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G-CSF's use in COVID-19 treatment and the role of hematopoietic growth factors in its pathophysiology: a systematic review

Usos do G-CSF no tratamento da COVID-19 e o papel de fatores de crescimento hematopoiético na fisiopatologia da doença: uma revisão sistemática

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ABSTRACT

Introduction: Hematopoiesis is controlled by specific growth factors, and its isolation leads to a new type of therapeutic agents such as the granulocyte colony-stimulating factor, that acts on neutrophils. **Aims:** In light of the importance of this drug and the COVID-19 pandemic, this review aims to discuss the possible benefits and risks of granulocyte colony-stimulating factor use on COVID-19 treatment, in addition to the role of hematopoietic growth factor on the disease pathophysiology. **Method:** A systematic review was conducted using the United States National Library of Medicine (PubMed), Scientific Electronic Library Online (SciELO) and Centro Latino-Americano e do Caribe de Informação em Ciências da Saúde (BIREME) as databases, utilizing the keywords COVID-19 and granulocyte colony-stimulating factor. **Results:** From Biblioteca Virtual em Saúde ten papers were selected. No study was retrieved from SciELO. From the PubMed database, only one paper fit the inclusion criteria. **Conclusion:** After literature review and analysis, it was not possible to verify the efficacy of granulocyte colony-stimulating factor on COVID-19 treatment, even though it seems to be safe and have few side effects.
Keywords: Filgrastim, COVID-19, Granulocyte colony-stimulating factor, SARS-CoV-2.

RESUMO

Introdução: A hematopoese é controlada por determinados fatores, e o isolamento destes leva a uma nova classe de agentes terapêuticos como o fator estimulador de colônias de granulócitos, que age nos neutrófilos. **Objetivo:** Tendo em vista a importância deste medicamento e da pandemia da COVID-19 atualmente, essa revisão tem como objetivo discutir os possíveis benefícios e riscos do uso do fator estimulador de colônias de granulócitos no tratamento da COVID-19, assim como o papel de fatores de crescimento hematopoiético na fisiopatologia da doença. **Método:** Foi feita uma revisão sistemática usando como base de dados o PubMed, SciELO e Biblioteca Regional de Medicina, utilizando as palavras-chave: COVID-19 e Granulocyte Colony-stimulating Factor. **Resultados:** Na ferramenta Biblioteca Virtual em Saúde, foram selecionados dez artigos. Não foi recuperado nenhum estudo da ferramenta SciELO. Na pesquisa pela base de dados PubMed, um artigo se encaixou nos critérios de inclusão. **Conclusão:** Após análise da literatura, não foi possível comprovar a eficácia do uso de fator estimulador de colônias de granulócitos no tratamento da COVID-19, apesar de, ao que tudo indica, seu uso ser seguro e com poucos efeitos colaterais.
Palavras-chave: Filgrastim, COVID-19, Fator estimulador de colônias de granulócitos, SARS-CoV-2.

INTRODUCTION

Hematopoiesis is controlled by certain growth factors, and their definition leads to a new type of therapeutic agents[(1)]. The granulocyte colony-stimulating factor (G-CSF) is one of them, which acts on neutrophils, one of the most important body defenses against infection[(1)]. It was approved for cancer patients undergoing chemotherapy in the United States in 1991, and ever since, its use has been expanded for different medical uses[(1)].

G-CSF is a cytokine that acts on the bone marrow, promoting the release of mature neutrophils to peripherical blood, leading to the proliferation of these cells and reducing the granulocyte predecessors' growth time, aside from acting with other hematopoietic factors

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like erythropoietin and stem cell factor (SCF)[2,3]. Furthermore, it increases neutrophil function by improving phagocytic and chemotactic capacity, and it is specific to the cell lineage, exercising a big role in granulopoiesis[2].

G-CSF's clinical use is mainly associated with neutropenic patients. Currently, the growth factors made by the pharmaceutical industry are Filgrastim and Lenograstim, which attach to myeloid predecessors' receptors, raising the production and differentiation of neutrophilic lineages and activating mature neutrophil's phagocytic and cytotoxic functions[4]. These kinds of drugs have already been used to decrease neutropenic-associated infections that could have been caused by chemotherapy, radiotherapy, and myeloid cells suppressor drugs, which are responsible for the high morbidity and mortality of those infections[4]. Moreover, other G-CSF functions include increase of the immune system in patients with HIV, pneumonia, diabetes-caused infections, leukemia, and febrile neutropenia[4].

GM-CSF (granulocyte and macrophage colony stimulating factor) is another type of hematopoietic growth factor that, even though it has different types of receptors in the human body, is also used as an adjuvant for oncological therapies such as immunotherapy, post-transplant graft failure therapy, and treating pulmonary diseases such as acute respiratory distress syndrome (ARDS) and pneumonia[5].

Recently, during the coronavirus disease 2019 (COVID-19) pandemic, numerous hypotheses were studied about the use of G-CSF in patients infected by SARS-CoV-2. On the one hand, some papers described a possible relationship between febrile neutropenia prevention and treatment in oncological patients with worse COVID-19 outcomes, approaching G-CSF use as a determining factor for the neutrophil increase and posterior and subsequent respiratory worsening[6]. Other studies grant the worse outcome of the disease because of an exaggerated inflammatory reaction that involves a higher release of IL-6 and TNF, leading to a cytokine storm that would contribute to multi-system failure[7]. Nevertheless, other papers propose that G-CSF's use would counteract lymphocytopenia, a worse COVID-19 prognosis factor, and could improve outcomes[6].

These applications are extremely important; since the beginning of the pandemic, over 18 million cases of COVID-19 have been confirmed in Brazil, and over 500000 deaths have been reported according to the World Health Organization[8]. The search for new safe therapies is still necessary as long as the pandemic continues to affect a large part of the population and the country seeks vaccination as a way to decrease the virus' circulation[9].

OBJECTIVE

In light of the importance of this drug and COVID-19 pandemic, this review aimed to discuss the possible benefits and risks of G-CSF's use in COVID-19 treatment, in addition to the role of hematopoietic growth factors in the disease's pathophysiology.

METHODS

An active search was made in the literature, on June 2021, in three different databases (Figure 1). The inclusion criteria were as follows: books, documents, clinical trials, case reports, and randomized clinical trials fully published in Portuguese and English that approached G-CSF's use in COVID-19 treatment and had open access. The exclusion criteria included narrative reviews, systematic reviews, letters to the editor, and meta-analysis. The following DeCS/MeSH descriptors were used: COVID-19 e Granulocyte Colony-stimulating Factor.

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist recommended for systematic reviews was used[10].

RESULTS

There were 42 studies on Biblioteca Virtual em Saúde (BVS). After reading the titles of the papers, there were 18 studies left, of which 10 were selected after reading the abstracts. None were retrieved from the SciELO database. Throughout the search in PubMed, 96 papers were obtained, of which 11 were chosen after title reading and 1 fit the inclusion criteria (Table 1).

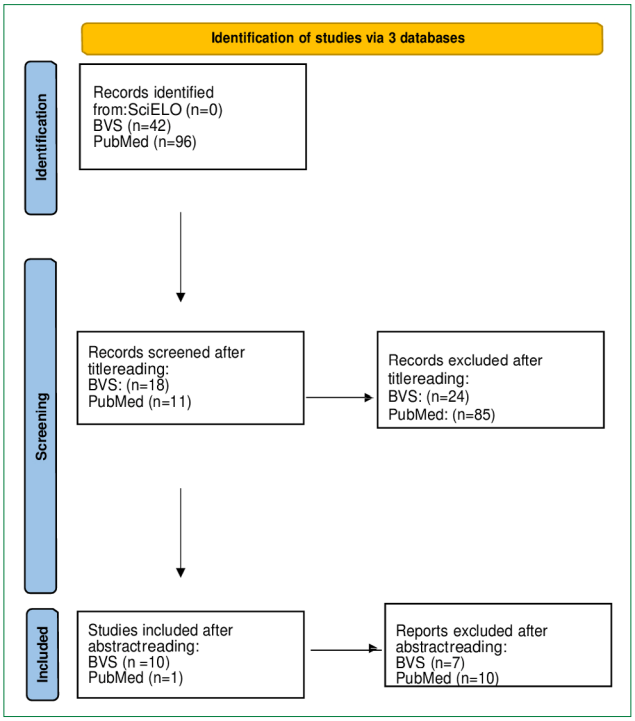

Figure 1 – Flow diagram of methodology[9].

Table 1 – Results.

Author	Study design	Sample	Results
Cheng et al.[11]	Randomized controlled trial	200 patients with pneumonia without comorbidities, 100 treated with standard care for COVID-19, 100 with standard care, and 3 doses of rhG-CSF	Statistically, time for clinical improvement was not different between the two groups. The percentage of patients that developed critical conditions was lower in the group that used rhG-CSF. On day 5, the median lymphocyte count was significantly higher in the group that used rhG-CSF. Respiratory failure, ARDS, sepsis, and septic shock were more common in the group that used standard care.
Devi et al.[12]	Case report	76-year-old male with systemic arterial hypertension and diabetes mellitus	On the 32nd day of COVID-19, the patient developed fever (38.6°C) and worsening of the leucopenia and neutropenia (absolute neutrophil count 0.33×10^9/L). Antibiotic therapy was used with piperacillin and tazobactam for 5 days and 300 µg filsgrastim for 2 days. There was improvement in the neutrophil levels with G-CSF and fever dropped after 2 days.
Lutfi et al.[13]	Case report	39-year-old male with heart failure with reduced ejection fraction, hypertension, type 2 diabetes mellitus, gout, morbid obesity, and stage 3 chronic kidney disease	On the 23rd day of hospital stay, the patient developed worsening of neutropenia and thrombocytosis, with an absolute neutrophil count reaching 0 and platelets reaching 478000/mcL. 480 mcg TBO-filgrastim was used for 5 days, with rapid neutrophil reconstitution, with an absolute neutrophil count reaching 5300 mcL on the 28th day.
Zhang et al[14]	Cohort	304 hospitalized patients with COVID-19, 16 of which used G-CSF	G-CSF use led to a higher number of hospital admissions (95% confidence interval, p-value [CI]: 0.017). In hospitalized patients, G-CSF's use was associated with an increase of the need for high levels of oxygen and death (95%CI, p-value: 0.024). That was seen in patients with a high response for G-CSF with regard to the increase of the absolute neutrophil count after medication use (95%CI, p-value: 0.004).
Meizlish et al[15]	Cohort	49 COVID-19 hospitalized patients, 40 in the ICU, and 9 in the ward	ICU patients had higher levels of activation neutrophil markers than patients in the ward on the first day of hospital stay. The levels were also higher on the first day in the ward patients than after they were transferred to the ICU.
Chi et al.[16]	Cross-sectional study	70 patients infected by COVID-19 and 4 convalescent cases	Levels of IL-7, IL-10, and IP-10 were significantly higher in asymptomatic patients than in the control group. Levels of IL-1β, IL-1ra, IL-2, IL-2Rα, IL-6, IL-7, IL-8, IL-9, IL-10, IL-13, IL-15, IL-17, IL-18, G-CSF, M-CSF, IFN-α2, IFN-γ, TNF-α, TRAIL, basic FGF, HGF, PDGF-BB, VEGF, GRO-α, IP-10, MCP-1, and MIG were higher in symptomatic patients. Compared to milder cases, severe cases had higher levels of IL-6, IL-7, IL-10, G-CSF, M-CSF, IP-10, MCP-1, MCP-3, MIG, and MIP-1α.

Continue...

Table 1 – Continuation.

Author	Study design	Sample	Results
Burgos-Blasco et al.[17]	Cross-sectional study	Teardrop samples of 41 healthy patients and 62 COVID-19 infected patients	An increase of IL-9, Il-15, G-CSF, GM-CSF, IFN-γ, PDGF, and VEGF levels was found, and an eotaxin reduction in the tears of COVID-19 patients. IL-1RA and GM-CSF had lower levels in patients that were more severe and in those who needed treatment targeted to the immune system (p<0.05).
De Luca et al.[19]	Prospective cohort	13 patients that did not need mechanical ventilation that received mavrilimumab and 26 patients in the control group that received standard care	No patients in the mavrilimumab group died, while 7 (27%) patients in the controlled group died (p=0.086). On the 28th day, all patients in the mavrilimumab group and 17 (65%) in the control group showed clinical improvement (p=0.03).
Cremer et al.[18]	Randomized controlled trial	40 COVID-19 hospitalized patients in 7 hospitals on the United States	Mavrilimumab's use did not lead to a statistically significant increase in the percentage of patients free of the use of supplementary oxygen on the 14th day of hospital stay among those with pneumonia due to severe COVID-19, hypoxemia and systemic hyperinflammation. On the 28th day of hospital stay, patients that got mavrilimumab were also numerically more likely to be alive and without respiratory failure.
Temesgen et al.[20]	Cohort	12 hospitalized patients with pneumonia due to COVID-19 and unfavorable outcomes risk factors treated with lenzilumab and 27 patients in the same conditions that were not treated with lenzilumab	Patients treated with lenzilumab got fewer days for clinical improvement and hospital discharge and bigger temperature reduction than the control group (p<0.05). Increase of the absolute lymphocyte count was higher of the group treated with lenzilumab (p<0.05). Patients treated with monoclonal antibody also had significant drop in the PCR compared to the basal number.
Zhao et al.[21]	Cohort	9 severe COVID-19 patients and 5 patients with bacterial pneumonia	TCD4 and TCD8 cells went through clonal expansion and activation on the bronchoalveolar lavage fluid in both groups. An increase in GM-CSF levels was seen on peripheral blood of COVID-19 patients.

rhG-CSF: recombinant human granulocyte colony stimulating factor; ARDS: acute respiratory distress syndrome; G-CSF: granulocyte colony-stimulating factor; TBO-filgrastim: name of a drug; ICU: intensive care unit; IL: interleukin; IP: inducible protein; M-CSF: macrophage colony stimulating factor; IFN: interferon; TNF: tumor necrosis factor; TRAIL: TNF-related apoptosis inducing ligand; FGF: basic fibroblast growth fator; HGF: hepatocyte growth factor; PDGF-BB: platelet-derived growth fator; VEGF: vascular endothelial growth factor; GRO: growth related oncogene; MCP: monocyte chemoattractant protein; MIG: monokine induced by interferon-γ; MIP: macrophage-inflammatory protein; GM-CSF: granulocyte and macrophage colony stimulating factor; VEGF: vascular endothelial growth factor; PCR: polymerase chain reaction.

DISCUSSION

After careful reading of the data obtained after the literature review, it is important to reflect upon certain items.

Granulocyte colony-stimulating factor use during and after COVID-19

In a randomized controlled trial, G-CSF's use in patients showing lymphopenia during COVID-19 did not change the time for clinical improvement[11]. However, the percentage of ill patients advancing to complications such as ARDS, sepsis, or septic shock was lower than in individuals who were on G-CSF[11]. Moreover, a lower percentage of patients who used G-CSF died during the study in comparison with those who had standard care[11]. That would lead to the understanding that, even though that was not a faster clinical improvement, the number of patients that developed severe disease was reduced[11].

Furthermore, another interesting finding is a case report in which febrile neutropenia due to COVID-19 infection developed on the 32nd day of disease and was successfully treated with two filgrastim doses[12]. This kind of complication is rarely reported in patients infected by SARS-CoV-2, even though it is very common on several viral infections[12].

In addition, an agranulocytosis case was reported after COVID-19 recovery, which was treated with filgrastim with a good response[13]. That would imply on a chronological event, possibly due to the viral infection. However, more studies are essential for a better understanding of this possible complication.

On the contrary, other evidence can make one wonder about the medication's possible risks and benefits. A study with oncological patients showed an association between G-CSF's use and an increase in the need for high-level supplementary oxygen and death[14]. These outcomes happened especially in patients with a higher absolute neutrophil count after drug administration[14]. Even though there were limitations in this paper, such as involving different types of cancer in the same study, it is worth considering the possible risks of using G-CSF.

Cytokines profile in patients hospitalized with COVID-19

In the United States, higher levels of G-CSF, as well as IL-8, IL-6, IL-10, TNF-α, IL-1RA, and M-CSF were significantly associated with mortality[15]. Another important finding was that high levels of neutrophil activation markers (resistin, lipocalin-2, hepatocyte growth factor, MMP8, IL-8, and G-CSF) were found on the first day of hospitalization in patients that would later be transferred to the ICU, which would lead to the conclusion that this alteration would precede critical illness and could predict COVID-19 mortality[15].

Likewise, in China, higher levels of IL-6, IL-7, IL-10, G-CSF, M-CSF, IP-10, MCP-1, MCP-3, MIG, and MIP-1α were seen in the blood serum of severe patients in comparison to milder cases[16]. The cytokine levels went back to normal after recovery[16]. This discovery supports the idea that infection by SARS-CoV-2 is a strong inducing force for pro-inflammatory cytokine production, promoting the development of the cytokine storm that would lead to multi-systemic failure.

Similarly, another study center reported an increase in IL-9, IL-15, G-CSF, GM-CSF, IFN-γ, PDGF, and VEGF levels in the tears of infected patients[17]. Even though the paper has limitations, such as the absence of patients with mild disease, these results contribute to a better understanding of the disease's pathophysiology and endorse previous findings in cytokine levels in COVID-19 patients[16,17].

Use of granulocyte and macrophage colony stimulating factor inhibitors during COVID-19

According to Cremer et al., hyperinflammation and its consequent excessive cytokine production were identified as the worst prognosis factor in patients with pneumonia due to SARS-CoV-2 infection[18]. The GM-CSF can contribute to this condition, since it is high in COVID-19 patients' bronchoalveolar lavage that developed ARDS, it is increased in patients' serum who died due to COVID-19, and it regulates pro-inflammatory responses in the lungs[18].

Taking into account this hypothesis, studies were conducted with GM-CSF's monoclonal antibodies, like mavrilimumabe and lenzilumabe, in patients infected by SARS-CoV-2.

In all papers, monoclonal antibodies were well tolerated without any side effects [18-21]. In some study centers, patients treated with monoclonal antibodies had less time to clinical improvement than the control group ($p<0.05$)[19,20]. In a different paper, it was stated that there was improvement in inflammatory markers (PCR and IL-6) and in the disease's severity, through total lymphocyte count, in patients that used lenzilumabe[20]. However, in a study performed on seven hospitals in the United States, in which mavrilimumabe was used in patients with severe COVID-19, there was no significant difference in the percentage of patients alive and without oxygen therapy compared to the control group[18].

Although there are certain limitations to previous papers, these findings strengthen the hypothesis that hyperinflammation contributes to the disorders already known to COVID-19 and emphasize a possible treatment focused on reducing the cytokine storm.

CONCLUSION

After literature analysis, it was not possible to state the efficacy of G-CSF use in COVID-19 treatment, even though it seems its use is safe and has less side effects. Contrariwise, there is a possible benefit to the use of GM-CSF's monoclonal antibodies, given the development of hyperinflammation in COVID-19 pathophysiology. Nonetheless, larger studies are necessary to prove new therapies for the treatment of the illness.

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