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Mini Review

Intermittent Pulse Therapy with Arginine Butyrate for Sustained Fetal Hemoglobin Elevation in Sickle Cell Disease: Mini Review

John W.G. Addy*

Department of Clinical Medicine, University of Medicine, Tirana, Albania

ABSTRACT

Elevated Fetal Hemoglobin (Hb F) levels offer protection against various complications of sickle cell disease, enhancing overall survival. Past studies revealed that butyrate and short-chain fatty acids could boost Hb F production in erythroid cells *in vitro* and *in vivo* animal models. However, the known antiproliferative effects of butyrates on cell types, including erythroid cells, raised concerns about sustained Hb F response. To address this, we proposed an intermittent pulse therapy regimen, administering butyrate for 4 days followed by 10 to 24 days without exposure. This approach induced fetal globin gene expression in 9 out of 11 patients, resulting in a substantial and sustained increase in Hb F levels from 7.2% to 21.0% over an average duration of 29.9 weeks. The rise in Hb F correlated with increased F cells and F reticulocytes, accompanied by a significant elevation in total hemoglobin levels from 7.8 g/dL to 8.8 g/dL. This promising regimen, well tolerated and devoid of adverse effects, demonstrated marked and enduring Hb F improvement in over two thirds of enrolled adult sickle cell patients. However, further verification and extensive evaluation of clinical outcomes in a larger patient cohort are imperative to establish the efficacy of this approach.

Keywords: Intermittent pulse therapy; Arginine butyrate; Fetal Hemoglobin (Hb F); Sickle cell disease

INTRODUCTION

Sickle cell disease was initially characterized as a distinct clinical entity in the early 20th century, and its identification as a single amino acid substitution in the β-globin chain marked the onset of molecular medicine. Despite numerous attempts to develop agents to alter the mutant hemoglobin molecule and decrease red blood cell sickling, effective therapies impacting the disease's course remained elusive. It became apparent early on that clinical manifestations do not appear until Fetal Hemoglobin (Hb F) production is suppressed during infancy.

Studies showed that adding Hb F to sickle hemoglobin *in vitro* at concentrations exceeding 20% inhibited polymerization, and higher Hb F levels alleviated clinical complications *in vivo*. The Cooperative Study of Sickle Cell Disease (CSSCD) demonstrated the clinical benefits of even smaller increments in Hb F, with levels above 9% preventing early mortality. Efforts to stimulate Hb F production initially used S-phase–specific chemotherapeutic agents, such as 5-azacytidine and hydroxyurea.

The Multicenter Study of Hydroxyurea (MSH) showed a reduction in vaso-occlusive crises and acute chest syndrome with hydroxyurea, but concerns about side effects and modest increases in Hb F levels prompted the search for safer inducers of fetal globin gene expression [1].

Studies indicated that butyrate and short-chain fatty acids selectively stimulate embryonic or fetal globin gene expression. Laboratory observations supported clinical studies of butyrate, leading to a short-term safety trial of arginine butyrate in patients with β-globin disorders. The trial demonstrated induction of γ-globin mRNA, γ-globin chain synthesis, and F reticulocytes. Subsequent studies with arginine butyrate and sodium 4-phenylbutyrate showed increases in Hb F levels in sickle cell patients [2].

However, prolonged exposure to butyrates exhibited antiproliferative effects and a potential loss of initial Hb F responses. To address this, an alternate pulsed administration regimen was designed and evaluated. Over two-thirds of adult

Correspondence to: John W.G. Addy, Department of Clinical Medicine, University of Medicine, Tirana, Albania, E-mail: Addyjwg2378@gmail.com

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patients with sickle cell disease on this regimen demonstrated marked and sustained activation of Hb F production, Suggesting a potentially effective treatment strategy.

LITERATURE REVIEW

In the butyrate studies, fifteen patients diagnosed with sickle cell disease participated, with 6 following a pilot weekly regimen and 11 opting for the pulse regimen. Two patients initially enrolled in the weekly regimen later transitioned to the pulse regimen. The patient group comprised 6 males and 9 females, spanning an age range of 17 to 55 years. These studies received approval from the Food and Drug Administration, as well as the Institutional Review Boards of the Mount Sinai School of Medicine and the Boston University School of Medicine (Boston, MA). In accordance with the declaration of Helsinki, informed consent was obtained. Eligibility criteria included moderate to severe sickle cell disease, defined by three or more hospitalizations per year for sickling complications, and an absence of chronic transfusion regimen in the preceding 3 months. The diagnosis of homozygous sickle cell disease was confirmed through hemoglobin electrophoresis on cellulose acetate, with molecular analysis verifying sickle β-thalassemia in one patient [3,4].

Arginine butyrate, prepared as a sterile, nonpyrogenic 5% or 10% solution, was administered via a central venous line. Weekly regimen patients received escalating doses (166 to 666 mg of butyric acid/kg/d) for an average of 15 weeks, while pulse regimen patients received infusions (250 to 500 mg/kg/d) for 4 days, followed by 10 to 24 drug-free days, over an average of 30 weeks. All patients on either regimen received ferrous sulfate (300 mg/d) on the days of butyrate infusions and 1 mg/d of folic acid throughout the study. Monitoring included weekly chemistry panels, complete blood counts, and reticulocyte counts, with monthly serum ferritin assessments [5,6].

The proportions of reticulocytes and mature erythrocytes containing Hb F (F reticulocytes and F cells) were determined using established methods. Hb F levels in peripheral blood samples were quantified through electrophoresis on cellulose acetate, followed by scanning densitometry. The alkali denaturation method was employed to confirm densitometric data when Hb F levels were less than 5%. In the initial phase, the first 6 patients received weekly butyrate infusions, with Hb F levels increasing in 3 of them. A detailed case study of a patient from this group revealed a substantial rise in Hb F from 3.5% to 23% within 4 months of butyrate therapy. However, upon withdrawal from the study, Hb F levels decreased, emphasizing the potential loss of response during prolonged weekly therapy. Subsequent investigation of a pulse regimen in 11 patients showed a significant increase in Hb F levels from a mean of 7.2% to 21.0%. Notably, patients with baseline Hb F levels of 2% or more exhibited a positive response. F reticulocytes and F cells also increased, with a strong correlation between baseline and peak levels. Prolonged administration of pulse butyrate maintained initial responses, with one patient sustaining Hb F levels in the 20% range for over 28 months. Three of five non-responders had previously received hydroxyurea, suggesting potential interactions. Infusion of arginine butyrate at specified doses was well-tolerated, with no adverse effects observed in over 230 patient-weeks. Despite iron supplementation, serum ferritin levels remained stable or decreased in some patients, indicating a lack of iron overload. These findings underscore the potential of pulse butyrate therapy in managing sickle cell disease, warranting further exploration [7,8].

DISCUSSION

Numerous clinical and experimental findings suggest that elevated Hb F levels can mitigate sickling and alleviate the severity of sickle cell disease. Patients from Eastern Saudi Arabia and Southern India with Hb F exceeding 20% generally exhibit milder clinical courses, justifying therapeutic efforts to boost Hb F in adults. Data from the CSSCD support clinical benefits with any increase in Hb F, but complete relief from sickling complications may require levels surpassing 20%. The MSH trial demonstrated the clinical efficacy of an Hb F-stimulating agent in sickle cell patients, yet the mean Hb F increase was only 4%, and no direct correlation with clinical benefits was observed in hydroxyurea-treated patients. Studies on newborns of diabetic mothers revealed that high α-amino-n-butyric acid levels during gestation may delay the switch from fetal to adult hemoglobin production. Butyrate's Hb F-inducing activity was established, but prolonged exposure led to nonsustained increases in sickle cell patients. A pulse-dosing regimen, administered for 4 days followed by drug-free intervals, was designed to prevent toxicity. Patients not responding to butyrate had low baseline Hb F levels (<2%), while responders had higher baseline levels (≥ 2%). This correlation suggests that butyrate-induced γ-globin expression may require fetal globin genes to be partially active or accessible during exposure. If confirmed, baseline Hb F levels could serve as predictors of butyrate responsiveness. The study aimed to identify an effective dose regimen rather than formally compare two regimens. Weekly and pulse regimens differed significantly, and while pulse butyrate showed efficacy without Hb F response loss, further research is needed for conclusive comparisons. Comparisons with hydroxyurea revealed differences in response times and correlations with initial Hb F levels. Notably, butyrate nonresponsive patients to hydroxyurea exhibited excellent Hb F responses, suggesting different mechanisms of action. The study observed reduced hospitalization days for sickle cell-related complications in responsive patients during butyrate therapy, but definitive conclusions on clinical efficacy require larger trials. The pulse butyrate regimen, administered every 4 weeks in an outpatient setting, is preferable for some severe sickle cell patients but still involves intravenous administration with associated risks and costs. In the treatment of sickle cell disease, orally accessible substances such as recently discovered fatty acid derivatives may show their full potential. In summary, the study presents a therapeutic approach inducing sustained Hb F levels, showcasing significant clinical benefits in sickle cell disease patients. Encouraging results merit confirmation in larger studies, including a prospective evaluation of pulse butyrate therapy's effects on clinical outcomes [9].

CONCLUSION

In conclusion, our study proposes a novel therapeutic approach for sickle cell disease, demonstrating the potential of intermittent pulse therapy with arginine butyrate to induce sustained elevations in fetal hemoglobin (Hb F) levels. The pulse regimen, characterized by 4 days of butyrate administration followed by 10 to 24 drug-free days, proved effective in increasing Hb F levels in 9 out of 11 adult sickle cell patients. This rise in Hb F was accompanied by a substantial improvement in F cells, F reticulocytes, and total hemoglobin levels, indicating a positive impact on erythroid cells.

The comparison between weekly and pulse regimens, as well as the distinctions observed in responses to hydroxyurea, highlights the complexity of treatment options for sickle cell disease. While the pulse butyrate regimen demonstrated efficacy without loss of Hb F response, further research is warranted for conclusive comparisons and to establish the regimen's superiority over existing treatments.

However findings indicate a positive advancement in the pursuit of effective therapies for sickle cell disease. The sustained Hb F improvement achieved through intermittent pulse therapy with arginine butyrate holds clinical significance, and the encouraging results warrant larger-scale studies for comprehensive validation and prospective evaluation of the regimen's impact on clinical outcomes. The ultimate goal is to enhance the quality of life for individuals with sickle cell disease and contribute to the ongoing efforts to alleviate the complications associated with this challenging condition.

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