Intramesenteric Steroid Treatment for Steroid-Refractory Gastrointestinal Graft Versus Host Disease

Steroid Dirençli Gastrointestinal Graft Versus Host Hastalığında İntramezenterik Steroid Uygulaması

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Abstract

Currently, steroid-refractory severe gastrointestinal (GI) graft versus host disease (GVHD) is among the most important complications of allogeneic transplantation, and as yet there is no standard approach to its treatment. Herein we report two cases with steroid-refractory GI GVHD that received intramesenteric steroid treatment. In both cases the frequency and volume of diarrhea resolved completely following intramesenteric methylprednisolone (MP) injection. In conclusion, intra-arterial steroid injection might be an alternative treatment approach for steroid-refractory GI GVHD.

Key Words: Steroid-refractory GVHD, Intramesenteric steroid

Özet

Günümüzde, steroid dirençli gastrointestinal (GI) graft versus host hastalığı (GvHH) allogeneik transplantasyon yapılan hastalarda izlenen en sık komplikasyonlardan biridir ve henüz standart bir tedavi yaklaşımı yoktur. Burada, steroid refrakter GvHH olan iki vakamin intramezenterik steroid uygulamasına dair sonuçları bildirilmiştir. Her iki hastada intramezenterik metilprednizolon (MP) enjeksiyonu takiben diarenin sıklığı ve miktarı tamamen düzelmiştir. Sonuç olarak, intra-arteriel steroid verilimi bu tip olgularda alternative bir tedavi yaklaşımı olabilir.

Anahtar Sözcükler: Steroid dirençli GvHH, İntramezenterik steroid

Introduction

Steroid-refractory severe gastrointestinal (GI) graft versus host disease (GVHD) is one of the most challenging complications of allogeneic hematopoietic cell transplantation (allo-HCT), and is associated with very high morbidity and mortality rates. Treatment with various salvage regimens has been used, but the results have not been satisfactory. In recent years, regional administration of steroids directly through the arteries that supply blood to the liver and intestines has resulted in varying degrees of effectiveness [1-3]. Herein we present 2 cases with steroid-refractory severe GI GVHD in which significantly stable recovery followed a single intra-arterial injection of methylprednisolone (MP) through the superior and inferior mesenteric arteries.

Case 1

A 44-year-old male patient with AML underwent allo-HCT from an HLA-identical sister following a myeloabla-
tive conditioning regimen. Symptoms of grade III (skin, liver, and GI) acute GVHD emerged on d 30 of hematological recovery, which were confirmed based on pathological examination. Skin symptoms resolved following IV MP 2 mg·kg$^{-1}$·d$^{-1}$, but frequent diarrhea (maximum volume: 6 L·d$^{-1}$) persisted. Due to exacerbation of GI symptoms, i.e. severe abdominal pain and hematochezia, antithymocyte globulin was initiated on d 35 of hematological recovery. As the patient’s diarrhea did not abate and he had an elevated bilirubin level and metabolic disorders, 4 weeks of infliximab 10 mg·kg$^{-1}$ QWK was started on d 41 of hematological recovery.

Despite of all the immunosuppressive treatments, the patient’s diarrhea continued at the rate of 3 L·d$^{-1}$; therefore, intramesenteric arterial MP infusion was administered on d 54 of hematological recovery. Briefly, under digital subtraction angiography (DSA) guidance (Multistar Plus/T.O.P., Siemens AG, Forchheim, Germany), via the right femoral artery No. 5 French catheters (Contra 2, Imager II, Boston Scientific/Medi-Tech, Annacotty, Limerick, Ireland) were placed with their mesenteric tips. Selective views were obtained via injection of 6-8 mL of non-ionic contrast agent (Iomeron 400 mg/dl, Bracco SpA, Milan, Italy) in order to precisely visualize the vascular supply of the superior and inferior mesenteric arteries. Additionally, selective celiac angiography was performed in order to determine if there was anatomical variation. Selectively, 1 mg·kg$^{-1}$ of MP in 10 mL of sterile saline was infused over the course of 3 min into the superior and inferior mesenteric arteries (Figures 1 and 2).

The patient’s diarrhea decreased in volume and frequency (1 L·d$^{-1}$·2 d) after administration of intra-arterial steroid. The patient’s metabolic and clinical status began to recover on the fourth day. The symptoms of GI GVHD were completely resolved 90 d post treatment (Figure 3) and he was discharged with CsA alone as immunosuppressive therapy. Unfortunately, the patient died due to systemic infection 224 d post treatment.

**Case 2**

A 56-year-old male with idiopathic myelofibrosis underwent allo-HCT from an HLA identical sibling donor and non-myeloablative conditioning in November 2005. Donor lymphocyte infusion was administered on 10 May 2006 because of increasing-donor type chimerism. The patient developed grade II acute GVHD in the skin and liver 1 month after donor lymphocyte infusion (DLI). Steroid plus CsA was administered, but acute GVHD progressed to extensive chronic GVHD, involving the eyes, the GI system, and bone marrow. The results of skin and colon biopsies confirmed grade III skin and GI GVHD.

Oral budesonide, mycophenolate mofetil, sirolimus, and extracorporeal photopheresis (ECP) were added for the treatment of GVHD. Despite all treatment, GI GVHD could not be controlled. We administered intramesenteric steroid infusion, as described in case 1. Marked improvement in the patient’s symptoms and a decrease in the volume of diarrhea was noted 72 h following the procedure. Complete resolution of diarrhea occurred 15 d after steroid infusion. As of 3 years following the procedure (at

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**Figure 1:** Digital subtraction angiography of the hepatic artery.

**Figure 2:** Digital subtraction angiography of the superior mesenteric artery.
Steroid-Refractory GI GVHD and Intramesenteric Steroid Infusion

Rogler and Schottelius reported a decrease in the number and affinity of steroid receptors in GI tract mucosa in patients with inflammatory bowel disease [8,9]. Administration of regional steroid infusion versus systemic may cause higher concentration of steroids in the mesenteric circulation and inflammatory mucosa in patients with GI GVHD. Hence, regional steroid application may overcome the refractoriness caused by a decrease in the number and affinity of steroid receptors.

In conclusion, the two presented cases with severe GI GVHD, and refractoriness to steroid and secondary salvage therapies responded dramatically to regional administration of steroids via the mesenteric artery. A single dose of intramesenteric artery steroid infusion appears to be effective, even in patients that have not responded to multiple treatment regimens, and is not associated with extensive systemic immunosuppression. Nonetheless, we cannot exclude that the treatment responses observed in the two presented cases were not due to the delayed therapeutic effect of their initial steroid treatment or other immunosuppressive agents. However, the resolution of GI symptoms within 72 h of intra-arterial administration demonstrate the efficiency of this novel treatment. Based on the present findings, intra-arterial administration of steroids is easy, reliable, and safe, and can be considered a first-line treatment, especially for avoiding severe systemic immunosuppression in patients with severe GI GVHD. On the other hand, controlled studies are required to exclude the role of previous immunosuppressive treatments.

Informed consent was obtained.

Conflict of Interest Statement

The authors of this paper have no conflicts of interest, including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included.

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