LETTER TO THE EDITOR

Comment on ‘Reported Severe Hypersensitivity Reactions after Intravenous Iron Administration in the European Economic Area (EEA) Before and After Implementation of Risk Minimization Measures’

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To the Editor,

In response to the recently published article by Nathell et al. [1], we draw attention to the fact that this is a second publication (the first being Ehlken et al. [2018] [2]) by members of the same author group, focusing on iron isomaltoside (IIM), this time evaluating the impact of risk minimization measures (RMMs) implemented by the European Medicines Agency (EMA) on the rate of hypersensitivity reactions (HSRs) associated with different intravenous (IV) iron products.

In their introduction, Nathell et al. cite a selection of low-level evidence sources (spontaneous reporting to regulatory authorities, single-centre cohort/retrospective studies, pharmacoepidemiological data) to suggest that IIM is associated with a greater risk of HSRs than ferric carboxymaltose (FCM). Not only do the authors fail to consider the available strong clinical trial data [3–6], the weight of information presented in the introduction for IIM is not fairly balanced with data for other IV iron products; indeed, no review of other products is included in the introduction. For example, the authors could have discussed the systematic review and meta-analysis by Avni et al. [7] summarising the safety of IV preparations, including risk of infusion reactions, based on over 100 randomized clinical trials, and the literature review of clinical trial data by Kalra and Bhandari [6] describing serious or severe HSRs based on standardised Medical Dictionary for Regulatory Activities (MedDRA) Query (SMQ) terms for anaphylactic reactions for IIM, FCM and iron sucrose.

Such a targeted approach presents a critical review of IIM that fails to consider all other relevant data (as advocated by the EMA) [8]. Having evaluated the risk of severe HSRs for IV iron products before and after the implementation of the EMA’s RMMs, and concluding that the RMMs had no clear impact on reporting rates, the Nathell et al. report harbours a biased view of IIM.

The negative view of IIM, communicated in the article by Nathell et al., is entirely contrasted by data from large head-to-head randomized controlled trials (RCTs) (i.e., the gold standard) that demonstrate a good safety profile for IIM that is at least comparable to other IV iron products (Fig. 1).

Whilst we acknowledge that Nathell and colleagues may not have been aware of the recent data from the PHOSPHARE and FERWON trials at the time of submitting the report, the findings of the PROVIDE and PROPOSE trials were published in 2015 and 2017, respectively, and therefore appear to have been overlooked. The PHOSPHARE trials are the first published trials of IIM versus FCM and demonstrated low incidences of serious or severe HSRs for IIM (0.8%) and FCM (1.7%) [9]. The FERWON trials were powered (n = 3008 patients) and designed ( adjudicated and confirmed serious or severe HSRs) to detect the low frequency of serious or severe HSRs associated with IIM (0.3%) and iron sucrose (0.2%) [3, 10, 11].

The data from these RCTs are consistent with a recent thorough approach to analysing the comparative risk of serious or severe HSRs conducted by Pollock and Biggar [12]. This indirect comparison utilized data from 21 prospective clinical trials of IIM, FCM and iron sucrose, covering 8599 patients, and reporting serious or severe HSRs using the SMQ for anaphylactic reactions [12]. Three statistical approaches were used to compare HSR incidence rates between the IV iron products [12]. The primary Bayesian analysis showed a reduction in the odds of experiencing a serious or severe HSR of 59% with IIM relative to FCM [12]. The naive pooled analysis found the incidence...

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of serious or severe HSRs to be at least as low for IIM as for FCM and iron sucrose: 0.6% (23/3922), 1.5% (28/1892) and 1.2% (33/2785), respectively [12]. The indirect treatment comparison approach produced similar results [12]. These results are in close agreement with the previously mentioned head-to-head PHOSPHARE trials of IIM versus FCM [9]. Taken together, these results provide strong evidence that IIM is not associated with a higher risk of serious or severe HSRs than FCM, and strongly refute the findings of the Nathell et al. analysis. With respect to making product comparisons, these head-to-head trials and indirect treatment comparisons take precedence over retrospective data on spontaneously reported severe HSRs (methodology that is considered by the EMA to be fundamentally flawed [8]).

The product labels for IV iron products highlight the risk of HSRs, emphasize the need for careful monitoring during and after each infusion, and provide a level of advice on the different types of HSRs that can occur and how to manage them [13–16]. Supplementary to this information, published guidelines and algorithms exist to help healthcare professionals who prescribe and administer IV iron to recognize and manage HSRs [17–20]. In particular, these resources show how to distinguish the rare, severe HSRs from the mild-to-moderate, self-limiting infusion reactions, and how to manage such reactions should they occur [17–19]. Indeed, it is the lack of understanding of minor acute infusion reactions, such as Fishbane reactions, and their management that has perpetuated the misperception that IV iron products are associated with a high risk of severe HSRs. Often, the symptoms of a minor reaction abate within minutes of stopping the infusion—after a short period of time, the infusion can be restarted, and patients can go on to receive the remaining infusion of iron without further complication [17, 19].

Drawing attention to the US product label for FCM (Injectafer®), in particular, it is stated that, “In clinical trials, serious anaphylactic/anaphylactoid reactions were reported in 0.1% (2/1775) of subjects receiving Injectafer,” and that, “Other serious or severe adverse reactions potentially associated with hypersensitivity which included, but not limited to, pruritus, rash, urticaria, wheezing, or hypotension were reported in 1.5% (26/1775) of these subjects” [21]. These observations were obtained from two US randomized clinical trials of FCM, in which a total dose of 1500 mg (two separate infusions of 750 mg each) was administered [22, 23]. In contrast, the Nathell et al. analysis reports the rate of severe HSRs (anaphylactic reaction, anaphylactic shock, anaphylactoid reaction, or anaphylactoid shock) with FCM in the range of 0.18–1.47 per 100,000 defined daily doses (DDD [1 DDD = 100 mg]), corresponding to a rate of 0.0027–0.022% for a 1500 mg dose of FCM. Although there are differences between the two sources in the categories used to define a severe HSR, the Nathell et al. analysis clearly underestimates the risk of severe HSRs following treatment with FCM by at least one order of magnitude, meaning that any comparison of rates is meaningless, and clearly illustrating the issues with their analysis.
Compliance with ethical standards

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Conflict of interest Philip Schaffalitzky de Muckadell and Claes Christian Strom are employees of Pharmacosmos A/S.

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References

1. Nathell L, Gohlike A, Wohlfeil S. Reported severe hypersensitivity reactions after intravenous iron administration in the European Economic Area (EEA) before and after implementation of risk minimization measures. Drug Saf. 2019. https://doi.org/10.1007/s40264-019-00868-5.

2. Ehiken B, Nathell L, Gohlike A, Bocuk D, Toussi M, Wohlfeil S. Evaluation of the reported rates of severe hypersensitivity reactions associated with ferric carboxymaltose and iron (III) isomaltoside 1000 in Europe based on data from EudraVigilance and VigiBase™ between 2014 and 2017. Drug Saf. 2019;42(3):463–71.

3. Bhandari S, Thomsen LL. A single 1000 mg infusion of iron isomaltoside 1000 demonstrates a more rapid hemoglobin response and reduced risk of cardiovascular adverse events compared to multiple doses of IV iron sucrose in the FERWON trials [Abstract SP342]. Nephrol Dial Transplant. 2019;34(Suppl 1):i475–i486.

4. Derman R, Roman E, Modiano MR, Achebe MM, Thomsen LL, Auerbach M. A randomized trial of iron isomaltoside versus iron sucrose in patients with iron deficiency anemia. Am J Hematol. 2017;92(3):286–91.

5. Bhandari S, Kalra PA, Kothari J, Ambühl PM, Christensen JH, Essaiaan AM, et al. A randomized, open-label trial of iron isomaltoside 1000 (Monofer®) compared with iron sucrose (Venoferr®) as maintenance therapy in haemodialysis patients. Nephrol Dial Transplant. 2015;30(9):1577–89.

6. Kalra PA, Bhandari S. Safety of intravenous iron use in chronic kidney disease. Curr Opin Nephrol Hypertens. 2016;25(6):529–35.

7. Avni T, Bieber A, Grossman A, et al. The safety of intravenous iron preparations: systematic review and meta-analysis. Mayo Clin Proc. 2015;90(1):12–23.

8. European Medicines Agency. Rapid response to BMJ. Re: Pandemrix vaccine: why was the public not told of early warning signs? (EMA/659264/2018). 26 September 2018. Available at: https://www.ema.europa.eu/documents/other/european-medicines-agency-rapid-response-british-medical-journal-pandemrix.pdf. Accessed 18 Jan 2019.

9. Wolf M, Rubin J, Achebe M, Econs MJ, Peacock M, Imel EA, et al. Effects of iron isomaltoside vs ferric carboxymaltose on hypophosphatemia in iron deficiency anemia: two randomized clinical trials. JAMA. 2020;323(5):432–43.

10. Auerbach M, Henry D, Derman RJ, et al. A prospective, multicenter, randomized comparison of iron isomaltoside 1000 versus iron sucrose in patients with iron deficiency anemia: the FERWON-IDA trial. Am J Hematol. 2019;94(9):1007–14.

11. Bhandari S, Kalra PA, Berkowitz M, et al. Safety and efficacy of iron isomaltoside 1000/ferric derisomaltose versus iron sucrose in patients with chronic kidney disease: the FERWON-NEPHRO randomized, open-label, comparative trial. Nephrol Dial Transplant. 2020. https://doi.org/10.1093/ndt/gfaa011.

12. Pollock RF, Biggar P. Indirect methods of comparison of the safety of ferric derisomaltose, iron sucrose and ferric carboxymaltose in the treatment of iron deficiency anemia. Expert Rev Hematol. 2020;13(2):187–95.

13. Monofer® (iron isomaltoside). Summary of product characteristics. Pharmacosmos UK Ltd. 9 July 2019.

14. Ferinject® (ferric carboxymaltose). Summary of product characteristics. Vifor Pharma UK Ltd. 12 December 2018.

15. Venofer® (iron sucrose). Summary of product characteristics. Vifor Pharma UK Ltd. 8 May 2019.

16. CosmoFer® (iron dextran). Summary of product characteristics. Pharmacosmos UK Ltd. 23 January 2019.

17. Rampton D, Folkersen J, Fishbane S, Hedeus M, Howaldt S, Locatelli F, et al. Hypersensitivity reactions to intravenous iron: guidance for risk minimization and management. Haematologica. 2014;99(11):1671–6.

18. Macdougall IC, Bircher AJ, Eckardt KU, Oberлад GT, Pollock CA, Stenvinkel P, Conference Participants, et al. Iron management in chronic kidney disease: conclusions from a “Kidney Disease: Improving Global Outcomes” (KDIGO) Controversies Conference. Kidney Int. 2016;89(1):28–39.

19. Lim W, Aif W, Knowles S, Lim G, Lin Y, Mothersill C, et al. Canadian expert consensus: management of hypersensitivity reactions to intravenous iron in adults. Vox Sang. 2019;114(4):363–73.

20. Gómez-Ramírez S, Shander A, Spahn DR, Auerbach M, Liambrou GM, Vaglio S, Münoz M. Prevention and management of acute reactions to intravenous iron in surgical patients. Blood Transfus. 2019;17(2):137–45.

21. Injectafer® (ferric carboxymaltose injection). Prescribing information. February 2020. Available at: https://injectafer.com/prescribing-information-portlet/getDocument?product=IF&inline=true. Accessed 25 Feb 2020.

22. Onken JE, Bregman DB, Harrington RA, Morris D, Acs P, Akright B, et al. A multicenter, randomized, active-controlled study to investigate the efficacy and safety of intravenous ferric carboxymaltose in patients with iron deficiency anemia. Transfusion. 2014;54(2):306–15.

23. Onken JE, Bregman DB, Harrington RA, Morris D, Buerkert J, Hamerski D, et al. Ferric carboxymaltose in patients with iron-deficiency anemia and impaired renal function: the REPAIR-IDA trial. Nephrol Dial Transplant. 2014;29(4):833–42.