

ORIGINAL PAPER

# Correction of iron deficiency anaemia using IV CosmoFer in CKD patients with asthma: a prospective study

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## Summary

**Background:** Intravenous (IV) iron is commonly used for correcting iron deficiency anaemia in patients with chronic kidney disease (CKD). There remains a concern for its use in patients with asthma as it may trigger an acute exacerbation. Pre-treatment with a single dose of parenteral hydrocortisone may obviate this risk.

**Method:** We carried out a prospective study of known asthmatic patients with CKD requiring single-dose iron repletion therapy. We analysed the efficacy and safety of IV CosmoFer (low molecular weight iron dextran). Twenty non-dialysis CKD patients with iron deficiency anaemia and a history of asthma were enrolled. Severity of asthma and level of control were recorded as per British Thoracic Society Guidelines and Royal Collage of Physician questionnaire, respectively. All patients received IV hydrocortisone 30 min before the test dose of CosmoFer followed by the remaining total dose. Patients were monitored for adverse reactions. Haemoglobin, serum ferritin levels and estimated glomerular filtration rate were measured pre and 6-weeks post-infusion. All patients were followed up until 6 weeks to assess the control of their asthma.

**Results:** All 20 patients completed the study. No patient experienced acute hypersensitivity or infusion reactions. At 6 weeks follow-up, no patient reported worsening of their asthma. There was an increase in mean haemoglobin from 10.1 to 11.1 g/dl and mean ferritin from 93.5 to 302.6 ng/ml.

**Conclusions:** This study demonstrates that IV CosmoFer may be administered safely in asthmatics by administering a single 50 mg dose of hydrocortisone pre-infusion.

## Introduction

Anaemia is common in patients with chronic kidney disease (CKD) and its incidence increases with decreasing glomerular filtration rate (GFR).<sup>1,2</sup> After exclusion of blood loss, the primary causes of anaemia in CKD are a decreased erythropoietin secretion from the renal parenchyma, followed by iron deficiency

(either functional or absolute).<sup>3</sup> The latter can be replaced either orally (which is poorly tolerated by patients) or intravenously (IV).<sup>4,5</sup> The advantage of using the IV route is that it is relatively well tolerated and most importantly is more efficacious with a mean rise in haemoglobin (Hb) of ~0.8 g/dl in comparison to 0.3 g/dl with oral iron.<sup>6</sup> This is due to the ability of parenteral iron

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to bypass the hepcidin-ferroportin system, which reduces the absorption from the duodenum and mobilization of iron from stores. Also for CKD patients, a single total iron dose can be given reducing the number of attendances and improving quality of life.<sup>7</sup> Currently, five IV iron preparations are licensed for use in Europe: low molecular weight iron dextran (CosmoFer), iron sucrose (Venofer), ferric carboxymaltose (Ferinject), iron isomaltoside 1000 (Monofer) and ferumoxytol (Reinso).

CosmoFer was developed to reduce hypersensitivity allergic reactions (including anaphylaxis), which were historically noted to be more common but still relatively rare with high molecular weight iron dextran preparations.<sup>8</sup> The safety of these relatively newer preparations is positive<sup>9–11</sup>; however, the summary of product characteristic suggests caution or contraindication in patients with asthma. Currently, there is no consensus on how to treat these patients and whether pre-treatment with steroids, H1 blockers or other agents is necessary.

The prevalence of asthma globally is estimated to be 334 million<sup>12</sup> and percentage prevalence in the UK population is estimated to be 5.9%.<sup>13</sup> Therefore a significant number of patients with CKD have additional asthma. Hypersensitivity reactions are extremely rare but potentially more common in patients with asthma. Death and other severe consequences related to the use of IV iron are also very rare. Data from the US National Centre for Health Statistics (1979–2005) showed that there were 3 deaths/year ascribed to iron infusions in the USA, approximating 1 for every 5 million doses of IV iron sold.<sup>14,15</sup> The European Medicines Agency (EMA) suggests caution with use of IV iron in patients with severe asthma,<sup>16</sup> there is no data on the use of IV iron in this group of patients.

We therefore carried out a prospective study in non-dialysis CKD (ND-CKD) patients who had a known history of asthma, requiring asthmatic agent therapy and referred for CosmoFer total dose iron. The aim was to establish whether pre-treatment with a single dose of parenteral hydrocortisone was sufficient to allow the safe administration of IV iron without exacerbating asthmatic symptoms either acutely or chronically.

## Methods

A prospective study of 20 ND-CKD patients referred for CosmoFer total dose iron who had a known history of asthma and requiring asthmatic treatment.

The study was approved by the Hull and East Yorkshire Hospitals NHS Trust, Drugs and therapeutics committee. In this group of patients, oral therapy was tried before IV Iron was considered. All patients underwent a detailed discussion of the risk/benefit before consent to prescribe parenteral iron. Twenty patients were selected as an initial pilot of safety before a larger cohort could be treated.

The severity and level of asthma control was assessed in each patient pre-infusion of parenteral iron as per British Thoracic Society guidelines<sup>17</sup> and the Royal College of Physicians (RCP) questionnaire,<sup>18</sup> respectively (Tables 1 and 2). All the infusions were administered in the hospital medical day unit by a specialist nurse, trained in parenteral iron administration and experience with resuscitation. In addition, full resuscitation facilities were available. Patients were monitored as per protocol every 15 min with monitoring of blood pressure, pulse and respiratory rate.

## Treatment regime

All patients received 50 mg of IV hydrocortisone 30 min before the test dose of CosmoFer (100 mg in 100 ml of 0.9% saline at

**Table 1.** British Thoracic Guidelines<sup>18</sup>

| Severity | Medication                                                                                                                            |
|----------|---------------------------------------------------------------------------------------------------------------------------------------|
| Step 1   | Mild intermittent asthma on inhaled short acting $\beta_2$ agonist, as required.                                                      |
| Step 2   | Regular inhaled steroid therapy.                                                                                                      |
| Step 3   | On initial add on therapy e.g. inhaled long acting $\beta_2$ agonist or leukotriene receptor antagonist or slow release theophylline. |
| Step 4   | Persistent poor control on high dose inhaled steroid (up to 2000 mcg/day) and addition of a fourth drug.                              |
| Step 5   | Continuous or frequent use of oral steroids.                                                                                          |

**Table 2.** RCP Questionnaire<sup>19</sup>

|   |                                                                                              |
|---|----------------------------------------------------------------------------------------------|
| 1 | Any difficulty sleeping because of asthma symptoms (including cough)?                        |
| 2 | Any usual asthma symptoms during the day (cough, wheeze, chest tightness or breathlessness)? |
| 3 | Has your asthma interfered with your usual activities (e.g. housework, work, school, etc)?   |

The 'yes/no' responses for the above questions are scored with 1 for each positive answer giving a total score between 0 and 3. Score zero is good control and a score 2 or 3 is poor control. A score of 1 has good sensitivity but poor specificity for suboptimal control.

rate of 100 ml/h). If there were no acute reactions or exacerbation of asthma symptoms, the remaining total dose was given (900 mg CosmoFer in 250 ml of 0.9% saline at the rate of 150 ml/h). Any adverse drug events were recorded on a database.

All patients were followed up by the anaemia nurse specialist for 6 weeks via telephone consultation to check asthma control using the RCP questionnaire.

## Results

The mean age of the cohort was 62.9 years (SD 18), with a female to male ratio of 1.2:1. Eighty percent of these patients had their diagnosis made by their general practitioner and 20% by a specialist chest physician. All patients had stable control of their asthma symptoms scoring zero on the RCP questionnaire, pre-treatment. The level of treatment of the asthma was Step 1 in 30%, Step 2 in 50% and Step 3 in 20% of patients. Patients remained stable throughout the administration of parenteral iron with no reported adverse reactions or asthmatic symptoms. No patient required use of their inhaler either during or after the infusion. The respiratory rate remained stable with no significant increase during or after the infusion. Six weeks after treatment, both severity and symptom control remained stable and no patient reported acute or delayed deterioration of asthma and hypersensitivity reactions. There were also no reported admissions to hospital with exacerbation of asthma. The mean values of Hb, serum ferritin (SF) and estimated GFR at baseline and follow-up are summarized in Table 3. There was significant increases in Hb (mean increase of 1 g/dl;  $P < 0.01$ ) and SF (from a mean of 93.5 to 302.6 ng/ml;  $P < 0.01$ ) in patients with various grades of asthma severity. There were no hypersensitivity reactions and no patient experienced any acute or delayed deterioration of asthma.

## Discussion and conclusion

This prospective safety study has demonstrated that total dose parenteral iron can be safely administered to known asthmatic

**Table 3.** Summary of mean (SD) baseline and follow-up biochemical measures

|                                    | Severity of asthma | Mean values pre CosmoFer | Mean values post CosmoFer | P      |
|------------------------------------|--------------------|--------------------------|---------------------------|--------|
| Hb (g/dl)                          | Step 1             | 10.3 (SD 1.4)            | 11.2(SD 1.7)              | <0.001 |
|                                    | Step 2             | 10.2 (SD 1)              | 11.3 (SD 1.4)             |        |
|                                    | Step 3             | 9.5 (SD 1.4)             | 11.4 (SD 1)               |        |
|                                    | All patients       | 10.1 (SD 1.2)            | 11.1 (SD 1.4)             |        |
| SF (ng/ml)                         | Step 1             | 61.8 (SD 24)             | 168.8 (SD 94.9)           | <0.001 |
|                                    | Step 2             | 93.2 (SD 57.8)           | 397.6 (SD 266)            |        |
|                                    | Step 3             | 142.5 (SD 68)            | 332.5 (SD 173.5)          |        |
|                                    | All patients       | 93.5 (SD 55.8)           | 302.6 (SD 198)            |        |
| eGFR (ml/min/1.73 m <sup>2</sup> ) | Step 1             | 20.8 (SD 9.4)            | 21.2 (SD 10.6)            | 0.54   |
|                                    | Step 2             | 19.8 (SD 12)             | 19.2 (SD 10.5)            |        |
|                                    | Step 3             | 24.5 (SD 9.3)            | 22.25 (SD 8.9)            |        |
|                                    | All patients       | 21 (SD 10)               | 20.5 (SD 9.5)             |        |

eGFR, estimated GFR.

patients after pre-treatment with a single IV dose of 50 mg of hydrocortisone.

Although there is lack of causal association of iron treatment in iron deficiency anaemia and asthma, it has been observed that patients with asthma have high plasma iron compared with healthy individuals.<sup>19</sup> In animal models, there remains conflicting results on the association between iron and allergic manifestations.<sup>20,21</sup>

Parenteral iron in patients with CKD and indeed other chronic disorders has become a significant treatment option for anaemia, especially when oral iron is not tolerated. The latest recommendations to manage risk of allergy from IV iron from European Medicines Agency (EMA) resulted from concerns raised from an allergic reaction in pregnant non-CKD patients.<sup>16</sup> It had several conclusions including that all IV iron preparations have a relatively low risk of causing allergic reactions and other risk minimization measures are considered during therapy. This latter suggestion, however, is vague and without more detailed advice. Therefore, one method to reduce potential reactions maybe pre-treatment of high risk groups where avoidance may not be possible. Indeed, there are no current guidelines how to manage or prevent adverse events.

There are no existing recommendations for pre-treatment in patients with bronchial asthma requiring parenteral iron therapy. This is not surprising in view of the extremely rare occurrence of anaphylaxis. The only available information comes from retrospective information.<sup>22</sup> Hence, prospective studies may allow a more evidenced based approach to the development of guidance. The rational for caution in bronchial asthma relates to the potential of nanoparticles within iron to induce an allergic reaction. The pathogenesis of anaphylaxis is considered multifaceted and includes activation of complement (C), mast cells and basophils<sup>23,24</sup> either directly or via anaphylatoxins (C3a and C5a) resulting in the production of several substances including histamine, thromboxanes, leukotrienes and platelet-activating factor. If severe enough, this will lead to smooth muscle contraction, increased capillary permeability and loss of fluid from the intravascular space with the clinical sequelae of bronchospasm, laryngeal oedema, tachycardia, hypo- or hypertension, hypoxia and reduced tissue perfusion.

Our study provides some initial evidence but is limited by the lack of a control population with no pre-treatment as we felt this would be unethical, although we must concede this is without an evidence basis.

There is no consensus on how to reduce these potential reactions. This study has taken a pragmatic view in pre-treatment and suggests this simple approach is feasible but requires validation in a larger cohort.

The frequency of serious cases of anaphylaxis reactions to commercial IV iron drugs is rare but probably under reported. With differential reporting and incomplete use of (denominator) data, it is difficult to conclude on the prevalence.<sup>14</sup> Indeed, a large study involving over 6000 patients is necessary to compare IV iron compounds.<sup>25</sup>

In 1996, Fishbane reported a retrospective clinical study of iron dextran, in which several variables were analysed as possible predictors of adverse reactions. A history of allergy (odds ratio, 2.4;  $P=0.03$ ) was the only variable that was found to be predictive of adverse events (not including allergy to iron dextran). In patients with a history of multiple drug allergies, there was a significantly increased risk of an adverse drug reaction (odds ratio, 5.5;  $P=0.0004$ ).<sup>26</sup>

Fletes et al.<sup>11</sup> observed that a history of (any) drug allergy was reported in 45 out of 150 cases (30%) and therefore concluded it to be a risk factor. In the ferumoxytol phase III program, more than one drug allergy was an exclusion criterion. Because of error, one patient made it into the study, he had several drug allergies—and the patient suffered a major anaphylactic reaction in the study.<sup>27</sup>

Corticosteroids and H1 blockers are the basic components of most premedication regimes for patients at high risk for an anaphylactoid reaction or with a history of anaphylactic reaction who need a specific drug or a contrast enhancing agent.<sup>28</sup> An extensive *post hoc*—literature evaluation of clinical trials involving a total of 10000 patients exposed to X-ray contrast agents, evaluated the efficacy of general prophylactic treatment with antihistamines and steroids. None of these trials were performed solely with allergic patients. The review concluded that 'In unselected patients the usefulness of premedication is doubtful and data to support the general use of premedication are lacking'.<sup>29</sup>

EMA suggests that there is an increased risk in patients with allergies or immune or inflammatory conditions including a history of severe eczema or other atopic allergy. Unfortunately, the EMA recommendation does not take into account the medical need for iron repletion in some patients with mild-moderate hypersensitivity reactions, where such reactions may be prevented with premedication. We therefore recommend that such decisions are left for individual clinical judgement and the preferences of the well-informed patient but provide this data as further reassurance.

## Limitations

Although the study is small and our group of patients did not have severe asthma, the findings still provide a degree of reassurance that in a relatively 'high risk' group of patients (potentially allergenic) who are intolerant to oral iron, use of total dose parenteral iron can be administered with good affect safely. Unfortunately, we did not measure the peak expiratory flow rate before and after the treatment. However, there was no objective worsening of heart rate, blood pressure, respiratory rate and oxygen saturation. These all strengthen the potential safety issues.

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