Poster #134

Dose Cycling Patterns In Epoetin Alfa Use In United States Hemodialysis Patients

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INTRODUCTION

- Dose cycling (DC) refers to the within-patient variation in erythropoietin stimulating agent (ESA) doses from week-to-week and month-to-month in response to oscillations in patient hemoglobin (Hb) concentration **(Figure 1)**. DC occurs for a number of reasons, including the lag time between ESA administration and Hb response and the lack of an optimal dose/response algorithm.
- For most patients, ESA response typically varies over time and may change due to a variety of causes and illnesses, including iron deficiency, infection, volume overload and missed dialysis sessions[1].
- When adjusting doses, physicians must take multiple factors into consideration, including both the level and rate of change in Hb. Thus, ESA doses are routinely adjusted with the clinical goals of limiting Hb fluctuations, preventing excessive Hb rates of change and preventing Hb overshoot.

OBJECTIVE

- To describe patterns of within-patient month-to-month dosing variations in U.S. hemodialysis patients taking epoetin alfa between January 2010 and July 2014.

METHODS

- Dosing data were taken from the OutcomesPlus datamart, an Amgen proprietary database of clinical data which contains information on approximately 80-85% of the entire U.S. dialysis population. This analysis was based on in-center hemodialysis patients only. Cohorts of patients who had dosing data for at least 7 consecutive months from January or from July of each year were selected from sampling frames of all patients in the database as of the index month (January or July).
- Doses were tracked for six months after the index month. Average weekly doses of epoetin alfa were calculated for each month. The top and bottom 1% average weekly dose outliers for each month were removed from the analysis.
- Doses were categorized into 8 ranges (units/week) based on ranges defined for dose conversions in the Aranesp® product insert: 0, 1-1499, 1500-2499, 2500-4999, 5000-10999, 11000-17999, 18000-33999, 34000+. Dose category changes were counted for any month that the dose category was different from the previous month's category. Dose consistency was counted as the number of consecutive months that the dose category was the same as the index month category. Patterns of changes and consistency in dose categories were examined for each cohort, and across cohorts.

RESULTS

- The mean(SD) cohort size was 205,911(8,667) patients. The sampling frames at each index month had a mean(SD) of 304,724(12,399). On average, one-third of the patients in the sampling frames did not have complete/eligible data for the following 6 months. Table 1 shows the number of patients and mean(SD) weekly dose for each sampling frame from which the cohorts were drawn. Mean weekly doses declined by 40% from January 2010 to January 2014.
- In the January 2014 cohort, the average number of dose category changes over six months was 3.4, with only 4% of patients having 0 dose category changes and 7% of patients changing dose category every month **(Figure 2)**. Only 42% of patients remained in the Index Month dose category a month later and only 22% of patients after 2 months **(Figure 3)**.
- Patterns of dose cycling were mostly consistent across the four and a half years covered by the study, with the exception of the July 2011 cohort, coincident with a FDA label change for epoetin alfa, when dose cycling peaked and dose consistency declined slightly **(Figures 4-5)**.

Table 1: Patient Counts and Mean Weekly Doses at Each Index Month

Index Month		Jan-10	Jul-10	Jan-11	Jul-11	Jan-12	Jul-12	Jan-13	Jul-13	Jan-14
Number of Patients		309,736	317,056	300,815	322,153	284,980	301,413	288,107	306,125	312,130
Weekly Dose	Mean	16,260	16,498	13,978	13,167	11,149	10,163	9,609	10,439	9,824
	St Dev	15,714	15,889	13,505	12,757	10,900	9,923	9,435	10,039	9,516

RESULTS

- Dose cycling is also consistent across dose categories. For example, in the January 2014 cohort, the percent of patients remaining in their index month category six months later ranged from 17% in the 1500 to <2500 category to 38% in the 5000 to <11000 category **(Figure 6).**

Figure 1: Dose Cycling in Sample Patients

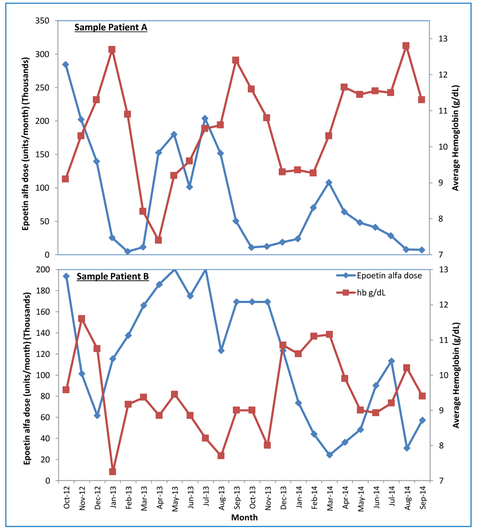


Figure 2: Dose Category Changes over 6 Months

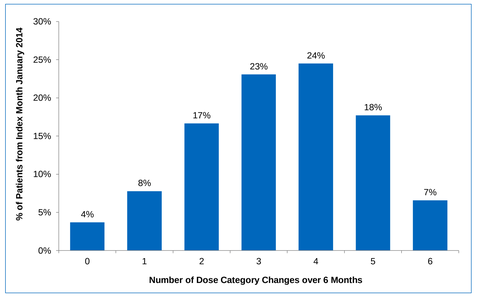


Figure 3: Dose Category Consistency over 6 Months

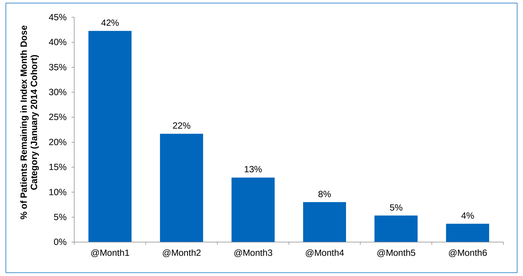


Figure 4: Dose Category Changes 2010-2014

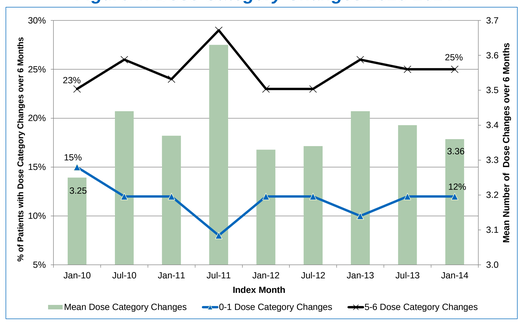


Figure 5: Dose Category Consistency 2010-2014

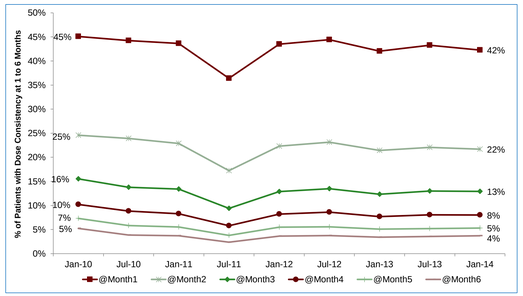
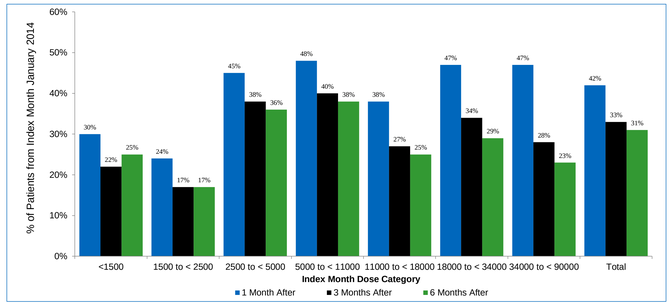


Figure 6: % Patients Who Were in Index Month Dose Category 1, 3 and 6 Months Later



DISCUSSION

- Between 2010 and 2014, in our large samples of U.S. hemodialysis patients, about 1 out of 4 patients experienced at least 5 ESA dose changes over six months, with 5% or less experiencing no dose changes.
- Contrary to common references in the literature to "low dose" and "high dose" patients[2] and "hypo-responsive" or "ESA-resistant" patients[3,4], the reality is that most patients on dialysis have varying ESA response over time and most receive regular, sometimes dramatic, ESA dose changes to manage their Hb.
- Given the frequency of dose adjustments for most dialysis patients, management of anemia may be more difficult to achieve with less frequently dosed ESAs[5,6].
- A limitation of this study was that we could only observe total monthly doses administered at each reporting facility. Intra-month dose category changes were not reported. In addition, we did not have access to data on missed dialysis sessions, which may influence month-to-month dose category changes. Finally, sampling methods have inherent limitations which may misrepresent the phenomena being studied.
- Future research could build upon our work by (1) providing a more granular look at dose category changes through the use of weekly dosing data, and (2) examining the impact of missed dialysis sessions.

CONCLUSION

- At least monthly ESA dose adjustments are routine in the anemia management of U.S. dialysis patients. Few patients experience what could be described as steady, maintenance doses of ESAs over extended time periods.

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