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ORIGINAL ARTICLE

Comparative outcomes of predominant facility-level use of ferumoxytol versus other intravenous iron formulations in incident hemodialysis patients

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ABSTRACT

Background. Ferumoxytol was first approved for clinical use in 2009 solely based on data from trial comparisons with oral iron on biochemical anemia efficacy end points. To compare the rates of important patient outcomes (infection, cardiovascular events and death) between facilities predominantly using ferumoxytol versus iron sucrose (IS) or ferric gluconate (FG) in patients with end-stage renal disease (ESRD)-initiating hemodialysis (HD).

Methods. Using the United States Renal Data System, we identified all HD facilities that switched (almost) all patients from IS/FG to ferumoxytol (July 2009–December 2011). Each switching facility was matched with three facilities that continued IS/FG use. All incident ESRD patients subsequently initiating HD in these centers were studied and assigned their facility exposure. They were followed for all-cause mortality,

cardiovascular hospitalization/death or infectious hospitalization/death. Follow-up ended at kidney transplantation, switch to peritoneal dialysis, transfer to another facility, facility switch to another iron formulation and end of database (31 December 2011). Cox proportional hazards regression was then used to estimate adjusted hazard ratios [HR (95% confidence intervals)].

Results. In July 2009–December 2011, 278 HD centers switched to ferumoxytol; 265 units (95.3%) were matched with 3 units each that continued to use IS/FG. Subsequently, 14 206 patients initiated HD, 3752 (26.4%) in ferumoxytol and 10 454 (73.6%) in IS/FG centers; their characteristics were very similar. During 6433 person-years, 1929 all-cause, 726 cardiovascular and 191 infectious deaths occurred. Patients in ferumoxytol (versus IS/FG) facilities experienced similar all-cause [0.95 (0.85–1.07)], cardiovascular [0.99 (0.83–1.19)] and infectious mortality [0.88 (0.61–1.25)]. Among 5513 Medicare (Parts A + B) beneficiaries, cardiovascular events [myocardial infarction, stroke and cardiovascular death; 1.05 (0.79–1.39)] and infectious events [hospitalization/death; 0.96 (0.85–1.08)] did not differ between the iron exposure groups.

Conclusions. In incident HD patients, ferumoxytol showed similar short- to mid-term safety profiles with regard to cardiovascular, infectious and mortality outcomes compared with the more commonly used intravenous iron formulations IS and FG.

Keywords: cardiovascular, infection, intravenous iron, mortality, safety

INTRODUCTION

Ferumoxytol was introduced as an alternative intravenous iron formulation and was approved 'for the treatment of iron deficiency anemia in adult patients with chronic kidney disease' (CKD) by the US Food and Drug Administration (FDA) on 30 June 2009 [1]. The three registrational trials supporting the approval were limited in scope and size, essentially comparing the efficacy of ferumoxytol with oral iron fumarate on the end point of hemoglobin concentration (as was customary for FDA approval of anemia drugs) in patients with nondialysis CKD (two trials) or dialysis-requiring CKD (one trial) [1–3]. Over 35 days of follow-up, ferumoxytol was superior compared with oral iron in all three trials in the efficacy end point of change from baseline hemoglobin concentration and appeared generally safe in these trials as well as another (crossover) trial of 713 patients [1, 4]. However, no head-to-head comparisons with other available intravenous iron products were required and quality data on the longer term safety remain limited [4–6].

Ferumoxytol differed from the other intravenous iron formulations available at the time in that a larger iron dose of 510 mg could be administered in a single, short injection. In contrast, previously available iron formulations required repeated injections or infusions of smaller iron doses. While this clinical advantage of ferumoxytol is particularly appealing for its use in patients with CKD not requiring dialysis or those undergoing peritoneal dialysis, its use has also been adopted by several US hemodialysis providers [6]. However, studies comparing the safety of ferumoxytol versus other intravenous iron formulations are limited.

Intravenous iron preparations differ in the way they envelop the iron core and there are likely differences in the amount of free iron that may get released into the blood stream ('labile iron') [7]. Free iron may put patients at acute risk of anaphylactic reactions and—in the longer term—exert clinically important toxicity with particular concerns about cardiovascular or infectious risks [7].

We conducted the present study to examine the safety of ferumoxytol use compared with other available intravenous iron products in real life practice. We applied an innovative study design that exploits the natural experiment, which occurs when individual dialysis facilities make formulary decisions and provide a single intravenous iron product to all or almost all of their patients.

MATERIALS AND METHODS

Study rationale

Most dialysis facilities restrict the choice among available intravenous iron formulations to a single one, which is then used for most or all of its patients. For the purpose of this study, we considered the choice among ferumoxytol, iron sucrose (IS) and sodium ferric gluconate (FG) as potentially random with regard to patient characteristics because such decisions, particularly at the introduction of a new drug, are often based on contracts with drug suppliers. Since it is not expected that patients choose a facility based on whether it uses one intravenous iron formulation or another, we have the opportunity to exploit these facility-level decisions as a natural experiment. Specifically, we used administrative data to mimic a cluster-randomized design, with clustering based on facility by assigning facilities and their incident hemodialysis patients to a treatment arm based on the predominant practice pattern of their facility. We have recently applied this design in a comparative safety study among erythropoiesis-stimulating agents [8].

Study population—patient selection, exposure assignment and follow-up

From the United States Renal Data System (USRDS), the national registry of persons with end-stage renal disease (ESRD), we identified all intravenous iron administrations from billing codes to Medicare between 1 January 2009 and 31 December 2011. We then defined for each hemodialysis facility and calendar month the proportion of intravenous administrations that were for ferumoxytol versus IS versus FG. For each facility, we termed a calendar month a ferumoxytol facility-month if ≥90% of administered intravenous iron administrations in that facility and month were ferumoxytol; correspondingly, if ≥90% of administrations were IS (or FG), we considered it an IS (or FG) facility-month. All other facility-months were categorized as 'mixed'. Beginning with the approval of ferumoxytol by the US FDA for the US market on 30 June 2009, we identified all facility-level switches from IS (or FG) to ferumoxytol.

We conducted all analyses using two approaches. One approach considered non-ferumoxytol facilities predominantly

using IS as well as facilities predominantly using FG as matching candidates. This approach yielded better opportunities to match ferumoxytol facilities and enabled us to use a higher matching ratio (1:3). However, this approach assumes that IS and FG are equally safe with regard to the outcomes studied. Some studies have challenged this class assumption between IS and FG and so we repeated our analyses only considering IS facilities; for these analyses, we used a matching ratio of 1:2. (Corresponding analyses between ferumoxytol and FG facilities were not conducted due to the relative paucity of FG facilities and our subsequent inability to match most ferumoxytol facilities.) Facilities were matched on the index month, geographic region (Census Division), chain (versus non-chain) affiliation and facility type (free standing versus hospital based) as reported in the USRDS.

From the first day of the matching month onward, we identified all patients regardless of their insurance status who initiated hemodialysis in a ferumoxytol facility and its matched IS (or FG) facility. If a facility switched back from predominant ferumoxytol to predominant IS (or FG) use, all matched facilities in the set were no longer eligible to contribute new incident patients to the study and all existing patients in the matching set were censored for further follow-up. Conversely, if a matching IS (or FG) facility switched to ferumoxytol, the matching set of the ferumoxytol facility and the remaining IS (or FG) facility continued to contribute patients and person time until all remaining IS (or FG) facilities switched upon which all patients arising from this matching set were censored. Since iron therapy is usually intermittent, depending on iron status measurements, dosing approach (bolus versus maintenance) and potential temporary contraindications (e.g. infections), patients may have received continuous, intermittent or no iron treatment, but most always with the intravenous iron formulation identified as predominantly used by their facility at the time.

We used the ensuing cohort to study mortality outcomes, which are recorded in the USRDS regardless of payer. Patients were censored at the end of available data (31 December 2011), upon switching to peritoneal dialysis, upon receipt of a kidney transplant, when switching to another hemodialysis facility, or when their facility or its match switched to predominant use of another intravenous iron formulation as described in detail above.

For analyses on nonfatal outcomes, we relied on claims-based data. Therefore, we restricted the cohort to patients who survived 90 days after the start of dialysis and who had Medicare Parts A + B as their primary payer on that day. In the USA, most patients with ESRD are eligible for Medicare benefits after a 90-day waiting period from the date of ESRD incidence certified in the Medical Evidence Report (form CMS-2728). Patients were followed from Day 91 after initiation of hemodialysis until censoring for the reasons listed above, as well as death (for nonfatal outcomes), or loss of Medicare Parts A + B coverage.

To examine the validity of using facility preference as the proxy for true exposure over time, as well as to illustrate other key anemia practice parameters, we plotted for each month of follow-up the mean dose of intravenous iron formulations received, the mean dose of erythropoiesis-stimulating agents received and the mean hemoglobin concentration achieved for each exposure group among incident patients who had Medicare Parts A + B.

Patient characteristics

From the USRDS patient file, we ascertained patients' age, sex, race (White, Black, Asian, Native American/Pacific Islander and other), ethnicity (Hispanic versus non-Hispanic) and whether they were covered by Medicaid (a means-tested federal program administered on the state level, which serves as a proxy for low-socioeconomic status). From the Medical Evidence Report, we ascertained the reported presence of several comorbidities (diabetes, hypertension, arteriosclerotic heart disease, heart failure, peripheral artery disease, cerebrovascular disease, chronic obstructive lung disease, cancer, inability to ambulate or transfer, tobacco use, drug use and alcohol use) as well as body mass index, serum hemoglobin and serum albumin concentrations and the reported estimated glomerular filtration rate at initiation of dialysis.

Outcomes

Mortality from any cause, cardiovascular mortality and mortality from an infectious cause were ascertained from the death file in the USRDS, which collates pertinent information from several sources. Nonfatal outcomes of interest were ascertained from International Classification of Diseases (9th Revision; ICD-9) diagnosis codes from inpatient Medicare claims using validated algorithms and included stroke (ICD-9: 430, 431, 432.x, 433.x1, 434.x1, 436, 437.1), myocardial infarction (MI; ICD-9: 410.x1), as well as a composite of stroke, MI and cardiovascular mortality. In addition, we investigated infectious outcomes using a composite of infectious hospitalization and death reportedly due to an infectious cause [9].

Table 1. Characteristics of ferumoxytol and matched IS or sodium FG complex facilities

Variable	Ferumoxytol		IS or sodium FG complex	
	n = 265	%	*n* = 795	%
Facility type[a]				
Non-chain	152	57.4	456	57.4
Chain	113	42.6	339	42.6
Facility type[a]				
Free standing	254	95.8	762	95.8
Hospital based	11	4.2	33	4.2
Profit status				
Missing			2	0.3
Not for profit	64	24.2	130	16.4
For profit	201	75.8	663	83.4
Facility size				
0–49	96	36.2	289	36.4
50+	169	63.8	506	63.6
Region[a]				
Northwest	49	18.5	147	18.5
Midwest	57	21.5	171	21.5
South	93	35.1	279	35.1
West	66	24.9	198	24.9

[a]From among 278 facilities that switched from IS or sodium FG complex to ferumoxytol between July 2009 and December 2011, we hard-matched three dialysis units each that remained with IS or sodium FG complex on facility type (hospital based versus free standing), chain (versus non-chain) affiliation and geographic region in the month and year of the switching event. We were able to match 265 (95.3%) of facilities that switched to ferumoxytol.

Table 2. Characteristics of patients initiating dialysis in matched ferumoxytol and IS or sodium FG complex facilities

Variable (% missing)	All patients		Ferumoxytol		IS or sodium FG complex		SD
	n or median, 14 206	% or IQR	*n* or mean, 3752	% or IQR	*n* or mean, 10 454	% or IQR	
Age (years)	65	55–76	65	54–75	66	55–76	−2.9
Female sex	6220	43.8	1658	44.2	4562	43.6	−1.1
Race (0.2%)							
White	9457	66.6	2620	69.8	6837	65.4	1.7
Black	3612	25.4	858	22.9	2754	26.3	−7.8
Asian	959	6.8	239	6.4	720	6.9	−2.1
Other	138	1.0	26	0.7	112	1.1	−4.0
Hispanic ethnicity (0.7%)	2311	16.3	703	18.7	1608	15.4	8.9
Medicaid eligibility	4161	29.3	1087	29.0	3074	29.4	−1.0
Comorbidities							
Diabetes	8006	56.4	2109	56.2	5897	56.4	−0.5
Hypertension	12 307	86.6	3275	87.3	9032	86.4	2.6
Arteriosclerotic heart disease	3429	24.1	987	26.3	2442	23.4	6.8
Heart failure	4848	34.1	1387	37.0	3461	33.1	8.1
Peripheral vascular disease	2017	14.2	620	16.5	1397	13.4	8.9
Cerebrovascular disease	1465	10.3	431	11.5	1034	9.9	5.2
Chronic obstructive lung disease	1544	10.9	404	10.8	1140	10.9	−0.5
Cancer	1206	8.5	310	8.3	896	8.6	−1.1
Unable to ambulate	1305	9.2	367	9.8	938	9.0	2.8
Unable to transfer	694	4.9	173	4.6	521	5.0	−1.8
Tobacco use	897	6.3	244	6.5	653	6.2	1.0
Drug use	213	1.5	68	1.8	145	1.4	3.4
Alcohol use	274	1.9	85	2.3	189	1.8	3.2
Reported measurements							
Body mass index, kg/m^2 (2.2%)	27.7	23.7–33.0	27.8	23.7–33.3	27.7	23.6–32.9	3.6
<18.5	510	3.6	142	3.8	368	3.5	1.5
18.5–24.9	4171	29.4	1078	28.7	3093	29.6	−1.8
25.0–29.9	3956	27.8	1032	27.5	2924	28.0	−0.9
≥30.0	5268	37.1	1415	37.7	3853	36.9	2.0
Hemoglobin, g/dL (7.3%)	9.7	8.8–10.7	9.7	8.8–10.6	9.7	8.8–10.7	−0.2
Serum albumin, g/dL (22.2%)	3.2	2.7–3.6	3.2	2.7–3.6	3.2	2.7–3.6	−1.9
eGFR at time of dialysis initiation, mL/min per 1.73 m^2 (3.0%)	10.4	7.6–14.0	10.6	7.8–14.2	10.4	7.5–13.9	5.3

All incident hemodialysis patients in these facilities were captured for analysis of mortality end points regardless of their health insurance status. eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; IQR, interquartile range; SD, standardized difference.

Statistical analysis

We first tabulated the characteristics of the matched ferumoxytol and IS (or FG) facilities. We then tabulated the characteristics of all enrolled incident hemodialysis patients by whether they dialyzed in a ferumoxytol versus an IS (or FG) facility. Groups were compared using standardized differences with <10%, indicating good balance [10]. We examined cumulative incidence plots for all outcomes for any differences in event rates or censoring events. We used Cox proportional hazards regression stratified on matching set to estimate unadjusted hazard ratios (HR) and corresponding 95% confidence intervals (95% CI). Schoenfeld residual plots were examined to identify any violations of the proportionality assumption. Since a few characteristics were slightly unbalanced between groups, we also fit demographics-adjusted models and models that included all reported comorbidities and biometric/laboratory characteristics. Missing data were addressed with multiple imputation by chained equation using the MICE package in R [11].

We conducted statistical analyses using SAS software, version 9.3 (www.sas.com) and R (www.r-projects.org). The Stanford University School of Medicine and Baylor College of Medicine Institutional Review Boards approved the study.

RESULTS

Between July 2009 and December 2011, 278 US small-chain or independent hemodialysis facilities adopted predominant use of ferumoxytol for their patients, of which we matched on facility type, chain status and geographic region 265 units (95.3%) with 3 units each that had continued to predominantly use IS or FG in the same month and year. Their facility characteristics are shown in Table 1. After the index date and prior to censoring of the matched facility pair, 14 206 patients initiated hemodialysis in these centers, 3752 (26.4%) in ferumoxytol and 10 454 (73.6%) in IS or FG facilities. Patient characteristics were quite similar among patients initiating hemodialysis in ferumoxytol versus IS or FG facilities (Table 2); all measured characteristics had a standardized difference of <10, indicating good balance. Patient-level separation of iron exposure during follow-up, assessed from monthly prevalent patients with Medicare coverage in these units, was excellent: 89.3% of patients received only IS/FG in this exposure group (1.8% received only ferumoxytol and 8.8% received both IS/FG and ferumoxytol), whereas 83.9% of patients received only ferumoxytol in

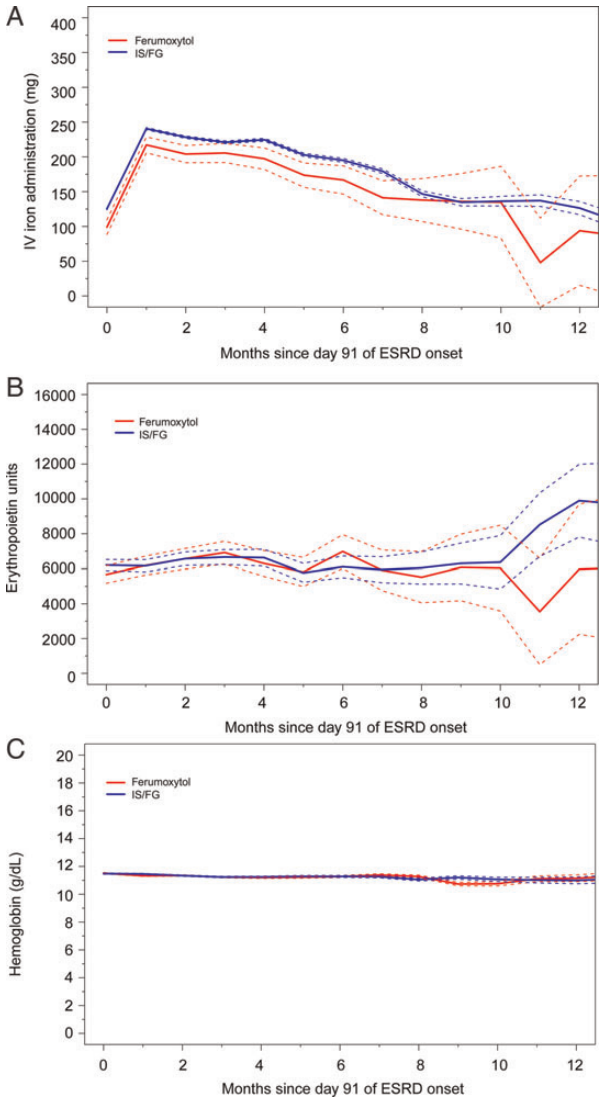

FIGURE 1: Comparison of anemia treatment characteristics during follow-up between patients initiating dialysis in ferumoxytol and matched IS or sodium FG complex facilities (IS/FG; patients on Medicare A and B in the corresponding month). (**A**) Mean monthly intravenous iron dose (in mg). (**B**) Mean monthly erythropoiesis-stimulating agent dose (in units). (**C**) Mean achieved hemoglobin concentration (in g/dL).

this corresponding exposure group (6.9% received only IS/FG and 9.2% received both IS/FG and ferumoxytol). Mean dose of administered intravenous iron was marginally lower in the ferumoxytol group and the mean erythropoiesis-stimulating agent dose administered was comparable and the mean hemoglobin concentration that patients achieved during follow-up was essentially identical between the two exposure groups (Figure 1), thus validating that other anemia practices were not meaningfully different between ferumoxytol facilities and those predominantly using IS or FG.

During follow-up over a total of 6433 person-years, 1929 deaths, 726 cardiovascular deaths and 191 infectious deaths occurred for incidence rates of 300, 113 and 30 per 1000 person-years, respectively (Table 3). Compared with patients who initiated dialysis in IS or FG facilities, patients in ferumoxytol facilities experienced similar all-cause mortality (HR: 0.95; 95% CI: 0.85–1.07), cardiovascular mortality (HR: 0.99; 95% CI: 0.83–1.19) and mortality from infectious causes (HR: 0.88; 95% CI: 0.61–1.25). These results were robust to adjustment for demographic or clinical characteristics (Table 3).

For analyses of nonfatal end points that were ascertained from medical claims, we identified 5513 incident hemodialysis patients who were alive and covered by Medicare Parts A + B at 90 days after the reported ESRD date: 1545 (28.0%) in ferumoxytol and 3968 (72.0%) in IS or FG facilities. There were fewer Black and more Hispanic individuals in ferumoxytol facilities; all other characteristics were once again balanced with standardized differences <10 (Table 4). Over 1848 person-years, 297 cardiovascular events (MIs, strokes and cardiovascular deaths) occurred for an incidence rate of 161 per 1000 person-years, with no difference between the iron exposure groups (HR: 1.05; 95% CI: 0.79–1.39; Table 3). Infectious hospitalizations occurred in 1792 individuals for an incidence rate of 1266 per 1000 person-years, also not different between patients treated in ferumoxytol versus in IS or FG facilities (HR: 0.96; 95% CI: 0.85–1.08; Table 3). These results were insensitive to adjustment for any recorded baseline characteristics.

In sensitivity analyses that restricted the comparison group to facilities predominantly using IS, we matched all 278 ferumoxytol with 556 IS facilities (Supplementary Table S1). Mortality analyses were conducted in 12 881 incident patients and outcomes that included nonfatal events were evaluated in 4940 incident patients who survived to Day 90 from their ESRD incidence date. In these analyses, there were fewer Blacks and more Hispanics in ferumoxytol facilities. In addition, certain cardiovascular comorbidities were more common among patients in ferumoxytol facilities (Supplementary Tables S2 and S3), while all other characteristics were balanced. Similar to the main analyses, outcomes were generally similar between patients initiating dialysis in a ferumoxytol versus an IS facility (Supplementary Table S4) whether adjusted or not.

DISCUSSION

We used the national US ESRD registry to compare the outcomes of hemodialysis patients treated at facilities using ferumoxytol with other patients treated at facilities that almost exclusively used either IS or FG. Using the observed preference of predominantly using one specific iron product as an instrument, we observed no difference between ferumoxytol and the other commonly used intravenous iron formulations with regard to mortality, cardiovascular or infectious outcomes.

Contract negotiations for the, often exclusive, addition of a specific drug to the provider's formulary recur repeatedly leading entire facilities to switch all of their patients to another product if the new contract is with another manufacturer. As a result, most US facilities used either sodium FG complex (approved by the FDA on 18 February 1999) or IS (approved by the FDA on 6 November 2000) for almost all of their patients for more than a decade. (Iron dextrans had essentially been abandoned due to their risk of rare, but severe side effects.) On 30 June 2009, ferumoxytol was approved by the FDA as

Table 3. Follow-up time, number of events, incidence rates and HR; incident patients in hemodialysis centers using ferumoxytol versus IS or sodium FG complex

Outcome	Sample size	Follow-up time (person-years)	Number of events	Incidence rate (per 1000 person-years)	Unadjusted HR (95% CI)	Model 1, HR* (95% CI)	Model 2, HR** (95% CI)
Mortality	14 206	6432.7	1929	299.9	0.95 (0.85, 1.07)	0.98 (0.88, 1.10)	0.97 (0.87, 1.09)
Cardiovascular mortality	14 206	6432.7	726	112.9	0.99 (0.83, 1.19)	1.07 (0.89, 1.28)	1.09 (0.91, 1.31)
Cardiovascular composite (stroke, MI and cardiovascular mortality)	5513	1848.0	297	160.7	1.05 (0.79, 1.39)	1.09 (0.82, 1.46)	1.10 (0.82, 1.48)
Infectious mortality	14 206	6432.7	191	29.7	0.88 (0.61, 1.25)	0.86 (0.61, 1.23)	0.88 (0.61, 1.28)
Infectious hospitalization	5513	1415.1	1792	1266.3	0.96 (0.85, 1.08)	0.96 (0.85, 1.07)	0.96 (0.85, 1.08)
Infectious composite (infectious hospitalization and infectious morality)	5513	1415.1	1793	1267.0	0.96 (0.85, 1.07)	0.95 (0.85, 1.07)	0.95 (0.85, 1.07)

Patients in IS/FG facilities constitute the reference group. Time-to-event analyses started on the day of reported incidence of ESRD for mortality outcomes and on Day 91 after ESRD for nonfatal and composite outcomes. *Model 1 adjusted for age, sex, race, Hispanic ethnicity, Medicaid eligibility and incidence year. **Model 2 additionally adjusted for all comorbidities, body mass index, serum albumin concentration and estimated glomerular filtration rate. Multiple imputation was used to address missing data. Results from complete case analyses were not materially different (not shown).

Table 4. Characteristics of patients initiating dialysis in ferumoxytol and matched IS or sodium FG complex facilities among Medicare Parts A + B patients

Variable (% missing)	All patients	Ferumoxytol	IS or sodium FG complex				SD
	n or median, 5513	% or IQR	*n* or median , 1545	% or IQR	*n* or median, 3968	% or IQR	
Age (years)	68	57–77	68	57–77	68	57–77	−0.3
Female sex	2478	44.9	709	45.9	1769	44.6	−2.6
Race (<0.1%)							
White	3815	69.2	1154	74.7	2661	67.1	5.5
Black	1321	24.0	301	19.5	1020	25.7	−14.6
Asian	307	5.6	77	5.0	230	5.8	−3.3
Other	68	1.2	13	0.8	55	1.4	−4.9
Hispanic ethnicity (0.3%)	861	15.6	292	18.9	569	14.3	12.2
Medicaid eligibility	1855	33.6	496	32.1	1359	34.2	−4.8
Comorbidities							
Diabetes	3173	57.6	885	57.3	2288	57.7	−1.2
Hypertension	4857	88.1	1357	87.8	3500	88.2	−2.2
Arteriosclerotic heart disease	1493	27.1	440	28.5	1053	26.5	4.1
Heart failure	2076	37.7	634	41.0	1442	36.3	9.4
Peripheral vascular disease	864	15.7	269	17.4	595	15.0	6.4
Cerebrovascular disease	616	11.2	188	12.2	428	10.8	4.2
Chronic obstructive lung disease	666	12.1	184	11.9	482	12.1	−0.9
Cancer	481	8.7	123	8.0	358	9.0	−3.9
Unable to ambulate	505	9.2	143	9.3	362	9.1	0.3
Unable to transfer	274	5.0	70	4.5	204	5.1	−2.9
Tobacco use	355	6.4	109	7.1	246	6.2	3.3
Drug use	72	1.3	23	1.5	49	1.2	2.1
Alcohol use	87	1.6	29	1.9	58	1.5	3.2
Reported measurements							
Body mass index, kg/m^2 (1.6%)	27.6	23.6–32.7	27.7	23.5–32.8	27.6	23.7–32.7	−0.02
<18.5	179	3.2	53	3.4	126	3.2	1.4
18.5–24.9	1668	30.3	480	31.1	1188	29.9	2.4
25.0–29.9	1572	28.5	408	26.4	1164	29.3	−6.7
≥30.0	2005	36.4	581	37.6	1424	35.9	3.5
Hemoglobin, g/dL (8.0%)	9.7	8.8–10.7	9.8	8.8–10.7	9.7	8.8–10.7	2.2
Serum albumin, g/dL (21.0%)	3.2	2.7–3.6	3.1	2.7–3.6	3.2	2.7–3.6	−3.0
eGFR at time of dialysis initiation, mL/min per 1.73 m^2 (2.8%)	10.6	7.8–14.1	10.8	7.9–14.6	10.5	7.8–14.0	5.9

Incident hemodialysis patients in the study facilities who had Medicare Parts A and B coverage on Day 90 after initiation of dialysis were captured for analysis of claims-based end points. eGFR, estimated glomerular filtration rate; IQR, interquartile range; SD, standardized difference.

an additional choice for intravenous iron therapy in ESRD. Since these negotiations do not consider the types of patients cared for and—conversely—patients do not select dialysis facilities for the specific iron formulation they use, this 'natural experiment' provides a suitable instrument to comparative effectiveness questions, especially for medications that may not be given continuously.

Head-to-head comparisons of intravenous iron formulations are rare and the assumption of a treatment class regarding similar effectiveness and safety appears commonly accepted.

However, at least one small trial provides evidence that this class assumption may not be appropriate and pointed toward a potential increase in infectious risk with IS [12].

A recent Phase II efficacy trial randomized 162 anemic and iron-deficient patients with CKD, 43% of whom were on dialysis, to 1.02 g of ferumoxytol (2 administrations) or 1 g of IS (5 or 10 administrations) [13]. No difference in the hemoglobin response after 5 weeks was observed. Rates of serious adverse events were 9% (ferumoxytol) and 7% (IS), respectively, and related serious adverse events occurred in 1% in both groups. Clearly, this study was not powered to detect any differences in important clinical outcomes such as cardiovascular or infectious events. We are aware of at least three other randomized head-to-head trials of other agents than ferumoxytol (IS versus sodium FG complex [14], iron gluconate versus iron saccharate [15], iron dextran versus IS versus sodium FG complex [16]). The former two studies were very small and focused on hemoglobin as the study end point. The latter study was larger ($n = 339$) and focused on safety and found the odds for serious adverse drug events (all) to be significantly higher with iron dextran compared with IS.

We are unaware of any observational studies comparing the safety of ferumoxytol with other iron agents. One single-arm study of 8666, mostly prevalent, patients who received ferumoxytol at three US chains found effectiveness and safety patterns that were consistent with expectation [6]. Only 126 patients (1.45%) experienced a total of 375 adverse events, including 45 severe adverse events. Only two (0.02%) patients experienced a serious anaphylactoid reaction, which is remarkable since the FDA's Adverse Event Reporting System (AERS) had registered unusual activity associated with ferumoxytol (serious cardiac disorders) as stated in the AERS Q2/2010 Report [17]. The label was subsequently amended in November 2010 to include these new concerns about life-threatening hypersensitivity reactions [18]. However, this study did not draw any informal or formal comparison with other cohorts of patients using IS or FG. Therefore, the findings from our study are informative in that we did not find any major differences in death and important nonfatal outcomes in rather similar cohorts of patients cared for in settings where ferumoxytol versus another intravenous iron formulation was used for anemia treatment.

Certain limitations of our study require consideration. Our comparisons of ferumoxytol and IS or FG were not randomized and therefore residual confounding remains possible. However, we used an intuitive quasi-experimental approach that mimicked a cluster-randomized trial in which facilities rather than individual patients are randomized to receiving one treatment or another. While the current study was not randomized, treatment with ferumoxytol versus IS or FG was evidently determined by formulary decisions at the facility level and independent of patient characteristics. Indeed, after matching facilities by specific criteria such as location, type and profit status, patients were similar between ferumoxytol facilities and those that predominantly used another iron formulation. Furthermore, we did not conduct a per protocol analysis in which we would only compare patients based on the drug received. For the specific case of intravenous iron injections, such an approach is impractical since treatment is often not at regular intervals, especially for ferumoxytol in which higher doses are given with each injection than with other iron preparations, and gets initiated dependent on iron status parameters and often stopped upon intercurrent (infectious) events. This per protocol analysis would be prone to time-dependent confounding which a facility-level analysis can avoid. While we were able to demonstrate similar anemia practices (mean administered iron and erythropoesis-stimulating agent dose, achieved hemoglobin concentration) between the exposure groups, we had no information on other iron status parameters (e.g. ferritin and transferrin saturation). Finally, we were unable to study the rather rare event of anaphylactoid reactions, for which our study was vastly underpowered and for which a different study design would have been more appropriate.

We conclude that in the typical hemodialysis care setting, ferumoxytol possess similar short- to mid-term safety profiles with regard to cardiovascular, infectious and mortality outcomes compared with the more commonly used intravenous iron formulations IS and FG.

SUPPLEMENTARY DATA

Supplementary data are available online at http://ndt.oxfordjournals.org.

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CONFLICT OF INTEREST STATEMENT

W.C.W. reports having served within the past 3 years as a scientific advisor to Affymax, Amgen, Astra-Zeneca, Astellas, Bayer, Fibrogen, GlaxoSmithKline, Keryx, Mitsubishi-Tanabe, Rockwell Pharma and Sandoz and on data safety monitoring boards for Medgenics and Medtronic. M.A.B. has received investigator-initiated research funding from Amgen and has served as a scientific advisor to Amgen, Merck, Pfizer and Rockwell Pharma. None of the remaining authors have anything to disclose.

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ORIGINAL ARTICLE

Impact of extracorporeal blood flow rate on blood pressure, pulse rate and cardiac output during haemodialysis

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ABSTRACT

Background. If blood pressure (BP) falls during haemodialysis (HD) [intradialytic hypotension (IDH)] a common clinical practice is to reduce the extracorporeal blood flow rate (EBFR). Consequently the efficacy of the HD (Kt/V) is reduced. However, only very limited knowledge on the effect of reducing EBFR on BP exists and data are conflicting. The aim of this study was to evaluate the effect and the potential mechanism(s) involved by investigating the impact of changes in EBFR on BP, pulse rate (PR) and cardiac output (CO) in HD patients with arteriovenous-fistulas (AV-fistulas).

Methods. We performed a randomized, crossover trial in 22 haemodynamically stable HD patients with AV-fistula. After a conventional HD session each patient was examined during EBFR of 200, 300 and 400 mL/min in random order. After 15 min when steady state was achieved CO, BP and PR were measured at each EFBR, respectively.

Results. Mean (SD) age was 71 (11) years. Systolic BP was significantly higher at an EBFR of 200 mL/min as compared with 300 mL/min [133 (23) versus 128 (24) mmHg; $P < 0.05$], but not as compared with 400 mL/min [133 (23) versus 130 (19) mmHg; $P = 0.20$]. At EBFR of 200, 300 and 400 mL/min diastolic BP, mean arterial pressure, PR and CO remained unchanged.