Ferric Gluconate Reduces Epoetin Requirements in Hemodialysis Patients with Elevated Ferritin

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ABSTRACT

The *D*ialysis Patients *R*esponse to *IV* Iron with *E*levated Ferritin (DRIVE) study demonstrated the efficacy of intravenous ferric gluconate to improve hemoglobin levels in anemic hemodialysis patients who were receiving adequate epoetin doses and who had ferritin levels between 500 and 1200 ng/ml and transferrin saturation (TSAT) ≤25%. The DRIVE-II study reported here was a 6-wk observational extension designed to investigate how ferric gluconate impacted epoetin dosage after DRIVE. During DRIVE-II, treating nephrologists and anemia managers adjusted doses of epoetin and intravenous iron as clinically indicated. By the end of observation, patients in the ferric gluconate group required significantly less epoetin than their DRIVE dose (mean change of −7527 ± 18,021 IU/wk, $P = 0.003$), whereas the epoetin dose essentially did not change for patients in the control group (mean change of 649 ± 19,987 IU/wk, $P = 0.809$). Mean hemoglobin, TSAT, and serum ferritin levels remained higher in the ferric gluconate group than in the control group ($P = 0.062$, $P < 0.001$, and $P = 0.014$, respectively). Over the entire 12-wk study period (DRIVE plus DRIVE-II), the control group experienced significantly more serious adverse events than the ferric gluconate group (incidence rate ratio = 1.73, $P = 0.041$). In conclusion, ferric gluconate maintains hemoglobin and allows lower epoetin doses in anemic hemodialysis patients with low TSAT and ferritin levels up to 1200 ng/ml.

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In patients with chronic kidney disease, an erythropoiesis stimulating agent (ESA) and iron must be present in sufficient quantities to effectively produce red blood cells. These 2 factors are easily modifiable, and nephrologists are adept at manipulating these therapies. However, controversy remains as to how to optimize iron and ESA administration and under which circumstances benefits exceed risks. This is especially true for ESAs, which have recently acquired a boxed warning.[1–3]

Studies in hemodialysis patients have repeatedly shown greater use of intravenous iron invariably results in lower epoetin doses while maintaining or increasing hemoglobin (Hb)/hematocrit levels.[4–9] However, these studies are hampered by various limitations, including small sample size, lack of a proper control group, and inclusion of few or no patients with baseline ferritin levels more than 500 ng/ml. Furthermore, those studies tended to in-

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clude patients who required relatively low epoetin doses. Therefore, there is little information in the published literature on the effect of intravenous iron on epoetin doses of hemodialysis patients who are anemic despite baseline ferritin levels more than 500 ng/ml and larger epoetin doses, a picture commonly encountered in clinical practice.

Minimizing the dose of ESAs may be beneficial for patients. A recent safety advisory about ESAs by the U.S. Food and Drug Administration recommended using the lowest dose possible of ESA when treating patients.[1–3] The 2006 anemia guidelines by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative recommend that dose of ESA be considered as one of several factors when deciding to administer intravenous iron to patients.[10]

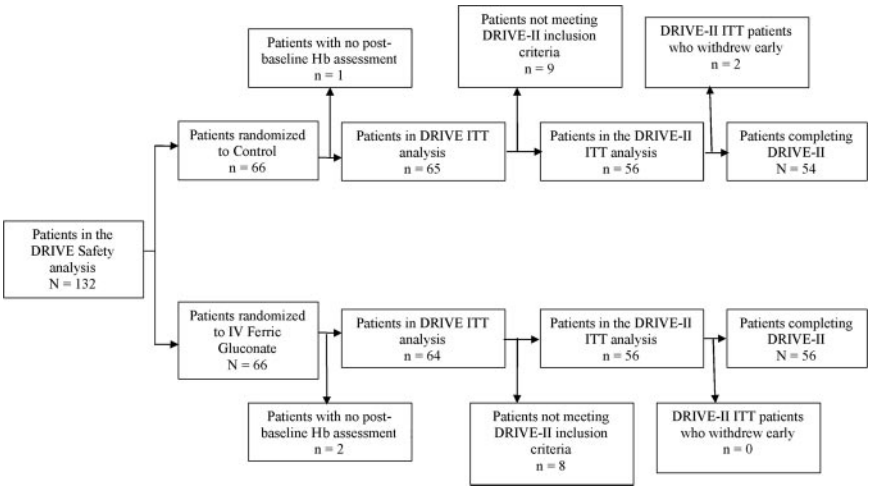

Figure 1. A schematic of patient disposition in DRIVE-II.

The Dialysis Patients Response to IV Iron with Elevated Ferritin (DRIVE) study was a randomized controlled trial that showed that intravenous ferric gluconate was effective in improving anemia in hemodialysis patients with ferritin of 500 to 1200 ng/ml, transferrin saturation (TSAT) $\leq$ 25%, and adequate epoetin doses,[11] disproving the widely held belief that patients with ferritin more than 500 ng/ml are unlikely to benefit from intravenous iron administration.[10,12,13] In the context of an increased epoetin dose, intravenous ferric gluconate patients were more likely to mount a hematologic response than controls, regardless of baseline levels of ferritin, TSAT, C-reactive protein, Hb, soluble transferrin receptor, epoetin dose, or reticulocyte Hb content.[14]

However, because of study design, DRIVE could not answer several important questions. The 6-wk duration of the DRIVE study did not permit evaluation of the sustainability of the hematologic response to intravenous iron or its effects on iron indices over a longer observation period under usual clinical anemia management. More importantly, the study could not evaluate epoetin-sparing effects of intravenous iron because epoetin dose adjustments were prohibited.

The DRIVE-II study was a 6-wk, observational extension of the DRIVE study, designed to investigate the extended effects of a 1-g course of intravenous ferric gluconate on epoetin doses, as well as Hb, TSAT, and serum ferritin under usual clinical management.

RESULTS

Of the 129 patients who were in the intent-to-treat (ITT) analysis of DRIVE, 11 patients did not participate for at least one of the following reasons: site did not participate in this follow-up study (1), transfer to another hemodialysis unit (1), transplantation (1), vacation (1), inability/refusal to provide informed consent (5), and death before receiving any dialysis treatments during DRIVE-II (2). Thus, 118 patients participated in DRIVE-II. Of those, 6 patients were considered unevaluable because they did not have at least 1 wk of epoetin doses before dropping out of the study or switching to darbepoetin. Therefore, 112 patients (56 in the control group and 56 in the intravenous ferric gluconate group) were included in the ITT analysis of the DRIVE-II study (Figure 1).

Table 1 summarizes the demographics, renal history, pre-DRIVE baseline epoetin doses, DRIVE epoetin doses, and end-of-DRIVE Hb, TSAT, and serum ferritin values. Patients in the 2 groups had similar demographics, renal history, and DRIVE epoetin doses. As previously reported, end-of-DRIVE Hb, TSAT, and serum ferritin were higher in the intravenous ferric gluconate group, but end-of DRIVE C-reactive protein levels were similar in the 2 groups.[11]

During the 6-wk DRIVE-II observation period, 33 (59%) patients (16 ferric gluconate; 17 iron sucrose) assigned to the control group received supplemental intravenous iron (median dose, 200 mg; range, 0–1250 mg; mean $\pm$ SD, 326 $\pm$ 372 mg), compared with 22 (39%) patients (13 ferric gluconate; 9 iron sucrose) in the intravenous ferric gluconate group (median dose, 0 mg; range, 0–875 mg; mean $\pm$ SD, 131 $\pm$ 214 mg).

Efficacy Variables

By the end of DRIVE-II, patients in the intravenous ferric gluconate group required significantly lower epoetin doses compared with their DRIVE dose (change of $-7527 \pm 18{,}021$ IU/wk, $P = 0.003$; median, -5700 IU/wk; interquartile range, $-18{,}525$ to 0 IU/wk), whereas epoetin doses were essentially unchanged in the control group (change of $649 \pm 19{,}987$ IU/wk, $P = 0.809$; median, 0 IU/wk; interquartile range, -375 to 8250 IU/wk) (Figure 2). The difference between the 2 groups in their change in weekly epoetin dose was statistically significant ($P = 0.017$, Figure 2). On average, patients who received intravenous ferric gluconate during DRIVE required 466 IU/kg per wk of epoetin (decreased from 568 ± 293 IU/kg per wk) com-

Table 1. Characteristics of patients in the DRIVE-II intent-to-treat analysis[a]

	Control ($n = 56$)	IV Ferric Gluconate ($n = 56$)
Age, yr	58.8 ± 15.5	60.7 ± 13.5
Females, n (%)	32 (57.1)	25 (44.6)
Weight, kg	74.9 ± 22.9	78.6 ± 21.2
Height, cm	168.2 ± 9.5	167.4 ± 10.5
Race, n (%)		
white	17 (30.4)	19 (33.9)
black	28 (50.0)	27 (48.2)
Hispanic	8 (14.3)	7 (12.5)
Asian/Pacific Islander	2 (3.6)	3 (5.4)
other	1 (1.8)	0 (0.0)
Etiology of CKD stage 5, n (%)		
diabetes	21 (37.5)	22 (39.3)
hypertension	21 (37.5)	20 (35.7)
glomerulonephritis	7 (12.5)	7 (12.5)
cystic disease	2 (3.6)	0 (0.0)
other	6 (10.7)	8 (14.3)
Type of HD access, n (%)		
AV graft	18 (32.1)	17 (30.4)
AV fistula	25 (44.6)	28 (50.0)
temporary catheter	3 (5.4)	2 (3.6)
permanent catheter	10 (17.9)	9 (16.1)
DRIVE epoetin dose, 1000 IU/wk	45.0 ± 23.5	43.7 ± 22.4
median (interquartile range)	37.7 (29.7–54.6)	37.5 (26.9–54.8)
hs-CRP at end of DRIVE, mg/L		
median (interquartile range)	16.9 (5.5–38.6)	13.2 (4.6–25.3)

HD, hemodialysis; AV, arteriovenous; CRP, high sensitivity C-reactive protein.
[a]Except where stated, all continuous variables are summarized in the form of mean ± SD. For between-group comparisons, all *P* values >0.245.

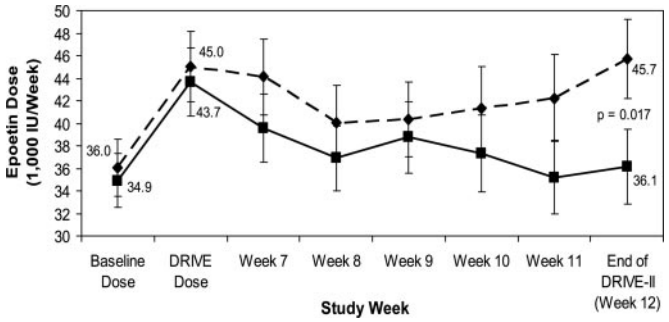

Figure 2. Epoetin dose throughout DRIVE-II. Baseline weekly epoetin doses were similar in the 2 groups, resulting in similar DRIVE epoetin doses. By wk 12, epoetin doses had dropped significantly lower in the intravenous ferric gluconate group (solid line) than the control (dashed line) ($P = 0.017$). Final epoetin doses were similar to their baseline (pre-25% epoetin dose increase) counterparts in the intravenous ferric gluconate group (P = not significant), whereas they were significantly higher in the control group ($P < 0.05$).

pared with 644 IU/kg per wk in their control counterparts (essentially unchanged from 639.2 ± 360.5 IU/kg per wk). By the end of DRIVE-II, weekly epoetin doses had decreased to levels similar to pre-DRIVE doses in the intravenous ferric gluconate group while remaining significantly higher in the control group (Figure 2). The reduction in epoetin dose was not related to the patient's initial ferritin stratum (≤800 ng/ml *versus* >801 ng/ml) (Table 2). Despite the reduction in epoetin doses, significantly more of the intravenous ferric gluconate patients maintained their Hb above 11.0 g/dl (83.9%) than control patients (67.9%; $P < 0.05$).

Hemoglobin, TSAT, and serum ferritin levels remained higher in the intravenous ferric gluconate group (Figures 3 through 5) than in the control group ($P = 0.062$, $P < 0.001$, and $P = 0.014$, respectively) at the end of DRIVE-II. Comparing the changes from the end of DRIVE (wk 6) to DRIVE-II endpoint (wk 12), there were no significant differences between groups in the change in Hb, TSAT, or serum ferritin. Hemoglobin change from end-of-DRIVE was 0.2 ± 1.3 g/dl and 0.2 ± 1.2 g/dl in the control and intravenous ferric gluconate groups, respectively ($P = 0.432$). TSAT change from end-of-DRIVE was −1.6 ± 7.0% points in the control ($P = 0.13$) and −0.6 ± 14.9% points and intravenous ferric gluconate groups (P = not significant), respectively. Ferritin levels increased by 35 ± 241 ng/ml in the control group (P = not significant) and fell by 92 ± 217 ng/ml in the intravenous ferric gluconate group ($P = 0.009$).

In patients randomized to 1 g of ferric gluconate during DRIVE, as well as any additional iron that may have been given during the 6 wk of DRIVE-II, no significant increase in serum ferritin compared with baseline was noted at end of study, regardless of initial serum ferritin stratification (Table 2). Treatment during DRIVE and/or DRIVE-II had little impact on increasing the number of patients in higher ferritin ranges. Among patients initially in the lower ferritin stratum (baseline ferritin ≤800 ng/ml) who had at least one ferritin value during DRIVE-II, 3 of 26 (11.5%) and 6 of 27 (22.2%) patients in the control and intravenous ferric gluconate groups, respectively, had a ferritin level more than 800 ng/ml at the end of DRIVE-II. Similarly, in patients initially in the upper ferritin stratum (baseline ferritin >800 ng/ml) and who had at least one ferritin value during DRIVE-II, 2 of 16 (12.5%) control patients and 3 of 15 (20.0%) intravenous ferric gluconate patients had a ferritin level more than 1200 ng/ml at the end of DRIVE-II.

There were 23 patients in the control group who received no intravenous iron during DRIVE-II. Their target epoetin DRIVE dose and epoetin dose at the end of DRIVE-II were 49,626 ± 29,666 IU/wk and 52,195 ± 32,176 IU/wk, respectively ($P = 0.562$). By the end of DRIVE-II, their Hb values had not changed since the end of DRIVE (11.4 ± 1.8 *versus* 11.4 ± 1.7 g/dl; $P = 0.953$). Their serum ferritin tended to drop from 612 ± 218 ng/ml to 534 ± 245 ng/ml ($P = 0.077$) while their TSAT increased from 21.4 ± 2.8% to 24.9 ± 5.9% ($P = 0.033$). Although there was a trend toward lower epoetin dose in the control patients who received intravenous iron during DRIVE-II, this did not reach statistical significance. The mean change in epoetin dose between the 33 who received intravenous iron during DRIVE-II was −690 ± 19,231 IU/wk (median, 0 IU/wk; interquartile range, 0–6800 IU/wk) *versus* 2570 ± 20,455 IU/wk (median, 0 IU/wk; interquartile range,

Table 2. Summary of epoetin, hemoglobin, transferrin saturation, and serum ferritin throughout DRIVE and DRIVE-II stratified by baseline serum ferritin

Baseline Ferritin Stratum	Control			IV Ferric Gluconate		
	Baseline	End of DRIVE	End of DRIVE-II	Baseline	End of DRIVE	End of DRIVE-II
≤800 ng/ml						
n		33			34	
epoetin dose, IU/kg per wk	543 ± 329	679 ± 411	671 ± 451	438 ± 253	548 ± 317	445 ± 281
Hb, g/dl	10.2 ± 0.7	11.4 ± 1.1	11.5 ± 1.1	10.3 ± 0.9	11.9 ± 1.4	12.0 ± 1.4
TSAT, %[a]	18.7 ± 3.6	19.9 ± 6.4	17.6 ± 6.2	18.7 ± 3.6	25.5 ± 6.1	23.7 ± 12.8
serum ferritin, ng/ml[a]	631 ± 86	453 ± 172	506 ± 274	622 ± 89	798 ± 184	698 ± 179
> 800 ng/ml						
n		23			22	
epoetin dose; IU/kg per wk	466 ± 216	582 ± 271	605 ± 346	480 ± 207	600 ± 257	500 ± 354
Hb, g/dl	10.1 ± 0.8	11.4 ± 1.6	11.7 ± 1.8	10.3 ± 0.7	12.0 ± 1.3	12.3 ± 1.3
TSAT, %[b]	19.6 ± 4.5	22.5 ± 4.6	21.9 ± 6.3	17.5 ± 4.8	26.4 ± 8.6	25.9 ± 18.3
serum ferritin, ng/ml[b]	923 ± 135	762 ± 292	717 ± 278	968 ± 122	1139 ± 288	995 ± 345

Hb, hemoglobin; TSAT, transferrin saturation.
[a]Based on 31 patients in the control group and 33 patients in the IV ferric gluconate group.
[b]Based on 22 patients in each treatment group.

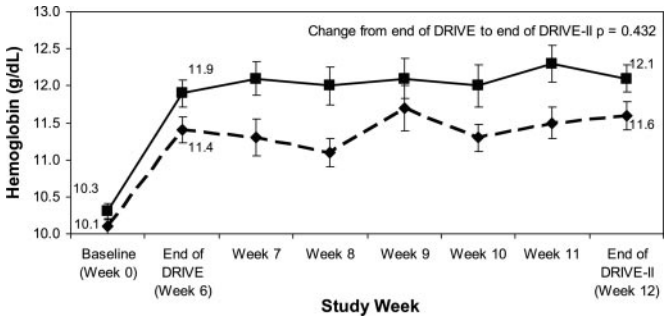

Figure 3. Hemoglobin values throughout DRIVE-II. Ferric gluconate (solid line); control (dashed line).

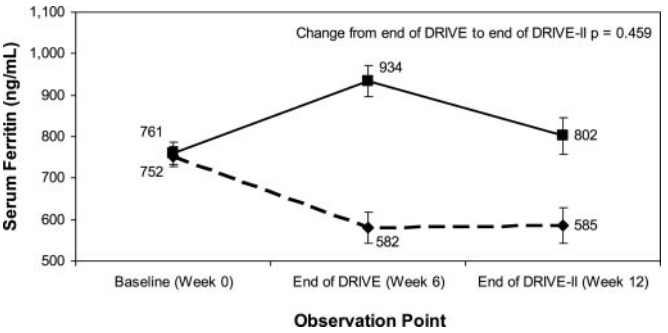

Figure 5. Serum ferritin at baseline, end of DRIVE (wk 6), and end of DRIVE-II (wk 12). Ferric gluconate (solid line); control (dashed line).

−2475 to 16,050 IU/wk) in the 23 patients who did not (P = 0.401, analysis of covariance controlling for DRIVE-II baseline epoetin dose).

A total of 39 intravenous ferric gluconate patients received the entire 1 g of ferric gluconate and experienced no major protocol deviations during DRIVE. Median amount of intravenous iron received by this subgroup during DRIVE-II was 0 mg (interquartile range, 0–187.5 mg). In this subgroup, epoetin doses dropped from 42,119 ± 21,174 IU/wk to 33,124 ± 24,815 IU/wk (P = 0.004). Hemoglobin levels were stable from end of DRIVE to end of DRIVE-II (12.0 ± 1.2 g/dl *versus* 12.0 ± 1.3 g/dl; P = not significant). Serum ferritin dropped from 916 ± 285 ng/ml to 556 ± 280 ng/ml ($P < 0.001$), and TSAT was unchanged (end of DRIVE 26.3 ± 6.2% *versus* end of DRIVE-II 27.1 ± 17.4%; P = 0.755).

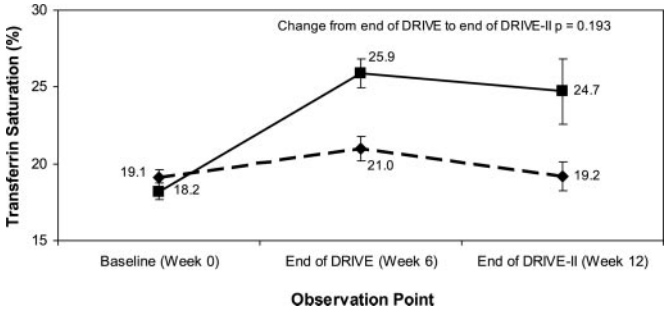

Figure 4. Transferrin saturation at baseline, end of DRIVE (wk 6), and end of DRIVE-II (wk 12). Ferric gluconate (solid line); control (dashed line).

Safety Analyses

Table 3 summarizes the observed serious adverse events (SAEs) by body system. During the entire 12-wk study period, 38 SAEs were experienced by 20 patients in the control group and 22 SAEs were experienced by 15 patients in the intravenous ferric gluconate group. Of those, 24 SAEs occurred in 13 control patients and 10 SAEs occurred in 8 intravenous ferric gluconate patients during DRIVE-II. There was no significant difference in the incidence of serious adverse events occurring during the 6-wk DRIVE-II period alone. However, a *post hoc* analysis using Poisson regression over the entire 12-wk study period (DRIVE plus DRIVE-II) demonstrated a 0.58 incidence rate ratio for hav-

Table 3. Serious adverse events occurring during the entire 12-wk observation period (DRIVE and DRIVE-II) by MedRA classification

	Control ($n = 66$)	IV Ferric Gluconate ($n = 66$)
Cumulative observation period, patient-wk	679	680
Serious adverse events,[a] patients (events)	20 (38)	15 (22)
Cardiac events, patients (events): cardiac arrest, CHF and aggravation thereof, cardiorespiratory arrest, endocarditis, MIs, pulmonary edema, and arrhythmias	9 (10)	6 (6)
Gastrointestinal disorders, patients (events): abdominal pain, ischemic colitis, gastric erosions, acute pancreatitis, and peritonitis	4 (4)	1 (2)
Vascular disorders, patients (events): gangrene, hematoma, hypertension, hypotension, and TIA	4 (4)	3 (3)
Infections, patients (events): cellulitis, clostridial gastroenteritis, implant infections, pneumonia, sepsis, and skin and subcutaneous abscesses	10 (12)	4 (4)
Others, patients (events)	8 (8)	7 (7)

CHF, congestive heart failure; MedRA, Medical Dictionary for Regulatory Activities; MIs, myocardial infarctions; TIA, transient ischemic attack.
[a]Short-term adverse events were similar in both groups.

ing an SAE in the intravenous ferric gluconate group compared with the control group ($P = 0.041$).

DISCUSSION

These results show that administration of 1 g of intravenous ferric gluconate to patients meeting our inclusion criteria results in significantly lower epoetin requirements at 12 wk. Compared with those not initially given intravenous iron, administration of intravenous iron allowed achievement of a greater initial increase in Hb and TSAT, and patients maintained those differences for at least 12 wk. However, increases in Hb must be closely monitored to minimize the potential risks associated with a rapidly rising Hb as well as a concentration more than 12 g/dl.[14–16] The proportional reduction in the epoetin dose observed in our study is similar to that reported following iron administration to dialysis patients with overt iron deficiency (TSAT <20% and ferritin <100 ng/ml).[17,18] However, those studies were small (≤30 patients), and the absolute units of epoetin reduction were much smaller than achieved in our study, which selected patients on higher epoetin doses. Similarly, administration of intravenous iron to patients considered to be "iron-replete" (ferritin ≤600 ng/ml or TSAT >20%) has shown effective epoetin dose reductions and resultant cost savings.[4,5,7,19–21] Until now, there has been little information on the effect of intravenous iron on patients with ferritin levels more than 500 to 600 ng/ml.

A reduction in epoetin requirements is one benefit seen in patients who are treated with intravenous iron preparations. In DRIVE-II, this was accomplished without further rise in serum ferritin. After intravenous iron, mean ferritin increased from baseline (761 ng/ml) to 934 ng/ml at 6 wk, then fell to 802 ng/ml at 12 wk (P = NS *versus* baseline). The increase in ferritin at 6 wk is similar to that observed after 1 g of iron administered to iron-deficient patients.[22,23] The reduction in ferritin toward baseline over a 12-wk period is also similar to previous reports.[7,17]

Some experts have expressed concern that administration of intravenous iron to patients with an elevated ferritin may increase infection rate or infectious complications. The proposed risk of infections from intravenous iron should coincide with intravenous iron administration or follow shortly thereafter. Over the 12 wk of the DRIVE and DRIVE-II studies, we observed less risk of hospitalizations from infections among patients given 1 g of intravenous ferric gluconate compared with the control group. The lack of difference in rates of infections between intravenous ferric gluconate and control may not be generalizable to all intravenous iron preparations. Different rates of bacteremia have been reported with different intravenous iron preparations in patients on maintenance hemodialysis.[24]

DRIVE-II demonstrates that a 1-g load of intravenous ferric gluconate results in a significant reduction in epoetin dose. Randomized trials of higher *versus* lower Hb targets have repeatedly shown increased risk of cardiovascular events or death in the high target arm.[15,25] Because of design, the high target arm invariably requires substantially more epoetin.[26]

In March 2007, the U.S. Food and Drug Administration amended the labeling of all epoetin and darbepoetin products by adding a boxed warning instructing prescribers to "use the lowest dose of ESAs that will gradually increase the Hb concentration to the lowest level sufficient to avoid the need for red blood cell transfusion."[1–3] The statement warns prescribers that, ". . . ESAs increased the risk for death and for serious cardiovascular events when dosed to achieve a target a Hb of greater than 12 g/dl." The dosage instructions were amended to advise against allowing Hb levels to exceed 12 g/dl.[1–3]

Regardless of serum ferritin or TSAT values, administration of intravenous iron to patients on hemodialysis has been shown to be associated with lower risk of all-cause and cardiovascular mortality.[27] Furthermore, to date, no studies have shown an increased risk of mortality with use of intravenous iron at any TSAT or ferritin value. Over a 12-wk period, we observed a significantly lower incidence of SAEs among pa-

tients receiving intravenous iron during DRIVE. The finding that there were more adverse events in the control group, although counterintuitive, may suggest that iron deficiency can be associated with worse and/or more frequent adverse events. The DRIVE-II study demonstrates using intravenous ferric gluconate in patients with ferritin between 500 and 1200 ng/ml minimizes their ESA dose requirements while maintaining Hb levels. No safety concerns were raised in this trial.

This study has several weaknesses. DRIVE-II was a 6-wk observational trial during which adjustments to epoetin dose and intravenous iron therapy were at the discretion of the individual dialysis unit. Although the level of evidence provided by an observational study does not carry the same weight as a randomized control trial, DRIVE-II provides much needed clinical information in this subgroup of anemic hemodialysis patients. During the 6 wk of DRIVE-II, investigators were not restricted in their use of or type of iron product administered. More than half of the control group was given intravenous iron during DRIVE-II, and almost half of all iron administered was in the form of iron sucrose. In this study, the control group required more intravenous iron in addition to higher epoetin doses postintervention, which may indicate that the residual effect of depriving iron when needed may be prolonged. Because both DRIVE and DRIVE-II were unblinded, knowledge of treatment group may have influenced DRIVE-II treatment decisions. Although black patients were overrepresented (~50% of study population) in DRIVE-II, it is unknown if there are racial differences in patient responsiveness to epoetin and intravenous iron preparations. Finally, DRIVE-II relied on Hb, TSAT, and ferritin values that were obtained from the local laboratory of each individual dialysis unit. We did not collect data investigating the variability between local laboratory values and those of the central laboratory used in the DRIVE study. It is unclear if this may have influenced our findings.

Although we observed no difference in cardiovascular events or mortality between the 2 groups over the 12-week study period (DRIVE and DRIVE-II), this study is neither sufficiently long nor large to fully assess these risks. Another limitation of DRIVE-II is the fact that Hb, TSAT, and ferritin values collected depended on the patients' dialysis units' biochemical evaluation schedules. Data were available only if the scheduled biochemical assessments fell within the 6-wk DRIVE-II observation period. Although at least one Hb value was recorded for virtually every study participant, there were some who were missing less frequently assessed indices, such as TSAT and serum ferritin. It is possible, although unlikely, that the missing data may have qualitatively affected our conclusions. We also only tested ferric gluconate administered as 125 mg for 8 consecutive dialysis sessions. Other iron products or different administration regimens could have differing effects related to efficacy, safety, and the changes in TSAT, ferritin, and other iron markers.

Conclusion

A 1-g loading course of intravenous ferric gluconate effectively and safely reduces epoetin doses in hemodialysis patients with low TSAT and serum ferritin levels less than or equal to 1200 ng/ml while maintaining optimal Hb levels. The magnitude of this epoetin dose reduction is similar to that seen in many reports of patients having classic iron deficiency. Accordingly, this study provides additional evidence to support the conclusion of the DRIVE study that intravenous iron is beneficial in maintaining Hb concentration while decreasing epoetin doses in anemic hemodialysis patients with a low TSAT and ferritin levels up to 1200 ng/ml.

Table 4. Inclusion and exclusion criteria for DRIVE[11]

Inclusion criteria
age 18 yr or older
receiving chronic HD for at least 90 days
TSAT ≤ 25%, serum ferritin 500 ng/ml to 1200 ng/ml, and Hb ≤ 11.0 g/dl
epoetin dose ≥ 225 units/kg per wk or ≥22,500 units/wk, with no change in dose or method of administration for ≥14 days
received no more than 125 mg of IV iron in any of the 4 wk preceding screening
Exclusion criteria
use of any investigational agent within 30 days before first day of study treatment
lactating or positive pregnancy test, if applicable
known sensitivity to ferric gluconate or any of its components
evidence of active infection requiring systemic antibiotic therapy at screening
surgical procedure planned within the next 8 wk
evidence of significant blood loss within the previous 6 wk
history of sickle cell or sickled hemoglobin C disease or hematologic malignancies
more than 3 missed hemodialysis treatments during the 8 wk before screening
blood transfusion within the previous 4 wk before screening
inpatient hospitalization within 2 wk before screening

HD, hemodialysis; TSAT, transferrin saturation; Hb, hemoglobin; IV, intravenous.

CONCISE METHODS

This study was conducted in compliance with the Declaration of Helsinki. All participating sites obtained approval of their respective institutional review boards before collecting any study data. All study participants provided informed consent before undergoing any study procedures. This trial was registered with the United States National Institutes of Health through the National Library of Medicine at http://clinicaltrials.gov.

Patient Selection

Patients who participated in DRIVE were eligible for participation in DRIVE-II once their involvement in DRIVE concluded. The DRIVE study design and population were previously described.[11] Briefly, this was an open-label, randomized, controlled, multicenter trial conducted in 37 centers across the United States. The inclusion and exclusion criteria are presented in Table 4.

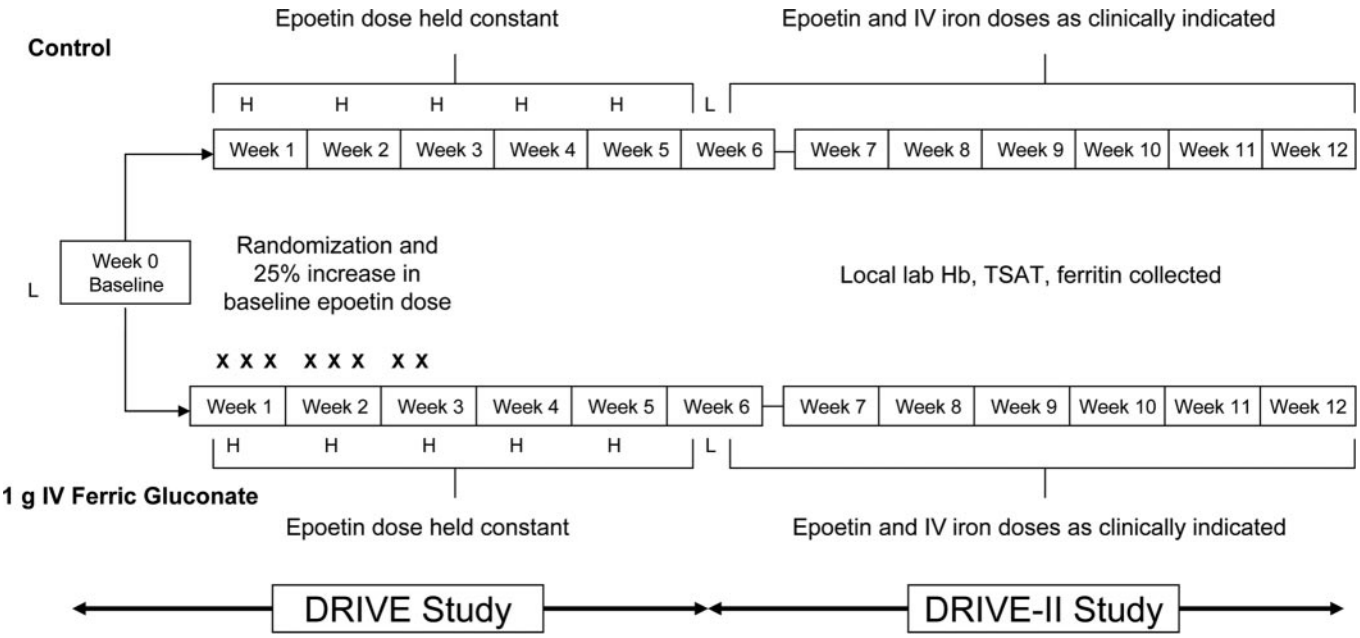

Figure 6. A schematic of the study procedures of DRIVE and DRIVE-II. L, comprehensive laboratory testing; H, hemoglobin and reticulocyte hemoglobin content (CHr) testing; X, 125 mg intravenous ferric gluconate administration.

Study Procedures

The study procedures of DRIVE and DRIVE-II are depicted in Figure 6. The DRIVE study procedures and results have been previously described in detail.[11] Participants were centrally randomized 1:1 to receive either no iron (control) or 1 g of ferric gluconate (Ferrlecit, Watson Laboratories, Morristown, NJ) administered as eight consecutive 125-mg doses beginning with the first hemodialysis session of wk 1 (intravenous iron group). Baseline epoetin doses were increased 25% in both groups at the first hemodialysis session of wk 1, then held constant throughout the DRIVE 6-wk duration except for safety reasons. No additional iron (intravenous or oral) or intravenous ascorbic acid was given during DRIVE. Comprehensive hematology and serum chemistry panels were obtained at baseline (wk 0) and endpoint (wk 6), and Hb was measured weekly.

Once patients completed their involvement in DRIVE (study completion at wk 6, or early withdrawal), they returned to the routine anemia management at their facility. The immediate 6 wk following exiting DRIVE constituted the observational study, DRIVE-II. During DRIVE-II, epoetin dose adjustments and use of intravenous iron therapy were at the discretion of anemia managers and the patients' physicians. Dialysis units were allowed to use any intravenous iron formulation (dextran, ferric gluconate, or sucrose). Hb, TSAT, and ferritin levels were obtained per the HD units' policies through their local laboratories. Information regarding the doses of administered epoetin and intravenous iron was collected, as were Hb, TSAT, and serum ferritin levels of each participant. SAEs were also recorded. The definition of an SAE was that adopted by the International Conference on Harmonization, which is any adverse event that results in any of the following outcomes: death, a life-threatening experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.[28]

Study Objectives

The predefined primary objective of the study was to compare the effects of study treatments given during DRIVE on the epoetin dose administered to patients at 12 wk after the start of treatment (*i.e.*, the difference between groups in change from weekly DRIVE epoetin dose to the wk 12 epoetin dose). In the event that a patient did not complete DRIVE-II or was switched to darbepoetin, the total of the final week of recorded epoetin doses was carried forward and considered the DRIVE-II endpoint dose (wk 12, last observation carried forward). Secondary objectives of DRIVE-II include comparisons between the groups in mean change from end-of-DRIVE Hb, TSAT, and serum ferritin to their corresponding measurements at DRIVE-II endpoint (wk 12 last observation carried forward).

Statistical Analysis

Patients who were in the ITT analysis of the DRIVE study and received at least 1 wk of epoetin doses during the DRIVE-II study period were included in the ITT analysis of DRIVE-II. Continuous variables were summarized using mean ± SD or medians and interquartile ranges. Categorical variables were summarized using frequencies and percentages. Change in weekly epoetin doses, Hb, TSAT, and serum ferritin were analyzed using analysis of covariance with the DRIVE epoetin dose, end-of-DRIVE Hb, end-of-DRIVE TSAT, and end-of-DRIVE serum ferritin as covariates. Comparisons between groups in DRIVE-II endpoint values of all continuous variables were conducted using unpaired *t* test, whereas within-group changes were conducted using paired *t* test. Statistical significance was determined at the alpha = 0.05 level. Statistical analyses were conducted using SAS 8.2 (SAS Institute, Cary, NC).

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REFERENCES

1. Amgen Inc: *Aranesp prescribing information*, Thousand Oaks, CA, Amgen, 2007
2. Amgen Inc: *Epogen prescribing information*, Thousand Oaks, CA, Amgen, 2007
3. Ortho-Biotech: *Procrit prescribing information*, Bridgewater, NJ, Ortho Biotech Products, 2007
4. Besarab A, Amin N, Ahsan M, Vogel SE, Zazuwa G, Frinak S, Zazra JJ, Anandan JV, Gupta A: Optimization of epoetin therapy with intravenous iron therapy in hemodialysis patients. *J Am Soc Nephrol* 11: 530–538, 2000
5. Chang CH, Chang CC, Chiang SS: Reduction in erythropoietin doses by the use of chronic intravenous iron supplementation in iron-replete hemodialysis patients. *Clin Nephrol* 57: 136–141, 2002
6. DeVita MV, Frumkin D, Mittal S, Kamran A, Fishbane S, Michelis MF: Targeting higher ferritin concentrations with intravenous iron dextran lowers erythropoietin requirement in hemodialysis patients. *Clin Nephrol* 60: 335–340, 2003
7. Fishbane S, Frei GL, Maesaka J: Reduction in recombinant human erythropoietin doses by the use of chronic intravenous iron supplementation. *Am J Kidney Dis* 26: 41–46, 1995
8. Kaneko Y, Miyazaki S, Hirasawa Y, Gejyo F, Suzuki M: Transferrin saturation versus reticulocyte hemoglobin content for iron deficiency in Japanese hemodialysis patients. *Kidney Int* 63: 1086–1093, 2003
9. Taylor JE, Peat N, Porter C, Morgan AG: Regular low-dose intravenous iron therapy improves response to erythropoietin in haemodialysis patients. *Nephrol Dial Transplant* 11: 1079–1083, 1996
10. National Kidney Foundation Kidney Disease Outcomes Quality Initiative: Clinical practice guidelines and clinical practice recommendations for anemia in chronic kidney disease. *Am J Kidney Dis* 47: S11-S145, 2006
11. Coyne DW, Kapoian T, Suki W, Singh AK, Moran JE, Dahl NV, Rizkala AR: Ferric gluconate is highly efficacious in anemic hemodialysis patients with high serum ferritin and low transferrin saturation: results of the Dialysis Patients' Response to IV Iron with Elevated Ferritin (DRIVE) Study. *J Am Soc Nephrol* 18: 975–984, 2007
12. Aronoff GR: Safety of intravenous iron in clinical practice: implications for anemia management protocols. *J Am Soc Nephrol* 15: S99-S106, 2004
13. Van Wyck DB, Bailie G, Aronoff G: Just the FAQs: frequently asked questions about iron and anemia in patients with chronic kidney disease. *Am J Kidney Dis* 39: 426–432, 2002
14. Singh AK, Coyne DW, Shapiro W, Rizkala AR: Predictors of response to anemia treatment in hemodialysis patients with high serum ferritin and low transferrin saturation. *Kidney Int* 71: 1163–1171, 2007
15. Singh AK, Szczech L, Tang KL, Barnhart H, Sapp S, Wolfson M, Reddan D, CHOIR Investigators: Correction of anemia with epoetin alfa in chronic kidney disease. *N Engl J Med* 355: 2085–2098, 2006
16. Drueke TB, Locatelli F, Clyne N, Eckardt KU, MacDougal IC, Tsakiris D, Burger HU, Scherhag A, CREATE Investigators: Normalization of hemoglobin level in patients with chronic kidney disease and anemia. *N Engl J Med* 355: 2071–2084, 2006
17. Fishbane S, Lynn RI: The efficacy of iron dextran for the treatment of iron deficiency in hemodialysis patients. *Clin Nephrol* 43: 238–240, 1995
18. Park L, Uhthoff T, Tierney M, Nadler S: Effect of an intravenous iron dextran regimen on iron stores, hemoglobin, and erythropoietin requirements in hemodialysis patients. *Am J Kidney Dis* 31: 835–840, 1998
19. Macdougall IC, Tucker B, Thompson J, Tomson CR, Baker LR, Raine AE: A randomized controlled study of iron supplementation in patients treated with erythropoietin. *Kidney Int* 50: 1694–1699, 1996
20. Schiesser D, Binet I, Tsinalis D, Dickenmann M, Keusch G, Schmidli M, Ambuhl PM, Luthi L, Wuthrich RP: Weekly low-dose treatment with intravenous iron sucrose maintains iron status and decreases epoetin requirement in iron-replete haemodialysis patients. *Nephrol Dial Transplant* 21: 2841–2845, 2006
21. Sepandj F, Jindal K, West M, Hirsch D: Economic appraisal of maintenance parenteral iron administration in treatment of anaemia in chronic haemodialysis patients. *Nephrol Dial Transplant* 11: 319–322, 1996
22. Nissenson AR, Lindsay RM, Swan S, Seligman P, Strobos J: Sodium ferric gluconate complex in sucrose is safe and effective in hemodialysis patients: North American Clinical Trial. *Am J Kidney Dis* 33: 471–482, 1999
23. Warady BA, Zobrist RH, Wu J, Finan E, Ferrlecit Pediatric Study Group: Sodium ferric gluconate complex therapy in anemic children on hemodialysis. *Pediatr Nephrol* 20: 1320–1327, 2005
24. Sirken G, Raja R, Rizkala AR: Association of different intravenous iron preparations with risk of bacteremia in maintenance hemodialysis patients. *Clin Nephrol* 66: 348–356, 2006
25. Besarab A, Bolton WK, Browne JK, Egrie JC, Nissenson AR, Okamoto DM, Schwab SJ, Goodkin DA: The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. *N Engl J Med* 339: 584–590, 1998
26. Vaziri ND: Cardiovascular effects of erythropoietin and anemia correction. *Curr Opin Nephrol Hypertens*; 10: 633–637, 2001
27. Kalantar-Zadeh K, Regidor DL, McAllister CJ, Michael B, Warnock DG: Time-dependent associations between iron and mortality in hemodialysis patients. *J Am Soc Nephrol* 16: 3070–3080, 2005
28. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guideline for Good Clinical Practice. http://www.fda.gov/cder/guidance/959fnl.pdf