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Using dynamic treatment regimes to understand erythropoietin stimulating agent hyporesponsiveness

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Abstract

Background: Erythropoietin stimulating agent hyporesponsiveness (ESAH) is associated with increased cardiovascular mortality in patients with end-stage renal disease (ESRD) on hemodialysis. Dynamic treatment Regimes (DTR), a type of clinical decision support (CDS) tool that guide the prescription of specific therapies in response to variations in patient states, have been used to guide treatment for chronic clinical problems that require frequent monitoring and therapy changes. Our objective is to explore the role of utilizing a DTR to reduce ESAH in pediatric hemodialysis patients.

Methods: Retrospective analysis of ESRD patients on hemodialysis who received ESAs. Dosing was adjusted using a locally developed protocol designed to target a hemoglobin between 10–12 g/dl. Analyzing this protocol as a DTR, we assessed adherence to the protocol over time measuring how the hypo-response index (ESA dose/hemoglobin value) changed due to varying levels of adherence.

Results: 18 patients met study criteria. Median hemoglobin was 11.4 g/dl (range: 6.1–15.4), and median weekly ESA dose (darbepoetin-equivalent) was 0.4 mcg/kg/dose (range: 0–2.1). Full adherence to the DTR was identified in 266 (71%) of the 4 week periods, with a median average adherence score of 0.80 (range: 0.63–0.91). As adherence to the DTR improved, ESAH decreased. During the last 12 weeks, 13 out of 18 patients had lower average ESA/hemoglobin ratio than the first 12 weeks.

Conclusion: A DTR appears to be well-suited to the treatment of anemia in ESRD and reduces ESAH. Our work shows the potential of DTRs to drive the development and evaluation of clinical practice guidelines.

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Keywords

Anemia; Hemoglobin; Dynamic Treatment Regime; End stage Renal Disease (ESRD); Pediatrics; Hemodialysis; Erythropoietin stimulating agent hyporesponsiveness (ESAH)

Introduction

Anemia secondary to chronic kidney disease (CKD) has been found in up to 90% of adult patients with a GFR <30 ml/min, and 95% of pediatric patients on hemodialysis [1]. Traditionally, it has been associated with three primary causes in patients with endstage renal disease (ESRD): erythropoietin deficiency (the target for erythrocyte stimulating agents (ESA)), reduced red blood cell survival, and inhibition of erythropoiesis by uremic toxins. ESAs play a significant role in improving both clinical and quality of life outcomes for patients with CKD [2, 3]. However, higher doses of ESA are also associated with increased mortality in both adults and children [4–7]. Those requiring higher ESA doses often have comorbidities that further contribute to ESA hyporesponsiveness (ESAH) [8]. Patients experience ESAH when one of the following conditions are met: (1) increasing ESA dose with a stable hemoglobin, (2) stable ESA dose with decreasing hemoglobin levels, or (3) increasing ESA dose and decreasing hemoglobin level.

Most studies have explored the relationship between ESA dosing and hemoglobin levels as a unidirectional relationship, where the ESA dose is the exposure variable and the hemoglobin level is the dependent outcome. However, the relationship is in fact bi-directional with both elements alternating as the exposure and outcome variables. This occurs as clinicians start a specific ESA dose (i.e. exposure), awaits a response in the hemoglobin (i.e. outcome) and then, based upon the resulting hemoglobin level (i.e. exposure), adjust the subsequent ESA dose (i.e. outcome). This pattern requires frequent monitoring and therapy adjustments over time, relying on a set of rules to guide clinicians in making necessary changes. Dynamic treatment regimes (DTR) consist of a series of rules, typically one per stage of intervention, that guide clinicians in individualizing treatment in response to patient status [9]. As a form of clinical decision support (CDS), DTRs not only provide guidance at the point of care, but also provide the necessary foundation to aid the development of clinical practice guidelines that support individual patient variations [10]. In addition, once in place, DTRs set the stage for more careful statistical evaluation of adherence to a set of clinical guidelines and remove potential confounders that results from variations in individual practice patterns.

In this study, we explore how a DTR framework can be used to evaluate (1) the presence of ESAH, and diminish the confounding effect due to the interdependence of hemoglobin and ESA dosing, and (2) the ability of a locally developed clinical practice guideline to reduce ESAH in a population of pediatric hemodialysis patients. We performed an observational, retrospective analysis from a single center pediatric hemodialysis patient population where the hemoglobin dosing guidelines that were in effect can be viewed as a DTR.

Methods

Overview and population

We performed an Institutional Review Board approved, retrospective, longitudinal cohort study of all pediatric hemodialysis patients at Seattle Children's Hospital between 6/2009 and 6/2014. All patients over 5 years of age who had been diagnosed with ESRD were screened for inclusion. Patients were excluded if they received home hemodialysis or were dialyzed at a non-Seattle Children's Hospital dialysis facility, as we could not verify medication doses. In addition, due to the dynamic changes that take place during hemodialysis initiation, patients were required to be on hemodialysis for a minimum of 91 days to be included in the study. We stopped following subjects when they discontinued hemodialysis for any reason, including transplant or change in modality to peritoneal dialysis, death, or at the end of the follow-up period (June 30, 2014) if it occurred earlier. We limited our study to those patients receiving darbepoetin alfa (DA), marketed by Amgen under the trade name Aranesp®, for at least part of the follow-up period. Patients with a history of having a previous or current malignancy were excluded from the study due to concerns of potential non-response to DA due to marrow suppressing from chemotherapeutics.

ESA dosing and monitoring

In 2009, Seattle Children's Hospital began to transition patients from epoetin alfa to DA, and utilized manufacturer conversion guidelines. The typical starting dose for ESA naïve patients was 0.45 µg/kg/dose, once weekly. Utilizing hemoglobin levels, doses were adjusted using a local, institutionally developed protocol (Table 1). Patients received an appropriate weight-based dose of DA. If hemoglobin levels fell below 10 g/dl or rose above 12 g/dl, ESA doses were adjusted appropriately. When such adjustments took place, hemoglobin monitoring frequency was increased. All doses of DA were administered in the hemodialysis unit by a licensed Registered Nurse and charted in the electronic medical record.

Data collection

Data was obtained from our institution's data warehouse. All potential subjects with a diagnosis of ESRD maintained on hemodialysis at Seattle Children's Hospital between our study dates were screened for inclusion. In addition, we queried the data warehouse to pull the following information for each potential subject: name, medical record number, date of birth, diagnosis list (ICD9 codes and descriptions), height, weight, hemodialysis order details (start date, dose, and frequency), ESA administrations (includes date, product, and dose), lab results, transfusion history, and reasons for stopping hemodialysis. The data pull allowed us to track the history of treatment changes for individual patients, such that all prescriptions for both ESA dosing and hemodialysis changes were recorded and used for analysis. In addition, we performed manual chart reviews to clarify transplant dates, when hemodialysis started if it began before 2009, and to exclude peritoneal dialysis patients.

Data preparation

For each subject, only data obtained >90 days after the start of hemodialysis was used for analysis. For each ESA order, the patient's most recent weight was matched to reconstruct the weight-adjusted dose. When patients had received some erythropoietin doses in addition to DA, those doses were converted according to the standard conversion 238.1 IU/microgram. ESA doses were summed over consecutive 4-week periods and normalized to a weekly weight-adjusted DA dose, to account for the relatively long half-life of DA. Lab measurements were averaged over corresponding 4-week periods, including only periods in which either hemoglobin or albumin were available. For each period, a hyporesponse index (hereafter: the ESA/Hgb index) was calculated by dividing the DA-equivalent dose in the prior time period, with the mean hemoglobin for the current period [11]. A higher index indicates more ESA used to remain at the target hemoglobin, a dropping hemoglobin in the absence of dose reduction, or a combination of both. An increase in the ESA/Hgb index over time can be interpreted as evidence for the development of ESAH. Patients with fewer than seven 4-week periods with hemoglobin data were excluded from the analysis. The datasets generated during and analyzed for the current study are available from the corresponding author on reasonable request.

Analysis and primary outcomes

We evaluated whether the Seattle Children's Hospital dose-adjustment guidelines described above were followed in each time period. Adherence was defined as increasing the dose by 10% or more soon after hemoglobin dropped below 10 g/dl, vice versa if it rose above 12 g/dl, and avoiding changes greater than 10% when hemoglobin stayed in the target range. Non-adherence was defined as reducing the dose following hemoglobin levels below 9.5 g/dl, increasing it following hemoglobin levels above 12.5 g/dl, or fluctuations larger than 25% when hemoglobin was in the target range. Time periods whose dosing did not meet the "Adherence" or "Non-adherence" definitions were labeled "Neutral".

An overall patient adherence score was calculated by counting a full point for each "Adherence" time period and a half point for each "Neutral" time period, and averaging over all time periods (including "Non-adherence") except the last 3. This score was then used as an explanatory variable in a multivariable regression model for the endpoint of a change in the "hyporesponse index" defined above, between the first 12 weeks (calculated as the average of the first three 4-week periods) and the last 12 weeks. Besides the score, the model also adjusted for time on hemodialysis and use of fistula access. In addition, we looked at the rate of success in staying between 10 and 12 g/dl, and how that rate had changed between the first and last 12 weeks.

Results

Of the 87 patients who received hemodialysis at Seattle Children's Hospital between 6/2009 and 6/2014, 18 (20.6%) met all inclusion criteria (Figure 1). Demographic characteristics of the included patients are summarized in Table 2. Age ranged between 5 and 20 years, with seven between 5 – 11, five between 12 – 17, and six were 18 – 20. Median time on hemodialysis after the first 90 days was 17.6 months (range: 6.7 – 49.7). During the study,

there were 391 four-week data periods across all 18 patients with a median of 19 periods for each patient (range: 8 – 51).

385 (98%) of the four-week periods had at least one documented ESA dose and 6 (2%) periods had no DA administered. The median weight-based dose was 0.4 µg/kg/week (range: 0 – 2.1). In addition, during 43 (11%) of the four week periods at least a portion of the ESA dose was administered as erythropoietin, typically in the beginning of follow up for individual patients. The median hemoglobin level was 11.4 (range: 6.1 – 15.4) and 52 periods (13%) were classified as low (e.g. hemoglobin <10 g/dl) and 123 (31%) had a hemoglobin equal to or greater than 12 g/dl. 372 (95%) of the two-week periods had at least one albumin result and the median albumin was 4.1 (range: 2.3 – 5.0).

Protocol adherence was seen in 71% of the 4-week time periods, while non-adherence was observed in 9%, and 19% were neutral (Table 3). The median subject-specific adherence score was 0.80 (range: 0.63 – 0.91). A higher percentage of hemoglobin levels were within the desired range during the last 12 weeks of treatment vs. the first 12 weeks (Figure 2A). In addition, both the weight-adjusted DA doses and the ESA/Hgb index decreased, albeit not significantly (Table 4). There was a significant association between an individual's overall adherence score and the change in their ESA/Hgb index over time: in both the univariate ($p=0.006$) and multivariable ($p=0.01$) models, as adherence increased, the ratio between final and initial ESA/Hgb indices was lower (Figure 2B and Table 5). Specifically, for only 5 of 18 patients this ratio was greater than 1 (a potential sign for ESAH), and all 5 had an adherence score lower than the study population's median (0.80). Finally, we explored the relationship between the standard DA dose and hemoglobin over time and found that plots which move in a counterclockwise and tightening pattern suggest that individual patients do not have ESAH, and furthermore that dosing decisions for those patients had stabilized around a dose that successfully maintains hemoglobin in the target range (Figure 3). By contrast, potential ESAH cases are apparent as a curve that continues to trend down or to the right (e.g., Patient M in Figure 3).

Discussion

Anemia management plays a key role in the treatment of patients with ESRD on hemodialysis, requiring that patients maintain their hemoglobin levels within a tight range to minimize both morbidity and mortality. Yet, for individual patients, maintaining control can be challenging, especially due to the potential negative consequences associated with ESAH. Our results demonstrate that a well-defined protocol, for anemia management, one example of a dynamic treatment regime, increases the probability of patients achieving and maintaining a desirable hemoglobin level as well as reducing ESAH in a subset of children maintained on hemodialysis for at least 9 months.

When exploring the factors that contribute to ESAH, one needs to consider not only the clinical risk factors that lead to resistance (e.g. hypoalbuminemia, hyperthyroidism, inflammation, etc.) but also variations in clinical practice patterns. The implementation of a DTR in the form of a CDS tool not only helps to distinguish between these two factors, but also has the potential to significantly reduce the latter by creating standard practice

guidelines. In our study, we didn't see the benefit of the CDS tool until adherence to ESA protocol reached a level of at least 75%, suggesting that high rates of acceptance and usage of the tool are required to reach the desired outcome. Therefore, policies that encourage adherence to the protocol including support for non-prescribing providers, such as dialysis nurses or pharmacists to adjust ESA dosing based on institutional protocol may further reduce ESAH rates.

With the trend towards providing more personalized medical care, evidence-based dynamic treatment regimes provide a way to operationalize and personalize standardized data driven decision making at the point of care [10]. DTRs have been used in a variety of clinical settings to help improve outcomes, from anticoagulation management [12] to ADHD treatment [13]. Our current work demonstrates the effectiveness of a relatively simple DTR, implemented as a clinical practice guideline, illustrating the potential of these type of CDS tools to be utilized over a long period of time where multiple decisions are made in response to constantly changing outcome variables.

While the protocol utilized at our institution was empirically derived based on local expert opinion, work by Murphy provides the methods to derive optimal dynamic treatment regimes using experimental or observational data in order to obtain maximum results [14]. Cotton et al. have utilized a DTR to explore the ideal hematocrit target range that minimizes mortality in prevalent hemodialysis patients using USRDS data [15]. Ideally, future tools would leverage existing data to design ideal treatment protocols, as well as clinical practice guidelines, but if sufficient data does not exist, the methods used to build new DTRs support prospective evaluation and refinement. Therefore, to further drive down ESAH rates, teams can leverage existing data, as well as expert opinion to help design future guideline-based CDS tools. Our findings suggest that prospective studies should include long, contiguous observation periods, given the typical frequency of dosing decisions. In the case of ESAH, it appears that the minimal stable time-unit seems to be 4 weeks, and a series of these units are required to evaluate for the presence of ESAH. Finally, these tools should include clearly defined decision support rules that address other known ESAH risk factors, such as iron deficiency, hyperparathyroidism, or nutritional deficiencies. We have modified our own protocol to now include some of these other factors to further reduce ESAH.

In addition to showing the benefit of the CDS tool in reducing ESAH, we propose a novel visualization strategy to assist clinicians in identifying patterns of both ESA response and hyporesponse (Figure 3). We believe that plotting an individual patient's hemoglobin as a function of their ESA dose allows for quick identification and recognition of hyporesponsive time periods compared to typical reporting tools. First, traditional medical record systems typically take a system-oriented approach to storing data, such that lab results are separated from medication dosing, making it more difficult to associate changes in therapies to outcomes. However, our visualization takes a more problem-oriented approach, where the necessary data elements are co-located within the same area of the medical record, and the relationship between treatments and outcomes over time are much more readily observed. Second, patients that respond to ESA treatments, have a unique and predictable pattern (i.e. counter clock-wise spiral), while non-responders tend to have patterns that drift down and to the right. Finally, plotting the hemoglobin as a function of the ESA dose, as opposed to

plotting both over time, condenses the display of information and emphasizes the dynamic relationship between the two items. Therefore, after a brief introduction to the visualization, clinicians should be able to quickly review and interpret this data, to make well informed and clinically appropriate decisions.

While our work demonstrates the potential of leveraging a DTR to minimize ESAH, we also need to recognize its limitations. First, the retrospective analysis limits our ability to completely comment on how other known ESAH factors (e.g. parathyroid hormone or albumin levels), play a role in the functioning of the CDS tool, as these tests were not collected consistently or with enough frequency for all patients in our group and therefore were unable to be analyzed. In addition, it is possible that the observed correlation between ESAH and DTR adherence was due to an unrecognized improvement in one or more of these factors. Therefore, future work in this area should be prospective, which not only affords the ability to incorporate additional risk factors into the CDS tool, but would also allow different permutations of the independent components of a tool to be evaluated (i.e. frequency of lab tests, rate of ESA changes based on varying changes in hemoglobin levels, needs of different demographic groups such as age, etc.).

Second, this study was conducted with a relatively small group of patients at a single institution, which may limit its generalizability. Our sample size was impacted by the decision to only include subjects who had been on hemodialysis for a minimum of 9 months due to concerns of stability at the start of hemodialysis as well as the pharmacokinetics of DA and our analysis procedures. Given that almost half of the screened patients were excluded as a result of these timing requirements, one may wonder what impact a DTR would have, if the majority of pediatric ESRD patients remain on hemodialysis for less than 9 months. Yet, in the US the median waiting time for incident patients on hemodialysis is 11.1 months based on recent USRDS data [16] and pediatric patients who are maintained on hemodialysis for longer periods are the ones who have the most to gain from a DTR, as they are more likely to experience morbidity and mortality of ESAH and increased cumulative dosing of ESA [7].

Given the complexities and significant risks associated with anemia management in hemodialysis patients, tools that simplify and minimize these risks, have the potential to provide real world benefits for this patient population. Our work demonstrates the value of incorporating clinical practice guidelines in a simple CDS tool in reducing ESAH, and lays the ground work for future studies to investigate how such guidelines and tools can be optimized to reduce the complications associated with ESAH.

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Figure 1: Consort Diagram. 87 patients were originally screened for inclusion and 69 (79.3%) were excluded for various reasons as indicated in the figure.

HD – hemodialysis; SCH – Seattle Children’s Hospital

Figure 2:

Changes in hemoglobin as a function of the Dynamic Treatment Regime. A) Comparison of hemoglobin results at the start of treatment to the end of the investigation period. B) Association between an individual's adherence score and change in erythrocyte stimulating agent (ESA)/hemoglobin (Hgb) ratio index comparing the first 12 weeks of treatment to the final 12 weeks of the study period. As adherence to the ESA protocol increased, patients were significantly more likely to have a decrease in their ESA/Hgb index ($p=0.006$).

Figure 3:

Relationship between weight-based normalized dose of darbepoetin alfa (DA) versus hemoglobin (Hgb) over time for individual patients. The black circle represents each patient's first 4-week hemoglobin average vs. the DA dose during the 4-week period immediately prior. The line connects to the subsequent period, and so forth, with its color becoming lighter over time. Patients without erythrocyte stimulating agent hyporesponsiveness (ESAH) usually demonstrate a counterclockwise and tightening spiral, best exemplified by Patient N. In contrast, for Patient M ESAH is highly suspected as the plot trends right, with hemoglobin remaining below 10 ug/dl despite increasing DA doses towards the end of our follow-up period.

Table 1:

Seattle Children's Hospital's darbepoetin alfa dosing protocol

Hgb Level	ESA Dose Change	Monitoring Frequency
< 10	Increase dose by 25%	Weekly
10 – 12	No Change	Monthly
> 12	Hold dose until Hgb < 12 and then decrease dose by 25%	Weekly

ESA – erythrocyte stimulating agent; Hgb - hemoglobin

Table 2:**Patient Characteristics**

	Count (%)	Median (range)
Gender		
Female	8 (44%)	
Male	10 (56%)	
Age Group at Monitoring Start		14.8 (5.8 – 20.2)
5 to 11	7 (39%)	
12 to 17	5 (28%)	
18+	6 (33%)	
Number of data points per Patient		19.0 (8.0 – 51.0)
8–14	7 (39%)	
15–24	6 (33%)	
25+	5 (28%)	
Monitoring period (months)		17.6 (6.7 – 49.7)
6 – 12	6 (33%)	
12 – 24	6 (33%)	
24 – 60	6 (33%)	

Table 3:

Adherence to the darbepoetin alfa (DA) protocol for each four week period. Adherence can be defined as an appropriate response to the DA dose in response to hemoglobin levels for individual patients as defined in the methods.

Adherence to Protocol	4-week periods (%)
No	35 (9%)
Neutral	72 (19%)
Yes	266 (71%)
Total	373 (100%)

Table 4:

Comparisons in hemoglobin (Hgb), darbepoetin alfa (DA) dosing, and the hyporesponse index (ESA/Hgb) over time.

	Mean (SD) of individual patient averages		
	First 12 weeks	Final 12 weeks	p-value
Hemoglobin	11.3 (1.7)	11.0 (1.2)	0.48
Weight adjusted DA dose	0.7 (0.4)	0.5 (0.3)	0.11
ESA/Hgb index	0.06 (0.03)	0.05 (0.03)	0.11

Table 5:

Relationship between protocol adherence and erythrocyte stimulating agent (ESA)/hemoglobin (Hgb) ratio. There was a significant correlation between adherence to the dynamic treatment regime and a reduction in the ESA/Hgb ratio in both unadjusted and adjusted models. Fistula use and duration of time on hemodialysis was not associated with a significant change in the ESA/Hgb ratio.

Effect	Unadjusted			Adjusted		
	Change (%)	Confidence	P Value	Change (%)	Confidence	P Value
Adherence (excluding last 12 wks), per 1% improvement	-4.7	(-7.8,-1.5)	0.006	-5.1	(-8.8,-1.4)	0.010
Proportion of Time using Fistula (per 10%)	-1.0	(-9.2,7.2)	0.799	-3.6	(-11.5,4.4)	0.349
Monitoring Duration (per 6 months)	-8.3	(-24.2,7.7)	0.287	0.0	(-16.0,16.0)	0.999