At the Crossroads for Intravenous Iron Dosing

The recently published secondary analysis of the Proactive IV irOn Therapy in haemodiALysis patients (PIVOTAL) trial greatly clarifies the infectious risk of proactive versus reactive intravenous (IV) iron dosing in patients on hemodialysis.[1,2] Although the original study demonstrated that infection episodes, defined as hospitalizations for infections, occurred nearly equally among patients assigned to either the proactive group or the reactive group, the current analysis uses two additional prespecified outcomes of "all infections" and "death from infection." Consistent with the primary study findings, neither of these outcomes demonstrate a differential risk among individuals assigned to the proactive or reactive dosing approach. The analysis also finds no effect modification by vascular access type or difference in outcome by level of iron indices. We congratulate the authors on the completion of the landmark study and communication of the new analysis, which taken together, clearly demonstrates the safety and benefit of a proactive IV iron approach to a reactive IV iron approach.

Contemporary clinical practice of IV iron dosing in the United States, however, differs in two important ways than the approaches tested in the PIVOTAL trial. First, dialysis centers administer repletion doses of IV iron that often exceed 400 mg/mo, the maximum amount allowed in the proactive group. Forty percent of patients on dialysis receive ≥250 mg/mo; 20% are given ≥500 mg/mo.[3] Second, the thresholds of serum ferritin and transferrin saturation (TSAT) values to terminate IV iron therapy vary widely; protocols at some United States dialysis clinics call for treatment up to a serum ferritin value of 800 ng/ml but at many others, up to 1200 ng/ml.[4] Iron is also given up to a TSAT value of 50%. The proactive arm held iron dosing at a serum ferritin of 700 ng/ml and TSAT of 40%. Therefore, most United States–based nephrologists would consider the approach taken by the PIVOTAL as moderate to conservative with respect to absolute dose and termination thresholds.

We are now at a crossroads for IV iron management. One road forward is to rigorously test the proactive approach to high-dose repletion strategies that commonly administer IV iron above 400 mg/mo and with different termination thresholds. There may indeed be benefit from higher dosing approaches, but currently, it remains unproven. A second choice is the adoption of the proactive approach with the corollary that dosing strategies more or less aggressive than the proactive arm be halted. In these unprecedented times, a moderate approach may be the rational path forward.

DISCLOSURES

M. Brookhart has served as a scientific advisor for Amgen, Brigham and Women's Hospital, Merck, Rockwell Medical, and Vertex, and owns equity in NoviSci, Inc. B. Robinson is an employee of Arbor Research Collaborative for Health, which administers the DOPPS Program. Global support for the ongoing DOPPS Program is provided without restriction on publications by a variety of funders. For details see https://www.dopps.org/AboutUs/Support.aspx. B. Robinson has received consultancy fees or travel reimbursement since 2018 from AstraZeneca, GlaxoSmithKline, and Kyowa Kirin Co., all paid directly to his institution of employment. All remaining authors have nothing to disclose.

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See related Letter to the Editor, "Authors' Reply," on page 1654.

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Authors' Reply

On behalf of the entire Proactive IV IrOn Therapy in HaemodiALysis Patients (PIVOTAL) study team, we wish to thank Kshirsagar *et al.*[1] for their comments on our recently published secondary analysis of the PIVOTAL trial.[2] We agree with much of what they have said but have the following comments to make.

The choice of dosing regimens and safety cutoffs for the two arms in the PIVOTAL trial has been extensively discussed. We completely recognize that a large number of dialysis centers in the United States are already using iron protocols that are aligned to the high-dose arm.[3] However, it is important to point out that current clinical practice varies widely worldwide, and the majority of countries and dialysis centers adopt more modest iron dosing protocols than the United States. Indeed, in Japan, the standard of care is more aligned to the low-dose arm of the trial.[3,4]

The trial was originally designed to reflect the two extremes of iron dosing in the United Kingdom, and indeed, comprehensive pretrial research indicated that a ferritin safety cutoff >700 μg/L would not be acceptable to many potential investigators in the United Kingdom. We already recognized that the sample size for the study would need to be >2000 patients and that we would need "buy-in" from 40–50 centers. Thus, the choice of dosing protocols in the study was partly on the basis of current United Kingdom and European practice and partly on a pragmatic approach regarding study feasibility.

Next, we agree with Kshirsagar *et al.*[1] that the two options that dialysis physicians in the United States have are (*1*) to continue with their more aggressive iron protocols, aiming to rigorously test the benefits/safety of this approach (particularly because in the authors' own observational study of 13,249 United States patients on dialysis, intravenous iron administration strategies promoting more intensive iron treatment were associated with higher risks of mortality and infection-related events[5]); or (*2*) adopt the PIVOTAL high-dose arm approach with the corollary that dosing strategies more or less aggressive than this be halted. Which of these options to choose is not within our remit to comment, but we feel that this is where we need to defer to guideline bodies, such as Kidney Disease Improving Global Outcomes, to assess the evidence base and make recommendations because they have the expertise and methodology to do this properly.

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See related Letter to the Editor, "At the Crossroads for Intravenous Iron Dosing," on pages 1653–1654.

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