OPINION ARTICLE

Recruiting the innate immune system with GM-CSF to fight viral diseases, including West Nile Virus encephalitis and COVID-19 [version 1; peer review: 1 approved, 2 approved with reservations]

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Abstract

As the coronavirus disease 2019 (COVID-19) pandemic grows throughout the world, it is imperative that all approaches to ameliorating its effects be investigated, including repurposing drugs that show promise in other diseases. We have been investigating an approach to multiple disorders that involves recruiting the innate immune system to aid the body's healing and regenerative mechanism(s). In the case of West Nile Virus encephalitis and potentially COVID-19, the proposed intervention to stimulate the innate immune system may give the adaptive immune response the necessary time to develop, finish clearing the virus, and provide future immunity. Furthermore, we have found that GM-CSF-induced recruitment of the innate immune system is also able to reverse brain pathology, neuroinflammation and cognitive deficits in mouse models of Alzheimer's disease and Down syndrome, as well as improving cognition in normal aging and in human patients with cognitive deficits due to chemotherapy, both of which exhibit neuroinflammation. Others have shown that GM-CSF is an effective treatment for both bacterial and viral pneumonias, and their associated inflammation, in animals and that it has successfully treated pneumonia-associated Acute Respiratory Distress Syndrome in humans. These and other data strongly suggest that GM-CSF may be an effective treatment for many viral infections, including COVID-19.

Keywords

COVID-19, SARS-CoV-2, West Nile Virus, granulocyte-macrophage colony-stimulating factor, Alzheimer's Disease, inflammation, acute respiratory distress syndrome, neuroinflammation

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There is much debate about how to best treat disorders that include an inflammatory component. For example, in Alzheimer's disease (AD), inflammation is evidenced by the activation of microglia and astrocytes, the consequent over-expression of inflammatory cytokines and acute phase proteins in the brain, and by the presence of inflammatory markers in the blood[1,2]. Furthermore, in AD, some inflammatory proteins expressed in the brain, specifically α1-antichymotrypsin and apolipoprotein E (ApoE), especially ApoE4, clearly promote and, indeed, are necessary for amyloidogenesis that leads to cognitive decline in humans and/or animal models[3,4]. The finding that the introduction of pro-inflammatory molecules, such as lipopolysaccharide, into mouse models of AD exacerbated amyloid pathology and cognitive deficits also suggested that inflammation contributed essentially to the disease, possibly by a self-perpetuating feed-forward mechanism[5]. This idea was reinforced by the finding that people with rheumatoid arthiritis, who routinely take non-steroidal anti-inflammatory drugs (NSAIDS) to control the swelling and inflammation in their joints, have a much lower risk of developing AD, which suggested that their NSAID use was protective against, and might be used to treat, AD[6,7].

In the case of viral diseases, including West Nile Virus (WNV) encephalitis, bacterial and viral pneumonia, Severe Acute Respiratory Syndrome-coronavirus (SARS-CoV-1), Middle East Respiratory Syndrome-coronavirus (MERS-CoV), the development of inflammation has been cited as evidence that an effective treatment should include anti-inflammatory drugs, including steroids[8,9]. Indeed, steroids have been used in some human patients with WNV infection[10–13]. In respiratory diseases, an overactive innate immune reaction, termed a 'cytokine storm' may arise and has been treated with high dose steroids. Furthermore, use of minocycline to suppress microglial activation and promote expression of anti-inflammatory cytokines reduces neuronal cytotoxicity and mortality in WNV-infected mice[14,15]. Minocycline, has also been suggested as a treatment for AD based on experiments in cell culture and animal models, but its effects were complex and resulting changes to the peripheral and CNS immune system remain unclear[16,17].

Despite the logical and preclinical data-based arguments in favor of using anti-inflammatory drugs for treatment of inflammation-associated disorders, clinical trials showed that NSAIDs were unsuccessful and potentially detrimental in AD and mild cognitive impairment participants[7,18–20], and minocycline also failed in a recently-completed trial in participants with early AD[21]. In WNV and Japanese Encephalitis Virus infected mice, *reducing* microglia in the brain by blocking the receptor of Macrophage Colony Stimulating Factor (MCSF) with PLX5622[9] resulted in increased viral load and mortality, suggesting that microglia, traditionally considered to be an indication of a dangerous pro-inflammatory milieu may, in fact be beneficial in fighting the virus infection.

Such alternative, even opposing, views of the role of inflammation is particularly striking in recent discussions about treating COVID-19. For example, it is proposed that inflammation in COVID-19-associated SARS should be suppressed because the cytokine storm is thought to play a major role in the pulmonary damage that so greatly increases morbidity and mortality in SARS (also termed acute respiratory distress syndrome, ARDS), a feature of infection by both SARS-CoV-1 and SARS-CoV-2[22]. Recent studies report increased plasma levels of chemokines and cytokines, including CCL-2, CCL-3, RANTES, INFγ, IL-1β, IL-2, IL-6, IL-8, IL-10, G-CSF, IP10, TNFα, and others, in severe cases of COVID-19 as compared to mild cases[23,24], while decreased levels of lymphocytes are also commonly found in severe cases of SARS and COVID-19 patients[25–30]. Thus, it is unclear whether treatment with broad-acting immunosuppressant drugs to combat the increased cytokine and chemokine signaling would also exacerbate leukopenia, resulting in inhibited clearance of the virus and repair of tissue damage. Because no controlled trials using NSAIDs or steroids in COVID-19 patients have yet been reported, the CDC has taken a cautious stand, stating that "*Currently, there are no data suggesting an association between COVID-19 clinical outcomes and NSAID use*" and that "*Corticosteroids have been widely used in hospitalized patients with severe illness in China[31–34]; however, the benefit of corticosteroid use cannot be determined based upon uncontrolled observational data. By contrast, patients with MERS-CoV or influenza who were given corticosteroids were more likely to have prolonged viral replication, receive mechanical ventilation, and have higher mortality[35–39]. Therefore, corticosteroids should be avoided unless indicated for other reasons, such as management of chronic obstructive pulmonary disease exacerbation or septic shock.*"[40]

As another, more targeted approach, it is suggested that inflammation may be best prevented or reduced by using specific monoclonal antibodies to block either the IL-6 receptor[41–43] or the cytokine granulocyte-macrophage colony-stimulating factor (GM-CSF)[41,44]. The hypothesis that blocking IL-6 or GM-CSF will be beneficial is based in part on the finding that IL-6 and GM-CSF and/or the cells that express them are increased in the blood of COVID-19 patients[22,41] and on the beneficial results froma preliminary single-arm trial of an IL-6 receptor blocker, which reportedly lowered fever and improved oxygenation in COVID-19 patients[43]. Lowering IL-6 or other inflammatory cytokines in COVID-19 patients is reasonable, but the timing may be critical as early treatment may be detrimental. A multi-arm study including both early and later stage patients is essential to determine the clinical relevance of such intervention[30,42], especially for anti-IL-6 therapies, such as tocilizumab and sarilumab, as IL-6-mediated inflammation has been shown to play a critical role in effective cellular and humoral immunity against viral infections[45–48]. Thus, if anti-IL-6 therapies are used too early to treat patients with COVID-19, this strategy could potentially inhibit viral clearance and/or leave the patients susceptible to recurrent infection with SARS-CoV-2.

As an alternative to treatment approaches designed to block pro-inflammatory cytokine responses, we suggest that COVID-19-associated SARS may be better prevented or treated by instead increasing the activation and numbers of macrophages and microglia, in particular by *increasing* the levels of

GM-CSF. This innate immune system stimulant has been approved by the FDA as recombinant human GM-CSF (rHuGM-CSF/sargramostim/Leukine®) for almost 30 years as a therapy to increase white blood cell numbers by stimulating the division and differentiation of hematopoietic stem cells[49]. Approved indications for such treatment include reducing the incidence of severe and life-threatening infections after chemotherapy, accelerating myeloid reconstitution following hematopoietic cell transplantation (HCT), and treating cases of acute radiation syndrome. The finding of low white blood cell counts in patients with COVID-19[23] suggests that the ability of GM-CSF to increase select leukocyte populations, particularly phagocytes, may be of therapeutic value in COVID-19, especially given GM-CSF's ability to treat life-threatening infections, and as data from Wuhan, China have shown that half of all COVID-19 patients who died had evidence of secondary infections[50]. This concept is further supported by a previous study that found that the endogenous levels of GM-CSF were significantly higher in bronchoalveolar lavage fluid from patients with ARDS due to trauma or sepsis who *survived* compared to those who died[51], in contrast to the potential deleterious effects of GM-CSF that were inferred from the study cited above[41].

These results suggest to us that GM-CSF may be beneficial in the treatment of WNV infection and the inflammation that results, and by implication, other viral infections, potentially including COVID-19. In preliminary experiments, we have found that GM-CSF treatment improves survival in mice infected by footpad injection with the TX02 strain of WNV, from approximately 35% in untreated animals to 80% survival in mice treated with GM-CSF starting the day after viral inoculation (p=0.0034) (Clarke, Potter, Boyd, Tyler, manuscript in preparation). These findings are particularly important, as there are currently no effective treatments for WNV encephalitis, and the long safety history of rHuGM CSF/sargramostim in treating leukopenia and preventing life-threatening infections suggests that these preliminary findings, if confirmed, could quickly be translated into human trials.

Furthermore, the potential benefit of GM-CSF as a pulmonary therapy has been shown directly in several other animal models in which GM-CSF treatment was able to both protect against and treat bacterial and viral pneumonias[52–61], which, like COVID-19, induce a cytokine storm that can lead to respiratory distress and multi-organ failure. Notably, some of these studies showed that inhaled GM-CSF was particularly efficacious[57,58]. Inhaled GM-CSF has also been used successfully in humans off-label as a treatment for pulmonary alveolar proteinosis[62–65], and successfully as compassionate treatment for pneumonia-associated ARDS[66].

The recent report that injection of mesenchymal stem cells (MSCs) reverses clinical and peripheral manifestations of COVID-19[67] and the fact that GM-CSF is well known to stimulate the mobilization of MSCs from the bone marrow[68–70] provide further support for the argument that GM-CSF administration may effectively treat COVID-19.

It is also relevant that the unusually rapid onset of COVID-19-associated SARS after infection with the SARS-CoV-2 virus may be due to infection and inflammation in the central nervous system (CNS), including in the brain stem, which could contribute to respiratory failure, and neurological symptoms have been reported in COVID-19 patients, such as hypogeusia, hyposmia, neuralgia, dizziness, headache, ataxia, epilepsy, and others[71–77]. Additionally, in studies of SARS-CoV-1 and MERS-CoV, the presence of viral neuroinvasion has been identified in both animal studies[78,79] and in post-mortem human brain samples[80,81]. Significantly, GM-CSF can easily cross the blood-brain barrier[82], and our work with GM-CSF in both animals and humans indicates that it can ameliorate CNS disorders of various kinds that include an inflammatory component. For example, GM-CSF/sargramostim treatment is associated with improved cognition in:1) mouse models of Alzheimer's disease[83], which has since been replicated by others[84], 2) a mouse model of Down syndrome (Ahmed, Boyd, Potter *et al*., manuscript in preparation), 3) aged wild-type control mice[83] and (Ahmed, Boyd, Potter *et al*., manuscript in preparation), which has also been replicated by others[85], 4) a retrospective study of leukemia patients after immune system chemoablation and HCT, who acquire chemotherapy-associated cognitive impairment[86], and 5) mild-to-moderate Alzheimer's disease participants, based on one measure, the Mini-Mental State Exam (recombinant human GM-CSF/sargramostim, five days/week for three weeks (Potter, Woodcock, Boyd *et al*., NCT01409915; manuscript submitted), all of which are CNS disorders. These findings are relevant to COVID-19 because all of these disorders induce inflammation[1,8,9] and yet still benefit from treatment with GM-CSF, which *increases*, rather than decreases, the number and activation of microglia, the resident phagocytes of the CNS that are often cited as indicators of a dangerous pro-inflammatory milieu that must be suppressed to achieve successful treatment. Additionally, we have found that GM-CSF treatment reverses astrogliosis, which is also associated with CNS disorders and has been reported to be reversed by GM-CSF treatment that ameliorates spinal cord injury and inhibits glial scar formation[87,88]. Furthermore, multiple studies have shown that there is a very high prevalence of cognitive impairment in ARDS survivors, from between 70–100% at hospital discharge, to 46–80% at one year, and persisting in 20% at five years[89–91], which strongly argues for extended treatment with GM-CSF/sargramostim, given its ability to improve cognition in several animal models and reverse cognitive impairment associated with chemotherapy and neurodegeneration.

Because GM-CSF/Sargramostim has been safely and routinely used as a subcutaneous injection treatment and, off-label, as an inhalation treatment, we suggest that this long-FDA-approved drug should be tested for its ability to improve recovery in COVID-19 patients and/or after resolution of infection in severe ARDS survivors to ameliorate potential cognitive deficits. Although compassionate use is possible, it is more important that, either, or a combination, of these two routes of administration in a randomized, pilot trial be used to properly assess the possibility that the innate immune system stimulant, GM-CSF, may reduce morbidity

and mortality from COVID-19, as the studies discussed above suggest. Indeed, while an earlier version of this manuscript was being reviewed, a trial of sargramostim in COVID-19 patients with ARDS was announced in Europe using both inhaled/nebulized and/or injected administrations[92]. We hope that sites in the U.K., the U.S., and elsewhere will be invited to join that study, and welcome comments and data at: https://medschool.cuanschutz.edu/GMCSF-COVID

If GM-CSF/sargramostim proves to be beneficial as a treatment for COVID 19, the fact that the U.S. Department of Health and Human Services maintains a stock of rHuGM-CSF/sargramostim to be used in the event of a nuclear accident may provide short-term resources[93].

Data availability

No data is associated with this article.

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The commentary of Potter *et al.* draws parallels from their finding that GM-CSF ameliorates intrinsic and viral neuro-inflammation induced in the course of Alzheimer's disease and West Nile Virus infection, respectively. The authors propose that the application of GM-CSF may have utility for the treatment of COVID-19. Neurotropism for SARS-CoV-2 and other respiratory coronaviruses has been documented, although this is not discussed in the present commentary as a relevant source of targetable neuroinflammation by GM-CSF administration.

Supporting a beneficial role of GM-CSF, there is an abundance of studies that supplementation of GM-CSF in the airway enhances resistance to viral and bacterial pneumonia and, furthermore, that therapeutic GM-CSF inhalation can stabilize critical illness by macrophages increasing the odds for survival. These beneficial effects are observed locally at a high GM-CSF dosage. It is well-established that the effects of GM-CSF on myeloid cell behavior, activation, and interactions interfacing innate and adaptive immunity are concentration- and source-dependent. Homeostatic functions of GM-CSF at local sites, such as surfactant metabolism by alveolar macrophages may contribute to anti-inflammatory scavenging and repair of tissue damage at a time of need. On the other hand, activated lymphocytes unloading their GM-CSF payload in inflammatory immune synapses during immune remediation against an infectious agent could deliver substantial collateral damage and tissue destruction. To this end, there is an abundance of studies that GM-CSF contributes to adverse inflammation in multiple sterile and non-sterile inflammatory models, autoimmune disease models, and in chronic inflammatory disease caused by chronic environmental exposures such as smoking.

Buttressing a detrimental contribution of GM-CSF in the development of COVID-19, there are a plethora of clinical trials underway to neutralize GM-CSF signaling. This, however, is evolving against a backdrop of disappointing data that IL-6 blockade in the Sanofi and Regeneron trials were not effective for the treatment of COVID-19. The article could be updated with this latest information, although the effects of GM-CSF in such trials remains to be seen.

The challenge in designing immuno-modulatory therapies for COVID-19 is the systemic nature of the

syndrome. Timing, disease stage, manifestation, and severity, dosage, and route of administration are critical parameters. Significant research effort is, therefore, required to inform the decision making process for GM-CSF supplementation or blockade gave the diverse functions of resident myeloid cell populations in different tissues. A more discerning argument on the compartmental utility of GM-CSF in preventing cognitive sequelae of COVID-19 is thus warranted.

Is the topic of the opinion article discussed accurately in the context of the current literature?
Yes

Are all factual statements correct and adequately supported by citations?
Yes

Are arguments sufficiently supported by evidence from the published literature?
Yes

Are the conclusions drawn balanced and justified on the basis of the presented arguments?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Mechanisms of infectious and noninfectious inflammatory syndromes of the lung, surfactant protein immune functions, GM-CSF in pulmonary homeostasis

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 10 July 2020

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In an interesting perspective on immune system-based strategies to combat COVID-19 and its accompanying cytokine storm, Potter *et al.* discuss the relationship of this disease—and particularly, the hyperinflammatory syndrome manifest in the most severe cases—to other disorders. While it may not be surprising to SARS-CoV-2 infections placed vis-à-vis with other viral infections such as West Nile Virus (WNV), some readers may be shocked to see the comparison extended to Alzheimer's disease (AD). But this is not an unreasonable stretch. The inflammatory hypothesis of AD has been around since the late 1980s, when we and others began to report the elevation of immune-system markers such as interleukin-1 and complement proteins[1,2,3,4]. We were reluctant to refer to these changes as "inflammation" at the time, as the brain's partial privilege from immune sequelae[5] puts a damper on the *calor, dolor,* and *rubor* classically associated with peripheral inflammation. Nevertheless, the cytokines

most closely associated with inflammation now appear to drive every element of AD pathology, as we proposed in the "cytokine cycle"[6] (which a more poetic turn of phrase might have rendered "cytokine cyclone" and thus provided the first such "storm").

The elaboration of cytokines during neurodegeneration must be presumed to arise from some program that would be otherwise appropriate and adaptive, and several findings indicate that it is modulation rather than wholesale suppression of immune mediators that will be beneficial in AD. Potter *et al.* touch on this in reference to the effects of lipopolysaccharide in mouse models of AD, though they could have helped their case by including the intriguing finding that such stimuli can attenuate amyloid pathology[7]. Many current therapeutic attempts are aimed at manipulating inflammatory pathways in AD, including the application of GM-CSF (or a clinical preparation known as "sargramostim") by Potter's group. The strange career of COVID-19 and the varied effects it has on multiple organ systems suggests a similar need for targeted manipulation of immune responses.

Evidence clearly indicates that SARS-CoV-2 promotes inflammation by augmenting actions of the innate immune system. In addition to the cytokine storm, the life-threatening form COVID-19 sometimes takes is associated with other inflammatory markers such as C-reactive protein, ferritin, and D-dimers, as well as elevation of the neutrophil:lymphocyte ratio[8]. It is possible that this reflects attempts by the innate immune system to pick up the slack left by virus's targeted suppression of acquired immunity via an exquisite ability to suppress interferon-dependent responses[9]. This provides one more similarity to AD via the changes in immune systems brought about by advanced age, which invariably results in lymphocyte decline and the elevation of inflammatory cytokines as a component of the senescence-associated secretory phenotype.

Potter *et al.* acknowledge this evidence of an overactive innate response in their criticism of treatments that would suppress the entire immune system, such as steroids and NSAIDS. This latter is also cited in relation to the ADAPT trial of naproxen or celecoxib in AD, halted due to untoward side effects of celecoxcib. However, it is interesting to note, as the authors do, that nondemented subjects who took naproxen for two or three years of the trial had reduced rates of developing AD. Such findings fit well with a VA database retrospective study of ibuprofen and naproxen use among almost 50,000 clinically and neuropathologically confirmed Alzheimer patients and 200,000 non-AD patients. The odds of being in the AD group was reduced from 1.03 to 0.56—i.e., more than 40 percent—among those who took ibuprofen for 5 years or longer[10].

Less compelling are the prospects for effectively guiding the immune system through a SARS-CoV-2 attack with GM-CSF. Potter *et al.* suggest that the success of sargramostim to treating some forms of leukopenia means it will boost lymphocyte actions leukopenia. However, the difference in CD4+ lymphocytes produced by sargramostim treatment was just 22 percent, and this was only after 6 months of treatment[11]. The vast majority of leukocytes that accumulate after GM-CSF/sargramostim administration are neutrophils, with a considerable number of eosinophils, monocytes, and macrophages; this would seem to be precisely contraindicated in COVID-19. Indeed, Zhou et al. (2020), cited by Potter et al., suggest suppression of GM-CSF among other strategies to restrain the innate immune system.

Thus, the logical argument for GM-CSF in SARS or COVID-19 is one that should raise red flags; there is a chance that it could worsen outcomes. Improved outcomes with GM-CSF in the WNV model is encouraging. However, it should be noted that WNV is in an entirely different phylum from coronaviruses. Thus, the WNV data may serve best as justification for conducting preclinical studies with a relevant coronavirus model. In the end, it is imperative that no stone is left unturned in the quest for effective

treatments for COVID-19 while we suffer without a vaccine. For regardless of how different that acute disease might be from AD and related disorders, there is every reason to believe that the inflammatory ravages triggered by SARS-CoV-2 will set in motion cyclones and cycles that will increase the rates of chronic neurodegeneration.

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Is the topic of the opinion article discussed accurately in the context of the current literature?
Yes

Are all factual statements correct and adequately supported by citations?
Partly

Are arguments sufficiently supported by evidence from the published literature?
Partly

Are the conclusions drawn balanced and justified on the basis of the presented arguments?
Partly

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 23 June 2020

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This opinion article by Potter *et al.* presents the provocative hypothesis that targeted stimulation of certain immune populations by the administration of GM-CSF could ameliorate certain neuroinflammatory conditions, such as Alzheimer's or West Nile Virus infection, or pulmonary conditions such as COVID.

There are many references drawn together to support this suggestion. However, there is insufficient clarity in the arguments to introduce the subject to readers unfamiliar with the literature.

Of largest concern is the casual mixing of very different immunomodulators, without discussion of the various mechanisms of action. The authors discuss steroids, NSAIDS, minocycline, monoclonal antibody therapies, and an experimental therapy called PLX5622 without an adequate introduction to the very different pathways inhibited by these modulators.

Additionally, the authors do not always distinguish between the different cell types affected. For instance, they comment that GM-CSF might help COVID by improving the "leukopenia" noted in severe cases. However, it is LYMPHOPENIA that marks the most severe cases of COVID, and systemic GM-CSF administration will not help that at all.

In terms of GM-CSF, the authors do not clearly distinguish between the likely different mechanisms of action when GM-CSF is administered systemically vs via inhalation. It is unlikely, for instance, that inhaled GM-CSF stimulates demargination of PMNs to the same extent that subQ does.

Finally, the combined discussions of auto-neuro-inflammation (e.g. Alzheimer's), WNV neuroinflammation, and pulmonary inflammation becomes confusing.

In short, this article would be vastly improved by separating the topic into multiple subheadings, and addressing one sub-topic (e.g. "Immunomodulators in Alzheimer's," "Immunomodulators in WNV,") at a time.

The information is good. The references are solid. The proposal of using GM-CSF therapeutically to modify inflammation is exciting. But the disorganization of this article currently obscures its strengths, and it should be rewritten for clarity.

Is the topic of the opinion article discussed accurately in the context of the current literature?
Yes

Are all factual statements correct and adequately supported by citations?
Yes

Are arguments sufficiently supported by evidence from the published literature?
Partly

Are the conclusions drawn balanced and justified on the basis of the presented arguments?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Pulmonary innate immunity

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.