Towards personalizing hydroxyurea treatment of sickle cell disease

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This work addresses sickle cell disease (SCD), a hereditary disorder caused by a single gene mutation in the beta-globin gene that produces abnormal hemoglobin and makes red blood cells sickle-shaped. Currently, SCD affects approximately 100,000 Americans and millions of people worldwide. Hydroxyurea (HU) is the most widely used disease-modifying drug for SCD, requiring daily oral doses over a patient's lifetime. The main challenges associated with HU treatment are substantial interpatient variability in pharmacokinetic (PK) and pharmacodynamic (PD) profiles, cytotoxicity, lack of an effective biomarker to predict treatment efficacy, and non-adherence.

HU gets cleared from the body within 24 hours, but the drug-related effects manifest on a timescale of days and take months to stabilize. Because of the short lifespan of HU inside the body, existing models have only captured HU trajectory inside the plasma over 24 hours; the relationship between daily drug dosage and the long-term effects of HU was not taken into account. In this work, we model the HU biomarkers trajectory on a timescale ranging from 1-8 years for pediatric SCD patients. In addition, we also model the effect of skipping drug intake on the biomarkers trajectory to investigate how different patterns of non-adherence can result in different physiological profiles.

We developed a semi-mechanistic compartmental PK model, which captures the temporal changes in the HU concentration in the plasma. The model calculations for AUC and AUMC match well with data with greater than 70% accuracy. The PK model is simulated every day with the given dose as input. The average drug concentration is computed for each day and plugged into the PD models, where we studied drug efficacy alongside drug side effects. For estimating efficacy, we modeled the effect of HU on biomarkers - fetal hemoglobin (HbF) and mean cell volume (MCV). For HbF, we modeled the HbF activation by HU through an intermediate that directly activates the HbF. For MCV, we modeled the erythropoiesis process to examine the effects of HU on the formation of red blood cells and its direct/indirect manifestation in the MCV. The HbF and MCV model performs well for both adherent as well as non-adherent patients. Further, the effect of HU on white blood cells (WBC) is a manifestation of its effect on the early precursor cells. Therefore, we modeled the leukopoiesis process for capturing myelosuppression, which

describes the formation of WBC in the blood circulation and how HU affects cells in different stages. For patients with myelosuppression effect, the model is able to mimic patient response.

We also observed that for many patients, the HbF and MCV indicated non-adherence; however, the dosing data did not contain the non-adherence information. We incorporated non-adherence in the patients' model using a probabilistic algorithm which led to improved model fits. In addition, to see how different forms of non-adherence affect HbF and MCV profiles, we imposed non-adherence in the model. We observed that missing the dose in a specific pattern is less harmful than missing the dose in a row. In summary, we developed mathematical models to simulate HU response in SCD patients and quantify non-adherence, which will eventually help clinicians differentiate treatment inefficacy from non-adherence.

Although HU has been beneficial in improving the life expectancy of patients and reducing sickle cell-related complications, there are challenges associated with the management of the drug. Our modeling approach is a key step towards understanding the long-term effects of HU on the patients' physiology within a shorter timeframe as compared to the clinical studies that can require years of monitoring. The models developed here can be helpful in not only predicting patients' PK-PD trajectory but also in understanding why some patients respond well while others do not and how we can maximize the treatment benefit for poor responders.