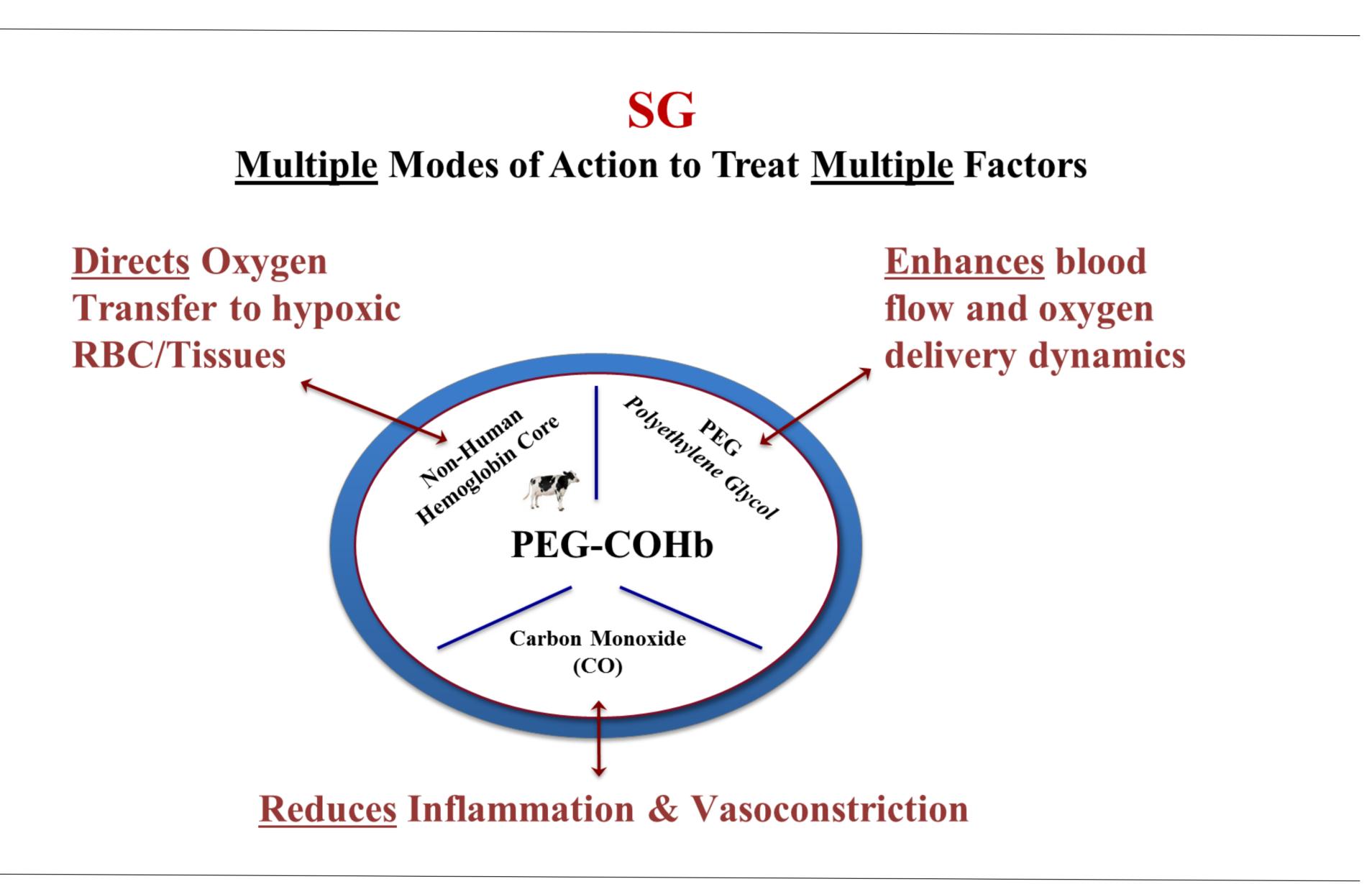
Use of a Pegylated Carboxyhemoglobin Bovine in Severe Life-Threatening Anemia

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Background:

Patients who cannot receive blood transfusions in the presence of severe anemia can sustain significant morbidity and mortality. Religious beliefs and hemolytic reactions are the most common reasons for not transfusing a patient. Pegylated bovine carboxyhemoglobin (Sanguinate; SG), a therapeutic drug, has been used in 5 such patients.



Aim:

Perform a post-hoc analysis of clinical findings and assess their relationship to individual patient diagnosis/associated comorbidities and SG intervention.

Methods:

Five patients with hemoglobin (Hb) levels under 3.5 g/dL were treated with repeated doses of SG. Diagnoses included AML, hemolytic reaction, acute chest syndrome and sickle cell disease (SCD) crisis. Patients ranged in age from 19 to 61. A unit of SG consists of 500 mL (40 mg/mL) given IV. Total doses ranged from 1 unit/day for 2 to 4 days up to 8 units given over 9 days.

Results:

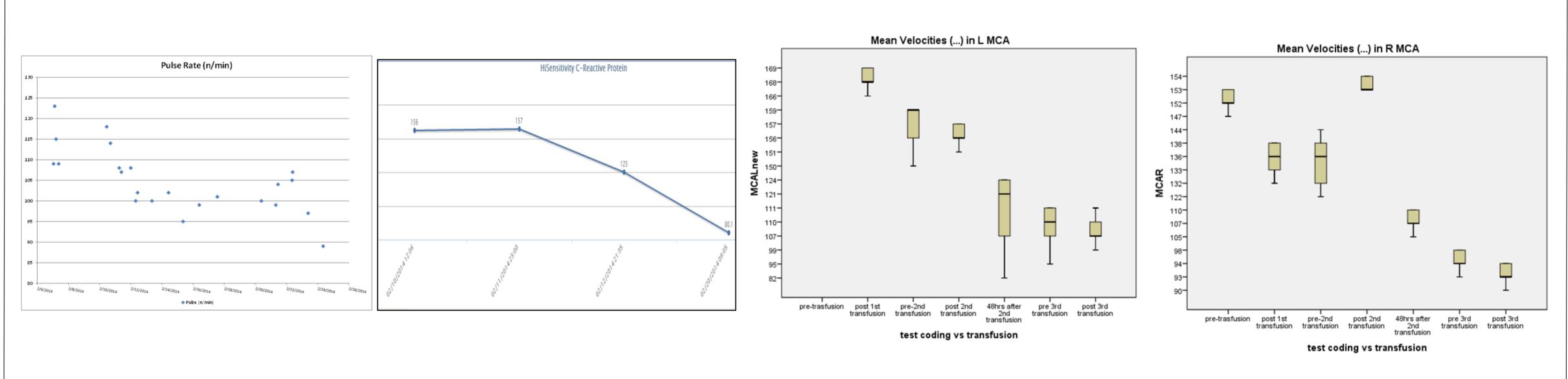
Patient	Diagnosis	Patient Characteristics	Nadir Hb level (g/ dL)	Number of doses	Clinical signs of improvement following SG infusion
1	SCD crisis	61 year old Jehovah witness female with SCD trait/thalassemia trait.	2.9	2	More alert; improved brain oxygenation; responsive to questions.
2	ACS	23 year old Jehovah Witness female with SCD/thalassemia trait.		4	Improved cerebral blood flow and CRP levels; improved breathing
3	Hyperhemolysis follow- ing allogenic blood transfusion	28 year old female with SCD	2.5	8	Reported feeling well with no pain and no shortness of breath
4	Anemia due to chemo- therapy	51 year old Jehovah witness female with acute myelogenous leukemia	2.5	2	Awake, alert, and oriented and no reported lethargy
5	Hyperhemolysis follow- ing stem cell transplant	19 year old male	<3	4	Absence of fatigue; improved clinical status

Patient 1

- •Hb of 2.9 and hematocrit 8.6%. Unresponsive to stimuli and tachypneic with agonal respirations requiring intubation. Fluid output <10%.
- •Within 12 hours of SG administration, patient was more alert with improved brain oxygenation (from 40-50 to mid upper 60s) and able to respond to questions.
- •Patient received a second dose but clinical status continued to decline with severe hypotension and neglible renal function. Life Support discontinued.
- Death was not attributed to SG.

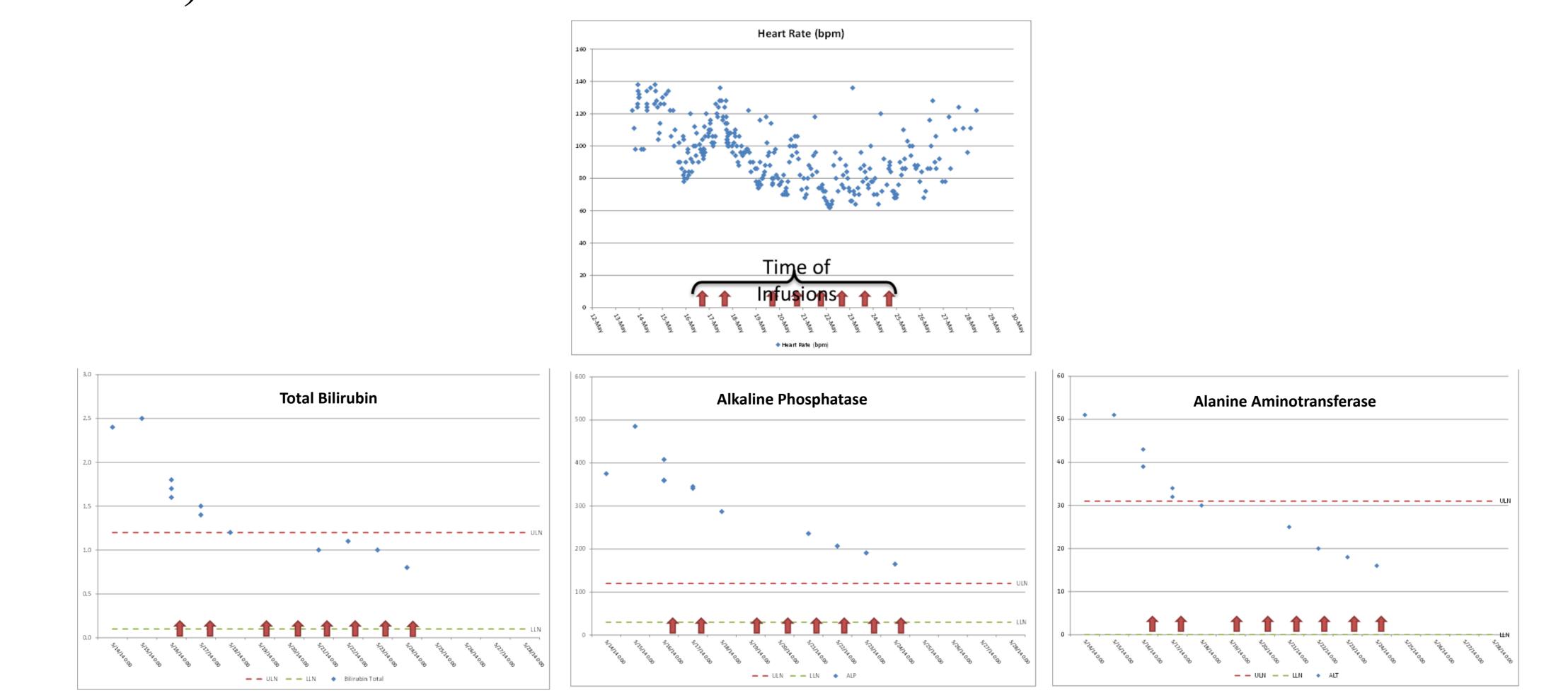
Patient 2

- •Hb 3.1. Intubated for respiratory distress. Transcranial Doppler (TCD) study revealed hyperemia with high cerebral blood flow rate.
- •SG was given and repeated in 24 hours. After initial extubation failure, two more units of SG were given to optimize extubation.
- •Patient was successfully extubated. Despite persistently low Hb, she reported improvement in her dyspnea. TCD velocities gradually normalized and CRP decreased.



Patient 3

- •Hb 3.5 g/dl and hematocrit 9.8%.
- -8 single dose infusions of SG were provided over 9 days.
- •Following the first 2 doses of SG, patient reported feeling well with no pain and no shortness of breath. Anemia remained severe (Hb 2.5).
- •Additional 6 daily doses of SG were given with continued reports of "feeling well" and improved mobility (shortness of breath upon mild exertion).

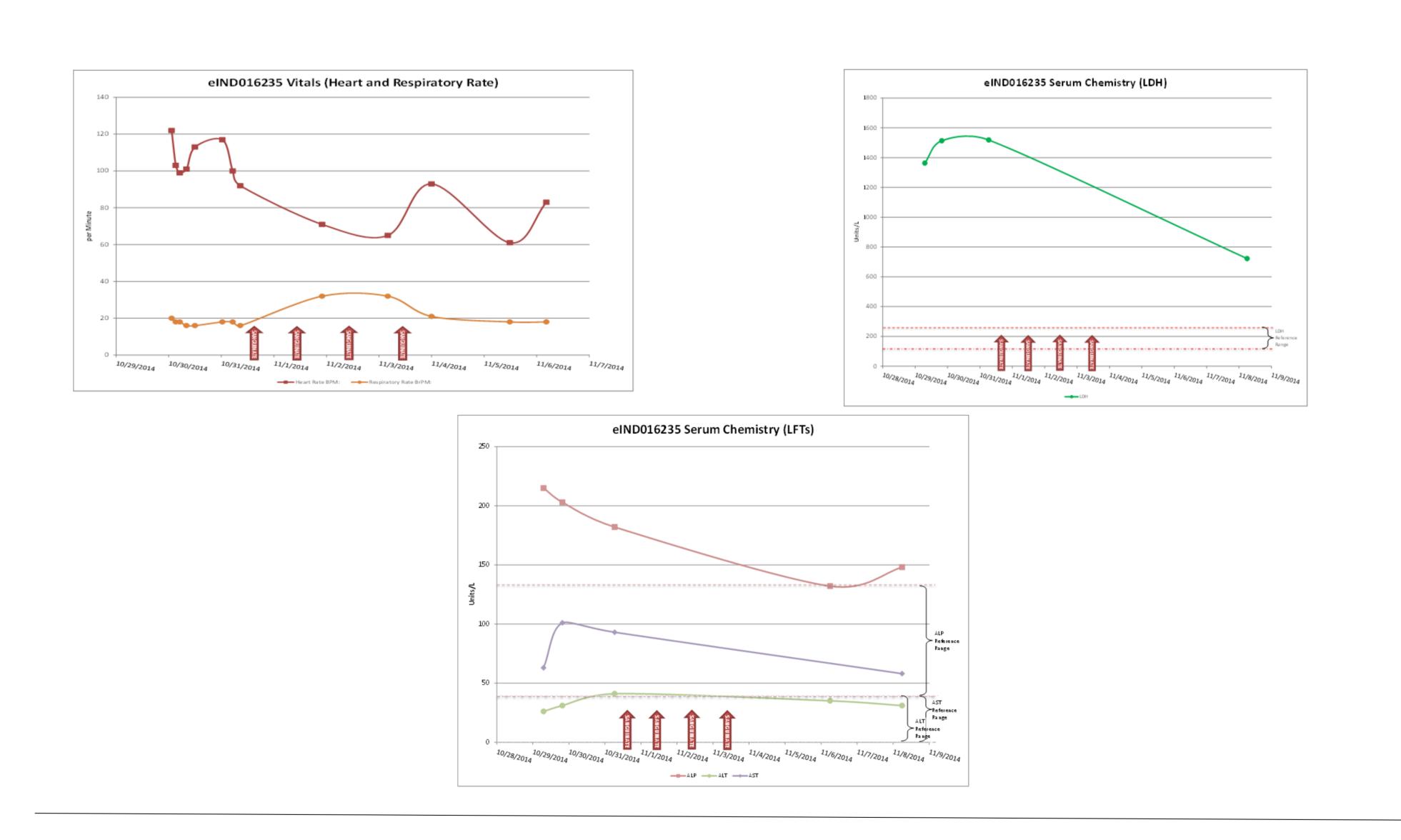


Patient 4

- •Following decitabine treatment, Hb dropped to 2.5. Patient was lethargic, dyspneic and mildly confused.
- •Immediately following infusion of SG, patient was awake, alert, and oriented. No further lethargy.
- •A second dose of SG was administered as clinical status of patient deteriorated the following day.
- •Patient died 2 hours later attributed to cardiac arrest secondary to complications of AML.

Patient 5

- •Hb 2.4. Severe fatigue and tachycardic.
- •Single doses of SG infused for 4 days.
- •Improvements in oxygenation, attributed to reduction of extreme fatigue, appeared to correlate with SG treatment.
- •The treating physician stated that SG likely played a role in stabilizing clinical condition until the donor cell erythropoiesis could occur.



Summary:

Evidence indicates that SG has potential therapeutic benefit in patients who have life-threatening anemia and cannot receive blood transfusions for personal or medical conditions. As vaso-constriction, inflammation, and oxygen deprivation are significant factors in severe hemolysis and ischemia, SG through the therapeutic actions of CO and oxygen may interrupt the ischemic cascade and improve clinical symptoms of hypoxia due to severely low hemoglobin levels. The improved clinical status in these patients suggests that SG may act as a bridge therapy providing oxygenation until patients regain hematopoietic function. Preclinical and *in vitro* studies with SG have been shown to demonstrate anti-inflammatory activity as well as active CO and oxygen transfer. SG is currently in clinical development for various anemic and ischemic disorders.