

A Novel Anemia Management Protocol

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Objective

Report the performance of an adaptive protocol for management of anemia in end-stage renal disease design.

Background

- Anemia of end-stage kidney disease (ESRD) is characterized by multiple factors:
 - Endogenously produced erythropoietin (EPO) is inappropriately low for the level of anemia.
 - Reduced red blood cell lifespan.
 - EPO resistance.
 - Inflammation.
 - Loss of blood.
- Erythropoiesis is a dynamic process. Its interaction with an anemia management protocol results in a *new* dynamic system, whose behavior can be very different from that observed in pharmacokinetics/pharmacodynamics (PK/PD) studies.
- Current anemia management protocols fail to achieve desired response.
- Anemia management should be viewed as a feedback control system, with new protocols designed using feedback control principles.

Methods

Pharmacokinetics Model

- Single pool of EPO in blood, intravenous doses modeled as impulsive inputs, and Michaelis-Menten function capturing nonlinear clearance.

Pharmacodynamics Model

- Stimulatory effects of EPO on differentiation, maturation, and proliferation of hematopoietic stem cells into reticulocytes modeled using a nonlinear, time-delayed function of EPO concentration.
- Reticulocyte and RBC dynamics are described using cellular lifespan probability distributions.

Parameter Estimation

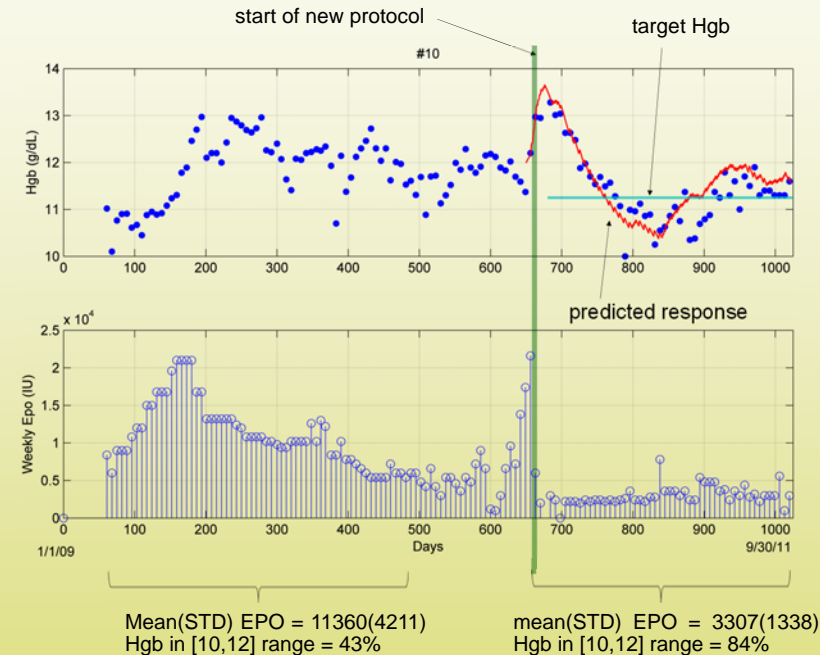
- Simulink Design Optimization Tool (The MathWorks, Inc.) for estimating nominal PK/PD parameters.
- Quantify uncertainty in PK/PD parameters.

Model Simplification and AMP Design

- Pharmacokinetics and cell production represented as nonlinear function of EPO dose.
- Apply feedback control principles (Quantitative Feedback Theory) to design individualized protocols that maintain target Hgb level in ESRD patients with different EPO responsiveness and time-varying erythropoiesis properties.

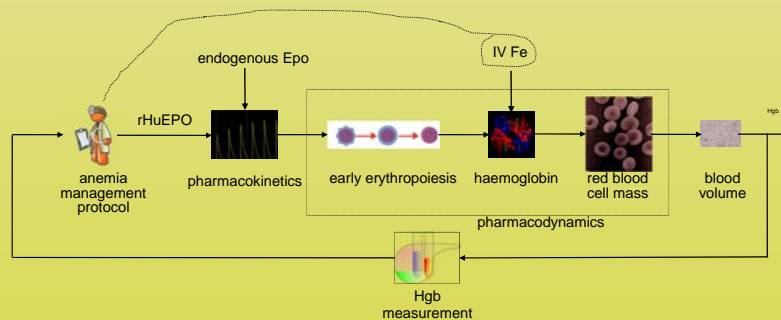
Results

- Hgb levels and EPO doses in subject #10. New AMP initiated at day 661.
- New AMP controls Hgb level to target with reduced EPO doses.



Discussion

- Model-based, feedback control principles offer an improved approach for designing individualized anemia management protocols which can achieve improved Hgb management with reduced EPO doses.
- Intercurrent events (e.g., inflammation, blood loss) place significant constraints on achievable AMP performance.
- We hypothesize that:
 - Short-term Hgb variability is largely due to fluid volume variations that cannot be controlled using anemia management protocols.
 - Long-term Hgb variability is largely due to poorly designed anemia management protocols.



Anemia Management as Feedback Control System