Gastroenterology and Hepatology From Bed to Bench.
2023 **RIGLD**, Research Institute for Gastroenterology and Liver Diseases

BRIEF REPORT

Granulocyte colony-stimulating factor does not improve mortality in severe alcoholic hepatitis: a single-center experience from the United States

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ABSTRACT

Aim: To assess the role of granulocyte colony-stimulating factor (GCSF) in the patients with severe alcoholic hepatitis (SAH) using real world experience in the United States.

Background: There are few effective treatments for severe alcoholic hepatitis, which has a significant fatality rate. GCSF has been associated with improved survival in a small number of Indian studies, while there is a dearth of information from other parts of the globe.

Methods: We performed a single-center retrospective study of consecutive patients admitted to a tertiary care, liver transplant center with severe alcoholic hepatitis from May 2015 to February 2019. The patients receiving GCSF (5µg/kg subcutaneously every 12 hours for 5 consecutive days) (n=12) were compared to the patients receiving standard of care (n=42).

Results: Thirty-day, 90-day and 1-year mortality rates was similar among groups (25% vs. 17%, P=0.58; 41% vs 29%, P=0.30; 41% vs 47%, P=0.44, respectively). There was no difference in liver transplant listing and orthotopic transplantation among groups.

Conclusion: In this real-world, United States-based study, GCSF does not improved survival in the patient with several alcoholic hepatitis compared to standard of care.

Keywords: Alcoholic hepatitis, Granulocyte colony-stimulating factor, Liver failure.

(Please cite as: **Nahas J, Y. Tow C, R. Chacko K, Haider T, Massoumi H. Granulocyte colony-stimulating factor does not improve mortality in severe alcoholic hepatitis: a single-center experience from the United States. Gastroenterol Hepatol Bed Bench 2023;16(1):524-526. https://doi.org/10.22037/ghfbb.v16i1.2639).**

Introduction

The patients with severe alcoholic hepatitis (SAH) have limited therapeutic options and high short-term mortality (1). Highly selected candidates may be eligible for early liver transplantation (LT), but the majority of the patients do not meet the psychosocial criteria necessary for listing (2). Despite the lack of compelling evidence to support their use, glucocorticoids remain a mainstay of pharmacologic treatment. However, patients who are steroid non-responsive or ineligible due to conditions like active infection, gastrointestinal bleeding, or renal failure have few therapeutic options (3). Non-steroid-based therapies, such as pentoxifylline and N-acetylcysteine do not improve survival (4) Recent studies from India have demonstrated survival benefits using granulocyte colony-stimulating factor (GCSF) either as primary therapy or for patients who failed steroid therapy, though these studies were not replicated outside of Asia (5-7). This study aims to examine the role of GCSF on mortality in the patients with SAH using real world experience at a single liver transplant center in the United States.

Received: 01 November 2022 *Accepted*: 13 December 2022
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Methods

Using a tertiary care, single-center, prospectively maintained LT evaluation database from May 2015 to February 2019, consecutive referrals for adult inpatient LT for SAH were retrospectively examined. SAH was defined as a Maddrey discriminant function (MDF) ≥ 32 or MELD-Na score ≥ 20. GCSF administration was determined based on expert consultation of a transplant hepatologist. Patients who got GCSF as part of their treatment for SAH were contrasted with those who did not. 30-day mortality was the main result. A change in MELD-Na score at 30 days, 90-day and 1-year death rates, as well as the listing and receipt of orthotopic liver transplantation were secondary outcomes. Statistical analyses were performed using Mann-Whitney, Chi-squared, and log rank tests in IBM SPSS v.25.0. A p-value of < 0.05 was statistically significant. The study protocol was approved by Institutional Review Board of the Albert Einstein College of Medicine and Montefiore Medical Center.

Results

Fifty-four patients with SAH were evaluated for inpatient LT over a 4-year period (Table 1). The median age was 43 years old and 60% were men. Sixty-five percent of patients received steroids. Twelve patients (22%) received GCSF (5μg/kg subcutaneously every 12 hours for 5 consecutive days). Among GCSF patients, 5 were not candidates for steroids and 7 were on steroids for an average of 8 days prior to stopping due to non-responsiveness. Twenty patients were ultimately approved for LT listing via ultimately 15 were transplanted.

Compared to patient who did not receive GCSF, patients who received GCSF had no significant differences in MELD-Na scores (median 33 vs 32, P=0.11), serum creatinine (2.3 vs 1.6 mg/dL, P=0.96), and the rates of infection (50% vs 29%, P=0.17) at presentation. GCSF patients had higher MDF scores (median 90 vs 68, P=0.02). GCSF patients received first-line therapy with steroids at similar rates to non-GCSF patients (58% vs. 66%, P=0.58) and had similar duration of steroid exposure (7 vs. 13.5 days, P=0.19).

At 30 days, there was no difference in mortality rates between GCSF, and non-GCSF patients (25% vs. 17%, P=0.58). All deaths were due to multiorgan failure precipitated by hepatic failure and often infection. GCSF patients had higher serum creatinine (3.4 vs 2.1 mg/dL, P=0.04), and trended towards increased MELD-Na scores (median 36 vs 30, P=0.08).

Table 1. Demographic and clinical characteristics and the outcomes of patients with severe alcoholic hepatitis who received GCSF compared to those who did not.

Characteristic	GCSF (N=12)	Non-GCSF (N=42)	p-value
Demographics			
Median age (range) – year	44 (22-57)	43 (26-57)	0.84
Male sex – no. (%)	5 (41)	22 (52)	0.61
Clinical Characteristics at Admission			
Median MELD-Na (range)	33 (30-55)	32 (24-44)	0.11
Median discriminant function (range)	90 (54-123)	68 (38-98)	0.02
Ascites – no. (%)	8 (67)	35 (83)	0.21
Grade 3-4 hepatic encephalopathy – no. (%)	1 (8)	3 (7)	0.89
Infection – no. (%)	5 (50)	12 (29)	0.17
GI bleed – no. (%)	3 (25)	7 (17)	0.51
Renal replacement therapy – no. (%)	3 (25)	11 (26)	0.93
ICU stay – no. (%)	4 (33)	17 (40)	0.65
Treatment Received for Alcoholic Hepatitis			
Corticosteroids – no. (%)	7 (58)	28 (67)	0.60
Pentoxifylline – no. (%)	1 (8)	2 (5)	0.63
N-acetylcysteine	8 (67)	25 (57)	0.65
Mortality			
30 days – no. (%)	3 (25)	7 (17)	0.58
90 days – no. (%)	5(41)	9(29)	0.30
1 year – no. (%)	5 (41)	10 (47	0.44
Transplant			
Listed – no. (%)	5 (41)	15 (36)	0.71
Transplanted – no. (%)	3 (25)	12 (29)	0.81

Ninety-day (41% vs 29%, P=0.30) and 1-year mortality rates (41% vs 47%, P=0.44) were similar among groups. Kaplan Meier survival curves showed no statistically significant differences between the groups. Additionally, the rates of LT listings and procedures for GCSF and non-GCSF patients were comparable.

Discussion

GCSF-mobilized CD34+ hematopoietic stem cells, and subsequent engraftment into the liver gives hope for a well-tolerated therapy for SAH that is rather easy to administer (8). Randomized, double-blinded clinical trials of the patients with SAH from India have shown improvements in MELD-Na score, MDF, and Child-Turcotte-Pugh scores, and most importantly survival up to 90 days after administration (5-7). Benefits were observed even in patients who were steroid non-responders (7). The patient populations in these studies, however, were overall and homogenous with a significant predominance of male patients of South Asian descent.

Our study is the first to report real-world experience in the United States of using GCSF for the treatment of SAH. The results of earlier clinical studies were not replicated in our investigation. After 30 days, 90 days, or one year, GCSF did not reduce MELD-Na score, MDF, or death in patients with SAH. The use of GCSF had no effect on the listing of organs for transplant or LT. These results may reflect a narrow therapeutic window in which GCSF may have benefit, as the average MELD-Na of our patient population was much higher (low 30s) than reported in prior trials (mid-20s) (5-7). It may also be that GCSF if less effective in a more diverse patient population with regards to both sex and ethnicity.

Our study was limited by small sample size, lack of randomization and potential for selection bias in favor of using GCSF in sicker patients with higher MDF scores. While MELD scores were higher in the GCSF group (33 vs. 32 in the standard medical therapy group), this was not deemed to be clinically significant.

Conclusion

Due to the nature of the patient group and the dearth of safe and effective medical treatments, SAH is a difficult condition to manage. GCSF gives a slim chance of recovery in individuals who are not liver transplant candidates, who have steroid contraindications, or who are steroid non-responders. While our study has not found positive results, further real-world studies and studies with greater patient diversity are needed to better clarify the efficacy of this stem cell-based therapy in the general SAH population.

Acknowledgements

Melissa Fazzari, PhD, MS (Department of Epidemiology and Public Health, Albert Einstein College of Medicine, Bronx, NY).

Conflict of interests

The authors declare that they have no competing interests.

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