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# Efficacy and safety of intra-arterial steroid infusions in patients with steroid-resistant gastrointestinal acute graft-versus-host disease

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**There is no established second-line treatment for steroid-resistant acute graft-versus-host disease (GVHD). We prospectively assessed the safety and efficacy of intra-arterial steroid infusions (IASIs) for steroid-resistant acute gastrointestinal (GI) GVHD and compared the outcomes with those of historical controls at our institution. Nineteen consecutive, allogeneic hematopoietic stem cell transplantation subjects aged 31–67 years (median 52) were enrolled between October, 2008, and November, 2012. Acute GVHD was confirmed by biopsy in all cases. The enrolled patients were treated with infusions of methylprednisolone into the mesenteric arteries and/or gastroduodenal and left gastric arteries. Fourteen consecutive patients who developed steroid-resistant acute GI GVHD between 2001 and 2008 were used as controls. For the primary endpoint at day 28, the overall and complete responses in the IASI group trended higher (79% vs. 42%, $p = 0.066$) and were significantly higher (63% vs. 21%, $p = 0.033$) than those in the control group. Although not statistically significant, owing to the small population, the crude day-180-nonrelapse mortality rate was about 20% lower and the day-180-overall-survival rate tended to be higher than the control (11% vs. 29%, $p = 0.222$; 79% vs. 50%, $p = 0.109$, respectively). There were no serious IASI-related complications. Our results suggest that IASI can safely provide excellent efficacy for refractory acute GI GVHD without increasing infection-related complications and may improve prognosis.** 

Acute graft-versus-host disease (GVHD) remains the leading cause of nonrelapse mortality (NRM) following allogeneic hematopoietic stem cell transplantation (allo-HSCT). Approximately 50% of patients with grade II or greater acute GVHD have shown resistance to systemic corticosteroids [1–3], and the prognosis for steroid-refractory recipients is extremely poor [1–15]. There is a strong need to establish a standard treatment for severe GVHD and to make further progress in prevention strategies for GVHD.

Case series data on ulcerative colitis have stimulated speculation that local high-dose corticosteroids for acute gastrointestinal (GI) GVHD could be more effective than systemic moderate-dose corticosteroids [16]. In addition, because topical corticosteroid treatment can also prevent undesirable effects related to systemic immunosuppressive treatment, such as increased risk of infections or reduction in the graft-versus-leukemia effect [17], this approach may improve prognosis by decreasing NRM and malignancy relapse. Three prospective single-arm studies reported favorable responses to intra-arterial steroid infusions (IASIs) for treatment-resistant acute GI GVHD [18–20]. However, because these studies did not employ controls, the question as to whether IASI decreases NRM and improves survival could not be addressed.

We therefore prospectively examined the safety and efficacy of IASI as second-line treatment for treatment-resistant acute GI GVHD and compared the outcomes with those of historical controls.

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## Patients and methods

*Study design and selection of patients and historical controls*

This prospective, single-arm, single-center study was undertaken between October, 2008, and November, 2012, at our institution. Written, informed consent was obtained from all enrolled study patients, and the study protocol was approved by the institutional review board of our institution.

Eligible patients needed to be 18 years or older, diagnosed by colon biopsy, and have initial steroid-resistant acute GVHD. Exclusion criteria were as follows: uncontrolled skin and/or liver acute GVHD, serum creatinine level $>1.5$ mg/dL, and platelet counts that never exceeded 30,000/μL even after platelet cell transfusion. The historical control group consisted of patients with initial treatment-resistant acute, isolated GI GVHD of grade II or greater between September, 2001, and September, 2008, at our institution.

*Treatment plan*

In patients showing improvement after IASI, systemic corticosteroid administration was tapered by 10% every 5–7 days. If a significant response was obtained, the IASI was repeated weekly. If worsening of GVHD in any organ was observed, the case was classified as a treatment failure.

*Procedural technique*

Following arteriography to decide on variant arterial blood supplies to the gut, we administered methylprednisolone (mPSL) into the arteries mainly through three or four French microcatheters, as follows: When the main organ involved lower GI GVHD, mPSL (1.5 mg/kg) was infused into the superior mesenteric artery and mPSL (0.5 mg/kg) into the inferior mesenteric artery over approximately 1 min. In the case of upper GI GVHD, mPSL (0.5 mg/kg) was injected into both the gastroduodenal artery and left gastric artery over approximately 1 min.

*Definition and evaluation of endpoints*

The primary endpoint was set as the treatment response rate for acute GI GVHD at day 28 after the first IASI. A steroid-refractory endpoint was defined as progression after 3 days, no improvement after 5 days, or persistence after 14 days despite the use of systemic prednisolone (PSL) or mPSL (1–2 mg/kg). A steroid-dependent endpoint was defined as the inability to taper PSL or mPSL without progression of GVHD. Responses were evaluated according to the clinical improvement of GI symptoms as previously reported [1].

*Statistical methods*

A comparison of patient characteristics and treatment response was performed using the Mann-Whitney U test and Fisher's exact test. To compute the probabilities of NRM and primary disease relapse and compare them between the groups, cumulative incidence curves were drawn in a competing-risks model, and Gray's test was employed. The probability of overall survival was estimated from the start of second-line treatment using the Kaplan-Meier method and compared using the log-rank test. Recipients receiving second allo-HSCT owing to primary disease relapse were censored on the dates of second allo-HSCT. All statistical analyses were performed using EZR, a modified version of R commander (version 2.0-3) based on the statistical software environment R (version 3.0.2) [21].

## Results and discussion

A total of 19 consecutive transplants were enrolled, and all were eligible for this study. Fourteen consecutive patients were selected as historical controls (Table 1). After a median of one procedure (range = 1–4), 15 (79%) had an overall response. The complete response rate of the IASI group was significantly higher (Table 2). The median interval to initial response was 2 days (range = 1–9) after the procedure.

A median 36-month follow-up (range = 7–66) of survivors showed an overall survival rate of 50% (Fig. 1A). There were no IASI procedure-related complications, GI bleeding, or thrombotic microangiopathy. One patient in the IASI group suffered from enterocolitis due to *Candida* species and *Enterococcus* species at 4 and 61 days after the procedure, respectively. These were treated successfully with antifungal and antibacterial therapies. Although there were two deaths due to infection (fungal sepsis and pneumonia) without GVHD in the IASI group, these did not appear to be directly related to the procedure (Table 2).

Although progress in transplantation procedures has contributed to a decrease in transplant-related mortality, no improvement of prognosis for steroid-resistant acute GI GVHD has been clearly demonstrated to date [22]. Although antithymocyte globulin is one of the major treatment options, with a reported 18%–57% response rate, no improvement in overall survival has been shown [5–9]. A small retrospective evaluation of infliximab revealed a complete response (CR) rate of 62% with a 1-year-survival rate of 38% [10]. Additionally, three small studies [11–13] that examined the utility of mycophenolate mofetil reported CR rates of 26%–31% and 1-year-survival rates of 16%–40%. A recent small retrospective study of alemtuzumab reported a CR+partial response (PR) rate of 62% and a 1-year-survival rate of 33% [14]. A small-scale retrospective analysis of the utility of pentostatin reported a CR rate of 70% and a 2-year-survival rate of 43% [15]. Several factors may explain the poor survival rates even in responders, including increased severe infections or a reduction in the graft-versus-leukemia effect caused by excessive immunosuppression. Rather than employing such systemic immunosuppressive treatments, topical therapies such as IASI might resolve these problems. Clinically, a moderate dose of intra-arterial mPSL by one procedure is unlikely to have a significant impact on the systemic immune system. In an analysis of immune recovery after IASI therapy in seven evaluable patients, the kinetics data seemed similar to data reported previously (Fig. 1D) [23].

A higher survival rate was seen in our study than in previous studies [18–20]. Several reasons for this are offered. First, in this prospective study, earlier interventions might have been performed in some patients. Second, we infused a higher dose of mPSL into the superior mesenteric artery because it supplied a larger portion of the intestine than the inferior mesenteric artery.

We did not identify the reason that IASI overcame steroid refractoriness in patients with GVHD. Although