

Inadequate VTE Prophylaxis Makes Costs Soar

BY BRUCE JANCIN

SAN DIEGO — Partial venous thromboembolic event prophylaxis in at-risk medical and surgical inpatients is associated with a mean 2-day greater hospital length of stay and \$22,000 more per patient in total hospital charges than for recipients of best-practice appropriate prophylaxis, according to a large national study.

Thus, partial VTE prophylaxis—that is, any VTE prophylaxis not in accord with American College of Chest Physicians guidelines in terms of dose or duration—not only entails adverse clinical consequences, it also carries a significant economic price, Dr. Alpesh Amin observed at the annual meeting of the American College of Chest Physicians.

He presented a retrospective case-control study of economic and clinical outcomes in 21,001 medical and surgical inpatients around the nation who received VTE prophylaxis. The data were obtained from the Thomson Reuters MarketScan Hospital Drug Database.

The VTE prophylaxis was in step with ACCP guidelines in a mere 24.5% of patients, and such low rates have also been seen in numerous other studies. The in-hospital VTE rate in the appropriate-prophylaxis group was 1.9%, compared with 1.4% in the three-quarters of patients who got partial prophylaxis, according to Dr. Amin, professor and chairman of the department of medicine and executive director of the hospitalist program at the University of California, Irvine.

Mean hospital length of stay was 9.3 days in the appropriate-prophylaxis group, compared with 11.2 days with

partial prophylaxis. Mean hospital charges were \$47,981 with appropriate prophylaxis and \$69,997 with partial prophylaxis. After adjustment for patient variables and hospital characteristics, including bed count, teaching status, and geographic region, the adjusted mean difference in total charges in a multivariate analysis was \$21,260.

Total unadjusted hospital costs averaged \$17,386 per patient in the appro-

priate VTE prophylaxis group, compared with \$23,823 in the partial prophylaxis group. After adjustment, the mean difference in hospital costs was \$6,370 less in favor of the appropriate-prophylaxis group.

Venous thromboembolic events cost the U.S. health care system an estimated \$1.5 billion annually. The assumption is that most of the cost savings documented in this study in the appropriate-pro-

phylaxis group stemmed from VTEs avoided, although that wasn't formally studied. A randomized clinical trial would be required to rule out the possibility that the outcome differences were due to confounders that were not controlled for, the physician noted.

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enrichments

FIRST IN A SERIES ON IRON DEFICIENCY ANEMIA AND CHRONIC KIDNEY DISEASE

Evolving Safety in IV Iron Therapy

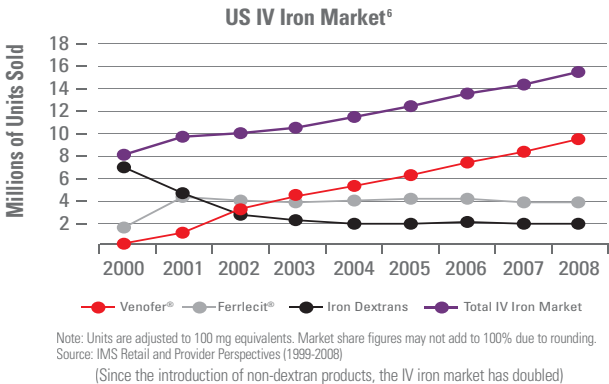
Iron deficiency anemia is generally accepted as one of the most significant complications of chronic kidney disease (CKD).¹ When erythropoiesis stimulating agents (ESAs) were introduced 20 years ago, the supporting use of intravenous (IV) iron therapy enabled improved correction of anemia in patients undergoing dialysis and in other stages of CKD, creating a surge in the use of IV iron therapy.^{1,2} Today, there are several choices in IV iron therapies, each with its own unique characteristics.

Early IV Iron Therapy

Parenteral iron therapy formulations were limited in the early 20th century and had precarious safety records.³ Early investigators prepared their own formulations, which were unprotected by a carbohydrate shell, and, thus, highly toxic. Eventually, researchers developed a formulation bound to carbohydrates, which represented a major advance in parenteral iron safety and led to the first commercially available iron-carbohydrate compounds.⁴ These compounds, most of which were introduced in the 1940s and 1950s, included iron dextran, iron sucrose, and sodium ferric gluconate.^{3,4} Until the late 1990s, iron dextran was the only IV iron available in the US market.

IV Iron Therapy and ESA

The advent of ESAs changed the IV iron landscape completely. Iron deficiency occurs in the majority of patients during ESA therapy because of the increase in the production of red blood cells and subsequent increase in iron demand.⁵ Shortly after the 1989 FDA approval of the first ESA, epoetin alfa, data emerged that indicated IV iron supplementation improved the response to ESA therapy, making it a critical component in the correction of anemia.²



Increased Use Creates Market Shift

Increased use of IV iron therapy drew increased scrutiny of safety issues related to these agents.⁷ Prior to 1992, the only IV iron product available in the US was Imferon®, (iron dextran injection, USP, Fisons, UK), a low molecular weight (LMW) iron dextran.⁸ Initially approved for intramuscular use, Imferon® was first used for IV iron administration in 1971 but withdrawn from the US market in 1990 due to manufacturing issues at their UK plant.⁹ Two more iron dextrans entered the market in the early

to mid 1990s. One was an LMW iron dextran, INFeD®, and another was the high molecular weight iron dextran, Dexferrum®. These were the only available IV iron agents in the US for several years.^{1,2,4,10,11}

Eventually, due to concerns of the risk of anaphylaxis, non-dextran forms of iron, Ferlecit® (sodium ferric gluconate complex in sucrose injection) and Venofer® (iron sucrose injection, USP) were submitted to FDA for approval.¹ Ferlecit® was approved by FDA in 1998 and Venofer® in 2000. Launched in 2000, Venofer® became the # 1 prescribed IV iron in the US in 2003, with a clinical safety and tolerability profile proven in iron deficient CKD patients including patients intolerant to other parenteral irons (iron dextrans and sodium ferric gluconate, or both).^{6,12} Recently, ferumoxytol, Feraheme™, was introduced into the US market; but data pertaining to its safety and tolerability in post approval environments have not yet been captured for historical review.^{1,13}

Dextran Derivatives / Non-dextrans	IV Irons Available in US		
		Year Approved	Molecular Weight
	Venofer® (iron sucrose injection, USP) ^{10,13}	2000	34,000 - 60,000 Da
	Ferlecit® (sodium ferric gluconate complex in sucrose injection) ^{14,15}	1999	289,000 - 440,000 Da
	MODIFIED* ¹² Feraheme™ (ferumoxytol) injection ^{11,16}	2009	750,000 Da
	UNMODIFIED Dexferrum® (iron dextran injection, USP) ^{4,17}	1996	265,000 Da
	INFeD® (iron dextran injection, USP) ^{4,18}	1992	165,000 Da

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*No detectable unmodified dextran.

A Proven Alternative

Unmodified iron dextran products are required to have a black box warning to emphasize the risk of hypersensitivity, including anaphylaxis. They also require a test dose, patient observation period and resuscitative equipment. Non-dextran IV irons have neither a black box warning, requirements for a test dose, nor an observation period. In fact, in an evaluation of 4 US clinical trials (2 pivotal and 2 postmarketing) on the safety of iron sucrose administered to iron deficient hemodialysis patients with a history of intolerance to previous parenteral iron dextran and/or sodium ferric gluconate therapy, there were no serious AEs and no treatment discontinuations reported.²⁰

Additionally, there is more to learn about the new subcategory of modified dextran derivatives. Feraheme™ is the latest entry to the IV iron market, approved in June, 2009. While Feraheme™ can be administered at high doses rapidly, making it potentially very convenient, further experience with this product will be instructive, especially in patients with a history of multiple drug allergies or in patients intolerant to other IV irons.^{18,21}

In review, there are differences in IV iron formulations that are well worth understanding. Being knowledgeable about the evolution of IV iron therapy is the best approach for ensuring that patients with CKD receive optimal care.

IMPORTANT SAFETY INFORMATION: Venofer® (iron sucrose injection, USP) is contraindicated in patients with evidence of iron overload, in patients with known hypersensitivity to Venofer® or any of its inactive components, and in patients with anemia not caused by iron deficiency. Hypersensitivity reactions have been reported with IV iron products. Hypotension has been reported frequently in hemodialysis dependent-chronic kidney disease (HDD-CKD) patients receiving IV iron, and has also been reported in non-dialysis dependent (NDD) and peritoneal dialysis dependent (PDD)-CKD patients receiving IV iron. Hypotension following administration of Venofer® may be related to rate of administration and total dose delivered.

In multi-dose efficacy studies in HDD-CKD patients (N=231), the most frequent adverse events (>5%), whether or not related to Venofer® administration, were hypotension, muscle cramps, nausea, headache, graft complications, vomiting, dizziness, hypertension, chest pain, and diarrhea. In post-marketing safety studies in HDD-CKD patients (N=1051), the most frequent adverse events reported (>1%), whether or not related to Venofer® administration, were congestive heart failure, sepsis, and taste disturbance. In multi-dose efficacy studies in NDD-CKD patients (N=91), the most frequent adverse events (>5%), whether or not related to Venofer® administration, were taste disturbance, peripheral edema, diarrhea, constipation, nausea, dizziness, and hypertension. In the study of PDD-CKD patients (N=75), the most frequent adverse events, whether or not related to Venofer®, reported by ≥5% of these patients were diarrhea, peritoneal infection, hypotension, pharyngitis, peripheral edema, and nausea.

References: 1. Fishbane S. Anemia in chronic kidney disease: status of new therapies. *Curr Opin Nephrol Hypertens*. 2009;18:112-115. 2. Shafer E. ESAs and IV iron: a perfect match? *HemOnc Today*. Available at: <http://www.hemonctoday.com/articlePrint.aspx?type=print&id=30191>. Accessed: August 7, 2009. 3. Auerbach M, Coyne D, Ballard H. Intravenous iron: from anathema to standard of care. *Am J Hematol*. 2008;83:580-588. Available at: <http://www.interscience.wiley.com/cgi-bin/home/35105>. Accessed: August 7, 2009. 4. Danielson BG. Structure, chemistry, and pharmacokinetics of intravenous iron agents. *J Am Soc Nephrol*. 2004;15:S393-S398. 5. Wish JB, Coyne DW. Use of erythropoiesis-stimulating agents in patients with anemia of chronic kidney disease: overcoming the pharmacological and pharmacoeconomic limitations of existing therapies. *Mayo Clin Proc*. 2007;82(11):1371-1380. 6. IMS data. Retailer and provider perspectives. 1999-2008. 7. Van Wyck DB, Danielson BG, Aronoff GR. Making sense: a scientific approach to intravenous iron therapy. *J Am Soc Nephrol*. 2004;15:S391-S392. 8. Lawrence R. Development and comparison of iron dextran products. *Pharm Sci Technol*. 1998;52(5):190-197. 9. SCRP: Fisons' "disappoints" FDA inspectorate. January 24, 1992, 18867. 10. Fishbane S, Ungureanu VD, Maesaka JK, et al. The safety of intravenous iron dextran in hemodialysis patients. *Am J Kidney Dis*. 1996;28:529-534. 11. Fishbane S, Maesaka JK. Iron management in end-stage renal disease. *Am J Kidney Dis*. 1997;29:319-333. 12. Venofer® [package insert]. Shirley, NY: American Regent, Inc. Rev. 10/08. 13. AMAG Pharmaceuticals. FDA approves Feraheme™ to treat iron deficiency anemia in adult chronic kidney disease patients. Available at: <http://www.snl.com/irweb/link/irfile.aspx?ID=4166432&FD=8015643>. Accessed: August 13, 2009. 14. Groman EV, Paul KG, Frigo TB, Bengel H, Lewis JM, inventors; Advanced Magnetix Inc., assignee. Heat stable colloidal iron oxides coated with reduced carbohydrates and carbohydrate derivatives. US Patent 6 599 498. July 29, 2003. 15. Tozzi V. Venofer® (iron sucrose injection, USP) receives FDA approval for the treatment of iron deficiency anemia in pre-dialysis patients. Available at: http://www.hdon.com/misc/Venofer_press_release_june_2005.htm. Accessed: August 9, 2008. 16. Business Wire. Ferlecit® approved: FDA approves new injectable iron for dialysis patients. Available at: http://www.thefreelibrary.com/_/print/PrintArticle.aspx?id=53910524. Accessed: August 9, 2009. 17. Ferlecit® [package insert]. Corona, CA: Watson Pharmaceuticals, Inc. Rev. 09/06. 18. Feraheme™ [package insert]. Lexington, MA: AMAG Pharmaceuticals, Inc. 06/09. 19. INFeD® [package insert]. Morristown, NJ: Watson Pharma, Inc. 03/06. 20. Charytan C, Schwenk MH, Al-Saloum MM, Spinowitz BS. Safety of iron sucrose in hemodialysis patients intolerant to other parenteral iron products. *Nephron Clin Pract*. 2004;96:c63-c66. 21. Coyne DW. Ferumoxytol for treatment of iron deficiency anemia in patients with chronic kidney disease. *Expert Opin Pharmacother*. 2009;10(15):1-6.

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What It Takes To Curb VTE

This is an important reminder that just doing "anything" for VTE prophylaxis is not the same as doing the "right" thing with respect to evidence-based medicine.

The current focus on VTE prophylaxis rates often misses the point that we need to improve our use of appropriate VTE prophylaxis. This means that we need to give the right method to the right patient at the right dose for the right duration of time. And for many patients, the intensity of VTE prophylaxis isn't commensurate with the VTE risk of the patient.

This study highlights how costly it is when physicians don't get VTE prophylaxis "right."

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