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Therapeutic Apheresis and Dialysis

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ORIGINAL ARTICLE

Novel adsorptive type apheresis device Immunopure for ulcerative colitis from clinical perspectives based on clinical trials: Japan and Europe

Yoshihiro Endo[1] | **Motoki Yonekawa**[2] | **Kazutaka Kukita**[2] | **Masaki Katagiri**[3] | **Takayuki Matsumoto**[4] | **Keisuke Kawasaki**[4] | **Shunichi Yanai**[4] | **Shingo Kato**[5] | **Kazuhito Kani**[5] | **Tomonari Ogawa**[6] | **Kazuya Kitamura**[7] | **Izumi Hasegawa**[8] | **Yusuke Inoue**[8] | **Takuya Doi**[8] | **Kazuhide Higuchi**[9] | **Ken Kawakami**[9] | **Kazuki Kakimoto**[9] | **Hiroki Nakamura**[10]

[1]Department of Clinical Nursing, Shiga University of Medical Science, Otsu, Japan

[2]Department of Surgery, Sapporo Hokuyu Hospital, Sapporo, Japan

[3]Department of Gastroenterology, Sapporo Hokuyu Hospital, Sapporo, Japan

[4]Division of Gastroenterology, Department of Medicine, Iwate Medical University, Yahaba, Japan

[5]Department of Gastroenterology and Hepatology, Saitama Medical Center, Saitama Medical University, Saitama, Japan

[6]Department of Nephrology and Hypertension, Saitama Medical Center, Saitama Medical University, Saitama, Japan

[7]Department of Gastroenterology, Kanazawa University Hospital, Kanazawa, Japan

[8]Department of Gastroenterology and Hepatology, Japan Community Health Care Organization Chukyo Hospital, Nagoya, Japan

[9]Second Department of Internal Medicine, Osaka Medical College, Takatsuki, Japan

[10]Division of Gastroenterology and Hepatology, Shin-Koga Hospital, Kurume, Japan

Correspondence
Yoshihiro Endo, Department of Clinical Nursing, Shiga University of Medical Science, Tsukinowa-cho, Otsu, Shiga 520-2192, Japan.
Email: yendo@belle.shiga-med.ac.jp

Abstract

Several adsorptive type devices for ulcerative colitis are used for the induction of remission in patients with active severe disease worldwide. In 2020, the novel apheresis device Immunopure for ulcerative colitis was launched in Japan. Immunopure, like the polyethylene terephthalate column, uses polyarylate, a type of polyester resin, as the adsorbent. Similar to the cellulose acetate column, Immunopure is filled with adsorbent beads and expected to provide ease of use, with minimal risk of column clogging. Immunopure adsorbs leukocytes and platelets, especially activated platelets and platelet-leukocyte aggregates. In this article, the capability of Immunopure is evaluated from clinical perspective based on a clinical trial in Japan/Europe. As a result, Immunopure is comparable to other products in clinical effectiveness and indicated for the treatment of patients with refractory moderate ulcerative colitis, making it highly useful in clinical practice.

KEYWORDS

adsorptive device, aggregation, granulocyte, leukocyte, moderate, monocyte, polyarylate resin, therapeutic apheresis, ulcerative colitis

1 | INTRODUCTION

Inflammatory bowel diseases, such as ulcerative colitis (UC) and Crohn's disease, have recently been considered major indications for therapeutic apheresis in the extracorporeal therapy area. In Japan, two types of apheresis devices, polyethylene terephthalate (PET) and cellulose acetate (CA) columns, have been approved for marketing and reimbursed by health insurance until recently (Table 1). In the treatment of UC, the PET type device is indicated for the induction of remission in patients with active severe or moderate disease, and the CA type device for the induction of remission in patients with active severe disease. On the other hand, the novel apheresis device Immunopure (NIKKISO Co., Ltd. Tokyo, Japan) (Figure 1) for UC was launched in March 2020, resulting again in two options and a product indicated for moderate cases becoming clinically available.

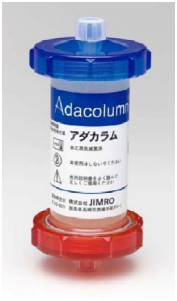
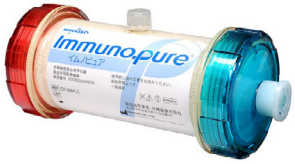
This article provides an overview of the features of the new option Immunopure and its clinical results obtained overseas and in Japan.

2 | MATERIALS AND METHODS

2.1 | Performance of materials

The adsorption performance of individual devices, including those which are no longer available in clinical practice, is concluded from any published literatures [1–4] for the CA and PET columns, and the results of previous clinical trials [5] for Immunopure is shown in Table 2. The CA column mainly removes monocytes (about 19.5% on average) and granulocytes (about 26% on average), which are involved in inflammation, with a low lymphocyte adsorption/removal rate of 0% to less than 7%. In contrast, the PET column provided higher treatment efficiency, having the ability to remove about 57% of platelets on average in addition to about 79% of monocytes and about 90% of granulocytes on average. However, the PET column had the disadvantage of removing as many as about 55% of lymphocytes on average. Immunopure is comparable to the PET column in terms of the ability to adsorb about 46% of monocytes, about 35% of granulocytes, and about 45% of platelets on average and has a low mean lymphocyte adsorption/removal rate of about 3%, offering an advantage similar to that of the CA column. Ramlow et al. [5] have reported changes in blood cell populations between the inlet and outlet of the Immunopure adsorber in a clinical study. After the initiation of treatment, platelets in the outlet were reduced to 31%, monocytes to 30%, and granulocytes to 53%, while lymphocytes only underwent a minor change. Waitz et al. [6] also evaluated changes in platelet-monocyte aggregates, platelet-T cell aggregates, and platelet-macrophage aggregates by flow cytometry. Compared with healthy subjects, patients with UC were found to have significant increases in aggregates of activated CD42+ platelets and CD14+

TABLE 1 Commercialized/commercial device for leukocyte/granulocyte apheresis

	CA column	PET column	Immunopure®
Appearance/shape			
Target disease	UC/CD Pustular psoriasisPsoriatic arthropathy	UC Chronic rheumatoid arthritis	UC
Indications	Granulocyte adsorption to induce remission in patients with active (only those with severe disease as defined by severity criteria)	Leukocyte adsorption to induce remission in patients with active (only those with steroid refractory severe or moderate panclotis or left-sided colitis)	For leukocyte apheresis to induce remission in patients with active (only those with refractory moderate disease)
Adsorbent	Cellulose acetate beads	Non-woven polyester fabric	Polyarylate resin beads
Adsorbate	Leukocytes (monocytes and granulocytes)	Leukocytes and Platelets (monocytes, granulocytes, and lymphocytes)	Activated leukocytes and platelets (monocytes and granulocytes)

monocytes, those of activated CD42+ platelets and CD3+ T cells, and those of activated CD42+ platelets and CD11b + macrophages. Of note, even after 60 min of treatment with Immunopure, significant reductions in aggregates of activated platelets and monocytes, those of activated platelets and T cells, and those of activated platelets and macrophages were maintained in the outlet of the adsorber compared with the inlet levels. The proper removal of these activated immune-related blood components is crucial in helping patients achieve clinical remission.

2.2 | Clinical performance

2.2.1 | Clinical trial in Germany

In a clinical trial of the Immunopure adsorber conducted by Ramlow et al. [5], Immunopure was used in the same manner as that applied in Japan in 2012, that is, once weekly for 5 consecutive weeks. The study population consisted of 10 patients with moderate UC (Rachilewitz Clinical Activity Index: 6–10). Clinical remission was achieved in 80% of patients, many of whom showed responses at the end of treatment, with a further reduction in clinical activity index (CAI) at Week 4 post-end of treatment.

2.2.2 | Prospective randomized multicenter controlled study in Germany

In addition, Kruis et al. [7] have reported the results of a prospective, randomized, multicenter, controlled study in 22 patients with UC with inadequate response to 5-aminosalicylic acid (5ASA) as a clinical result of Immunopure. Patients were randomized to either the Immunopure therapy (steroid-free) group (12 patients) or the conventional drug therapy withdrawal program (prednisolone tapering) group (10 patients). The primary endpoint was the steroid-free clinical remission rate at Week 12. Clinical response was assessed based on the disease activity index (DAI). Both groups exhibited a significant improvement in disease status at Week 7 post-end of treatment. After the end of treatment, the steroid group appeared to be headed toward disease reactivation following steroid withdrawal, whereas the improvement appeared to be sustained in the Immunopure therapy group. This suggests that apheresis may eliminate the need for steroids and allow patients to achieve sustained remission.

2.3 | Clinical trial in Japan

In Japan, a clinical trial involving 70 patients with refractory moderate UC at seven sites (Sapporo Hokuyu Hospital, Iwate Medical University, Saitama Medical Center, Kanazawa University Hospital, Japan Community Health care Organization Chukyo Hospital, Osaka Medical College Hospital, Shin-Koga Hospital) was planned from February 2015 to October 2019, but prematurely discontinued due to difficulty in patient recruitment. Immunopure was used twice weekly for 10 consecutive times. The primary endpoint was the clinical remission rate at Week 7. Clinical response was assessed based on Rachimilewitz CAI.

FIGURE 1 The novel apheresis device Immunopure [Color figure can be viewed at wileyonlinelibrary.com]

3 | RESULTS AND DISCUSSION

3.1 | Clinical trial in Japan

Table 3 summarizes the results from 13 patients with evaluable data. As a result from 11 patients who is efficacy analysis target population, that remission rate was achieved in 63.6% of patients (7/11). The effectiveness of Immnopure was also evaluated by comparing pooled

TABLE 2 Adsorption character of Immunopure in accordance with the result of previous clinical trials

	Platelets	Leukocytes	Lymphocytes	Monocytes	Granulocytes
Mean ± standard deviation (10 patients in a European clinical trial[a])	41.0 ± 22.3	29.6 ± 14.8	3.9 ± 7.0	42.6 ± 25.2	34.1 ± 17.8
Mean ± standard deviation (10 patients in a Japanese clinical trial)	49.3 ± 17.2	29.6 ± 16.4	2.8 ± 6.9	49.6 ± 18.7	35.6 ± 20.0

[a]Nikkiso internal data, not published.

TABLE 3 Clinical responsibility of Immunopure

Remission rates (moderate UC)				Remission rates (refractory UC)			
	Data type	Remission rate	Remarks		Data type	Remission rate	Remarks
Immunopure	Japanese clinical trial	63.6% (7/11)	• Moderate disease • 2 weeks post-end of treatment	Immunopure	Japanese clinical trial	63.6% (7/11)	• Moderate disease • 2 weeks post-end of treatment
	European clinical trials	80.0% (8/10)	• Moderate or severe disease • 5 weeks post-end of treatment		European clinical trials	75.0% (6/8)	• Moderate or severe disease • 5 weeks post-end of treatment
	European post-marketing data	66.7% (4/6)	• Moderate or severe disease • 5 weeks post-end of treatment		European post-marketing data	75.0% (3/4)	• Moderate or severe disease • 5 weeks post-end of treatment
	Japanese clinical trial	70.4% (19/27)			Japanese clinical trial	69.6% (16/23)	
	European clinical trials				European clinical trials		
	European post-marketing data				European post-marketing data		

Abbreviation: UC, ulcerative colitis.

results from this study and previous European clinical trials with the abovementioned data from publications concerning treatment with the CA and PET columns. Subgroup analyses of remission rates showed that remission was achieved in 70.4% of patients receiving Immunopure therapy vs. 61.8% to 67.3% of patients using other columns in the moderate disease population and in 69.6% vs. 51.7% to 74.1%, respectively, in the refractory disease population [2,5,6,8–14]. This demonstrates that Immunopure is comparable to existing products in terms of clinical effectiveness in refractory moderate disease.

Immunopure, which is covered by health insurance for use in patients with moderate UC, was launched around the same time that the marketing of the PET column was unfortunately discontinued. This is a welcome development, providing healthcare professionals with multiple treatment options in clinical practice. Although only a limited number of patients were treated in the Japanese clinical trial, the Immunopure apheresis device, which is supported by overseas post-marketing experience, became clinically available in 2020.

Drug therapy is evolving, but apheresis is well known to be safer than steroids. Immunopure thus offers a promising treatment option.

4 | CONCLUSION

Immunopure is comparable to other products in clinical effectiveness and indicated for the treatment of patients with refractory moderate ulcerative colitis, making it highly useful in clinical practice.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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