

GM-CSF: A Promising Target in Inflammation and Autoimmunity

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Abstract: The cytokine, granulocyte macrophage-colony stimulating factor (GM-CSF), was firstly identified as being able to induce in vitro the proliferation and differentiation of bone marrow progenitors into granulocytes and macrophages. Much preclinical data have indicated that GM-CSF has a wide range of functions across different tissues in its action on myeloid cells, and GM-CSF deletion/depletion approaches indicate its potential as an important therapeutic target in several inflammatory and autoimmune disorders, for example, rheumatoid arthritis. In this review, we discuss briefly the biology of GM-CSF, raise some current issues and questions pertaining to this biology, summarize the results from preclinical models of a range of inflammatory and autoimmune disorders and list the latest clinical trials evaluating GM-CSF blockade in such disorders.

Keywords: GM-CSF, inflammation, autoimmunity, therapeutic

Introduction

Granulocyte macrophage-colony stimulating factor (GM-CSF, CSF2) was originally defined as a hemopoietic growth factor due to its ability to form colonies of granulocytes and macrophages in vitro by proliferation and differentiation of bone marrow progenitor cells.¹ A number of reports have revealed that GM-CSF and the GM-CSF receptor (GM-CSFR) levels are elevated and correlated with disease severity in many inflammatory/autoimmune diseases, for example, rheumatoid arthritis (RA).² In addition, there is much preclinical data providing a strong rationale for the involvement of GM-CSF in such diseases. As a result, GM-CSF and GM-CSFR have both attracted great interest as potential therapeutic targets. This review provides a brief overview of the pleiotropic biology of GM-CSF and outlines some of the most recent preclinical findings and in particular the resultant clinical studies using GM-CSF- or GM-CSFR-targeting monoclonal antibodies (mAbs) in various diseases. It also summarizes some of the contentious issues and outstanding questions pertaining to GM-CSF biology. This review cannot obviously cover all aspect of the broad topic and further background information on GM-CSF biology and targeting can be found in earlier reviews (see, for example,²⁻⁶).

GM-CSF Biology

GM-CSF Receptor and Signaling

GM-CSF binds to the multimeric GM-CSFR, comprising a specific low-affinity ligand-binding α subunit (GM-CSFR α) and a signal-transducing β subunit (GM-CSFR β), the

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latter shared with the interleukin-3 (IL-3) and IL-5 receptors. The activation of GM-CSFR triggers (i) phosphorylation of the GM-CSFR β subunit, which commonly leads to the binding of signal transducer and activator of transcription 5 (STAT5) thereby initiating Janus Kinase (JAK) 2 signaling^{7–9} and (ii) activation of the MEK/ERK, phosphatidylinositol 3 kinase (PI3K) and NF κ B pathways.^{10,11}

The hemopoietic-specific transcription factor, interferon regulatory factor 4 (IRF4), is a key signaling molecule for the adoption of dendritic cell (DC)-like properties in GM-CSF-treated precursors, such as monocytes.^{12–16} Recently, it was reported that the GM-CSF stimulation of monocytes/macrophages in vitro leads to the formation of CCL17 via IRF4 as an important pathway, termed the GM-CSF/CCL17 axis (see below).¹⁷ Mechanistically, GM-CSF up-regulates IRF4 expression by enhancing JMJD3 demethylase activity.¹⁷ Additionally, GM-CSF-IRF4 signaling favours the polarization of pro-inflammatory macrophages and increased antigen presentation capability (ie increased MHC class II expression) during in vivo inflammation.¹⁸ In contrast, some literature indicates IRF5, but not IRF4, to be important for GM-CSF-induced macrophage polarization^{19,20} and IRF4 has been considered to have an anti-inflammatory role in macrophages (for example, enhanced interleukin (IL)-10 and reduced TNF production).^{21–23}

GM-CSF and the Lung

While GM-CSF appears to be dispensable for steady state myeloid cell development in vivo,²⁴ GM-CSF directly regulates the differentiation of liver-derived fetal monocytes into immature alveolar macrophages during embryonic development²⁵ and also promotes the development of functional alveolar macrophages via PU.1.^{25,26} GM-CSF gene-deficient mice develop pulmonary alveolar proteinosis,^{24,27} which can also occur in humans due to genetic mutations or endogenous neutralizing antibody (53).²⁸ This pathology results from compromised alveolar macrophage functions.²⁹ In addition, GM-CSF deficient mice have been reported to be more susceptible to lung infections.^{30,31} Inhaled GM-CSF can protect mice from such infections^{30,32} via enhancing macrophage and DC function.^{30,31} These studies suggest that the availability of excess GM-CSF could be beneficial in certain circumstances.

Sources of GM-CSF in Inflammation

A wide range of cells can produce GM-CSF.^{2–6} During inflammation, major sources of GM-CSF are both

hematopoietic, for example, T and B cells, and non-hematopoietic, for example, tissue resident cells.

T Cells

GM-CSF has been reported to be produced by T_{H1} and T_{H17} cells via STAT signaling^{33–35} and shown to be crucial for encephalitogenicity.³³ A distinct subset of T cells, known as GM-CSF-producing T_H cells, has recently been identified.³⁵ GM-CSF-producing T_H cells express undetectable T-bet, GATA-3, or ROR γ t and do not express a cytokine signature that other T cell subsets express.^{35,36} In humans, GM-CSF-producing T_H cells can be identified as CCR10⁺ CCR4⁺ CXCR3⁻ CCR6⁻ cells.³⁶ GM-CSF-producing T_H cells have been implicated in autoimmune brain disease as fewer GM-CSF-producing T_H cells correlated with less severe experimental autoimmune encephalomyelitis (EAE).³⁵

Innate Lymphoid Cells

The innate lymphoid cell (ILC) family encompasses the classic cytotoxic natural killer (NK) cells and the non-cytotoxic ILCs.^{37,38} NK cells have been recently reported to produce GM-CSF when infiltrating into joints for the maintenance of inflammatory arthritis.³⁹ Among the subsets of ILCs, type 3 ILCs have been shown to secrete GM-CSF in intestinal inflammation.^{40–42} In spondyloarthritis, type 3 ILCs are found to be enriched in the inflamed joint and are the predominate source of GM-CSF.⁴³

B Cells

A subset of B cells, namely innate response activator (IRA) B cells, resides in nonlymphoid sites, such as the peritoneal and pleural cavities, and provides a first line of defense against infection.⁴⁴ In a model of Toll-like receptor (TLR)-induced sepsis, IRA B cells, which produce GM-CSF and also reported to express the GM-CSFR, mediate a GM-CSF-dependent IgM protective mechanism against septic shock.^{44–46} Mixed chimeric mice with B cell-restricted GM-CSF deficiency had high bacterial titer morbidity after infection but did not develop alveolar proteinosis,⁴⁴ indicating that B cell-derived GM-CSF is dispensable for surfactant clearance by alveolar macrophages. Memory B cells isolated from multiple sclerosis (MS) patients produce high levels of GM-CSF, termed GM-CSF⁺ B cells, and co-culture of these cells with macrophage-colony stimulating factor (M-CSF)-generated, human blood monocyte-derived macrophages initiates proinflammatory responses.⁴⁷ Interestingly, dimethyl fumarate ameliorates MS

and depletes GM-CSF-producing B cells in these patients^{48,49} consistent with a pathogenic role for these cells.

Tissue Resident Cells

Tissue resident cells can also be a potential source of GM-CSF during inflammation. For example, it has been shown that fibroblast-like synoviocytes are important for the initiation of experimental autoimmune arthritis via their GM-CSF production.⁵⁰ GM-CSF has been reported to be expressed by cardiac fibroblasts in models of Kawasaki disease and myocarditis.^{51,52} Epithelial cells can produce GM-CSF in response to allergenic stimuli^{53,54} and such production can restore alveolar barrier function.⁵⁵ In addition, studies also reported that endothelial cells can produce GM-CSF in response to pro-inflammatory cytokine stimulation.^{56–58}

GM-CSF-Responsive Cells

In vitro, GM-CSF can regulate proliferation and/or activation of myeloid cells, namely monocytes, macrophages, DCs, neutrophils and eosinophils. At sites of inflammation, GM-CSF can be proinflammatory through recruitment of myeloid cells and/or by enhancing their survival and activation.^{6,59} However, it has been reported that prolonged exposure to GM-CSF can lead to the generation of monocyte-derived suppressor cells.⁶⁰

In addition to being able to control the development of monocytes and macrophages from bone marrow precursors in vitro, GM-CSF can regulate multiple functions in the differentiated cells, including cell survival, proliferation and maturation, via transcription factors, such as PU.1 and IRF4.^{17,26,61} During infection, GM-CSF has been shown to boost macrophage antimicrobial functions, such as enhanced phagocytosis⁶² and increased production of reactive oxygen species.^{63,64} GM-CSF stimulates monocytes/macrophages to secrete some pro-inflammatory cytokines (for example, IL-6, IL-23 and CCL17)^{17,65–67} and these cells are often hyperinflammatory (“primed”) when they encounter a second stimulus (for example, lipopolysaccharide (LPS)).^{68–70} Macrophages are remarkably plastic cells and have been classified into various so-called “polarization states” (for example, M1 vs M2) in different diseased tissues. As regards the expression of certain pro-inflammatory cytokines, GM-CSF has been considered to shift the phenotype of macrophages into a M1-like, pro-inflammatory polarization state;⁷¹ however, such cells have also been considered to have dual M1/M2 characteristics,^{53,67} and GM-CSF-activated monocytes have been reported to

alleviate experimental colitis.⁶⁷ As a result, it has been recommended that the M1/M2 polarization terminology not be applied to GM-CSF action.^{2,17,61,72}

GM-CSF also promotes the development of migratory CD103⁺ CD11b⁺ DCs,^{40,73} while negatively regulating the development of resident CD8⁺ DCs.⁷⁴ GM-CSF, often in combination with IL-4, is widely used to generate in vitro murine and human DC populations from bone marrow precursors and blood monocytes, respectively.^{11,75–77} Heterogeneity in GM-CSF-induced bone marrow DCs has been reported, comprising at least two populations, namely the Fms-like tyrosine kinase 3 (FLT-3)⁺ DC or the CD11c⁺ MHCII⁺ CD115⁺ monocyte-derived DC (MoDC).⁷⁸ There has been debate in the literature regarding the role of GM-CSF in the in vivo generation of MoDCs.^{79–85} Some studies have shown GM-CSF to be dispensable for the differentiation of MoDCs;⁸² in contrast, it has been demonstrated that NFκB-dependent GM-CSF production in CD4⁺ T cells is required for the generation of MoDCs.^{81,83,84} Very recently, to add fuel to this debate GM-CSF has been proposed⁸⁶ to differentiate a population of DC3s independently of conventional DCs (cDCs) or monocyte-restricted progenitors. Besides the regulation of DC numbers, there is evidence that GM-CSF also regulates their function, including antigen presentation (as indicated by increased MHCII expression⁷⁸) and inflammatory responses (as indicated by increased IL-6 and IL-23 secretion⁸⁷).

Neutrophils

GM-CSF can enhance the survival, adhesion and trafficking of neutrophils.^{88,89} During infection, GM-CSF also upregulates the antimicrobial functions of neutrophils, such as phagocytosis⁹⁰ and formation of extracellular traps.⁹¹ One study reported that the expression of PU.1 in neutrophils of pulmonary alveolar proteinosis patients was normal, indicating that GM-CSF is not involved in steady state neutrophil development.⁸⁹

GM-CSF/CCL17 Axis

The chemokine, CCL17 (formerly called thymus and activation-regulated chemokine [TARC]) was originally implicated in the preferential attraction of T_H2 cells;⁹² however, it can also attract regulatory T cells.⁹³ Its most recognized receptor is CCR4⁹⁴ although the atypical chemokine receptor 2 (ACR2) has also been reported to be a CCL17 receptor.⁹⁵ As mentioned above, GM-CSF in vitro upregulates CCL17 formation via an IRF4/JMJD3-dependent mechanism in human and mouse monocytes/macrophages,¹⁷ as well as in inflammation

models.^{18,80} It is to be noted that GM-CSF is not the only mediator that regulates CCL17 production in these populations; for example, IL-4 also upregulates the CCL17 expression in human monocytes and mouse macrophages via a similar mechanism.⁹⁶ This GM-CSF/CCL17 axis has been found to be important in controlling inflammatory arthritic and osteoarthritic pain in pre-clinical models,^{17,80,97–99} importantly, this axis appears to be active in humans, since a neutralizing GM-CSFR mAb in RA patients leads to a sustained reduction in circulating CCL17 levels.¹⁰⁰ Preclinical studies suggest that CCL17 may not necessarily be acting as a T cell chemokine in its control of inflammation and its associated pain.^{17,80,97–99} Mechanistically, whether CCL17 has a direct effect on neurons for pain induction remains an open question¹⁰¹ – there are conflicting reports as to whether CCR4, the CCL17 receptor, is expressed on neurons.^{101–104} However, whatever the mechanism, it is clear that neutralizing CCL17 peripherally with a mAb ameliorates inflammatory arthritic⁹⁹ and osteoarthritic^{97,98} pain. Additionally, other studies have also reported a non-chemotactic role for CCL17, for example, a role(s) in regulating inflammation by restricting regulatory T cell expansion.^{105,106}

GM-CSF Biology: Current Issues and Questions

There are still a number of issues and questions pertaining to GM-CSF biology, which need to be addressed as they have potential implications for the clinical targeting of GM-CSF in inflammation and autoimmunity. It should be borne in mind that this biology may vary depending on the processes and tissues involved in the particular clinical indication in question. Which responding cell type(s) is relevant and whether GM-CSF regulates their number and/or activation/differentiation status are important considerations — the latter issue may have implications for therapeutic delivery and dosing since the extent of GM-CSF neutralization/depletion is likely to be critical.⁶ There is still plenty of controversy around the role of GM-CSF in DC development *in vivo*.^{79–85} It would also be worth knowing how significant is GM-CSF-dependent IRF4 signaling in monocytes/macrophages, including the so-called GM-CSF/CCL17 axis discussed above. Depending on the particular model of inflammation/autoimmunity being studied, the relevant cell type(s) producing GM-CSF varies, again with possible implications for therapeutic strategies. GM-CSF administration systemically can have pro-inflammatory and anti-inflammatory effects — as discussed previously, these

responses to exogenous GM-CSF may or may not be predictive of the findings when endogenous (locally acting?) GM-CSF is neutralized/depleted.²

GM-CSF has been documented for its role in peripheral pain.^{17,99,107,108} However, whether in this capacity GM-CSF is acting directly on neurons (nociceptors), including acting centrally, remains unclear as conflicting reports have been published.^{101,109–115} Additionally, GM-CSF has also been reported to have neuroprotective effects following nerve injury.^{116,117} Further research is obviously needed to clarify how GM-CSF interacts with the nervous system.

GM-CSF in Disease Inflammatory Arthritis

Early studies measuring cytokines in synovial fluid and blood from patients with RA showed increased GM-CSF levels, as well as increased expression of GM-CSFR, in inflamed synovial tissue.^{118,119} Administration of GM-CSF to RA patients led to disease flares.¹²⁰ A genome-wide association study revealed that mutations in CSF2 (the gene that encodes GM-CSF) contribute to genetic susceptibility in RA.¹²¹ Based in part on the priming of blood monocytes with GM-CSF, it was recently suggested that GM-CSF neutralization be considered as a potential therapeutic approach for the treatment of ankylosing spondylitis.¹²²

The contribution of GM-CSF to the pathogenesis of experimental inflammatory arthritis is well documented in the literature. GM-CSF-deficient mice fail to develop arthritis and associated pain in several inflammatory arthritis models, including collagen-induced arthritis (CIA), antigen-induced arthritis (AIA), zymosan-induced arthritis (ZIA) and K/BxN serum-transfer arthritis (STA).^{17,39,108,123} The administration of neutralizing GM-CSF mAbs ameliorated existing disease in these models.^{99,124} Regarding the relevance of GM-CSF to arthritic pain, as mentioned earlier GM-CSF is implicated in regulating inflammatory and arthritic pain via downstream CCL17.^{17,98,99} Interestingly, high levels of circulating GM-CSF have been shown to correlate with the responsiveness of RA patients to anti-TNF agents.¹²⁵ Consistent with the concept of the GM-CSF/CCL17 axis (see above), RA patients treated with anti-GM-CSFR mAb (mavrilimumab) have reduced circulating CCL17 levels, suggesting that CCL17 could be a biomarker for anti-GM-CSF or anti-GM-CSFR treatment.¹⁰⁰

Osteoarthritis

Osteoarthritis (OA) was once considered a non-inflammatory arthropathy; however, it is now well-recognized that there can be a significant inflammatory component contributing to OA clinical symptoms, for example, chronic pain. The expression of GM-CSF and its receptor have been found in OA synovial tissue^{126,127} and reported to be negatively correlated with pain.¹²⁶ In contrast, in a collagenase-induced, joint instability OA model, GM-CSF-deficient mice were protected from associated pain and osteophyte development.¹⁰⁷ Consistent with this data, neutralizing anti-GM-CSF mAb effectively ameliorated pain in the same model.^{97,107} This pain amelioration was observed when the neutralizing mAb was administered early or late in this model but early administration was needed for it to be effective on joint damage.⁹⁷ This data has led to clinical trials in OA for targeting GM-CSF (see below) or CCL17 (<https://clinicaltrials.gov/show/NCT03485365>). Synovial inflammation, characterized by macrophage infiltration, is often more prominent in early OA lesions, while advanced OA is more commonly associated with structural changes (for example, cartilage degeneration and/or osteophyte formation).^{128–130} Given that GM-CSF regulates a wide range of macrophage functions (see above), it could be that optimal clinical improvement might be seen in patients with early OA as opposed to patients with advanced OA disease.

Multiple Sclerosis

Multiple sclerosis (MS) is a chronic autoimmune/inflammatory disease of the central nervous system (CNS) and is characterized by demyelination and subsequent axonal degeneration. While it is widely believed that T_H17 cells are the main encephalitogenic population in EAE,¹³¹ the most widely used MS model, it was reported that their key secreted cytokine, IL-17, is dispensable for the development of EAE.^{132,133} Instead, it was later shown that GM-CSF secreted by T_H17 cells is the main cytokine contributing to encephalitogenicity¹³⁴ via the activation of microglia within the CNS.¹³⁵ GM-CSF-activated microglia adopt a M1-like (inflammatory) phenotype¹³⁶ and produce highly neurotoxic molecules such as tumor necrosis factor (TNF), IL-1 and IL-6.¹³⁷ It has been proposed that GM-CSF promotes the breakdown of the blood brain barrier enabling entry of circulating Ly6C^{hi} monocytes and stimulates the differentiation of monocyte-derived antigen-presenting cells.^{138,139} These differentiated cells share a similar phenotype to macrophages

found in active MS lesions.^{140,141} Additional mouse studies have demonstrated that GM-CSF deletion results in fewer monocyte-derived cells in the CNS parenchyma following EAE induction,¹⁴² and GM-CSF administration leads to more cells migrating into the CNS parenchyma.¹⁴³ Elevated GM-CSF levels have been reported in the cerebrospinal fluid of patients with active MS.^{144,145} Glatiramer acetate, a FDA-approved drug to treat MS, has been shown to upregulate regulatory T cells and reduce GM-CSF levels in mice with EAE.¹⁴⁶ These reports demonstrate that GM-CSF plays a central role in EAE and indicate that GM-CSF might be a therapeutic target in MS.

Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) is a chronic immune-mediated disease affecting the gastrointestinal tract consisting of two main subtypes: Crohn's disease (CD) and ulcerative colitis (UC).¹⁴⁷ Impaired innate immunity plays a critical pathogenic role in IBD.¹⁴⁸ GM-CSF has been identified as a key mediator of chronic inflammation in models of colitis.^{41,149,150} Other studies using dextran sodium sulfate (DSS)-induced colitis reported that GM-CSF-deficient mice developed more severe colitis;^{151,152} mechanistically, it has been claimed that type 3 ILC-derived GM-CSF modulates the macrophage phenotype to prevent intestinal fibrosis.⁴² In line with a potential beneficial role of GM-CSF in IBD, GM-CSF administration can improve IBD experimentally¹⁵³ and in some patients;^{152,154} also, high levels of circulating anti-GM-CSF autoantibodies have been found to correlate with worse CD prognosis.^{155,156}

Interstitial Lung Disease

Interstitial lung disease (ILD) comprise heterogenous inflammatory lung parenchyma disorders that can lead to alveolitis and ultimately fibrosis.¹⁵⁷ It is also a serious complication associated with systemic rheumatic diseases.¹⁵⁷ Experimentally, the SKG mouse with a mutation in the *Zap-70* gene^{158,159} develops spontaneous arthritis, ILD and IBD.¹⁶⁰ The lungs of SKG mice develop fibrosis associated with intense infiltrates of GM-CSF⁺ IL-17A⁺ neutrophils, pathological features that are reminiscent of human ILD.¹⁶¹ GM-CSF blockade reduces these features, including the degree of fibrosis, in SKG mice, with IL-17 blockade being less effective.¹⁶² Interestingly, CCL17-expressing macrophages have been implicated in mediating peritoneal fibrosis.¹⁶³ Given these findings, together with the data in lung inflammation models wherein GM-CSF blockade

impaired CCL17 expression in alveolar macrophages,⁸⁰ in our view further studies examining the role of the GM-CSF/CCL17 axis in lung fibrosis are warranted.

Aortic Aneurysm

Dissecting aortic aneurysm is an important and often life-threatening condition. It was reported that mice deficient in *Klf6*, the gene encoding the transcription factor, Krueppel-like factor 6, developed worse aortic aneurysm.¹⁶⁴ In the same study, GM-CSF was identified to be an effector molecule downstream of Krueppel-like factor 6 and the administration of GM-CSF exacerbated aortic aneurysm formation, with GM-CSF antagonism having the opposite effect.¹⁶⁴ In the aortic root GM-CSF induces CD11b⁺ Gr-1⁺ Ly6C^{hi} inflammatory monocyte accumulation, with anti-GM-CSF mAb administration resulting in reduced inflammation and dilation.¹⁶⁵ These findings suggest that GM-CSF blockade might be an effective therapeutic approach in aortic aneurysm.

Allergic Disease

GM-CSF has been reported to be involved in the T_H2 response in allergic airway inflammation via activation of DCs.^{53,166,167} In a mouse model of asthma, allergen-exposed epithelial cells secrete GM-CSF, which activates DCs and also prolongs eosinophil survival.^{53,168} Administration of a GM-CSF neutralizing mAb also led to reduced allergic hyperresponsiveness.^{167,168} As a result, an anti-GM-CSF mAb has been tested in a Phase II trial for severe asthma (see below). Interestingly, it has been reported that alveolar DC-derived CCL17 is critical for airway inflammation^{169,170} and CCL17 airway expression correlates with asthmatic disease severity.^{171,172} In our view these data warrant a detailed study examining the role of the GM-CSF/CCL17 axis in asthma, with CCL17 being a potential target for treating allergic disease and/or a biomarker for patient selection.

Obesity and Its Associated Meta-Inflammation

Obesity is now widely considered as a low-grade, chronic inflammatory disease that contributes to metabolic dysfunction, ectopic lipid deposition and insulin resistance.^{173,174} With progressive obesity, adipose tissue macrophages (ATMs) have been considered to be a key cell type contributing to metabolic inflammation, insulin resistance and the impairment of adipocyte function.^{175–177} In response to

diet-induced obesity (DIO) in mice, elevated GM-CSF levels can be detected in serum,¹⁷⁸ peritoneal fluid,¹⁷⁹ and adipose tissue;¹⁸⁰ moreover, GM-CSF is required for DIO-induced adipose tissue inflammation, as GM-CSF gene-deficient mice had reduced number of infiltrating ATMs and crown-like features in adipose tissue,¹⁸⁰ in spite of increased adiposity and body weight.^{181,182} It was also reported that GM-CSF gene-deficient mice exhibited improved metabolic status, namely insulin sensitivity to glucose, compared with their wild-type counterparts,¹⁸⁰ and that GM-CSF-responsive myeloid cells play a key role in this improvement.¹⁸¹ As a result, GM-CSF has been proposed to be a key mediator whose actions might explain the difference between obese individuals with normal glucose tolerance (metabolically “healthy”) and those with type 2 diabetes (metabolically “unhealthy”).¹⁸¹ In addition to type 2 diabetes, GM-CSF has also been implicated in other obesity-exacerbated diseases, for example, in the obesity-mediated enhancement of breast cancer metastasis.¹⁸³ How GM-CSF plays a role during obesity-induced meta-inflammation remains to be explored.

Covid-19

In coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), there is a characteristic hyperactive immune response that leads to an overwhelming infiltration of inflammatory myeloid cells (particularly monocytes, macrophages and neutrophils) into the lungs.^{184–190} More recent studies have questioned the validity of referring to the COVID-19 hyperactive immune response as the “cytokine storm” seen in chimeric antigen receptor (CAR) T cell-related cytokine release syndrome (CRS).^{191,192} The COVID-19-related hyperactive immune response resembles a phenotype of secondary haemophagocytic lymphohistiocytosis, often referred to as “macrophage activation syndrome”.^{184–189} In COVID-19 patients, increased percentages of GM-CSF-expressing leukocytes have been found in the blood.¹⁹³ Inhibition of GM-CSF activity in models of hyperinflammatory conditions that share similar pathology to late stages of COVID-19, such as CAR T cell-related CRS and neurotoxicity,¹⁹⁴ graft versus host disease-associated CRS¹⁹⁵ and inflammatory lung diseases,^{162,196–198} was shown to be beneficial. The relevance of GM-CSF to COVID-19 and its potential as a therapeutic target have been reviewed recently.^{199,200}

Table 1 Past and Current Status of GM-CSF-Based Therapies

Drug	Company	Indication	Phase	Status	ClinicalTrials.gov Identifier
Otilimab	GlaxoSmithKline	RA	I/II	Completed	NCT01023256
		RA	II	Completed	NCT02799472
		RA	II	Completed	NCT02504671
		RA	III	Recruiting	NCT03970837
		RA	III	Recruiting	NCT03980483
		RA	III	Recruiting	NCT04134728
		RA	III	Recruiting	NCT04333147
		OA	II	Completed	NCT02683785
		MS	I/II	Completed	NCT01517282
		COVID-19	II	Recruiting	NCT04376684
Lenzilumab	Humanigen	RA	II	Terminated	NCT00995449
		CMML	I	Completed	NCT02546284
		Asthma	II	Completed	NCT01603277
		COVID-19	III	Recruiting	NCT04351152
		Large B-cell lymphoma	I/II	Recruiting	NCT04314843
TJM2	I-Mab	Healthy adult subjects	I	Completed	NCT03794180
		RA	I	Recruiting	NCT04457856
		COVID-19	I/II	Recruiting	NCT04341116
Namilumab	Izana	Healthy adult subjects	I	Completed	NCT02354599
		RA	I	Completed	NCT01317797
		RA	II	Completed	NCT02379091
		RA	II	Terminated	NCT02393378
		Psoriasis	II	Completed	NCT02129777
		Axial Spondyloarthritis	II	Completed	NCT03622658
Gimsilumab	Roivant	Ankylosing Spondylitis	I	Completed	NCT04205851
		COVID-19	II	Recruiting	NCT04351243

Abbreviations: RA, rheumatoid arthritis; OA, osteoarthritis; MS, multiple sclerosis; CMML, chronic myelomonocytic leukemia.

Clinical Studies with the Blockade of GM-CSF and Its Receptor

A number of clinical trials neutralizing GM-CSF (see Table 1) or GM-CSFR (see Table 2) using mAbs have been/are being carried out. Encouragingly, no serious adverse events have been noted so far, for example infections and compromised lung function, with the data from

a long-term open label extension (OLE) study in RA patients being particularly promising in this regard.¹⁰⁰

Otilimab

Otilimab (formerly known as MOR-103 and GSK3196165) is an IgG1 mAb, developed by MorphoSys AG, that binds to GM-CSF and prevents its interaction with GM-CSFR α ; it is

Table 2 Past and Current Status of GM-CSFR-Based Therapies

Drug	Company	Indication	Phase	Status	ClinicalTrials.gov Identifier
Mavrilimumab	Kiniksa	RA	I	Completed	NCT00771420
		RA	II	Completed	NCT01706926
		RA	II	Completed	NCT01715896
		RA	II	Terminated	NCT01712399
		Giant cell arteritis	II	Active, not recruiting	NCT03827018
		COVID-19	II	Recruiting	NCT04399980
		COVID-19	II	Not yet recruiting	NCT04397497

Abbreviation: RA, rheumatoid arthritis.

currently being produced by GSK for use in several randomized controlled trials (RCTs).

A short-term, dose-escalation phase Ib/IIa trial in randomized RA patients (n=96, NCT01023256) showed improved efficacy in all outcomes (ACR and European League Against Rheumatism (EULAR) response) compared with placebo with no pulmonary function test abnormalities being reported.²⁰¹ The subsequent double-blind, placebo-controlled phase IIa (NCT02799472) and IIb (NCT02504671) trials consistently showed clinical improvement in RA patients receiving otilimab and it was well tolerated. Circulating CCL17 levels declined only in the otilimab group, supporting the existence of the GM-CSF/CCL17 axis in humans. GSK has announced the start of a clinical development program (ContRAst) embracing three Phase III trials aiming to evaluate the efficacy and safety of otilimab in RA patients with inadequate response to i) conventional synthetic/biologic disease modifying anti-rheumatic drugs (DMARDs) (NCT03970837), ii) methotrexate (NCT03980483) and (iii) biologic DMARDs and/or JAK inhibitors (NCT04134728). A long-term safety and efficacy study with otilimab has also commenced (NCT04333147).

The results of an exploratory, 12-week, phase IIa study of otilimab in patients with hand OA (n=44, NCT02683785) have been reported and, while not statistically significant in this small study, reduction in pain, accompanied by improvement in functional impairment, was noted.²⁰² Patients have been recruited to determine the efficacy of otilimab in COVID-19 (NCT04376684).¹⁹⁹

Lenzilumab

Lenzilumab (formerly known as KB003) is an IgG1-neutralizing anti-GM-CSF mAb and has been tested successfully in a randomized phase II trial in RA (NCT00995449). A Phase I trial using lenzilumab in patients with chronic myelomonocytic leukemia (CMML) has been completed (NCT02546284); 33% of patients showed durable clinical benefit, which appears to be better in a distinct subtype of CMML patients, warranting further studies to identify CMML subtypes more likely to respond.²⁰³ A Phase II, randomized, double-blind, placebo-controlled, 24-week study in asthma patients (n=311; NCT01603277) has been performed; overall, there were no effects on asthma control although there appeared to be improvements in patients with eosinophilic asthma.²⁰⁴ Recently, lenzilumab was administered to a small cohort of patients (n=12) with COVID-19 pneumonia and found to

associate with improved clinical outcome with no mortality observed,²⁰⁵ a subsequent phase III study has commenced patient recruitment to evaluate efficacy and safety of lenzilumab (NCT04351152).

TJM2

TJM2 is an IgG1-neutralizing anti-GM-CSF mAb. Phase I trials in healthy subjects (NCT03794180) and in patients with severe COVID-19 (NCT04341116) have commenced.

Namilumab

Namilumab (formerly known as MT203), an IgG1-neutralizing anti-GM-CSF mAb, has been investigated in double-blind, placebo controlled, randomized trials in healthy individuals (NCT02354599)²⁰⁶ and in RA patients (NCT01317797),²⁰⁷ which established that namilumab has an acceptable tolerability profile.^{206,207} Phase 1b (NCT01317797) and phase II studies (NCT02379091) in RA demonstrated efficacy, with the latter study further reporting dose-response effects.^{207,208} A phase II trial investigating the efficacy of namilumab in plaque psoriasis was also completed (NCT02129777) with no significant difference being recorded for this end point between placebo-treated and namilumab-treated individuals.²⁰⁹ Patients are being recruited for a phase IIa trial using namilumab in axial spondyloarthritis (NCT03622658).

Gimsilumab

Gimsilumab (also known as KIN-1901), a fully human IgG1 mAb, has been investigated in a double-blind, placebo controlled, randomized trial in healthy subjects and subjects with ankylosing spondylitis (NCT04205851). Patients are being recruited for a phase II trial in COVID-19 (NCT04351243).

Mavrilimumab

Mavrilimumab (CAM-3001) is a humanized IgG4 mAb with high affinity to the GM-CSFR α chain.²¹⁰ The efficacy and safety profiles of mavrilimumab have been investigated in a phase I trial in 32 RA patients (NCT00771420) and in the subsequent EARTH clinical development program, including two phase IIa-IIb RCTs (EARTH EXPLORER 1 and EARTH EXPLORER 2).^{211,212} In the phase IIb, placebo-controlled EARTH EXPLORER 1 study (NCT01706926), moderate-to-severe active RA patients (n=236) with ongoing methotrexate treatment, received three different doses of mavrilimumab (150, 100 and 30 mg). The DAS28-CRP score among these RA patients was significantly decreased

in all mavrilimumab subgroups compared with placebo, with the optimal response being 150mg mavrilimumab.²¹² The EARTH EXPLORER 2 study (NCT01715896), which was a phase II, double-blind, randomized trial, evaluated the benefits of using mavrilimumab (100mg every other week, n=70) in long-standing, active RA patients (mean disease duration 6.7 years, and mean baseline DAS28-ESR 6.5), who had not responded to a conventional synthetic DMARD or TNF inhibitor.²¹¹ This study included a parallel treatment with an anti-TNF mAb (golimumab) (50 mg every 4 weeks, n=68). No statistical difference was seen between RA patients treated with mavrilimumab or golimumab, which could be due to the fact that a suboptimal mavrilimumab dose (100 mg every other week) was used in this trial as opposed to the most effective dose (150mg every other week), confirmed by the EARTH EXPLORER 1 study.²¹² Peripheral biomarkers and pathophysiological pathways modulated by mavrilimumab and golimumab were also assessed in the study. While a number of mediators were suppressed by both mAbs, mavrilimumab, but not golimumab, was able to suppress serum levels of CCL17 and CCL22 and to induce sustained differential suppression of peripheral disease markers in anti-TNF inadequate responders.²¹¹

The long-term efficacy and safety profile of mavrilimumab were also explored in an OLE study (NCT01712399). All patients (n=422), who completed the double-blind phase of EARTH EXPLORER 1 and 2 trials (study 1109; NCT01712399), had the opportunity to enter the study and receive mavrilimumab 100 mg every other week plus methotrexate for a 3-year follow-up period.¹⁰⁰ At week 122, 65.0% and 40.6% patients achieved a DAS28-CRP score of <3.2 and <2.6, respectively,¹⁰⁰ demonstrating a sustained benefit in measures of RA disease outcomes. The overall safety profile of mavrilimumab appears to be promising, particularly regarding pulmonary alveolar proteinosis. In this OLE study, biomarker analyses support the hypothesis that GM-CSF regulates CCL17 and CCL22 as sustained suppression of CCL17 and CCL22 was seen in mavrilimumab-treated patients over a longer follow-up period.

New clinical trials are underway to evaluate the benefits of mavrilimumab in patients with giant cell arteritis (NCT03827018) and in COVID-19 patients (NCT04399980 and NCT04397497).¹⁹⁹ It has recently been reported that mavrilimumab treatment was associated with improved clinical outcomes compared with standard care with patients with severe COVID-19.²¹³

Concluding Remarks and Future Perspectives

The preclinical rationale for targeting GM-CSF in inflammation/autoimmunity is solid, and the results from early phase clinical trials of GM-CSF or GM-CSFR blockade in RA patients, and possibly asthma and COVID-19, are encouraging. However, careful ongoing evaluation of adverse effects, particularly in the lungs and gut, is clearly paramount but, as mentioned above, it seems so far that the anti-GM-CSF and anti-GM-CSFR mAbs used in clinical trials are without major safety concerns. It is hoped that there are other indications (see Table 1) where GM-CSF targeting will turn out to provide potential benefit. The key role of GM-CSF in inflammatory pain was highlighted above. In this connection, the rapid and dramatic effect of mavrilimumab on RA pain has been highlighted^{211,212} and, intriguingly, it has been speculated that the dramatic effects of the JAK1/2 inhibitor, baricitinib, also on RA pain may be due to its inhibition of GM-CSF signaling.²¹⁴ Circulating biomarkers, such as CCL17, may aid in the selection of an indication for GM-CSF-based therapeutics and even of patients within such an indication, thus hopefully leading to better clinical outcomes. It is hoped that targeting GM-CSF is successful in patients who are non-responders to biologics, for example, those targeting other inflammatory mediators, such as TNF and IL-6.

Disclosure

The employer of K.M.-C. L., A.A.A and J.A.H., the University of Melbourne, has licensed patented technology relating to therapeutically targeting GM-CSF to MorphoSys AG, Germany.

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