

# G-CSF and GM-CSF Are Different. Which One Is Better for COVID-19?

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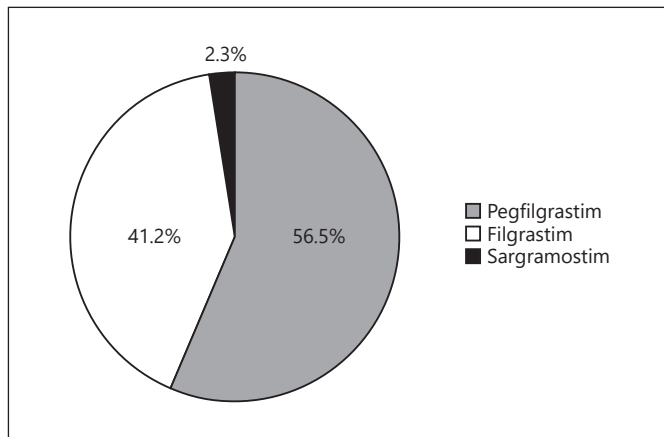
Development of molecularly cloned myeloid hematopoietic growth factors (e.g., granulocyte colony-stimulating factor [G-CSF] and granulocyte-macrophage colony-stimulating factor [GM-CSF]) more than 30 years ago increased safety and efficacy of intensive chemotherapy and radiation therapy by reversing damage to bone marrow function, thereby decreasing infections and bleeding and shortening hospitalizations. These drugs were also used to mobilize bone marrow hematopoietic progenitor cells into the blood facilitating their use as a graft for hematopoietic cell transplants. Other proposed uses included increasing efficacy of anti-leukemia chemotherapy and treating persons exposed to high doses of acute whole-body ionizing radiation [1, 2]. Safety and efficacy of G- and GM-CSFs, typically given intravenously or subcutaneously, are well-known. Practice guidelines and consensus statements on their use are available from many medical societies and organizations including the American Society of Clinical Oncology (ASCO), the European Society of Medical Oncology (ESMO), the American Society of Hematology (ASH), and the National Comprehensive Cancer Network (NCCN).

G-CSF (e.g., filgrastim and pegfilgrastim, and their biosimilars) and GM-CSF (e.g., sargramostim) are the two most common types of hematopoietic growth factors. These drugs (proteins) are sometimes thought as being interchangeable. This is wrong. Structure, receptors, receptor distribution, and biologic effects of these pro-

teins differ substantially. Filgrastim is a 19-kDa protein produced in *E. coli* which is not glycosylated. In contrast, sargramostim, a mixture of three GM-CSFs with molecular weights of 19.5, 16.8, and 15.5 kDa, is a glycosylated protein produced in *S. cerevisiae*. Glycosylation adds stability and degradation resistance [3]. Receptors for filgrastim and sargramostim belong to the cytokine receptor super-family. The G-CSF receptor (G-CSFR; CD114) is a homo-oligo-dimer, whereas the GM-CSF receptor (GM-CSFR; CD116) is a hetero-oligo-dimer sharing a  $\beta$ -chain with the IL-3 and IL-5 receptors. The G-CSFR is expressed primarily on neutrophils and bone marrow precursor cells. The GM-CSFR, more widely expressed than the G-CSFR, is present on neutrophils, monocytes, eosinophils, dendritic cells, basophils, and, possibly, B-cells, whereas the G-CSFR is expressed only on neutrophils and monocytes [4]. Differences in receptor expression account for most of the biologic differences between filgrastim and sargramostim. Importantly, G-CSF is the dominant colony-stimulating factor (CSF) released from lung cells in response to pro-inflammatory cytokines [5].

G-CSF is the most widely used molecularly cloned hematopoietic growth factor (shown in Fig. 1). GM-CSF has a broader range of biologic activities than G-CSF as well

Dedicated to Academician Andrei Vorobiev of the Russian Federation, the 2nd human to receive GM-CSF, who died recently.



**Fig. 1.** 2019 US market share distribution of hematopoietic growth factors. Data include pegfilgrastim (Neulasta<sup>®</sup>, FulphilaTM, Udenyca<sup>®</sup>), filgrastim (Neupogen<sup>®</sup>, Zarxio<sup>®</sup>, Granix<sup>®</sup>, Nivestym<sup>®</sup>), and sargramostim (Leukine<sup>®</sup>). Source: IQVIA National Sales Perspectives<sup>®</sup>, June 5, 2020.

as anti-bacterial, anti-fungal, and anti-viral properties via complex signaling [6]. GM-CSF has been used as an adjuvant for diverse anti-cancer therapies including immune therapy and anti-cancer vaccines [7–9]. Other uses of GM-CSF include therapy of post-transplant graft failure [10], reversal of immune paralysis (i.e., persistence of a marked compensatory anti-inflammatory innate immune response following an insult such as sepsis or trauma) [11–15], and treatment of lung diseases such as autoimmune pulmonary alveolar proteinosis, acute respiratory distress syndrome (ARDS), and pneumonia [11, 16].

In an uncontrolled clinical trial, Herold and colleagues [11] gave aerosolized GM-CSF (sargramostim), 125 µg for 2 doses 48 h apart to 6 subjects with moderate-to-severe community-acquired pneumonia or ventilator-associated ARDS. They reported improved oxygenation in subjects receiving GM-CSF compared with controls with a mean increase of about 40% in lung compliance [11]. GM-CSF promoted an M1 phenotype of alveolar macrophages and increased activation of alveolar mononuclear phagocytes without increasing neutrophils in the alveolar compartment. Similarly, safety of aerosolized sargramostim was reported in autoimmune pulmonary alveolar proteinosis [16]. A phase-2 Belgian, multi-center SARPAC study used aerosolized sargramostim in persons with COVID-19-related ARDS (EudraCT 2020-001254-22, NCT04326920) [17]. Preliminary data are most encouraging (unpublished observations).

Hematologists and oncologists are more familiar with G-CSF than GM-CSF, and as shown in Figure 1, G-CSF

accounts for >95% of the use of molecularly cloned myeloid hematopoietic growth factors. Consequently, many physicians may be more likely to use G-CSF than GM-CSF in persons with COVID-19-related ARDS. This may be a mistake based on the data we cite regarding G-CSF-induced influx of granulocytes in the lung, an effect not seen with GM-CSF. However, there are no comparative clinical data in this setting (see below).

Whether aerosolized molecularly cloned hematopoietic growth factors are safe and effective in COVID-19-related ARDS and in other SARS-CoV-2-infected persons is controversial and unknown. Several reports suggest not giving molecularly cloned hematopoietic growth factors to persons undergoing conventional chemotherapy and hematopoietic cell transplantation during the SARS-CoV-2 pandemic because of concerns of increasing lung inflammation or the hypothetical risk of increasing inflammatory cytokines such as interleukin-6 (IL-6) associated with an adverse outcome [18, 19]. However, these recommendations are not evidenced-based and there are no published data reporting such events in humans.

Several studies report systemic G-CSF can exacerbate lung injury in the setting of pulmonary infection. For example, Jing and colleagues [20] reported G-CSF increases lung injury in a mouse model of acute renal injury. Wang et al. [21, 22] reported blocking the G-CSF receptor in mouse models of infection and asthma reduced neutrophil infiltration and neutrophil-mediated inflammation. Tsantikos and associates [23] reported G-CSF was important in the pathogenesis of chronic obstructive pulmonary disease in some persons. Arimura and co-workers [24] described severe acute lung injury in a healthy hematopoietic cell transplant donor given G-CSF. Boujoukos and colleagues [25] reported that during the initial inflammatory response to endotoxin in humans, the alveolar space is relatively insulated from cytokine-induced effects of endotoxin including tumor necrosis factor, IL-6, and IL-8 but not G-CSF. Takatsuka et al. [26] reported five people developed ARDS whilst receiving G-CSF with chemotherapy or a hematopoietic cell transplant. These data suggest that giving G-CSF can worsen lung function by causing neutrophil infiltration. This effect is especially so in settings of inflammation such as infection and cytokine release syndrome. Because cytokine release syndrome is a feature of COVID-19-related ARDS, caution is needed.

These same adverse effects on lung function are not reported in mouse models or humans receiving sargramostim in similar settings. The favorable preliminary

data from the SARPAC study using aerosolized sargramostim are encouraging [17]. Several studies suggest G-CSF is likely to exacerbate lung injury in the setting of infection. Consequently, persons receiving intensive chemotherapy during the SARS-CoV-2 pandemic, especially those with COVID-19, may not be receiving G-CSF. Giving GM-CSF may be associated with less lung injury risk. Three clinical trials of GM-CSF in persons with COVID-19-related ARDS are in progress (SARPAC [EudraCT 2020-001254-22; NCT04326920], iLeukPulm [NCT04411680], and NCT04400929).

In summary, although G-CSF and GM-CSF are molecularly cloned myeloid growth factors, their biology and clinical effects differ. GM-CSF has a much wider activity spectrum in animals and humans. In persons with lung infection and/or ARDS, GM-CSF may be a safer drug than G-CSF. Whether this is so can only be definitively answered in a randomized comparison trial. Unfortunately, this is unlikely to be done and we may have to rely on indirect evidence of safety and efficacy.

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