Use of granulocyte and monocyte adsorption apheresis in dermatology (Review)

LAURA GNESOTTO*, GUIDO MIOSO* and MAURO ALAIBAC

Dermatology Unit, Department of Medicine, University of Padova, I-35128 Padova, Italy

Received March 7, 2022; Accepted May 24, 2022

DOI: 10.3892/etm.2022.11463

Abstract. Adsorptive granulocyte and monocyte apheresis (GMA) is an extracorporeal treatment that selectively removes activated myeloid lineage leukocytes from peripheral blood. This technique consists of a column with cellulose acetate beads as absorptive leukocytapheresis carriers, and was initially used to treat ulcerative colitis. A literature search was conducted to extract recently published studies about the clinical efficacy of GMA in patients with different skin disorders, reporting information on demographics, clinical symptoms, treatment and clinical course. Dermatological diseases, in which GMA has been performed, include generalized pustular psoriasis, pyoderma gangrenosum, palmoplantar pustular psoriasis, Behcet's disease, Sweet's syndrome, adult-onset Still's disease, impetigo herpetiformis, reactive arthritis, acne and hidradenitis suppurativa syndrome, cutaneous allergic vasculitis and systemic lupus erythematosus. In most patients, GMA was started after the failure of conventional therapeutic options and it was helpful in the majority of cases. Based on the information summarized, GMA could be considered a valid non-pharmacological treatment option for patients with several dermatological conditions, which are difficult to treat with other pharmacological preparations.

Contents

Correspondence to: Professor Mauro Alaibac, Dermatology Unit, Department of Medicine, University of Padova, 4 Via Vincenzo Gallucci, I-35128 Padova, Italy
E-mail: mauro.alaibac@unipd.it

*Contributed equally

Key words: granulocyte and monocyte apheresis, neutrophilic dermatoses, reactive arthritis, PASH syndrome, cutaneous allergic vasculitis, systemic lupus erythematosus

1. Introduction

General features of GMA. Adsorptive granulocyte and monocyte apheresis (GMA) is an extracorporeal apheresis technique that selectively removes about 65% of activated granulocytes and 55% of monocytes/macrophages with a small number of platelets, from the peripheral blood. Depletion of these activated cells could be considered a valid treatment option for several immune-related diseases, which do not respond to conventional treatments. Indeed, inflammatory cytokines such as interleukin (IL)-1β, IL-6, IL-8, IL-23, tumor necrosis factor (TNF)-α and others, are mostly produced by myeloid lineage leukocytes (1). GMA is usually performed once a week for 5-10 time sessions in a clinical setting, depending on the severity of the patient's disease and their response to treatment (2). This technique consists of a column filled with cellulose acetate (CA) beads, which selectively deplete activated myeloid lineage leukocytes (1). In each session of 60 min, 1,800 ml of blood is drained from the cubital vein of one arm, at a flow rate of 30 ml/min, through the GMA column and returned to the cubital vein of the contralateral arm (3). Anticoagulants must be used in patients undergoing GMA therapy, either nafamostat mesylate or heparin (4) (Fig. 1).

The first application of GMA was to treat ulcerative colitis (UC), although nowadays it is applicable in several skin diseases. These include generalized pustular psoriasis (GPP), pyoderma gangrenosum (PG), palmoplantar pustular psoriasis (PPP), Behcet's disease (BD), Sweet's syndrome (SS), adult-onset Still's disease (AOSD), impetigo herpetiformis (IH), reactive arthritis (ReA), PG, acne and hidradenitis suppurativa (PASH) syndrome, cutaneous allergic vasculitis (CAV) and systemic lupus erythematosus (SLE) (1). This therapeutical device has been increasingly used in dermatology in recent years due to its non-pharmacological feature, which makes GMA suitable for various settings and patients, especially with chronic disorders.

Mechanism of action. GMA has several effects, including granulocyte removal, reducing levels of pro-inflammatory cytokines, promoting anti-inflammatory molecules and stimulating specific cells with an immunomodulatory role, such as myeloid-derived suppressor cells (MDSC) and regulatory B-cells and T-cells. Nevertheless, not all the specific mechanisms of this apheresis technique have been completely understood yet (3,5).

Selective granulocytes/monocytes removal. Activated granulocytes and monocytes/macrophages express Mac-1, a cell-surface adhesive molecule that belongs to the integrin family. CA beads in the GMA column activate and absorb complement component iC3b, a ligand for Mac-1. Thus, the column selectively traps activated granulocytes by binding Mac-1 expressed on the granulocytes to iC3b on the beads (2). Furthermore, immunoglobulin G (IgG) on the CA beads mediates the adsorption through Fcγ receptors on the myeloid lineage cells (Fig. 2). GMA also removes CD11b+ activated neutrophils, reducing their infiltration into the inflamed regions (5,6). Yokoyama *et al* observed a decrease in peripheral CD14(+) CD16(+) monocytes (pro-inflammatory phenotype) and an increase in circulating levels of the CD4+ CD25high+/FOXP3 phenotype (functional regulatory T cells) in patients' blood after GMA treatment. This effect is significant since T regs actively suppress inflammatory responses by producing anti-inflammatory cytokines such as IL-10, IL-35 and transforming growth factor (TGF)-β (7). Despite removing granulocytes, peripheral leukocyte count after the entire process remains basically unchanged. In addition, it was noticed a significant reduction in CD10+ (mature and activated) and an increase in CD10-(immature, naive) granulocytes, provided by the bone marrow, which are physiologically less inflammatory (1,6).

Effects on pro-inflammatory and anti-inflammatory cytokines. *In vitro* studies on whole human blood showed that activated granulocytes and monocytes produce high levels of IL-1 Receptor Antagonist (IL-1Ra), Hepatocyte Growth Factor (HGF), soluble TNF Receptors I e II and L-selectin soluble receptor. The quantities of these anti-inflammatory cytokines were directly proportional to the number of cells that adhered to the carriers; when these cytokines reach the patient's circulation, they contribute to resolve inflammation (1). GMA also reduces the levels of IL-2Rα, IL-8 and Macrophage Migration Inhibitory Factor (MIF), a soluble lymphokine. This effect is significant because the IL-2/IL-2Rα axis is crucial for T cells differentiation and expansion while IL-8 is a potent chemotactic factor for granulocytes. MIF regulates the migration of macrophages and promotes the pro-inflammatory function of immune cells. In patients with Inflammatory Bowel Disease (IBD), GMA also contributes in regulating the inflammatory process by decreasing the levels of TNF-α, IL-1β, IL-6 (2). A recent *in vitro* study by Nishise *et al*, showed that CA beads inhibit IL-23, released from adsorbed granulocytes and monocytes (Fig. 2). IL-23 may promote the increase of IL-17, which is involved in the pathogenesis of various autoimmune diseases, autoinflammation and malignant neoplasms (8).

Stimulation of immunomodulatory cells. As explained previously, iC3b is selectively absorbed by the GMA column. iC3b, as a complement activation fragment, contributes to the development of MDSC. This kind of cells are involved in an immunomodulatory activity: they can express immunosuppressive molecules like Arginase 1, Inducible Nitric Oxide Synthase (iNOS), IL-10 and TGFβ, and they promote the differentiation of CD4+ T cells to T regs and suppress T cell response. T regs migrate from peripheral blood to local tissue to solve inflammation. Finally, the contact between neutrophils and CA beads stimulates the production of apoptotic cells, which re-enter the patient's bloodstream and raise the levels of regulatory B-cells (1,3).

Safety profile. One of the most important features of GMA is its safety profile (5). Data from clinical practice confirmed that no serious adverse events have been observed in patients treated with GMA. Domènech *et al* (1) have shown that more than a half of the reported events were related to the difficulty in performing blood access and adequate flow rate, elevation of venous pressure, coagulation and blood return problems. The most common clinical adverse events reported by patients were just mild ones, such as headache, fever, feeling of weakness and chills. Although GMA is a therapy targeting neutrophils, increased risk of infection has never been raised, since it does not cause any immunodeficiency (1). In conclusion, patients' perceptions about this technique are overall positive due to the procedure's convenience, as reported by Rodriguez-Lago *et al* (9).

GMA vs conventional therapies: effectiveness, cost and safety. Sparse studies are available in Europe comparing GMA with conventional medications. Tominaga *et al* (10) underlined the equivalent efficacy of GMA to the corticosteroids in UC patients. Nevertheless, the authors observed minor safety concerns, reported as adverse events, in GMA ($P<0.001$) and a better safety profile albeit a major average medical cost ($P<0.05$). In another study by Panés *et al* (11), the average annual cost per patient with UC treated with corticosteroids was 6740 euros and with 5 GMA sessions was 6959 euros. Moreover, the proportion of patients achieving clinical remission with GMA was 22.5% higher. Overall, a new course of corticosteroids and surgery was avoided in 18.5 and 4% of patients treated with GMA, respectively. Yoshino *et al* (12) described two groups of UC patients positive for Cytomegalovirus (CMV) after antiviral therapy. In the first group, 11 patients were treated with GMA, while the second group of 9 subjects took immunosuppressive therapies (IMT). As a result, 54.5% (6/11) of the GMA group achieved clinical remission, against 44.4% (4/9) of the IMT group. GMA did not induce CMV reactivation because it removes granulocytes and monocytes/macrophages, which CMV infects latently. In conclusion, the authors showed that GMA is safe and effective for this class of patients. To our knowledge, no studies comparing GMA and conventional treatments in dermatological diseases have been published.

2. Application of GMA in neutrophilic dermatoses

Neutrophilic dermatoses consist of a heterogeneous group of inflammatory skin conditions, characterized by the presence of a non-infectious infiltrate of mature neutrophilic leukocytes on histopathology. Clinical cutaneous features are heterogeneous, including vesiculo-pustules, papules, plaques, nodules, or ulcerations. In some cases, there could also be an extracutaneous involvement (13,14).

Generalized Pustular Psoriasis. Psoriasis is an immune-mediated, chronic, inflammatory disease, defined by keratoderma and hyperproliferation of keratinocytes. Its pathogenesis primarily involves T helper lymphocytes

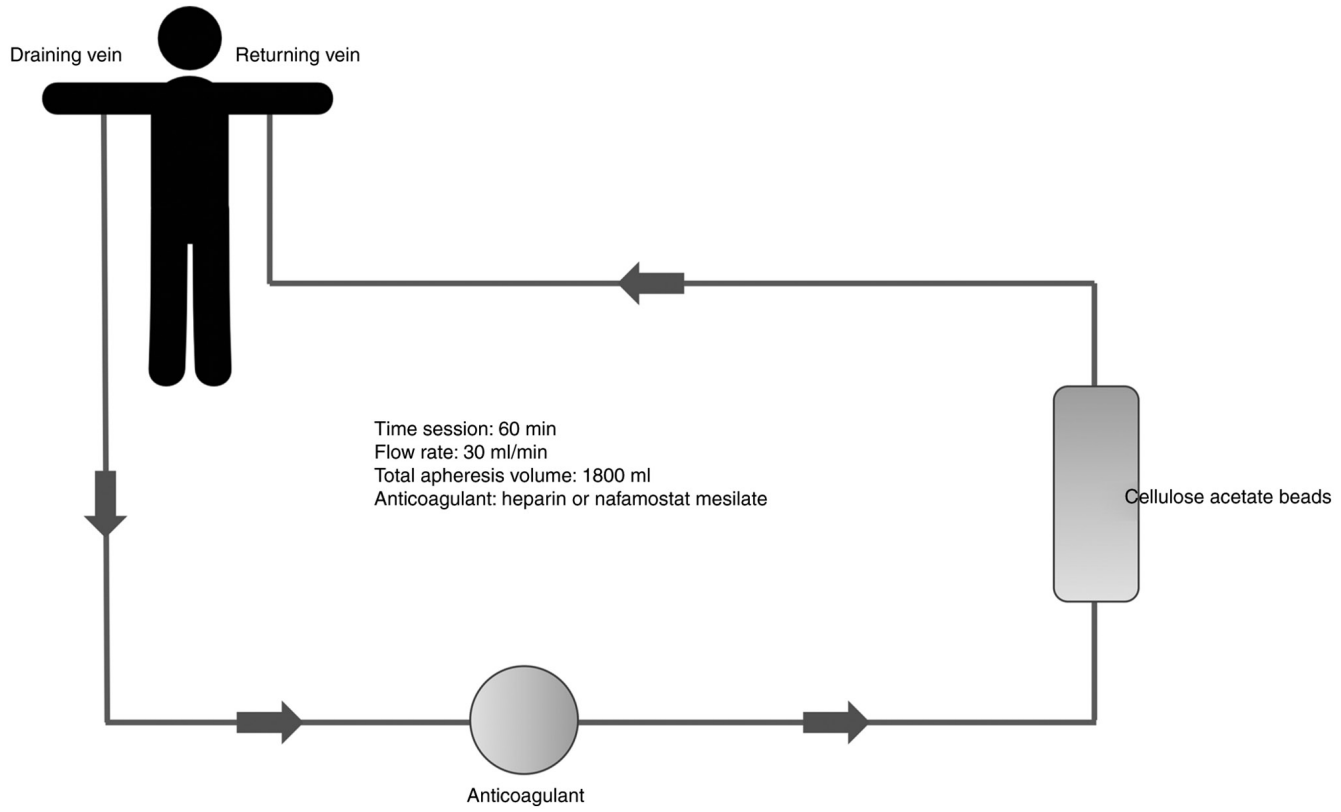

Figure 1. Granulocyte and monocyte apheresis system. In each session of 60 min, 1,800 ml of blood is drained from the cubital vein of one arm, at a flow rate of 30 ml/min to the cubital vein of the contralateral arm, passing through cellulose acetate beads in the column. Anticoagulants are necessary for this procedure.

and their related cytokines, although neutrophils could be variably expressed in psoriasis lesions, contributing to its definition (15,16) There are five types of psoriasis: psoriasis vulgaris, arthropathic psoriasis, psoriatic erythroderma, guttate psoriasis, pustular psoriasis (17). GPP is an unusual and severe variant of pustular psoriasis, clinically characterized by sterile pustules overlying painful, erythematous skin (18). Histologically, pustular psoriasis has spongiform pustules of Kogoj into the epidermis, formed by neutrophil infiltration. Moreover, the epidermis is characterized by an absent granular layer, parakeratosis, Munro's microabscesses, suprapapillary thinning and psoriasiform hyperplasia, while the dermis is characterized by dilated blood vessels with fewer neutrophils (18). Triggering factors of GPP include pyrogallic acid, infections, pregnancy, drugs, hypocalcemia (19). The mechanisms underlying the pathogenesis of GPP currently remain unclear (11). Certain monogenic autoinflammatory disorders clinically present as generalized variants of pustular psoriasis (CAMPS- *CARD14*-mediated pustular psoriasis-DIRA, DITRA-deficiency of IL-36 receptor antagonist-, those related to mutations in *AP1S3*) (18). First-line treatment options for adult GPP include retinoids, cyclosporine (CsA) and methotrexate (MTX). Second-line therapies include adalimumab (ADA), etanercept, topical agents and phototherapy. More recently, GMA has been employed in cases recalcitrant to other medications, or in special populations, such as very young or old patients, pregnant and those infected with hepatitis (18). Kanekura *et al* (20) showed that pustular psoriasis was dramatically ameliorated by GMA therapy, while psoriasis vulgaris responded minimally to this treatment. This aspect may be due to fewer infiltrated neutrophils in this pathology. In the largest study, Ohnishi *et al* (21) described 22 patients treated with GMA: 16 patients obtained effective response after the whole treatment, 5 patients maintained an unchanged condition and only in one case there was a worsening of the disease. Moreover, the majority of these subjects took concomitant therapies. Filosa and Filosa (13) observed that very few patients reported slight side effects (e.g. headache, dizziness, light headedness on standing, chills and feeling of weakness); one patient developed an allergic reaction to nafamostat mesylate, while another one developed pemphigoid. However, most of these effects are related to the use of anticoagulant, which is indispensable for the procedure (22). Overall, relapse of GPP after a complete course of therapy was seen in 6 patients. For patients who had a recurrence or did not respond to regular GMA, further sessions were disposed, also with an intensive regime (proposing therapy twice a week), obtaining remission in all patients (23-25). Mizutani *et al* (26) described two cases in which patients initially received regular GMA (5 sessions, once a week), and intensive GMA (5 sessions, twice a week) upon recurrence; the authors observed that increasing the number of sessions weekly, better results have been achieved in terms of clinical response. Furthermore, the same authors reported a case of a patient with GPP, who was pregnant during both regular and intensive GMA therapy. Her children were born with no anomalies but with low birth weights and at 33 and 36 weeks of pregnancy (19). Patients' features and results of GMA efficacy for treating GPP are shown in Table I (17,20,21,23,25-39).

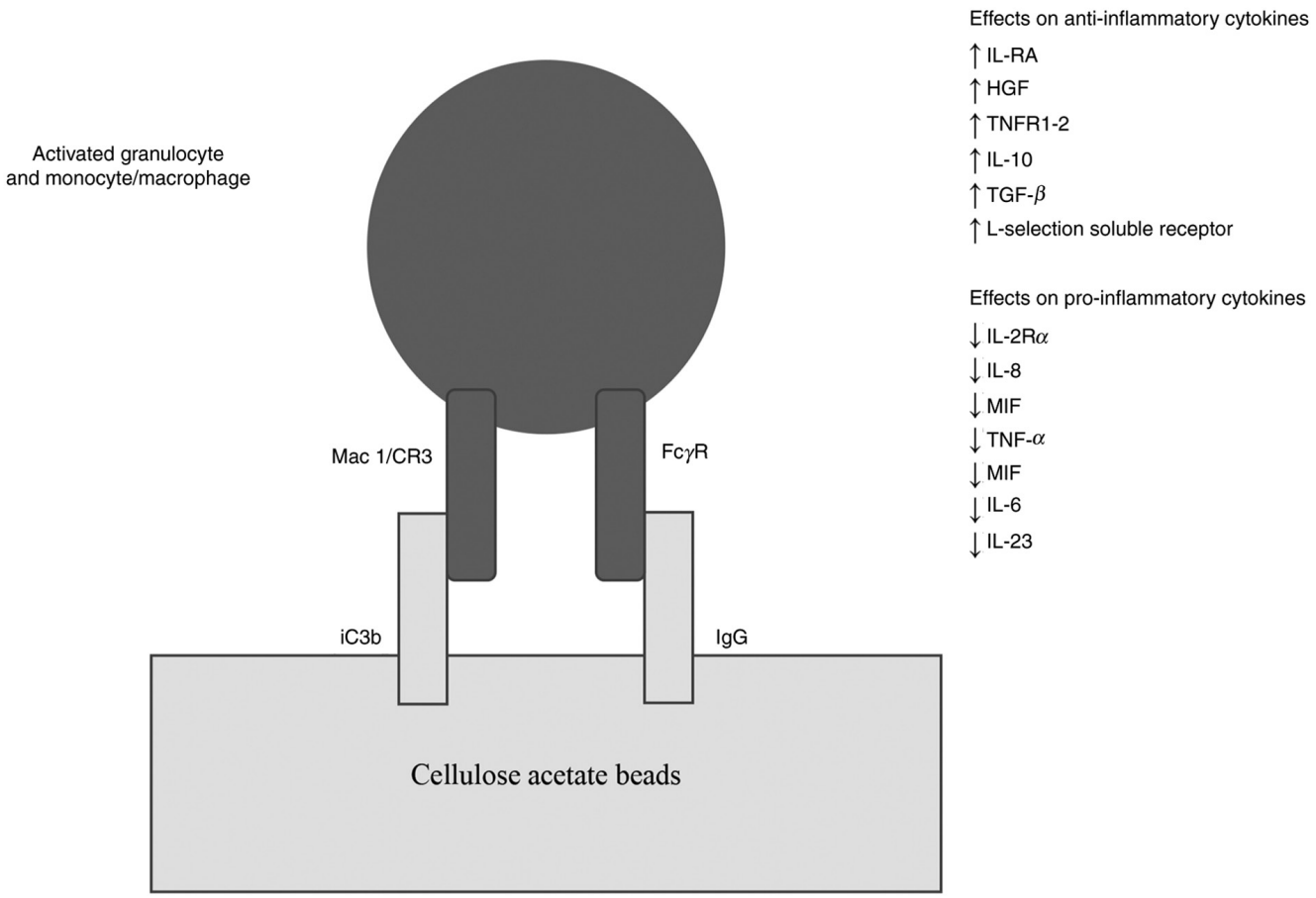

Figure 2. Diagram of granulocyte and monocyte selective removal and effects on cytokines. Activated granulocytes and monocytes/macrophages express Mac-1. Cellulose acetate beads in the column activate and absorb iC3b, a ligand for Mac-1. They also express immunoglobulin G, which bond Fcγ receptors on the myeloid lineage cells. Apheresis procedure modulates level of cytokines, as shown in the figure.

Pyoderma Gangrenosum. PG is an inflammatory disease, clinically characterized by painful skin ulcerations, especially on lower legs, with erythematous and undermined borders and histologically defined by the presence of a neutrophilic infiltrate in the dermis. PG is mostly associated with UC and Crohn's disease. However, other possible associations may include rheumatoid arthritis and hematological malignancies (40). Five clinical variants are currently recognized: classic or ulcerative, bullous, pustular, vegetative, and peristomal types (41). Treatment of PG usually comprise topical therapy (e.g. topical corticosteroids or topical tacrolimus), systemic treatment (e.g. oral corticosteroids, CsA, tacrolimus, colchicine, dapsone, MTX, intravenous immunoglobulin) and targeted therapy, including TNF-α inhibitors, anti IL-1 and IL-12/23 antagonists (42). Alternatively to current existing therapies, GMA is an effective option with minimal side effects, especially for steroid and immunosuppressant-resistant PG (43). Forty-nine cases of GMA application for PG have been summarized in Table II (28,43-62). In the main case series, Higashi *et al* (44) reported a complete response in eight patients, a nearly complete response in three patients and a partial response in two patients. Skin lesions remained stable in four cases, while a disease progression was observed in two cases. The same authors reported that in 12 patients, treatment outcomes were assessed 2 months after the final GMA session. During that post-GMA period, skin ulcers continued to shrink in eight patients and remained unchanged in three. Sakanoue *et al* (28) described an excellent response in three patients and a good response in one patient, all after 10 sessions of GMA, performed weekly. A moderate response was observed in two patients who underwent 5 time-sessions GMA, once a week. Russo *et al* (43) wrote the first case report in Europe, discussing the application of 10 sessions of GMA, scheduled weekly, for a patient with PG, whose ulcer started resolving after the 6th treatment. This patient did not experience any side effects or relapse of the disease during a 6-months follow up period. Moreover, Ikeda *et al* (45) showed an amelioration in patients' Dermatology Life Quality Index (DLQI), reflecting better daily function and quality of life after a course of GMA. Very few side effects occurred after GMA: Ishikawa *et al* (47) reported a case of a patient who developed a mild headache, while Higashi *et al* (44) described two episodes of non-serious transient hypertension and a failure in blood drainage for five patients, for whom however GMA was continued by decreasing the blood flow rate and changing the limb position. Overall, a relapse of PG after GMA was seen in four patients.

Palmoplantar pustular psoriasis. PPP is a chronic inflammatory disease, clinically characterized by erythema, scales and sterile pustules on the palms and soles. There is a higher prevalence between females, especially those who smoke (63).

Table I. Generalized pustular psoriasis: Demographics and clinical course.

First author	Reporting year	No. of patients	Age, years	Sex	Response to GMA	(Refs.)
Kanekura T	2003	1	62	M	Yes	(20)
Ohnishi H	2018	22	32-78	13F, 9M	16 Yes, 6 No	(21)
Shukuya R	2011	2	26-68	2 F	Yes	(23)
Suzuki A	2012	3	36-71	1F, 2M	Yes	(25)
Mizutani Y	2020	2	31-77	2 F	Yes	(26)
Fujii A	2017	1	79	F	Yes	(27)
Sakanoue M	2013	4	37-59	3F, 1M	Yes	(28)
Ikeda S	2013	15	50-13	4F, 11M	12 Yes, 3 No	(29)
Fujii A	2019	1	43	M	Yes	(30)
Koike Y	2017	1	13	M	Yes	(31)
Shindo E	2019	1	34	F	Yes	(17)
Fujisawa T	2013	1	60	F	Yes	(32)
Tominaga C	2015	1	78	F	Yes	(33)
Fujisawa T	2011	3	61-64	1F, 2M	Yes	(34)
Fujisawa T	2015	3	31-63	2F, 1M	Yes	(35)
Furusawa K	2012	1	42	F	Yes	(36)
Mabuchi T	2014	1	54	F	Yes	(37)
Seishima M	2008	1	44	F	Yes	(38)
Sugiura K	2014	1	65	F	Yes	(39)

M, male; F, female; GMA, granulocyte and monocyte apheresis.

Histologically, neutrophilic infiltration destroys epidermal microarchitecture and after the evacuation of the pus, pustules in PPP leave a visible cavity behind. When they are not evacuated, pustules dry up and form brownish scabs that subsequently exfoliate (19). PPP is usually resistant to treatment, with high rates of recurrence. A lot of systemic drugs have been tested, including colchicine, itraconazole, alitretinoin and biologics (64). Another therapeutic choice for PPP is GMA, as described by several authors. In the largest case series, Sakanoue *et al* (28) performed 5 sessions of GMA, once a week, resulting in two cases with excellent outcomes, seven cases with a good response, three with a moderate response and two patients were unresponsive. None of the patients reported side effects. Another report by Fujisawa *et al* (65) described an excellent response in three patients after 5 sessions of GMA, scheduled weekly. Kawakami *et al* (66) assessed the effect of the GMA at the end of treatment and after 3 months of follow up. In all patients GMA was conducted once a week, for 5 consecutive weeks. One patient showed a remarkable improvement immediately after GMA and two patients achieved the same result at a 3-month follow-up. Deterioration of skin symptoms was noted in two patients, at the follow up visit. The majority of patients were treated with several therapies before GMA, without efficacy. Patients' clinical features and results after therapy are shown in Table III (28,38,65-67).

Behcet disease. BD is a multisystem inflammatory chronic disorder, clinically characterized by recurrent oral and genital aphthosis, severe uveitis, cutaneous lesions such as erythema nodosum and pustules, in addition to multi-organ involvement and arthritis. The majority of patients are from Japan, the Middle East or the Mediterranean basin and the peak incidence is in the age between 20 and 35 (68). HLA-B51 is the allele with the best-known role in the pathogenesis, even if environmental triggers and immune cells and cytokines could be involved too (69). Histological features of cutaneous lesions could be a leukocytoclastic vasculitis with fibrinoid necrosis of postcapillary venules, a neutrophilic vascular reaction, or a lymphocytic perivasculitis (70). Pharmacological agents used to treat BD include colchicine, dapsone, corticosteroids and immunosuppressants such as azathioprine (AZA), MTX and CsA. The efficacy of TNF-α inhibitors in BD has been reported recently. In pregnant women, these systemic agents raise fetal risks such as teratogenicity, stillbirth and spontaneous abortion (68). GMA could be a valid treatment option in BD, since neutrophils are involved in its etiopathogenesis, as shown in Table IV (28,71,72). In their case series, Sakanoue *et al* (28) performed GMA five times, once a week, for the majority of patients. After this treatment, two patients had an excellent response, three a good one, one of them showed moderate results and in two cases there were no changes, compared with the beginning. Only one patient underwent GMA for 10 times, weekly, with a final moderate response to therapy. None of the patients experienced side effects. Different therapies were prescribed previously to GMA, including colchicine, loxoprofen, mefenamic acid and prednisolone (PSL). Higashi *et al* (71) reported a case of a 39-year-old woman, who was found to be pregnant during the therapy. She had no complications related to GMA and delivered a healthy newborn, underlining the lack of negative effects of this therapy. Finally, Kanekura *et al* (72) described two patients, a 21-year-old man and a woman of 50 years,

Table II. Pyoderma gangrenosum: Demographics and clinical course.

First author	Reporting year	No. of patients	Age, years	Sex	Response to GMA	(Refs.)
Sakanoue M	2013	6	21-76	1F, 5M	Yes	(28)
Russo I	2016	1	73	M	Yes	(43)
Higashi Y	2021	19	21-79	11F, 8M	13 Yes, 6 No	(44)
Ikeda K	2011	1	36	F	Yes	(45)
Ohmori T	2003	1	19	M	Yes	(46)
Ishikawa H	2004	1	30	M	Yes	(47)
Yoneda K	2005	1	39	F	Yes	(48)
Yanar-Fujisawa R	2005	1	31	F	Yes	(49)
Seishima M	2007	1	29	F	Yes	(50)
Fujino Y	2008	1	55	F	Yes	(51)
Kawakami T	2009	1	19	M	Yes	(52)
Doi R	2010	1	19	M	Yes	(53)
Kobayashi S	2011	1	29	M	Yes	(54)
Ohno M	2016	1	36	F	Yes	(55)
Okada M	2017	1	71	F	Yes	(56)
Yamashita A	2017	1	30	F	Yes	(57)
Tominaga K	2020	1	57	M	Yes	(58)
Shibuya T	2020	1	50	F	Yes	(59)
Kanekura T	2005	2	44-67	2M	Yes	(60)
Kanekura T	2002	1	38	M	Yes	(61)
Kawai M	2021	1	18	F	Yes	(62)
Kawakami T	2009	1	19	M	Yes	(52)

M, male; F, female; GMA, granulocyte and monocyte apheresis.

Table III. Palmoplantar pustular psoriasis: Demographics and clinical course.

First author	Reporting year	No. of patients	Age, years	Sex	Response to GMA	(Refs.)
Sakanoue M	2013	14	35-77	8 F, 6 M	12 Yes, 2 No	(28)
Seishima M	2008	1	66	M	Yes	(38)
Fujisawa T	2014	3	28-64	1 F, 2 M	Yes	(65)
Kawakami H	2019	5	48-77	5 F	4 Yes, 1 No	(66)
Kanekura T	2004	1	57	F	Yes	(67)

M, male; F, female; GMA, granulocyte and monocyte apheresis.

successfully treated with GMA. They underwent GMA 5 times and 8 times weekly, respectively. Both skin lesions and pain improved dramatically at the end of the therapy, and no side effects were experienced.

Sweet's syndrome. SS is an acute febrile neutrophilic dermatosis characterized by different clinical features, including fever, neutrophilia and tender erythematous skin lesions, asymmetrically distributed on face, neck and upper extremities. Classical SS has a worldwide distribution, usually affecting middle-aged women. It may be associated with infection of the upper respiratory or gastrointestinal tract, and with IBD (73). Histopathological diagnostic criteria include a dense neutrophilic infiltrate in the upper dermis. Occasionally, eosinophiles, lymphocytes or histiocytes may also be present (73). Systemic corticosteroids, colchicine and potassium iodide are considered as first-line treatments for SS. Second-line therapies include indomethacin, clofazimine, CsA and dapsone. The use of biologic agents has also been described (74). GMA may be a useful non-pharmacologic tool for SS, with no safety concerns. Fujii *et al* (75) reported a case of a 55-year-old woman affected by SS, previously treated with PSL, nonsteroidal anti-inflammatory drugs (NSAIDs) and colchicine, who underwent GMA for three times, once a

Table IV. Behcet disease: Demographics and clinical course.

First author	Reporting year	No. of patients	Age, years	Sex	Response to GMA	(Refs.)
Sakanoue M	2013	9	18-74	8 F, 1M	7 Yes, 2 No	(28)
Higashi Y	2013	1	39	F	Yes	(71)
Kanekura T	2004	2	21-50	1F, 1M	Yes	(72)

M, male; F, female; GMA, granulocyte and monocyte apheresis.

week, showing resolution of symptoms after the first session. This patient did not have any relapse of the disease during a 4 month's follow-up. Similarly, Sakanoue *et al* (28) described a 65-year-old male patient for whom GMA was performed 5 times, weekly, with good final response. He was previously treated with loxoprofen, without efficacy. No adverse effect was reported in both cases.

Adult-onset Still's disease. AOSD is a systemic inflammatory disorder of unknown etiology, characterized by a high spiking fever, transient skin rash, polyarthralgia, and hyperferritinemia. Other frequently observed clinical features include sore throat, hepatomegaly, splenomegaly, lymphadenopathy and serositis. Neutrophilic leukocytosis and granulocytosis are important diagnostic criteria too. This disease occurs worldwide and usually affects young adults (76). At present, AOSD therapeutic strategy aims to prevent organ damage and life-threatening complications and minimize adverse effects of treatment. However, therapies of AOSD remain largely empirical, lacking controlled clinical trials (77). Various drugs including NSAIDs, corticosteroids, MTX and other disease-modifying anti-rheumatic drugs (DMARDs) and biologic agents do not always guarantee complete remission of AOSD (76). Kanekura *et al* (78) suggested that GMA represents a promising treatment modality for AOSD, based on the positive outcome they obtained in the present case. More specifically, a 33-year-old woman was treated with GMA for 5 times, once a week, concomitantly taking corticosteroids and meloxicam. Both her laboratory findings and symptoms improved a lot after this treatment, fever decreased remarkably and skin lesions became faint in color and smaller in size. Furthermore, arthralgia dramatically improved. No adverse effects were observed and the patient suffered no relapse for the following 22-month period.

Impetigo Herpetiformis. IH is a rare systemic inflammatory disease occurring in pregnancy and it is considered as a subtype of GPP. IH's disease severity ranges from ‘severe’, a state sometimes accompanied by impaired placental function or electrolyte abnormalities, to ‘mild’, characterized by pustular skin eruptions (79). This condition mostly occurs in the third trimester of pregnancy and usually resolves after delivery. However, there is the possibility of recurrence in the following pregnancies (80). Patients with IH sometimes experience intrauterine growth restriction (IUGR), possibly due to lower oxygen and nutrition intake from the inflamed placenta (79). Conventional treatment for IH comprises topical steroid application or oral steroid administration. Second-choices therapeutic options include CsA, phototherapy and anti TNF-α drugs. Current reports indicate that GMA is useful in IH treatment to improve skin eruption and reduce placental inflammation and thus ameliorate IUGR (79,81,82). Iwasaki A (79) described a case of a 33-year-old woman with IH at 30 week's gestation of her first pregnancy. She was previously treated with topical and systemic steroids, then she performed 2 GMA sessions at 7-day intervals concomitantly with oral PSL. After the second GMA, skin eruption improved rapidly and almost resolved. The patient reported no relapse of the disease in the following months. Another case, observed by Fujii *et al* (81), involved a 28-year-old woman at her first pregnancy. Clinically, she experienced IH at 25 weeks of gestation and had a homozygous *CARD14* mutation. Two GMA sessions were performed: after the first one, skin lesions immediately improved and pustules disappeared. Following the second course, performed after 7 days, the eruption completely disappeared. In a report by Saito-Sasaki *et al* (82), a 30-year-old woman affected by IH at 10 weeks into her fourth pregnancy, was initially treated with methylprednisolone and CsA. She totally performed 14 courses of GMA, since IH relapsed twice in the meantime. Once she completed all the sessions, skin lesions disappeared. None of the three patients experienced side effects related to GMA therapy.

3. GMA in other skin disorders

Reactive arthritis. A triad of symptoms characterizes ReA, previously known as Reiter's syndrome: oligoarthritis of large joints, urethritis in men and cervicitis in women and conjunctivitis, usually occurring in young adults some weeks after a urogenital or gastrointestinal infection (83). Mucocutaneous features, including circinate balanitis, keratoderma blenorrhagicum, ulcerative vulvitis, nail changes, oral lesions, are often associated concomitantly or sequentially (84). Because patients test negative for rheumatoid factor, ReA is classified as a seronegative spondyloarthropathy. There are cases of familial aggregation of ReA which may be related to its association with HLA-B27 (84). NSAIDs are first-line drugs for the management of this disease. DMARDs, such as sulfasalazine, are effective for peripheral manifestations, while most experts consider glucocorticoids use in ReA contraindicated, except for an occasional intra-articular injection (83). As ReA is attributable to activated neutrophils and it is histologically similar to pustular psoriasis in its prominent neutrophil infiltration, therapy with GMA may be useful for treating this disease, as reported by Yoshifuku *et al* (85). Particularly, the authors described a case of a 73-year-old man with scaly, coalescent

erythematous macules with ulcers on penis and scrotum and a scaly erythematous plaque on his right hand. Moreover, he suffered from lumbar pain and multiple arthralgia, ulcer of the corneal epithelium and conjunctivitis and sterile urethritis. He did several treatments before apheresis, including ceftriaxone sodium, cefepime dihydrochloride, vancomycin hydrochloride and diclofenac sodium. The thrice-daily use of diclofenac sodium suppositories, which was required to ease the patient's pain before GMA therapy, was discontinued one week after the introduction of GMA. After the treatment, skin lesions improved dramatically and articular pain decreased. Ocular involvement and urethritis also ameliorated. The patient experienced no adverse effect related to GMA.

PASH syndrome. PASH syndrome is a recently proposed disease entity, belonging to the spectrum of autoinflammatory syndromes, similar to pyogenic sterile arthritis, pyoderma gangrenosum and acne (PAPA) syndrome and aseptic abscesses syndrome. However, in contrast to these two disorders, PASH syndrome shows a clear predilection for the skin and lacks arthritis and visceral involvement (86). Both PG and hidradenitis suppurativa (HS), are included in the spectrum of neutrophilic dermatoses. HS is a chronic-relapsing, debilitating inflammatory disease of the hair follicles that usually presents after puberty and affects apocrine gland-bearing skin (most frequently the axillae as well as the inguinal and anogenital regions). It is clinically characterized by recurrent, painful, deep-seated nodules that usually end in abscesses and sinus tracts with suppuration and hypertrophic scarring (87). Treatment of PASH syndrome could be challenging. Systemic glucocorticosteroids, AZA, CsA, dapsone and isotretinoin, may fail to control the disease satisfactorily. Biologic agents targeting IL-1 and TNF-α have been recommended to treat PASH syndrome, but their efficacy has not been well established because of its rarity (87). The efficacy of GMA on PASH syndrome has been observed in two case reports. Hatanaka *et al* (88) described a woman with a 15-years history of disease. Different therapies were prescribed prior to GMA, including systemic and topical antibiotics, oral PSL, and frequent surgical incisions. For this patient, GMA was performed twice a week for a total of five sessions; five additional sessions were scheduled at 7-day intervals. After the final session, a remarkable improvement of skin lesions was noticed and no relapse occurred during the following four years. Mizutani *et al* (89) reported a case of a male adolescent with clinical manifestations of PASH syndrome for two years, who failed to respond to treatments with oral PSL, CsA, dapsone and minocycline. For this reason, he received GMA sessions weekly for 10 consecutive weeks with a consequent great improvement of his condition. However, pustule formation did not completely disappear and thus ADA was administered.

Cutaneous allergic vasculitis. CAV is a disorder characterized by inflammation of small vessels, especially post capillary venules. Histologically, blood vessel necrosis is found with fibrinoid material deposits and inflammatory cellular infiltrate, nuclear dust, and erythrocyte extravasation (90). The most common clinical presentation of CAV consists of palpable purpura of the lower extremities. Less frequently, it reveals itself as nodular erythema, livedo racemosa, and punched-out ulcers (91). CAV may be idiopathic or may have a defined cause such as infection, medication, connective tissue disease, or malignancy. Extracutaneous disease or systemic vasculitis could also be related (92). An isolated episode of CAV associated with a known inciting factor may be managed by removal or treatment of the trigger, along with symptomatic measures. First-line systemic treatments for chronic, idiopathic CAV include colchicine or dapsone, used singly or in combination. Recurrent, chronic, or severely symptomatic CAV that does not respond to the aforementioned therapies may require initiation of an immunosuppressive agent such as AZA, mycophenolate mofetil, MTX, CsA, or rituximab (92). When these treatments are partially successful, GMA could be considered a therapeutic option. Kanekura *et al* (93) described a 49-year-old woman affected by CAV with intractable leg ulcers, which responded well to GMA therapy. GMA was carried out five times, once a week, simultaneously with loxoprofen. Ulcers were covered by regenerated skin at the end of all five treatment sessions, without relapse during a 5-months follow up period. No adverse event was reported. Also, Sakanoue *et al* (28) treated a case of CAV performing GMA, with an excellent response at the end of five sessions, scheduled once a week.

Systemic Lupus Erythematosus. SLE is a chronic autoimmune disease characterized by the production of autoantibodies directed against nuclear and cytoplasmic antigens, which may affect any organ. Skin is the most affected part of the body, especially in areas exposed to light, and main cutaneous manifestations comprises malar rash and discoid lesions. Other clinical features include photosensitivity, oral ulcers, arthritis, serositis, renal findings (persistent proteinuria, hematuria, cellular casts), neurologic disorders (seizures or psychosis), hematologic findings (thrombocytopenia, leukopenia, lymphopenia, or anemia). As far as laboratory findings concerned, clinicians should test for antinuclear antibodies (ANA), and if the result is positive, they should search for antigen-specific ANA, such as those targeting double-stranded DNA (dsDNA) or ribonucleoprotein complexes (Ro/SSA, La/SSB, Smith, and RNP), collectively referred to as extractable nuclear antigens. SLE is more common between adult women, with a higher peak of prevalence among African Americans. Several medications are used to treat SLE, including glucocorticoids, antimalarial agents, NSAIDs, immunosuppressive agents, and B cell-targeting biologics. However, the most important drug to treat SLE is hydroxychloroquine (94,95). Kanekura *et al* (96) posited that SLE patients could also benefit from GMA treatment. The authors described a male patient of 22-year-old, showing malar and discoid rash, leukocytopenia with lymphocytopenia, positive antibodies for dsDNA and Smith antigen (Sm) and ANA. He was previously treated using systemic corticosteroids. A total of five GMA sessions were scheduled once a week, without discontinuing patient's therapy with oral PSL. After the whole treatment, his skin rashes ameliorated dramatically and laboratory exams too. Demographic features and the therapeutic response of patients with SS, AOSD, IH, ReA, PASH syndrome, CAV and SLE are summarized in Table V (28,75,78,79,81,82,85,88,89,93,96).

Table V. Other diseases: Demographics and clinical course.

Disease	First author	Reporting year	No. of patients	Age (yr)	Sex	Response to GMA	(Refs.)
SS	Sakanoue M	2013	1	65	M	Yes	(28)
	Fujii A	2017	1	55	F	Yes	(75)
AOSD	Kanekura T	2004	1	33	F	Yes	(78)
IH	Iwasaki A	2018	1	33	F	Yes	(79)
	Fujii K	2020	1	28	F	Yes	(81)
	Saito-Sasaki N	2017	1	30	F	Yes	(82)
ReA	Yoshifuku A	2011	1	73	M	Yes	(85)
PASH Syndrome	Hatanaka M	2021	1	34	F	Yes	(88)
	Mizutani Y	2017	1	18	M	Yes	(89)
CAV	Sakanoue M	2013	1	34	F	Yes	(28)
	Kanekura T	2006	1	49	F	Yes	(93)
SLE	Kanekura T	2004	1	22	M	Yes	(96)

SS, Sweet's syndrome; AOSD, adult-onset Still's disease; IH, impetigo herpetiformis; ReA, reactive arthritis; PASH, pyoderma gangrenosum, acne and hidradenitis suppurativa; CAV, cutaneous allergic vasculitis; SLE, systemic lupus erythematosus; M, male; F, female; GMA, granulocyte and monocyte apheresis.

4. Conclusion

GMA is considered a promising and innovative treatment option for skin diseases linked to activated neutrophils and it represents an effective alternative to currently existing therapies, with minimal side effects compared to other systemic therapies. This review collected available publications regarding the effect of GMA in dermatologic disorders. The majority of patients underwent GMA treatments five or ten times, once a week, in relation to the severity of their disease and clinical response. Concomitant GMA therapy with other drugs (e.g. corticosteroids, CsA, etretinate) might shorten the time to remission and might increase the healing rate (62). Furthermore, GMA is useful to reduce systemic inflammation, not only to improve skin eruption, but also to reduce placental inflammation and thus ameliorate IUGR as reported in different cases of IH in pregnant women, who gave birth to healthy newborns (79,81,82). Another advantage of this technique concerns its safety profile, in contrast to multiple adverse events reported with conventional and biologic drugs. Despite the higher cost of GMA, compared with traditional medication, this therapeutical option could be cost-effective on a long-term perspective, decreasing hospitalization, surgery and reducing the overall cost of medical services. More research is needed before GMA would be accepted as first-line therapy, especially for particular groups of patients, such as pregnant women, children and adolescents. Moreover, it is sometimes difficult to estimate the effects of GMA alone since, in many cases, it was used in combination with other therapies. Another major issue of most studies is the short follow-up period. Further trials are required to evaluate GMA's safety and optimal therapeutic regimens for achieving long-lasting effects. On the basis of our results, we strongly suggest that this technique is a valuable choice for patients with intractable steroid and immunosuppressant-resistant skin diseases attributable to activated granulocytes. We hope that this non-pharmacological option could be applied as a first-line treatment to other chronic diseases for different medical purposes in the future.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

Not applicable.

Authors' contributions

LG, GM and MA made substantial contributions to conception and design, interpretation of data, participated in drafting the article and gave final approval of the version to be submitted and any revised version. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Domènech E, Grífols JR, Akbar A and Dignass AU: Use of granulocyte/monocytapheresis in ulcerative colitis: A practical review from a European perspective. World J Gastroenterol 27: 908-918, 2021.
2. Kanekura T: Clinical and immunological effects of adsorptive myeloid lineage leukocyte apheresis in patients with immune disorders. J Dermatol 45: 943-950, 2018.
3. Kanekura T, Hiraishi K, Kawahara K, Maruyama I and Kanzaki T: Granulocyte and monocyte adsorption apheresis (GCAP) for refractory skin diseases caused by activated neutrophils and psoriatic arthritis: Evidence that GCAP removes Mac-1-expressing neutrophils. Ther Apher Dial 10: 247-256, 2006.
4. Chen XL, Mao JW and Wang YD: Selective granulocyte and monocyte apheresis in inflammatory bowel disease: Its past, present and future. World J Gastrointest Pathophysiol 11: 43-56, 2020.
5. Cuadrado E: Granulocyte/monocyte apheresis as immunotherapic tool: Cellular adsorption and immune modulation. Autoimmun Rev 8: 292-296, 2009.
6. Hanai H, Takeda Y, Eberhardson M, Gruber R, Saniabadi AR, Winqvist O and Lofberg R: The mode of actions of the Adacolumn therapeutic leucocytapheresis in patients with inflammatory bowel disease: A concise review. Clin Exp Immunol 163: 50-58, 2011.
7. Yokoyama Y, Fukunaga K, Fukuda Y, Tozawa K, Kamikozuru K, Ohnishi K, Kusaka T, Kosaka T, Hida N, Ohda Y, *et al*: Demonstration of low-regulatory CD25High+CD4+ and high-pro-inflammatory CD28-CD4+ T-Cell subsets in patients with ulcerative colitis: Modified by selective granulocyte and monocyte adsorption apheresis. Dig Dis Sci 52: 2725-2731, 2007.
8. Nishise S, Abe Y, Nomura E, Sato T, Sasaki Y, Iwano D, Yoshizawa K, Yagi M, Sakuta K and Ueno Y: Effect of cellulose acetate beads on interleukin-23 release. Ther Apher Dial 20: 354-359, 2016.
9. Rodríguez-Lago I, Benítez JM, García-Sánchez V, Gutiérrez A, Sempere L, Ginard D, Barreiro-de Acosta M and Cabriada JL: Granulocyte and monocyte apheresis in inflammatory bowel disease: The patients' point of view. Gastroenterol Hepatol 41: 423-431, 2018 (In English, Spanish).
10. Tominaga K, Nakano M, Hoshino M, Kanke K and Hiraishi H: Efficacy, safety and cost analyses in ulcerative colitis patients undergoing granulocyte and monocyte adsorption or receiving prednisolone. BMC Gastroenterol 13: 41, 2013.
11. Panés J, Guilera M, Ginard D, Hinojosa J, González-Carro P, González-Lara V, Varea V, Domènech E and Badia X: Treatment cost of ulcerative colitis is apheresis with Adacolumn cost-effective? Dig Liver Dis 39: 617-625, 2007.
12. Yoshino T, Nakase H, Matsuura M, Matsumura K, Honzawa Y, Fukuchi T, Watanabe K, Murano M, Tsujikawa T, Fukunaga K, *et al*: Effect and safety of granulocyte-monocyte adsorption apheresis for patients with ulcerative colitis positive for cytomegalovirus in comparison with immunosuppressants. Digestion 84: 3-9, 2011.
13. Filosa A and Filosa G: Neutrophilic dermatoses: A broad spectrum of disease. G Ital Dermatol Venereol 153: 265-272, 2018.
14. Nelson CA, Stephen S, Ashchyan HJ, James WD, Micheletti RG and Rosenbach M: Neutrophilic dermatoses: Pathogenesis, Sweet syndrome, neutrophilic eccrine hidradenitis, and Behçet disease. J Am Acad Dermatol 79: 987-1006, 2018.
15. Nestle FO, Kaplan DH and Barker J: Psoriasis. N Engl J Med 61: 496-509, 2009.
16. Krueger JG and Bowcock A: Psoriasis pathophysiology: Current concepts of pathogenesis. Ann Rheum Dis 64 (Suppl 2): ii30-ii36, 2005.
17. Shindo E, Shikano K, Kawazoe M, Yamamoto T, Kusunoki N, Hashimoto Y and Nanki T: A case of generalized pustular psoriasis caused by hydroxychloroquine in a patient with systemic lupus erythematosus. Lupus 28: 1017-1020, 2019.
18. Hoegler KM, John AM, Handler MZ and Schwartz RA: Generalized pustular psoriasis: A review and update on treatment. J Eur Acad Dermatol Venereol 32: 1645-1651, 2018.
19. Navarini AA, Burden AD, Capon F, Mrowietz U, Puig L, Köks S, Kingo K, Smith C and Barker JN; ERASPEN Network: European consensus statement on phenotypes of pustular psoriasis. J Eur Acad Dermatol Venereol 31: 1792-1799, 2017.
20. Kanekura T, Yoshii N, Yonezawa T, Kawabata H, Saruwatari H and Kanzaki T: Treatment of pustular psoriasis with granulocyte and monocyte adsorption apheresis. J Am Acad Dermatol 49: 329-332, 2003.
21. Ohnishi H, Kadowaki T, Mizutani Y, Nishida E, Tobita R, Abe N, Yamaguchi Y, Eto H, Honma M, Kanekura T, *et al*: Genetic background and therapeutic response in generalized pustular psoriasis patients treated with granulocyte and monocyte adsorption apheresis. Eur J Dermatol 28: 108-11, 2018.
22. Sawada K, Ohdo M, Ino T, Nakamura T, Numata T, Shibata H, Sakou J, Kusada M and Hibi T: Safety and tolerability of nafamostat mesilate and heparin as anticoagulants in leukocytapheresis for ulcerative colitis: Post Hoc analysis of a large-scale, prospective, observational study. Ther Apher Dial 20: 197-204, 2016.
23. Shukuya R, Hasegawa T, Niwa Y, Okuma K and Ikeda S: Granulocyte and monocyte adsorption apheresis for generalized pustular psoriasis. J Dermatol 38: 1130-1134, 2011.
24. Sugiura K: The genetic background of generalized pustular psoriasis: IL36RN mutations and CARD14 gain-of-function variants. J Dermatol Sci 74: 187-192, 2014.
25. Suzuki A, Haruna K, Mizuno Y, Kuwae Y, Ono Y, Okumura K, Negi O, Kon Y, Takeuchi K, Takamori K, *et al*: Successful treatment of three cases of generalized pustular psoriasis with granulocyte and monocyte adsorption apheresis. Ther Apher Dial 16: 445-448, 2012.
26. Mizutani Y, Fujii K, Kawamura M, Inoue M, Mizutani YH, Matsuyama K, Doi T, Nagaya S and Seishima M: Intensive granulocyte and monocyte adsorption apheresis for generalized pustular psoriasis. J Dermatol 47: 1326-1329, 2020.
27. Fujii A, Ohnishi H and Seishima M: Generalized pustular psoriasis with IL-36 Receptor antagonist mutation successfully treated with granulocyte and monocyte adsorption apheresis accompanied by reduced serum IL-6 level. Ther Apher Dial 22: 92-93, 2018.
28. Sakanoue M, Takeda K, Kawai K and Kanekura T: Granulocyte and monocyte adsorption apheresis for refractory skin diseases due to activated neutrophils, psoriasis, and associated arthropathy. Ther Apher Dial 17: 477-483, 2013.
29. Ikeda S, Takahashi H, Suga Y, Eto H, Etoh T, Okuma K, Takahashi K, Kanbara T, Seishima M, Morita A, *et al*: Therapeutic depletion of myeloid lineage leukocytes in patients with generalized pustular psoriasis indicates a major role for neutrophils in the immunopathogenesis of psoriasis. J Am Acad Dermatol 68: 609-617, 2013.
30. Fujii A, Fujii K and Seishima M: Generalized pustular psoriasis with CARD14 Variant c.526G>C (p.Asp176His) successfully treated with granulocyte and monocyte adsorption apheresis. Ther Apher Dial 23: 298-299, 2019.
31. Koike Y, Okubo M, Kiyohara T, Fukuchi R, Sato Y, Kuwatsuka S, Takeichi T, Akiyama M, Sugiura K and Utani A: Granulocyte and monocyte apheresis can control juvenile generalized pustular psoriasis with mutation of IL36RN. Br J Dermatol 177: 1732-1736, 2017.
32. Fujisawa T, Moriya C, Shibuya Y, Kanoh H and Seishima M: Combination therapy of infliximab and granulocyte/monocyte adsorption apheresis for refractory pustular psoriasis with psoriatic arthritis. Acta Derm Venereol 93: 364-365, 2013.
33. Tominaga C, Yamamoto M, Imai Y and Yamanishi K: A case of old age-onset generalized pustular psoriasis with a deficiency of IL-36RN (DITRA) treated by granulocyte and monocyte apheresis. Case Rep Dermatol 7: 29-35, 2015.
34. Fujisawa T, Murase K, Okumura Y, Kanoh H, Doi T, Yoshida S, Ogura S and Seishima M: Generalized pustular psoriasis successfully treated with granulocyte and monocyte adsorption apheresis. Ther Apher Dial 15: 374-378, 2011.
35. Fujisawa T, Suzuki S, Mizutani Y, Doi T, Yoshida S, Ogura S and Seishima M: Granulocyte and monocyte adsorption apheresis for generalized pustular psoriasis: Therapeutic outcomes in three refractory patients. Ther Apher Dial 19: 336-341, 2015.
36. Furusawa K, Hasegawa T and Ikeda S: Immunosuppressant and infliximab-resistant generalized pustular psoriasis successfully treated with granulocyte and monocyte adsorption apheresis. Ther Apher Dial 16: 379-380, 2012.
37. Mabuchi T, Manabe Y, Yamaoka H, Ota T, Kato M, Ikoma N, Kusakabe Y, Komaba H and Ozawa A: Case of generalized pustular psoriasis with end-stage renal disease successfully treated with granulocyte monocyte apheresis in combination with hemodialysis. J Dermatol 41: 521-524, 2014.
38. Seishima M, Mizutani Y, Shibuya Y, Nagasawa C and Aoki T: Efficacy of granulocyte and monocyte adsorption apheresis for pustular psoriasis. Ther Apher Dial 12: 13-18, 2008.

39. Sugiura K, Haruna K, Suga Y and Akiyama M: Generalized pustular psoriasis caused by deficiency of interleukin-36 receptor antagonist successfully treated with granulocyte and monocyte adsorption apheresis. J Eur Acad Dermatol Venereol 28: 1835-1836, 2014.
40. Maverakis E, Marzano AV, Le ST, Callen JP, Brüggen MC, Guenova E, Dissemond J, Shinkai K and Langan SM: Pyoderma gangrenosum. Nat Rev Dis Primers 6: 81, 2020.
41. Ahronowitz I, Harp J and Shinkai K: Etiology and management of pyoderma gangrenosum: A comprehensive review. Am J Clin Dermatol 13: 191-211, 2012.
42. Alavi A, French LE, Davis MD, Brassard A and Kirsner RS: Pyoderma Gangrenosum: An update on pathophysiology, diagnosis and treatment. Am J Clin Dermatol 18: 355-372, 2017.
43. Russo I, Miotto S, Colpo A, Marson P, Tison T, Ferrazzi A and Alaibac M: Successful treatment of pyoderma gangrenosum with granulocyte and monocyte adsorption apheresis. Int Wound J 14: 282-284, 2017.
44. Higashi Y, Ibusuki A, Baba N, Hatanaka M, Tada KI and Kanekura T: Granulocyte and monocyte adsorptive apheresis for pyoderma gangrenosum. Ther Apher Dial 26: 450-455, 2022.
45. Ikeda K, Hamada T, Otsuka M and Iwatsuki K: Beneficial effects of neutrophil-targeted therapy for pyoderma gangrenosum associated with ulcerative colitis. Eur J Dermatol 21: 804-805, 2011.
46. Ohmori T, Yamagiwa A, Nakamura I, Nishikawa K and Saniabadi AR: Treatment of pyoderma gangrenosum associated with Crohn's disease. Am J Gastroenterol 98: 2101-2102, 2003.
47. Ishikawa H, Kumano T, Suzuki Y, Mabe K, Suzuki T, Momma S and Momma T: A case of successful treatment with granulocytapheresis (GCAP) for pyoderma gangrenosum complicating ulcerative colitis. Jap J Clin Dermatol 58: 1099-1101, 2004.
48. Yoneda K, Chino Y, Kamei K, Yamada T, Nagura K and You M: Four Cases of pyoderma gangrenosum associated with ulcerative colitis. Jap J Clin Dermatol 59: 263-266, 2005.
49. Yanaru-Fujisawa R, Matsumoto T, Nakamura S, Kochi S, Iida M, Kohda F, Hirahashi M, Yao T and Mibu R: Granulocyte apheresis for pouchitis with arthritis and pyoderma gangrenosum after restorative proctocolectomy for ulcerative colitis: A case report. Inflamm Bowel Dis 11: 780-781, 2005.
50. Seishima M, Mizutani Y, Shibuya Y, Nagasawa C and Aoki T: Efficacy of granulocyte and monocyte adsorption apheresis for three cases of refractory pyoderma gangrenosum. Ther Apher Dial 11: 177-182, 2007.
51. Fujino Y, Suzuki Y, Kohama R, Omoya T, Kitazoe K, Nakamoto J, Aoki H, Yano M, Sikiji T and Satake N: A case of Pyoderma Gangrenosum successfully treated by granulocytapheresis and steroid therapy. Tokushima J Med 30: 29-32, 2008.
52. Kawakami T, Yamazaki M and Soma Y: Reduction of interleukin-6, interleukin-8, and anti-phosphatidylserine-prothrombin complex antibody by granulocyte and monocyte adsorption apheresis in a patient with pyoderma gangrenosum and ulcerative colitis. Am J Gastroenterol 104: 2363-2364, 2009.
53. Doi R, Haga T, Fujita A, Saito C, Takeuchi S, Matsuoka A, Kawakami T, Soma Y and Kouro T. Rinsho Derma 52: 585-587, 2010.
54. Kobayashi S, Takeshita T and Furue M: A case of Pyoderma Gangrenosum with Ulcerative Colitis successfully treated with Granulocytapheresis, Skin grafting and Steroid therapy. Nishi Nihon Hifuka 73: 474-477, 2011.
55. Ohno M, Koyama S, Ohara M, Shimamoto K, Kobayashi Y, Nakamura F, Mitsuru K and Andoh A: Pyoderma gangrenosum with ulcerative colitis successfully treated by the combination of granulocyte and monocyte adsorption apheresis and corticosteroids. Intern Med 55: 25-30, 2016.
56. Okada M, Okawa T, Takashima R and Higashiyama M: A case of successful treatment with granulocytapheresis for pyoderma gangrenosum complicating ulcerative colitis. Skin Research 16: 150-154, 2017.
57. Yamashita A, Nakayama C, Tashiro J and Miwa J: Ulcerative colitis accompanied by pyoderma gangrenosum successfully treated with granulocyte monocyte apheresis: A case report. Prog Dig Endosc 90: 130-131, 2017.
58. Tominaga K, Kamimura K, Sato H, Ko M, Kawata Y, Mizusawa T, Yokoyama J and Terai S: Cytapheresis for pyoderma gangrenosum associated with inflammatory bowel disease: A review of current status. World J Clin Cases 8: 2092-2101, 2020.
59. Shibuya T, Haga K, Saeki M, Haraikawa M, Tsuchihashi H, Okahara K, Nomura O, Fukushima H, Murakami T, Ishikawa D, *et al*: Pyoderma gangrenosum in an ulcerative colitis patient during treatment with vedolizumab responded favorably to adsorptive granulocyte and monocyte apheresis. J Clin Apher 35: 488-492, 2020.
60. Kanekura T, Kawahara K, Maruyama I and Kanzaki T: Treatment of pyoderma gangrenosum with granulocyte and monocyte adsorption apheresis. Ther Apher Dial 9: 292-296, 2005.
61. Kanekura T, Maruyama I and Kanzaki T: Granulocyte and monocyte adsorption apheresis for pyoderma gangrenosum. J Am Acad Dermatol 47: 320-321, 2002.
62. Kawai M, Kawanami C, Fukuda A and Seno H: Pyoderma gangrenosum with primary sclerosing cholangitis-associated colitis successfully treated with concomitant granulocyte and monocyte adsorption apheresis with corticosteroids. Clin J Gastroenterol 14: 1561-1566, 2021.
63. Murakami M and Terui T: Palmoplantar pustulosis: Current understanding of disease definition and pathomechanism. J Dermatol Sci 98: 13-19, 2020.
64. Mrowietz U, Bachelez H, Burden AD, Rissler M, Sieder C, Orsenigo R and Chaouche-Teyara K: Secukinumab for moderate-to-severe palmoplantar pustular psoriasis: Results of the 2PRECISE study. J Am Acad Dermatol 80: 1344-1352, 2019.
65. Fujisawa T, Tawada C, Mizutani Y, Doi T, Yoshida S, Ogura S and Seishima M: Efficacy of granulocyte and monocyte adsorption apheresis for treatment of palmoplantar pustulosis. Ther Apher Dial 18: 238-243, 2014.
66. Kawakami H, Nagaoka Y, Hirano H, Matsumoto Y, Abe N, Tsuboi R, Kanno Y and Okubo Y: Evaluation of the efficacy of granulocyte and monocyte adsorption apheresis on skin manifestation and joint symptoms of patients with pustulotic arthro-osteitis. J Dermatol 46: 144-148, 2019.
67. Kanekura T, Kawabata H, Maruyama I and Kanzaki T: Treatment of psoriatic arthritis with granulocyte and monocyte adsorption apheresis. J Am Acad Dermatol 50: 242-246, 2004.
68. Bulur I and Onder M: Behçet disease: New aspects. Clin Dermatol 35: 421.434, 2017.
69. Tong B, Liu X, Xiao J and Su G: Immunopathogenesis of Behcet's Disease. Front Immunol 10: 665, 2019.
70. Alpsoy E, Zouboulis CC and Ehrlich GE: Mucocutaneous lesions of Behcet's disease. Yonsei Med J 48: 573-585, 2007.
71. Higashi Y, Shimokawa M, Kawai K and Kanekura T: Granulocyte and monocyte adsorption apheresis for Behçet's disease in a pregnant woman. J Dermatol 40: 1042-1044, 2013.
72. Kanekura T, Gushi A, Iwata M, Fukumaru S, Sakamoto R, Kawahara K, Maruyama I and Kanzaki T: Treatment of Behçet's disease with granulocyte and monocyte adsorption apheresis. J Am Acad Dermatol 51 (2 Suppl): S83-S87, 2004.
73. Villarreal-Villarreal CD, Ocampo-Candiani J and Villarreal-Martínez A: Sweet Syndrome: A review and update. Actas Dermosifiliogr 107: 369-378, 2016 (In English, Spanish).
74. Cohen PR: Sweet's syndrome-a comprehensive review of an acute febrile neutrophilic dermatosis. Orphanet J Rare Dis 2: 34, 2007.
75. Fujii A, Mizutani Y, Hattori Y, Takahashi T, Ohnishi H, Yoshida S and Seishima M: Sweet's syndrome successfully treated with granulocyte and monocyte adsorption apheresis. Case Rep Dermatol 9: 13-18, 2017.
76. Gerfaud-Valentin M, Jamilloux Y, Iwaz J and Sève P: Adult-onset Still's disease. Autoimmun Rev 13: 708-722, 2014.
77. Giacomelli R, Ruscitti P and Shoenfeld Y: A comprehensive review on adult onset Still's disease. J Autoimmun 93: 24-26, 2018.
78. Kanekura T, Terasaki K, Higashi Y, Yoshii N, Kawahara K, Maruyama I and Kanzaki T: Improvement of adult Still's disease with granulocyte and monocyte adsorption apheresis. Clin Exp Dermatol 29: 410-412, 2004.
79. Iwasaki A, Kawakami H and Okubo Y: Granulocyte/Monocyte adsorption apheresis as a novel therapeutic approach in the treatment of an impetigo herpetiformis case. Ther Apher Dial 22: 414-416, 2018.
80. Namazi N and Dadkhahfar S: Impetigo herpetiformis: Review of pathogenesis, complication, and treatment. Dermatol Res Pract 2018: 5801280, 2018.
81. Fujii K, Takahashi T, Matsuyama K, Fujii A, Mizutani Y, Ohnishi H and Seishima M: Impetigo herpetiformis with a CARD14 Thr79Ile variant successfully treated with granulocyte and monocyte adsorption apheresis. J Dermatol 47: e84-e85, 2020.
82. Saito-Sasaki N, Izu K, Sawada Y, Hino R, Nakano R, Shimajiri S, Nishimura I, Nakamura H, Sugiura K and Nakamura M: Impetigo herpetiformis complicated with intrauterine growth restriction treated successfully with granulocyte and monocyte apheresis. Acta Derm Venereol 97: 410-411, 2017.
83. Selmi C and Gershwin ME: Diagnosis and classification of reactive arthritis. Autoimmun Rev 13: 546-549, 2014.

84. Wu IB and Schwartz RA: Reiter's syndrome: the classic triad and more. J Am Acad Dermatol 59: 113-121, 2008.
85. Yoshifuku A, Oyama K, Ibusuki A, Kawasaki M, Sakanoue M, Matsushita S, Kawai K, Kawahara K, Maruyama I and Kanekura T: Granulocyte and monocyte adsorption apheresis as an effective treatment for Reiter disease. Clin Exp Dermatol 37: 241-244, 2012.
86. Braun-Falco M, Kovnerystyy O, Lohse P and Ruzicka T: Pyoderma gangrenosum, acne, and suppurative hidradenitis (PASH)-a new autoinflammatory syndrome distinct from PAPA syndrome. J Am Acad Dermatol 66: 409-415, 2012.
87. Cugno M, Borghi A and Marzano AV: PAPA, PASH and PAPASH Syndromes: Pathophysiology, presentation and treatment. Am J Clin Dermatol 18: 555-562, 2017.
88. Hatanaka M, Fujii K and Kanekura T: Successful treatment of pyoderma gangrenosum, acne, and suppurative hidradenitis syndrome with granulocyte and monocyte adsorption apheresis. J Dermatol 48: 376-377, 2021.
89. Mizutani Y, Okano T, Takahashi T, Ohnishi H, Ohara O, Sano A and Seishima M: Pyoderma gangrenosum, acne and suppurative hidradenitis syndrome treated with granulocyte and monocyte adsorption apheresis. Acta Derm Venereol 97: 275-276, 2017.
90. Tosca N and Stratigos JD: Possible pathogenetic mechanisms in allergic cutaneous vasculitis. Int J Dermatol 27: 291-296, 1988.
91. Chen KR and Carlson JA: Clinical approach to cutaneous vasculitis. Am J Clin Dermatol 9: 71-92, 2008.
92. Goeser MR, Laniosz V and Wetter DA: A practical approach to the diagnosis, evaluation, and management of cutaneous small-vessel vasculitis. Am J Clin Dermatol 15: 299-306, 2014.
93. Kanekura T, Yoshii N, Kawahara K, Maruyama I and Kanzaki T: Granulocyte and monocyte adsorption apheresis for cutaneous allergic vasculitis. Ther Apher Dial 10: 287-290, 2006.
94. Kiriakidou M and Ching CL: Systemic lupus erythematosus. Ann Intern Med 172: ITC81-ITC96, 2020.
95. Fortuna G and Brennan MT: Systemic lupus erythematosus: Epidemiology, pathophysiology, manifestations, and management. Dent Clin North Am 57: 631-655, 2013.
96. Kanekura T, Hashiguchi T, Mera Y, Katahira A, Nakamura I, Maruyama I and Kanzaki T: Improvement of SLE skin rash with granulocyte and monocyte adsorption apheresis. Dermatology 208: 79-80, 2004.