A predictive algorithm for the management of anaemia in haemodialysis patients based on ESA pharmacodynamics: better results for less work

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Abstract

Background. Many anaemia management algorithms recommend changes to erythropoiesis-stimulating agent (ESA) doses based on frequent measurement of haemoglobin levels in keeping with the ESA datasheets. We designed a predictive anaemia algorithm based on ESA pharmacodynamics, which we hoped would improve compliance with haemoglobin targets and reduce workload.

Methods. A new algorithm was designed which predicted the 3-month steady-state haemoglobin concentration following
a change in ESA dose and only recommended a change if it was outside the range 10.5–12.5 g/dL. Data were collected prospectively for 3 months prior and 15 months subsequent to implementing the algorithm.

**Results.** A total of 214 prevalent dialysis patients were included in the audit. After 12 months, the haemoglobin concentration was 11.4 g/dL, near the midpoint of the target range, with a narrowing of the distribution (SD 1.46 to 1.25 g/dL, \( P < 0.0001 \)). The proportion of patients with a haemoglobin level in the target range increased from 56% to 66% (\( P < 0.001 \)) principally due to a reduction in the number of patients with high haemoglobin levels. There was no significant change in the ESA dose over the audit period. The number of prescription changes fell from 1/2.5 months to 1/6.1 months after 12 months (\( P < 0.001 \)).

**Conclusions.** Switching prevalent haemodialysis patients to a predictive anaemia management algorithm improved compliance with haemoglobin targets, reduced the number of patients with high haemoglobin levels and reduced the number of ESA dose changes required.

**Keywords:** anaemia; haemodialysis

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**Introduction**

The management of anaemia in haemodialysis patients is centred on the administration of erythropoiesis-stimulating agents (ESAs). Guidelines recommend maintaining haemoglobin levels within a target range, which can be complex and time consuming. Several models exist for the delivery of anaemia care to dialysis patients. Some units adopt a physician-centred approach, with or without the aid of treatment algorithms, whereas others adopt a more rigorous standardized algorithmic approach. In both cases, a tendency to frequently check and respond to changing haemoglobin levels can promote haemoglobin cycling [1], which is associated with harm [2]. Additionally, frequent dose and prescription changes add to the already substantial workload and costs inherent in delivering dialysis services on a large scale.

Our dialysis service has used a computer-based system to inform ESA and iron dosing in our patients for the last 10 years as part of routine clinical care as previously published by Will et al. [3]. The universal application of an objective logic-based algorithmic approach allows six nephrologists to supervise the care of ~450 haemodialysis patients with standardization of anaemia practices. Because of these factors, we can easily test and compare the efficacy of different dosing strategies [4]. The algorithms used by the system have, until recently, used logic based on common clinical practice and the recommendations in the ESA product datasheet. The original algorithm recommended dose adjustments when the monthly haemoglobin was outside the target range of 11–12 g/dL and not moving towards this target range at a rate of at least 1 g/dL/month. This often required frequent dose changes leading to the phenomenon of haemoglobin cycling as has been reported previously by others [1].

In January 2009, we switched to a predictive anaemia management algorithm based on ESA pharmacodynamics and the altered red blood cell lifespan in dialysis patients as originally suggested by Uehlinger et al. in 1992 [5] and more recently advocated by Kalicki and Uehlinger [6]. The new algorithm predicts the eventual steady-state haemoglobin concentration and only recommends a change to the ESA dose if this predicted steady-state haemoglobin is outside the target range. The rationale being that the response to an ESA dose change should be fully evaluated before another is implemented. In addition, we widened the target haemoglobin range in line with the published guidance as intra-patient haemoglobin levels can vary by as much as 1 g/dL/month [7] making it difficult to maintain levels within a narrow range.

It was hoped that this new algorithm would limit the number of patients with high haemoglobin levels, increase compliance with haemoglobin targets and recommend fewer ESA dose changes. This paper presents the results of a prospective audit of ESA doses, the number of ESA dose changes and the haemoglobin levels before and after the change to the new algorithm.

**Materials and methods**

**Patients**

Three months after implementing the new algorithm, all ESA-dependent centre-based adult haemodialysis patients who had made the switch were screened for inclusion in the audit and followed prospectively. Patients were excluded if they had been on dialysis for <9 months prior to the algorithm change or dialysed at the one satellite unit where all patients had converted from darbepoetin alpha to a continuous erythropoietin receptor activator (CERA) shortly before the algorithm was introduced as part of a different service evaluation. Patients who left the dialysis programme within 15 months of the algorithm being introduced were not included in the analysis.

**Monitoring and supervision**

All patients as part of routine clinical care have monthly blood tests, which include measurement of the haemoglobin and ferritin concentrations and the percentage of hypochromic red cells. All drug prescriptions and test results are stored in a locally configured clinical information system (Proton; Clinical Computing Limited, London, UK). User-defined algorithms that analyse these data and recommend management changes were first established over a decade ago [3, 8]. The recommendations from the algorithm are issued in the form of a report which is passed to either the supervising physician or an independent nurse prescriber based at the dialysis unit to implement or reject any changes. In practice, the recommendations are followed almost without exception providing a stable platform for comparing regimens as described above and previously reported [4].

**ESA and dosing**

The ESA used for all patients was darbepoetin alfa (Aranesp®; Amgen, UK) and the intravenous iron was iron sucrose (Venofer®; Syner-Med Pharmaceuticals, UK). Both drugs were administered intravenously during dialysis by the dialysis nursing staff.

**The algorithms**

Prior to 2009, the algorithm recommended incremental ESA dose changes if the measured haemoglobin was outside the target range of 11–12 g/dL and not moving towards this target range at a rate of at least 1 g/dL/month. This was in accordance with the recommended dosing and monitoring described on the ESA datasheet. In January 2009, we implemented a new predictive algorithm and broadened the target haemoglobin range to 10.5–12.5 g/dL in keeping with the National Institute for Health and Clinical Excellence (NICE) recommendations in the UK [9] (Since this work was undertaken, NICE have issued new guidance recommending a target haemoglobin range of 10–12 g/dL [10]).

The main tenet of the new predictive algorithm is that it takes ~3 months for the haemoglobin level to reach a steady state following the
Predictive renal anaemia algorithm

initiation of an ESA or a change in the dose. The steady-state haemoglobin concentration is predicted using linear projection of two haemoglobin levels measured at 1 and 2 months following a change in ESA dose. The algorithm only recommends a change to the ESA dose if the predicted steady-state haemoglobin is outside the desired target range of 10.5–12.5 g/dL. No changes to the ESA dose are recommended if insufficient time has elapsed to predict the steady-state haemoglobin level, which in practice prevents dose changes at intervals <2 months. The magnitude of the dose change is proportional to the difference between the predicted steady-state haemoglobin and the population mean target of 11.5 g/dL (see Appendix for full explanation of the predictive algorithm). The prescription of intravenous iron, based on serum ferritin and the percentage of hypochromic red blood cells, was also determined by protocol and incorporated into the algorithm; this remained unchanged in the new algorithm.

Protocol and data analysis

Three months after the introduction of the new algorithm, all ESA-dependent patients who had made the conversion were identified. We followed these patients for 15 months during which we prospectively collected data on (i) monthly haemoglobin levels, (ii) the proportion of patients with a monthly haemoglobin level in the desired range of 10.5–12.5 g/dL, (iii) the ESA dose and (iv) the number of ESA dose changes per month. To avoid the periodicity that might be introduced by a system that normally allows dose changes at three monthly intervals, the data were analysed by calendar quarters. The prospectively collected data were compared on a quarterly basis with the baseline data, which was taken to be the last quarter prior to the change in algorithm.

A repeated measures analysis of variance design was used to examine differences in haemoglobin concentration or log-transformed ESA doses over time with a Bonferroni post hoc analysis. To look for differences in the variance of haemoglobin across time points, the F-test statistic was calculated. Chi-squared analysis was used to test for differences in the proportion of patients who were ESA-dependent and who were in the target range. To examine differences in the distribution of haemoglobin levels, the Wilcoxon signed-rank test was used with correction for multiple comparisons. All statistical analysis was carried out using SPSS 16 (IBM Corporation, New York) and a P value of <0.05 was considered significant.

Results

Three months after introducing the new algorithm, an audit group of 275 patients was identified. Of the 442 centre-based haemodialysis patients at the time of implementing the new algorithm, 85 had been on dialysis for <9 months, 34 were involved in the evaluation of a CERA, 21 did not require an ESA and 27 had left the programme in the 3 months following the change in algorithm. Of the 275 patients in the audit group, 214 were still on centre-based haemodialysis 15 months later as 38 patients had died, 18 received a transplant and 5 patients either switched renal replacement modality or left the region. An analysis of the 214 patients is presented here. Table 1 shows the baseline characteristics prior to switching to the new anaemia algorithm.

Table 1. Baseline characteristics of audit cohort

<table>
<thead>
<tr>
<th>n</th>
<th>Male/female (%)</th>
<th>Age (years)</th>
<th>Time on RRTa (years)</th>
<th>Mean haemoglobin concentration ± SD (g/dL)</th>
<th>Darbepoetin alfa dose (mcg/week)</th>
</tr>
</thead>
<tbody>
<tr>
<td>214</td>
<td>118/96 (55/45%)</td>
<td>68 (54–77)</td>
<td>3 (2–6)</td>
<td>11.8 (±1.5)</td>
<td>20 (10–40)</td>
</tr>
</tbody>
</table>

aData presented as median (Interquartile range) unless stated.
bRenal replacement therapy.

Haemoglobin concentration

The mean haemoglobin concentrations and SDs by quarter are shown in Figure 1. Following the change to the new algorithm for the first two quarters, there was a significant decrease in the mean haemoglobin level (P < 0.05), thereafter there were no significant changes between quarters [P = not significant (ns)]. After 12 months on the new algorithm, the mean haemoglobin concentration was 11.4 g/dL and near the mid-point of the target range. Comparing the 12-month data with baseline data, taken to be the last quarter before the new protocol was implemented, there was an increase in the number of monthly haemoglobin measurements in the target range 10.5–12.5 g/dL, rising from 56 to 66% (P < 0.001) and a reduction in the SD from 1.46 to 1.25 g/dL (P < 0.0001). The narrowing in the distribution of haemoglobin levels was principally due to a reduction in the number of patients having high haemoglobin levels with the proportion falling from 42 to 27% (P < 0.01) at a cut-off of 12.5 g/dL and from 10 to 3% (P < 0.01) at a cut-off of 14 g/dL over the same time period. There was no statistically significant change in the proportion of patients with haemoglobin levels below the target range following conversion to the predictive algorithm.

ESA dose

The median dose of darbepoetin alfa remained constant across all quarters at 20 mcg/week. The mean ESA dose following implementation of the new algorithm tended to be lower than that in the baseline period but the decrease was not statistically significant (P = n.s.). There were no significant changes in the prescribed intravenous iron dosages (mean 36 ± 33 mg/week) or serum ferritin levels (504 ± 206 µg/L) during the audit period.

Prescription changes

The number of ESA dose changes per month fell from a baseline of 1/2.5 months to 1/3.9 months (P < 0.01) immediately on switching algorithms. By the first quarter of 2010, the number of prescription changes per month had dropped further to 1/6.1 months (P < 0.001 compared to baseline)—see Figure 2.

![Fig. 1. Trend in mean haemoglobin concentration (± SD) by yearly quarter.](image-url)
Discussion

The use of computer-based anaemia management algorithms for dialysis patients are not new. The purported benefits being standardization of care, ease of service delivery on a large scale and importantly improved compliance with guidelines for haemoglobin levels. However, there is a lack of consensus on how best to design the algorithms. Different approaches that have been used include haemoglobin intervention ceilings and thresholds [8], the use of neural networks [11], monthly changes in haemoglobin levels [7] and reliance on individual haemoglobin measurements [14] are all important contributors to this process.

Previous investigators have suggested that anaemia management algorithms may be improved by taking into account red blood cell lifespan and ESA pharmacodynamics rather than reacting to short-term changes in haemoglobin concentration [6]. In an attempt to address these concerns, we designed and implemented a predictive algorithm which used linear extrapolation to predict the steady-state haemoglobin concentration 3 months after an ESA dose change and did not recommend any changes before the effect of the last ESA dose change could be fully assessed. By adopting this approach, we achieved the desired increase in compliance with haemoglobin targets. This was accompanied by a narrowing of the distribution of haemoglobin levels, which may confer additional benefits as a recent study has highlighted that higher haemoglobin variability, as measured by standard deviation, is associated with increased mortality [15].

The summary of product characteristics for darbepoetin alpha recommends that ‘after every dose or schedule adjustment the haemoglobin should be monitored every 1 or 2 weeks’ [16]. In our experience, and that of others [17], adjusting ESA doses on the basis of changes in haemoglobin levels over short periods such as this leads to a tendency for over compensation. For example, if a patient’s haemoglobin level rises above the upper limit of the target range, many algorithms recommend a reduction in the ESA dose. If ESA doses are reviewed and adjusted monthly it is likely, based on the pharmacodynamics of darbepoetin alfa [18] and the life cycle of red blood cells in this setting [5], that the haemoglobin level will not have dropped into the desired range before the next review. If a further dose reduction is made, it could result in a precipitous drop in the haemoglobin level. A similar sequence of events could occur in reverse and drive the haemoglobin too high when the levels drop below the target range.

Excursions to high and low haemoglobin levels are inevitable in ESA-dependent dialysis patients but the new algorithm was expected to reduce the number caused by over or under dosing of ESA. The audit indicated that the reduction was principally in the excursions to high levels suggesting that these are almost always iatrogenic. It is perhaps not surprising that there was little impact on excursions to low haemoglobin levels as this can be caused by any of the myriad of factors, many transient, known to influence ESA responsiveness [19] besides ESA under dosing. The reduction in the number of patients with high haemoglobin levels also led to a slight decrease in the mean haemoglobin level, bringing it closer to the midpoint of the target range.

Results using different computer-assisted anaemia management algorithms have recently been published. The approach by Ho et al. [13] was to increase the frequency of haemoglobin measurements to every dialysis session to inform ESA dosing and they reported an improvement in compliance with haemoglobin targets. More frequent haemoglobin checks may have a role in reducing inter-individual haemoglobin variation [20], such as occurrences with perturbations in fluid balance or lab assays for example, but in our opinion, a ‘pooled’ or averaged haemoglobin level may offer advantages for determining ESA dose adjustment rather than reacting to individual measurements taken over a short-time period. The question of whether using a pooled haemoglobin value in conjunction with our predictive algorithm would result in further improvements remains unanswered. The use of neural networks for renal anaemia management may have a place [11, 21] but in our opinion, the pharmacodynamic basis of our model and its simplicity make it a more practicable solution.

By adopting a predictive algorithm, we increased compliance with haemoglobin targets, reduced the number of patients with high haemoglobin levels and narrowed the haemoglobin distribution. This was achieved with no increase in blood sampling, a reduction in staff workload in terms of the number of ESA prescription changes required and with no increase in ESA usage. The fact that these results were obtained through a change in routine clinical practice with dose changes implemented by any member of staff qualified to prescribe ESAs rather than in the setting of a closely monitored clinical trial, highlights the potential utility and widespread applicability of this approach.

Conflict of interest statement. S.W.L., E.J.L. and J.E.T. have no conflicts of interest to declare. M.J.W. has previously received hospitality from Amgen, Roche and Ortho-biotech although has no ties to these organizations at present. The results of this work have not been published except in abstract form at the American Society of Nephrology, European Renal Association, British Renal Society and Renal Association meetings.
Predictive renal anaemia algorithm

References


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Appendix—Predictive algorithm for ESA dose changes

Any recommended change to the ESA dose is relative and proportional to the difference between the target and steady-state haemoglobin (Hb) level as defined below. The ESA used in our algorithm was darbepoetin alfa (Aranesp®; Amgen, UK). For all starting doses and dose adjustments, the ESA dose is rounded up or down to the nearest pre-filled syringe size.

Definitions

(All Hb measurements in g/dL)

\[ \text{Hb}_{\text{target}} \]
- Midpoint of target range (In this study, \( \text{Hb}_{\text{target}} = 11.5 \text{ g/dL} \))

\[ \text{Hb}_{\text{steady state}} \]
- Either:
  - Measured \( \text{Hb} > 90 \) days after last ESA dose change
  - Predicted \( \text{Hb} \) at 90 days after the last ESA dose change by linear extrapolation of \( \text{Hb} \) levels measured \( \geq 14 \) and \( \geq 42 \) days following a change in dose.

\( \Delta \text{Hb} \)
- \( \text{Hb}_{\text{target}} - \text{Hb}_{\text{steady state}} \)

Starting dose
- \( 10 \times \Delta \text{Hb} \) (Maximum starting dose darbepoetin alfa 30 mcg/week)

Dose adjustments

<table>
<thead>
<tr>
<th>Current dose</th>
<th>New dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{Aranesp} ) doses increase</td>
<td></td>
</tr>
<tr>
<td>2.5 mcg/week</td>
<td>5 mcg/week</td>
</tr>
<tr>
<td>5 mcg/week</td>
<td>7.5 mcg/week if ( \Delta \text{Hb} &lt; 3 \text{ g/dL} ), otherwise 10 mcg/week</td>
</tr>
<tr>
<td>10 mcg/week</td>
<td>15 mcg/week if ( \Delta \text{Hb} &lt; 3 \text{ g/dL} ), otherwise 20 mcg/week</td>
</tr>
<tr>
<td>15 mcg/week</td>
<td>20 mcg/week if ( \Delta \text{Hb} &lt; 3 \text{ g/dL} ), otherwise 30 mcg/week</td>
</tr>
<tr>
<td>20 mcg/week</td>
<td>30 mcg/week</td>
</tr>
<tr>
<td>&gt;20 mcg/week</td>
<td>((\Delta \text{Hb} \times 0.17) + 1 ) \times \text{Current dose} [Max increase 50%]</td>
</tr>
</tbody>
</table>

Aranesp doses decrease

<table>
<thead>
<tr>
<th>Current dose</th>
<th>New dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5 mcg/week</td>
<td>Stop ESA</td>
</tr>
<tr>
<td>5 mcg/week</td>
<td>7.5 mcg/week</td>
</tr>
<tr>
<td>&gt;5 mcg/week</td>
<td>((\Delta \text{Hb} \times 0.17) + 1 ) \times \text{Current dose} [Max decrease 50%]</td>
</tr>
</tbody>
</table>

The lowest dose for Aranesp is 10 mcg given every 4 weeks i.e. 2.5 mcg/week

NB
- If \( \text{Hb}_{\text{steady state}} \) is outside the target range but the current \( \text{Hb} \) is within the target range, \( \Delta \text{Hb} \) is fixed at \( \pm 1 \text{ g/dL} \).