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## Adsorptive granulocyte and monocyte apheresis: A potentially relevant therapeutic option for COVID-19

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### ARTICLE INFO

#### Article history:

Received 16 June 2020

Received in revised form 15 July 2020

Accepted 21 July 2020

#### Keywords:

SARS-CoV-2

COVID-19

Adsorptive granulocyte and monocyte apheresis

### ABSTRACT

The overproduction of proinflammatory cytokines and subsequent thromboembolism are major problems of coronavirus disease 2019 (COVID-19). Adsorptive granulocyte and monocyte apheresis (GMA), used for ulcerative colitis, is an extracorporeal therapy designed to remove activated myeloid lineage cells. Previous studies have demonstrated that GMA decreases proinflammatory cytokines and neutrophil–platelet aggregates. The effect of GMA on COVID-19 in a patient with ulcerative colitis was recently reported. The modes of action of GMA together with the findings of this case report indicate that GMA could be a relevant treatment option for COVID-19.

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Coronavirus disease 2019 (COVID-19), caused by infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has become a pandemic throughout the globe over a short period of time. As of July 13, COVID-19 had been diagnosed in over 12 910 000 people and there had been 569 128 associated deaths worldwide.

The lung is the primary site of infection by SARS-CoV-2 (Zhou et al., 2020). Pulmonary symptoms range from mild flu-like symptoms to respiratory failure and acute respiratory distress syndrome (ARDS). Severe ARDS is induced by a condition described as a cytokine storm, an overproduction of proinflammatory cytokines such as interleukin (IL)-1 $\beta$ , IL-6, and tumor necrosis factor alpha (TNF- $\alpha$ ), which leads to uncontrolled vasodilation, vascular hyperpermeability, and activation of neutrophils, platelets, and coagulation pathways (Jose and Manuel, 2020). Activated neutrophils induce platelet micro-clots in combination with thrombin (Piccardoni et al., 2001). Thrombin generation is elevated during a cytokine storm, but is negatively regulated by anti-coagulants such as antithrombin III, tissue factor pathway inhibitor, and protein C, which are impaired during a cytokine storm, and further aggravate the procoagulant condition (Jose et al., 2020). Therefore, the cytokine storm and a coagulation–anticoagulation imbalance promote the formation of microthrombi, disseminated intravascular coagulation, multi-organ failure, and fatality in COVID-19 patients.

Adsorptive granulocyte and monocyte apheresis (GMA) with the Adacolumn is an established extracorporeal circulation therapy designed for selective depletion of elevated and activated myeloid lineage cells. The Adacolumn used for GMA is filled with cellulose acetate beads, which serve as the adsorptive leukocytapheresis carriers (Saniabadi et al., 2003). GMA has shown efficacy in patients with ulcerative colitis, Crohn's disease, pustular psoriasis, and psoriatic arthritis (Saniabadi et al., 2003; Ikeda et al., 2013; Kanekura et al., 2017). GMA has been shown to have diverse immunomodulatory effects. The primary action of GMA is adsorptive depletion of elevated and activated myeloid lineage cells, but this is followed by favorable immune responses, including down-modulation of the inflammatory cytokine profile, generation of the anti-inflammatory cytokine IL-10, and changes in leukocyte surface molecules (Saniabadi et al., 2003; Kanekura, 2018). Since activated myeloid lineage cells are a major source of inflammatory cytokines, a marked decrease in IL-1 $\beta$ , IL-6, and TNF- $\alpha$  has been reported in patients with inflammatory bowel diseases (Kashiwagi et al., 2002).

Activated myeloid lineage leukocytes express a cell surface adhesive molecule, Mac-1 (integrin  $\alpha$ M $\beta$ 2). The carrier cellulose acetate beads activate and adsorb complement component iC3b, which is a ligand for Mac-1 on the proinflammatory leukocytes. Thus, the cellulose acetate beads selectively deplete Mac-1-expressing cells by binding of Mac-1 with iC3b (Kanekura et al., 2006). Additionally, Mac-1 contributes to the formation of neutrophil–platelet aggregates, termed platelet satellitism, which are seen in inflammation or infection, thus contributing to the thromboembolism complications discussed above. Further,

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platelet satellitism is mediated by binding of neutrophil Mac-1 to GPIIb/IIIa (integrin  $\alpha$ IIb/ $\beta$ 3) on platelets (Piccardoni et al., 2001). In line with these assertions, the frequency of platelet satellitism is significantly decreased by GMA, which removes Mac-1-expressing neutrophils. In healthy individuals, 20–25% of peripheral neutrophils are involved in platelet satellitism, whereas the mean frequency in eight patients with neutrophilic skin lesions was found to be 41%, which decreased to 22% after GMA treatment (authors' unpublished data). Therefore, based on the known action of GMA, it is believed that this is a relevant treatment option for patients with COVID-19.

In June 2020, the effect of Adacolumn on an ulcerative colitis patient who was infected with SARS-CoV-2 was reported (Roldán et al., 2020). A 36-year-old Spanish man with ulcerative colitis had fever and a cough in March 2020. His virus test was positive for SARS-CoV-2 and a chest X-ray showed bilateral sub-pleural infiltration. Diagnoses of COVID-19 and associated pneumonia were made. Laboratory values were as follows: white blood cell (WBC) count  $16 \times 10^9/l$ , lymphocyte count  $1.1 \times 10^9/l$  (6.9% of WBC), C-reactive protein (CRP) 18.8 mg/dl, and  $pO_2$  68 mmHg. He received five treatment sessions of GMA over five consecutive days with the aim of controlling his ulcerative colitis. Unexpectedly, his pulmonary symptoms and systemic inflammation improved, together with his ulcerative colitis. Symptoms of pneumonia, fever, and cough subsided and his WBC count returned to  $4.9 \times 10^9/l$ , lymphocyte count to  $2.1 \times 10^9/l$  (42.9% of WBC), and CRP to 3.4 mg/dl.

To our knowledge, GMA has a good safety profile; serious adverse effects are rarely reported. Its modes of action together with the findings of this case report support our notion that GMA is a relevant therapeutic option for patients with COVID-19 and warrants an immediate clinical trial to evaluate its full therapeutic efficacy in a large cohort of COVID-19 patients.

#### Funding source

None.

#### Ethical approval

Ethical approval was not required.

#### Conflict of interest

No conflict of interest to declare.

#### References

- Ikeda S, Takahashi H, Suga Y, 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* 2013;68(4):609–17.
- Jose RJ, Manuel A. COVID-19 cytokine storm: the interplay between inflammation and coagulation. *Lancet Respir Med* 2020;8(6):e46–7.
- Kanekura T, Hiraishi K, Kawahara K, et al. 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* 2006;10(3):247–56.
- Kanekura T, Seishima M, Honma M, et al. Therapeutic depletion of myeloid lineage leukocytes by adsorptive apheresis for psoriatic arthritis: efficacy of a non-drug intervention for patients refractory to pharmacologics. *J Dermatol* 2017;44(12):1353–9.
- Kanekura T. Clinical and Immunological effects of adsorptive myeloid lineage leukocyte apheresis in patients with immune disorders. *J Dermatol* 2018;45:943–50.
- Kashiwagi N, Sugimura K, Koiwai H, et al. Immunomodulatory effects of granulocyte and monocyte adsorption apheresis as a treatment for patients with ulcerative colitis. *Dig Dis Sci* 2002;47(6):1334–41.
- Piccardoni P, Sideri R, Manarini S, et al. Platelet/polymorphonuclear leukocyte adhesion: a new role for SRC Kinases in Mac-1 adhesive function triggered by P-selectin. *Blood* 2001;98(1):108–16.
- Roldán FP, Martín MEB, Carro PG. The effect of Adacolumn® on ulcerative colitis with COVID-19. *Rev Esp Enferm Dig* 2020;112(6):511.
- Saniabadi RA, Hanai H, Takeuchi K, et al. Adacolumn, an adsorptive carrier based granulocyte and monocyte apheresis device for the treatment of inflammatory and refractory diseases associated with leukocytes. *Ther Apher Dial* 2003;7(1):48–59.
- Zhou F, Yu T, Du R, et al. Clinical Course and Risk Factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020;395(10229):1054–62.