (Table 1).

Adverse Events

Hypotension was the most common adverse event (n = 76 events, 2.04 per 1000 iron infusions). Bronchospasm was the least prevalent adverse event (n = 7 events, 0.19 per 1000 iron infusions).

Infusion-Level Analysis

There were 92 encounters for any adverse events in 37 168 IV iron infusions (2.48 adverse events per 1000 IV iron infusions). The incident rate for having any adverse event was highest during ferumoxytol (2.54; 95% confidence interval [CI], 1.26–5.11) and lowest during iron dextran (0.96; 95% CI, 0.43–2.13) infusions. When separated by disease type, ferric gluconate had the highest (2.33; 95% CI,

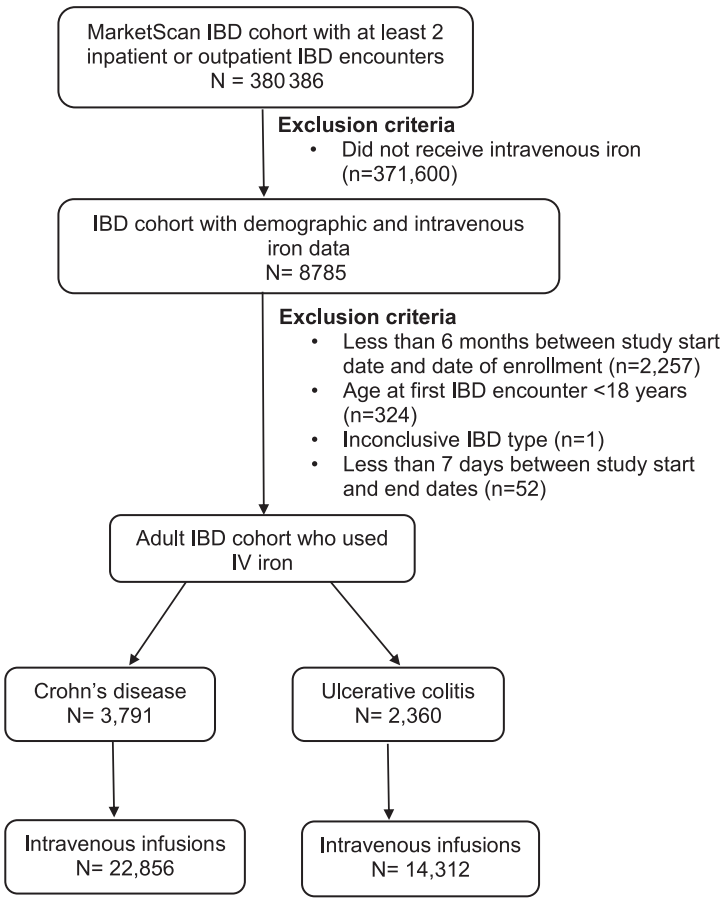

FIGURE 1. Flow chart for inflammatory bowel disease patients receiving intravenous iron in MarketScan, 2010–2014.

TABLE 1: Demographic Characteristics of Crohn's Disease and Ulcerative Colitis Patients in MarketScan, 2010–2014

	Crohn's Disease (n = 3791)	Ulcerative Colitis (n = 2360)
Age at first IBD encounter, median (min–max), y	43 (18–64)	44 (18–64)
18–34	32%	29%
35–49	34%	34%
50–64	34%	37%
Female	69%	66%
Median length of follow-up after first IV iron infusion (min–max), y	1.13 (0.02–4.48)	1.08 (0.02–4.48)
Median number of IV iron infusions (min–max)	3 (1–131)	3 (1–127)
Types of intravenous iron Median number of IV iron infusions (min–max)		
Ferric carboxymaltose	0% 1 (1–1)	0.03% 1 (1–3)
Ferric gluconate	17.8% 5 (1–109)	18.7% 5 (1–82)
Ferumoxytol	8.9% 2 (1–30)	8.4% 5 (1–48)
Iron dextran	15.6% 2 (1–131)	15.2% 5 (1–47)
Iron sucrose	57.8% 4 (1–97)	57.6% 4 (1–127)
Ever use of adalimumab, certolizumab, infliximab, natalizumab, vedolizumab	46.6%	28.6%

1.20–4.55) rate of adverse events during CD infusions, but the lowest (0.80; 95% CI, 0.21–3.12) during UC infusions (Table 2). The incident rate ratio (IRR) for any adverse event was highest among CD patients receiving ferric gluconate infusions (IRR, 1.50; 95% CI, 0.80–2.82) and UC patients receiving ferumoxytol infusions (IRR, 1.89; 95% CI, 0.77–4.65) compared with iron sucrose (Fig. 2). There were 0.24 anaphylactic shock events per 1000 IV iron infusions (n = 9 events) before adjustment. The lowest incidence rate for anaphylactic shock was found among iron sucrose (IBD, 0.14; 95% CI, 0.04–0.43; CD, 0.24; 95% CI, 0.06–0.97; UC, 0.12; 95% CI, 0.02–0.87) per 1000 IV iron infusions (Table 3). Anaphylactic shock rates were highest among CD patients receiving ferumoxytol (1.63; 95% CI, 0.41–6.59) and UC patients receiving ferric gluconate (1.09; 95% CI, 0.34–3.56). This rate could not be assessed in UC patients receiving iron dextran because there were no events (Table 3). All anaphylactic shock events occurred in females, preventing us from adjusting for sex in the model. Similarly, no events occurred in individuals who received biologic on the same day as the iron infusion.

Person-Level Analysis

Eight-one individuals had 92 adverse events. Individuals who had any adverse event (n = 81; 47 CD and 34 UC) after IV iron infusion made up 1.3% of our study cohort. Anaphylactic shock was present in 0.08% (n = 5) of CD and 0.05% (n = 3) of UC patients.

DISCUSSION

IBD patients receiving IV iron infusions had extremely low rates of adverse events. Out of 37 168 IV iron infusions in 6151 patients, there were 92 adverse events and only 9 cases of anaphylactic shock. About 1.3 out of every 100 IBD patients developed any adverse event after receiving IV iron infusion. The rate of anaphylactic shock was very low across all IV iron formulations. Several studies examining the rates of anaphylaxis among infliximab infusions showed similar or slightly higher rates (0.3–2.6 per 1000 infliximab infusions) compared with anaphylaxis from iron in our study (0.24 per 1000 iron infusions).[39–42]

The mechanism for infusion reactions to IV iron remains unknown, with theories including immunological IgE-mediated response and complement activation triggered by iron nanoparticles.[43] Chronic kidney disease patients, who are also at high risk of anemia, have low rates of infusion-related adverse events (<2% of infusions).[41, 42] Our study suggests that adverse reactions to IV iron in IBD are also rare. Two systematic reviews, both including 5 trials (n = 694[17] and n = 1143[44]), that examined IV iron formulations also found that adverse effects were rare. Serious adverse events in trials are often defined by sufficient seriousness to result in discontinuation of the medication, regardless of the potential association with the medication's mechanism of action. In contrast, the adverse events in this study are known potential adverse events of iron itself, including hypotension, bronchospasm, and anaphylaxis. The consistency of the rarity of adverse events across trials and diseases suggests that not administering iron because of the fear of adverse events is inconsistent with the evidence from both trials and a cohort study.

There were fewer adverse events recorded among patients who received iron dextran compared with the other types of IV iron in our study, which corresponds to the findings from the reviews. This finding was not statistically significant, suggesting that further studies may find different results. In the trials, this finding may be partially attributed to trial design with fewer iron dextran infusions, administration of a test dose, and premedication with steroids. In practice, iron dextran patients are routinely premedicated.

There may be advantages of treating patients with IV rather than oral iron, including fewer gastrointestinal symptoms, fewer infusions for newer formulations, and the opportunity to treat during a scheduled infusion of biologics. Although iron deficiency anemia is prevalent in IBD, there is uncertainty on the ideal route (oral vs IV) for treatment.[13, 17, 20, 37] Oral iron

TABLE 2: Adjusted[a] Incident Rate for Any Adverse Event[b] per 1000 Intravenous Iron Infusions Among Crohn's Disease and Ulcerative Colitis Patients in MarketScan, 2010–2014

	No. of Events/No. of Infusions Incident Rate per 1000 IV Iron Infusions (95% CI)[c]		
	Inflammatory Bowel Disease[a]	Crohn's Disease[d]	Ulcerative Colitis[d]
Ferric carboxymaltose	0/6[e]	0/1[e]	0/5[e]
Ferric gluconate	18/6748 1.85 (1.03–3.35)	14/4066 2.33 (1.20–4.55)	4/2682 0.80 (0.21–3.12)
Ferumoxytol	12/3225 2.54 (1.26–5.11)	6/2027 1.87 (0.73–4.77)	6/1198 2.86 (0.83–9.86)
Iron dextran	8/5739 0.96 (0.43–2.13)	3/3559 0.56 (0.16–1.89)	5/2180 1.25 (0.34–4.57)
Iron sucrose	54/21 450 1.74 (1.09–2.78)	31/13 203 1.56 (0.89–2.73)	23/8247 1.52 (0.54–4.29)
Received infusion on same day as biologic[f]	6/4202 1.29 (0.56–2.97)	5/3107 1.11 (0.43–2.91)	1/1095 0.86 (0.12–6.22)
No same day biologic	86/32 966 2.17 (1.60–2.95)	49/19 749 1.74 (1.11–2.74)	37/13 217 2.41 (1.54–3.78)
Male	22/13 845 1.21 (0.68–2.16)	10/8301 0.88 (0.40–1.92)	12/5544 1.23 (0.40–3.74)
Female	70/23 323 2.31 (1.44–3.71)	44/14 455 2.22 (1.26–3.90)	26/8768 1.69 (0.59–4.88)
Age at first IBD encounter, y			
18–34	20/9423 1.53 (0.84–2.77)	12/6064 1.21 (0.56–2.59)	8/3359 1.46 (0.46–4.68)
35–49	27/12 822 1.46 (0.83–2.56)	19/8042 1.40 (0.70–2.79)	8/4780 0.96 (0.29–3.21)
50–64	45/14 923 2.10 (1.24–3.54)	23/8750 1.60 (0.82–3.14)	22/6173 2.13 (0.73–6.21)

[a]Adjusted for type of IBD, type of IV iron, sex, age at first IBD encounter, and receiving biologic infusion on same day as IV iron.
[b]Any adverse effect is defined as experiencing either anaphylactic shock, hypotension, or bronchospasm.
[c]*P* value <0.0001.
[d]Adjusted for type of IV iron, sex, age at first IBD encounter, and receiving biologic infusion on the same day as IV iron.
[e]No rate was calculated when no event was observed.
[f]Biologics: adalimumab, certolizumab, infliximab, natalizumab, vedolizumab.

is associated with dyspepsia, abdominal pain, nausea, vomiting, and constipation, which may be confused with changes in IBD symptoms complicating treatment and patient satisfaction. Gastrointestinal side effects are less common with IV than oral iron,[9] and IV iron users are less likely to discontinue treatment.[17]

The number of infusions may impact formulation choice for some patients. The total number of infusions for IV iron varies depending on the formulation of iron received and the patient's hemoglobin status: 2 infusions for ferric carboxymaltose; up to 8 infusions of ferric gluconate; 2 infusions of ferumoxytol; single or multiple infusions of iron dextran; and up

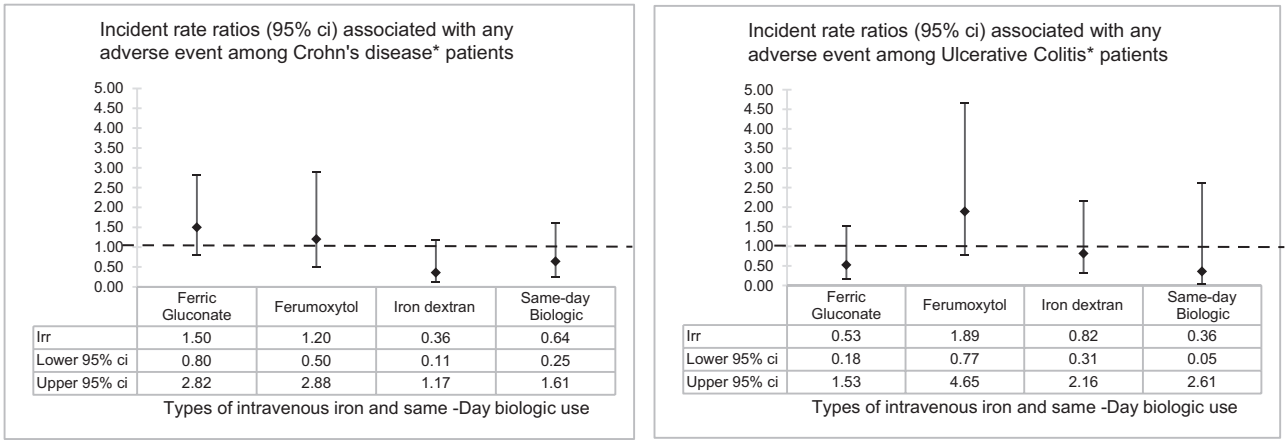

FIGURE 2. Adjusted* incident rate ratios for any adverse event† among Crohn's disease and ulcerative colitis patients in MarketScan, 2010–2014. *Adjusted for type of intravenous iron (reference group: iron sucrose), sex, age at first IBD encounter,and receiving biologic infusion on same day as IV iron. †Any adverse effect is defined as experiencing either anaphylactic shock, hypotension, or bronchospasm.

TABLE 3: Adjusted[a] Incident Rate and Incident Rate Ratios for Anaphylactic Shock Events per 1000 Intravenous Iron Infusions Among Crohn's Disease and Ulcerative Colitis Patients in MarketScan, 2010–2014

	Inflammatory Bowel Disease		Crohn's Disease[b]		Ulcerative Colitis[c]	
	No. of Events/No. of Infusions Incident Rate per 1000 Iron Infusions (95 % CI)[d]	Incident Rate Ratio (95% CI)	No. of Events/No. of Infusions Incident Rate per 1000 Iron Infusions (95% CI)[d]	Incident Rate Ratio (95% CI)	No. of Events/No. of Infusions Incident Rate per 1000 Iron Infusions (95% CI)[d]	Incident Rate Ratio (95% CI)
Ferumoxytol	2/3225 0.60 (0.15–2.44)	4.41 (0.74–26.39)	2/2027 1.63 (0.41–6.59)	6.89 (0.97–49.06)	0/1198[e]	No event[e]
Iron dextran	1/5739 0.17 (0.02–1.23)	1.25 (0.13–12.06)	1/3559 0.45 (0.06–3.18)	1.89 (0.17–20.94)	0/2180[e]	No event[e]
Ferric gluconate	3/6748 0.44 (0.14–1.38)	3.23 (0.65–16.00)	0/4066[e]	No event[e]	3/2682 1.09 (0.34–3.56)	9.13 (0.95–87.90)
Iron sucrose	3/21 450 0.14 (0.04–0.43)	1.00	2/13 203 0.24 (0.06–0.97)	1.00	1/8247 0.12 (0.02–0.87)	1.00
Ferric carboxymaltose	0/6[e]	No event[e]	0/1[e]	No event[e]	0/5[e]	No event[e]
Age at first IBD encounter, y						
18–34	4/9423 0.50 (0.18–1.41)	3.19 (0.58–17.44)	3/6064 1.21 (0.56–2.59)	2.16 (0.36–12.99)	1/3359 0.39 (0.05–3.03)	0.97 (0.09–10.65)
35–49	3/12 822 0.28 (0.09–0.89)	1.76 (0.29–10.54)	2/8042 1.40 (0.70–2.79)	1.00	1/4780 0.30 (0.04–2.26)	0.73 (0.07–8.09)
50–64	2/14 923 0.16 (0.04–0.66)	1.00	0/8750 1.60 (0.82–3.14)	No event[e]	2/6173 0.41 (0.09–1.83)	1.00

[a]Adjusted for type of IBD, type of IV iron (except ferric carboxymaltose), and age at first IBD encounter.
[b]Adjusted for type of IV iron (reference: iron sucrose) and age at first IBD encounter (reference, 35–49 years).
[c]Adjusted for type of IV iron (reference: iron sucrose) and age at first IBD encounter.
[d]*P* value <0.0001.
[e] No rate/ratio was calculated when no events were observed.

to 5 infusions of iron sucrose.[45] Patients scheduled to receive biologics can safely receive IV iron the same day based on our findings of no anaphylactic events.

A limitation of this study is the inability to appropriately compare differences in rates of adverse events, by type of IV iron formulation or type of IBD, due to the small number of encounters for these outcome measures.

In summary, only 1% of IBD patients developed anaphylaxis, bronchospasm, or hypotension after IV iron. Adverse events, including anaphylactic shock, were rare (1.3 per 1000 patients). Administration of IV iron on the same day as biologics was safe. Health care providers should be encouraged to use IV iron according to recommended guidelines for iron replacement among IBD patients with anemia.

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