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Citation: Ataga KI, Kutlar A, Kanter J, et al. Crizanlizumab for the prevention of pain crisis in sickle cell disease. *N Engl J Med*, 2016, 376:429-439

Question:

What is the safety and efficacy of Crizanlizumab (a P-selectin antibody) in decreasing the rate of sickle cell related pain crises over the course of 1 year?

Background

In patients with sickle cell disease, pain crises related to vaso-occlusion account for the number one cause of health care encounters. Due to the end organ damage that can occur during these pain episodes, vaso-occlusive pain crises not only decrease the quality of life for patients but also increase the risk of death. Vaso-occlusion occurs due to sickle erythrocytes and leukocytes sticking to the endothelium. P-selectin has been found to initiate the adhesion of leukocytes to the endothelium during pain crises. Crizanlizumab was created to specifically bind P-selectin in the hopes of decreasing painful vaso-occlusive crises.

Methods

Prospective, multicenter, randomized, placebo-controlled, double-blind, 12 month study, phase 2 trial assessing the safety and efficacy of Crizanlizumab.

Pt with sickle cell disease between the ages of 16-65 with 2-10 pain crises a year were eligible for the study. The patient were divided into subgroups based on 2-4 vs 5-10 pain crisis a year, whether or not the patient was taking hydroxyurea or not, high dose vs low dose vs placebo. Patients received doses every 4 weeks for 50 weeks resulting in 14 total doses. Every 4 weeks the patient's also underwent a physical exam, questionnaire and lab testing.

Results

Primary endpoint of median crisis rate per year was 1.63 in the high does group (45.3% less with $p=0.01$), 2.01 in the low dose group (32.6% less with $p=0.18$) and 2.98 in the placebo group. Secondary outcomes: Days hospitalized: 4 per year in high dose vs 6.87 in placebo (41.8% less) but $p=0.45$. Time to first crisis: 4.07 months in the high dose vs 1.38 months in the placebo ($p=0.001$). Time to second crisis was 10.32 months in the high dose vs 5.09 months in the placebo ($p=0.02$). No statistically significant differences noted between low dose and placebo though trend present in all outcomes. No differences noted in brief pain inventory questionnaire between all groups.

Discussion

High dose Crizanliqumab, which is a P-selectin inhibitor, shows great promise at decreasing the number of yearly pain crisis. This therapy showed decreased rates of pain crisis regardless of hydroxyurea use or sickle cell disease genotype. Safety analysis of the study revealed similar incidences of adverse events between both the treatment and placebo groups. Limitations include lack of long term follow up for detection of neutralizing antibodies. Conflicts of interest include the study being funded by the pharmaceutical company producing the antibody as well as the authors receiving grant support from companies and owning stock in Selexys pharmaceuticals.
