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ORIGINAL ARTICLE

Therapeutic strategies for severe alcoholic hepatitis

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Summary
Background and aims: Severe alcoholic hepatitis (SAH) is an inflammatory response with multiple morbidity factors like leucocytosis, hepatomegaly, renal failure, hepatic encephalopathy, endotoxemia, and has a high mortality rate. Accordingly, identifying therapeutic interventions that can support prognosis is the goal of research.
Methods: Questionnaires were sent to 1234 medical institutions asking for information on patients with SAH during 2004 to 2008 including patients' demography, disease profile and the therapeutic interventions patients had received during hospitalization.
Results: Twenty-nine hospitals had treated SAH patients, and provided full demographic data on 62 patients. Twenty-seven patients had received no treatment, 10 patients had received granulocytes/monocytes apheresis (GMA) to deplete elevated myeloid linage leucocytes, the rest had received one or more of the following treatments, corticosteroids, plasma exchange (PE) and haemodialysis (HD). Further, 23 patients had died and 39 had survived within 100 days of hospitalization. Serum creatinine (Cr) was higher in patients who had died vs patients who had survived ($P = 0.026$). Likewise, patients with white blood cells (WBC) $\geq 10^4/\mu L$ had higher mortality rate vs patients with WBC $< 10^4/\mu L$ ($P = 0.039$). GMA in patients with WBC $\geq 10^4/\mu L$ showed 100% prognosis vs patients with WBC $\geq 10^4/\mu L$ who did not receive GMA ($P = 0.0007$). Corticosteroids, PE and HD did not significantly impact prognosis of SAH patients.
Conclusions: Our perception is that, patients with elevated myeloid leucocytes benefit most from GMA, while PE appears to support patients with coagulation deficiency or high plasma bilirubin and HD has indication in patients with high Cr.

Abbreviations: SAH, Severe alcoholic hepatitis; GMA, granulocytes/monocytes apheresis; PE, plasma exchange; HD, haemodialysis; Cr, creatinine; WBC, white blood cells; TNF, tumor necrosis factor; IL, interleukin; PSL, prednisolone; TB, total bilirubin; PLT, platelet; Hb, haemoglobin; PT, prothrombin; GI, gastrointestinal; DIC, disseminated intravascular coagulation; HGF, hepatocyte growth factor; IL-1ra, IL-1receptor antagonist.

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Introduction

SAH is an acute chronic inflammatory response affecting the liver, and reflects a spectrum of health disorders that result from alcohol-induced liver injury, ranging from the most common asymptomatic fatty liver disease to fulminant hepatitis and cirrhosis in the long term. However, it is difficult to predict the clinical course in an individual patient that leads to SAH as only a minority of people who consume large amount of alcohol develop SAH [1,2]. The seriousness of SAH lies in its morbidity and mortality rates; in hospital mortality rates are very high [3]. Intake of large amount of alcoholic liquor along with malnutrition and female gender are some of the factors that are known to be associated with a more severe disease [4]. Identification of patients at a high risk of death is vital not only for decisions related to the management of individual patients, but also for the design of clinical trials to find effective treatments for SAH. As yet, it is not well understood why only a minority of alcoholics progress to SAH. Understanding environmental and host factors which increase the likelihood of progression to SAH should help to reduce mortality rate [5].

Up to now, treatment options for patients with SAH have been very limited due to the severity of the condition at the time patients become hospitalized and the diversity of the pathologic factors acting simultaneously at the SAH stage. In clinical setting, corticosteroids have shown limited benefit, albeit in the short term [5,6]. In 1992, only 2% of European gastroenterologists administered corticosteroids as a standard medication and 66% used these occasionally [7]. However, there are discrepancies in the literature as several randomized trials and meta-analyses have reached contradictory outcomes [6]. Other treatment options which are reported to improve the prognosis of SAH patients include PE, HD, and pentoxifylline [8—10]. Additionally, one pilot study reported efficacy for the anti-TNF-α antibody in patients with alcoholic hepatitis [11], but subsequent studies found anti-TNF biologics to be either ineffective [12] or increase mortality rate [13], which is paradoxical given that there is convincing evidence for a dysregulated inflammatory response in patients with SAH [14—16]. In line with this knowledge, plasma levels of pro-inflammatory cytokines including TNF-α, IL-1, IL-6 and IL-8 were elevated in acute alcoholic hepatitis [15,16]. Associated with an inflammatory response, many patients with SAH present with vastly elevated WBC counts, mainly due to an elevated neutrophils in the circulation [17—21]. Accordingly, single case studies have indicated that reducing the extra load of circulating neutrophils benefits the prognosis of patients with SAH [18—20]. With this in mind, the present investigation was to assess the efficacy of therapeutic granulocytes/monocytes apheresis (GMA) along with hitherto strategies used to treat patients with SAH.

Methods

Objectives

Our objective in the present work was to assess the efficacy of selective depletion of the elevated myeloid leucocytes by GMA in patients with SAH. Additionally, endeavour was made to better understand the prognostic effects of other few conventional options which have been tested in SAH patients including PE, HD, and corticosteroids. The outcomes were expected to enable us to present an algorithm, which may serve as a consensus for the management of SAH patients.

Survey of severe alcoholic hepatitis patients

Questionnaires were sent to 1234 medical institutions in Japan, which are certified by the Japanese Society of Gastroenterology. The questionnaires asked about the number of patients with SAH diagnosed according to the Diagnostic Criteria for Alcoholic Liver Disease set by Takada, et al. [22], and were admitted to each hospital between April 2004 and March 2008. In the Takada's Criteria, SAH is defined as having the following characteristics: presence of numerous alcoholic hyaline bodies; extensive neutrophil infiltration of the liver; severe hepatic cell necrosis; prothrombin activity is less than 50% of the normal level; leucocytosis; endotoxemia is common; liver size does not decrease in spite of abstinence from intake of alcoholic liquor; many patients die within a month due to multiple organ failure like encephalopathy, renal failure, and pneumonia. The questionnaires also asked about the patients' demographic variables, clinical laboratory data including hepatitis virus markers, and the form of therapeutic interventions SAH patients had received during hospitalization. Retrospectively, we investigated the associations of various demographic variables and disease profile with the patients' prognosis.

Therapeutic interventions

Ninety-nine medical institutions retuned the questionnaires. Twenty-nine of these 99 hospitals had treated patients with SAH, and provided us with full data on 62 patients. Patients could be subdivided into five groups based on the therapeutic interventions they had received during hospitalization. Twenty-seven patients had received none of the listed treatments, 10 patients had received GMA, the rest had received one or more of the following treatments, corticosteroids, PE or HD. Corticosteroids were PSL (30—50 mg/day) for $\geq$ 2 weeks or iv methylprednisolone (500—1000 mg/day) for 2—4 days and then replaced with PSL, to be tapered. Conventional PE and HD were done by using validated methods [23,24]. Regarding GMA, as stated above, most patients with SAH and other inflammatory disorders present with elevated and activated circulating WBC counts due to an elevated granulocytes [18—21,25,26]. In the GMA group, patients had WBC counts $\geq 10^4/\mu$L and all had agreed to cover the cost of this new intervention. GMA was undertaken with the Adacolumn (JIMRO, Takasaki, Japan) which can selectively adsorb myeloid linage leucocytes (granulocytes and monocytes/macrophages) from the blood in the column [21,25,26]. Each patient had received up to five GMA sessions, at one or two sessions/week as a basic treatment course.