Granulocyte and monocyte adsorption apheresis is effective for refractory neutrophilic disorders and induces myeloid-derived suppressor cells

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Granulocyte and monocyte adsorption apheresis (GMA) is an extracorporeal apheresis unit designed to remove pathogenic myeloid lineage cells. GMA involves a column containing cellulose acetate (CA) beads that serve as adsorptive leukocyte apheresis carriers. Myeloid-derived suppressor cells (MDSCs) are a heterogeneous population comprised of cells at several stages of myeloid lineage differentiation, that differentiate into macrophages, neutrophils, and dendritic cells. MDSCs play an important role in the regulation of the immune response and have immunosuppressive and anti-inflammatory properties. We previously demonstrated that CA beads activate complement component (iC3b). Recently, iC3b was shown to induce differentiation of myeloid cells to MDSCs. Based on these facts, we hypothesized that GMA induces MDSC differentiation. The purpose of this study was to investigate the clinical effectiveness of GMA for neutrophilic skin diseases and related arthropathy including pustular psoriasis and psoriatic arthritis and whether GMA induces MDSC.

For the assessment of clinical effectiveness, 68 patients with skin lesions and 41 with arthropathy were enrolled. Skin and joint lesions were assessed by overall lesional assessment (OLA) and visual analog scale (VAS), respectively. The incidence of MDSCs was analyzed by FACS in 8 patients and the effect of GMA on MDSC induction was examined using an *in vitro* mini-column system that mimics GMA. GMA was effective in 57 of 68 patients (83.8%) with skin lesions and 36 of 41 (87.8%) with arthropathy. The incidence of MDSCs in the patients was significantly increased by GMA. In the *in vitro* mini-column system, MDSCs were induced in the blood of 5 healthy volunteers and the induction was inhibited by inactivation of iC3b.

In conclusion, GMA is effective for neutrophilic disorders and the effect might be attributed, at least in part, to the induction of MDSCs via iC3b activation by the CA beads in the GMA column.

Granulocyte and monocyte adsorption apheresis (GMA)

GMA is an extracorporeal-type apheresis unit which uses a column (Adacolumn®, JIMRO, Takasaki, Japan) containing 3×10^4 pieces of 2 mm-diameter cellulose acetate beads. In the current series, GMA was performed 5 or 10 times at a week intervals. If the lesion showed amelioration but persisted at the completion of the 5th treatment, five more treatment sessions were added. In each session, 1800 mL of blood are drained from the cubital vein of one arm, passed at a flow rate of 30 mL/min through the GMA column, and returned to the cubital vein of the other arm. The GMA column, its circuit lines, and circuit system consisting of a regular dialysis circuit and a pump, were provided by JIMRO (Takasaki, Japan).

GMA remove activated neutrophils

Clinical Efficacy of GMA

Response of skin lesions to GMA (N=68)

	excellent	good	moderate	unchanged
Palmoplantar pustulosis (N=29)	6	11	7	5
Behçet's disease (N=11)	2	5	2	2
Pyoderma gangrenosum (N=10)	4	3	3	
Psoriasis vulgaris (N=8)		1	5	2
Acrodermatitis continua of Hallopeau (N=2)		1		1
SLE skin rash (N=2)		2		
Sweet's syndrome (N=2)		1		1
Cutaneous allergic vasculitis (N=1)	1			
Erythema nodosum (N=1)		1		
RA* leg ulcer (N=1)		1		
Reiter's disease (N=1)		1		
	13	27	17	11

Response of arthropathy to GMA (N=41)

	excellent	Good	moderate	unchanged
Psoriasis arthropathy (N=32)	6	14	8	4
Behçet's disease (N=4)	4			
Adult Still's disease (N=1)	1			
Cutaneous allergic vasculitis (N=1)	1			
RA* leg ulcer (N=1)		1		
Reiter's disease (N=1)		1		
Sweet's syndrome (N=1)				1
	12	16	8	5

*RA: rheumatoid arthritis

Patient: 57 F. Psoriatic arthritis

Monocytic/Granulocytic MDSCs Flow Cytometry

Frequency of MDSCs in preripheral blood

*P<0.05 **P<0.005

Frequency of MDSCs in the mini-column system

*P<0.05

Treatment outcome in patients treated with GMA

Patient no.	Age/sex	Diagnosis	Treatment sessions	VAS before/after	Response of skin lesions	Response of arthropathy
1	33/M	Palmoplantar pustulosis+ Arthropathy	5	5/4	Good	Unchaged
2	53/F	Palmoplantar pustulosis + Arthropathy	5	6/2	Good	Good
3	60/M	Palmoplantar pustulosis + Arthropathy	5	8/1	Good	Excellent
4	63/M	Palmoplantar pustulosis + Arthropathy	5	3/2.5	Unchanged	Unchnged
5	82/F	Erythema nodosum	5	8/2	Modelate	Excellent
6	63/M	Behçet disease	10	n.a.	Excellent	n.a.
7	34/F	pyoderma gangrenosum, acne, suppurative hidradenitis (PASH)	10	n.a.	Good	n.a.
8	40/F	palmoplantar pustulotic arthro-osteitis (PAO)	5	7.5/3	Excellent	Good