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GM-CSF as a therapeutic target in autoimmune diseases

Aoi Shiomi*, Takashi Usui and Tsuneyo Mimori

Abstract

Granulocyte-macrophage colony-stimulating factor (GM-CSF) has been known as a hematopoietic growth factor and immune modulator. Recent studies revealed that GM-CSF also had pro-inflammatory functions and contributed to the pathogenicity of Th17 cells in the development of Th17-mediated autoimmune diseases. GM-CSF inhibition in some animal models of autoimmune diseases showed significant beneficial effects. Therefore, several agents targeting GM-CSF are being developed and are expected to be a useful strategy for the treatment of autoimmune diseases. Particularly, in clinical trials for rheumatoid arthritis (RA) patients, GM-CSF inhibition showed rapid and significant efficacy with no serious side effects. This article summarizes recent findings of GM-CSF and information of clinical trials targeting GM-CSF in autoimmune diseases.

Keywords: GM-CSF, IL-17, Autoimmune disease, Multiple sclerosis, Rheumatoid arthritis, Crohn's disease, Th17 plasticity, GM-CSF target therapy

Background

Granulocyte-macrophage colony-stimulating factor (GM-CSF) was originally defined by its ability in vivo to generate colonies of both granulocytes and macrophages from bone marrow precursors [1]. It has also been shown to act on mature myeloid cells as pro-survival, activation, and differentiation factors [2]. Recent studies suggest that GM-CSF also has many pro-inflammatory functions and plays critical roles in the development of autoimmune and inflammatory diseases [3, 4].

Function of GM-CSF

Myeloid cell

GM-CSF promotes the survival and activation of macrophages, neutrophils, and eosinophils, as well as dendritic cell (DC) maturation [2]. On the other hand, GM-CSF-deficient mice have relatively normal myelopoiesis with abnormal lung histology that is indistinguishable from human pulmonary alveolar proteinosis (PAP) [5], indicating a redundant role of GM-CSF in myeloid cell development and its differentiation and critical roles in the maturation and surfactant catabolism of alveolar macrophages [6]. In addition to these functions, GM-CSF is reported to have diverse functions on mature myeloid cells, including enhancement of pro-inflammatory cytokine production [7], antigen presentation [8], induction of phagocytosis [9–11], and promotion of leukocyte chemotaxis and adhesion [12, 13].

GM-CSF can polarize macrophages into M1-like inflammatory macrophages, which produce a variety of inflammatory cytokines such as TNF, IL-6, IL-12p70, IL-23, or IL-1β, and thus promote Th1-Th17 responses [7, 14, 15]. On the other hand, the association of GM-CSF and Th2 immunity is also reported in allergic airway inflammation [16, 17].

GM-CSF positively regulates the development of dermal migratory $CD103^{+}CD11b^{-}$ and gut migratory $CD103^{+}CD11b^{+}$ DCs [18, 19] but negatively regulates the development of plasmacytoid DCs (pDCs) [20] and resident $CD8^{+}$ DCs [19]. GM-CSF is also reported to induce the development of inflammatory monocyte-derived DCs (moDCs) in vitro [21], but its effect in vivo has not been established well. It was reported that GM-CSF transgenic mice have increased the number of moDCs [22] and GM-CSF-deficient mice with inflammatory arthritis have markedly reduced the number of moDCs [23]. On the other hand, in the other reports,

* Correspondence: ashiomi@kuhp.kyoto-u.ac.jp
Department of Rheumatology and Clinical Immunology, Graduate School of Medicine, Kyoto University, 54-Kawahara-cho, Shogoin, Sakyo-ku, Kyoto 606-8507, Japan

GM-CSF was shown to be dispensable for the differentiation of moDCs, at least during acute infections [19, 24].

In neutrophils, GM-CSF upregulates the antimicrobial functions such as phagocytosis, reactive oxygen species (ROS) production, or expression of the integrin CD11b which increases cellular adhesion and tissue entry [12, 25].

The effect of GM-CSF on osteoclast differentiation is quite complex, for it has both enhancing and suppressive actions. Under the steady state, osteoclasts are known to differentiate from hematopoietic precursors of the monocyte/macrophage lineage in the presence of M-CSF and receptor activator of NFκB ligand (RANKL) [26]. GM-CSF induces shedding of M-CSF receptor, resulting in disruption of osteoclast differentiation [27]. On the other hand, the differentiation of osteoclast precursors generated in the presence of GM-CSF or GM-CSF plus TNFα was not inhibited by GM-CSF in vitro, indicating that a different set of osteoclast precursors is available in inflammatory arthritis and that they respond to a variety of pro-inflammatory cytokines which compensate for the loss of M-CSF signaling [28, 29]. GM-CSF is also reported to induce fusion of prefusion osteoclasts to form the bone-resorbing osteoclasts and induce bone erosion [30]. Conversely, other report suggested that GM-CSF inhibited the resorption ability of osteoclasts, indicating the existence of another osteoclastic pathway [28].

B cell

Among B cells, innate response activator (IRA) B cells, a B1a B cell-derived inflammatory subset, produce GM-CSF and also express GM-CSF receptors [31, 32]. GM-CSF controls IgM production from IRA B cells in an autocrine manner which is essential to protect from bacterial infection [31, 32].

Neuron

Sensory nerves express GM-CSF receptors, and GM-CSF is reported as a key mediator in bone-cancer pain [33], osteoarthritis pain, and inflammatory arthritic pain [34, 35]. A sensory nerve-specific knockdown of GM-CSF receptors attenuated tumor-evoked pain [33]. GM-CSF deficiency or neutralization also abolished osteoarthritis pain and inflammatory arthritic pain [34, 35].

GM-CSF receptor

GM-CSF receptor consists of an α-subunit which binds GM-CSF with low affinity (GMRα) and a signal-transducing βc-subunit which is shared with the IL-3 and IL-5 receptors [36]. The binary complex of GM-CSF and GMRα interacts with a free βc-subunit and forms the high-affinity hexamer complex [37]. Dodecamer complexes formed by lateral aggregation of two hexamer complexes enable Jak2 associated with a βc-subunit to dimerize and transphosphorylate, but the hexamer complexes do not [38]. This structure leads to dose-dependent responses of GM-CSF receptor activation. Low concentration of GM-CSF, as in normal condition, causes βc Ser^{585} phosphorylation and activates 14-3-3/PI-3 kinase pathway which only leads to cell survival. Higher concentration of GM-CSF, as in inflammatory condition, turns off βc Ser^{585} phosphorylation and mediated βc Tyr^{577} phosphorylation and activation of Jak2/STAT5 pathway, Ras/mitogen-activated protein kinase pathway, and PI-3 kinase pathway, resulting in promotion of cell survival, proliferation, and activation [37].

The membrane-bound GM-CSF receptor is expressed on myeloid cells [39] and on some non-myeloid cells, such as epithelial cells [40], endothelial cells [41], and neurons [33]. There also exists a soluble GM-CSF receptor alpha subunit [42]. The function of this soluble GM-CSF receptor is unclear, but it may be required to inhibit ligand binding to cells which express membrane-bound GM-CSF receptors [43].

Production of GM-CSF

A wide variety of cells can produce GM-CSF. Major sources of GM-CSF are T and B cells, monocyte/macrophage endothelial cells, and fibroblasts. Neutrophils, eosinophils, epithelial cells, mesothelial cells, Paneth cells, chondrocytes, and tumor cells can also produce GM-CSF [44]. The production of GM-CSF is stimulated by various factors, including TNF, IL-1, toll-like receptor agonists, and prostaglandin E2 [45, 46]. Recently, the pathogenicity of GM-CSF-producing CD4 T cells in autoimmune and inflammatory diseases is clarified and gaining increasing attention [3, 4].

Recently, Th17 cells were clarified to have high plasticity [47]. The "classical" Th17 cells driven by transforming growth factor-β1 (TGFβ1) and IL-6 have been reported to be weak inducers of inflammation [48, 49]. Conversely, IL-23 together with IL-1β induces the differentiation of highly pathogenic Th17 cells (Th1/17 cells) which also express CXCR3 and T-bet and produce IL-17, IFN-γ, and GM-CSF in mice [48, 49]. Recent studies clarified the production of GM-CSF is critical for the pro-inflammatory function of Th17 cells [3, 4]. In humans, IL-12, instead of IL-23, together with IL-1β is reported to promote the differentiation of Th1/17 cells [50]. Th1/17 cells can be distinguished from Th1 cells by the expression of CD161, a hallmark of Th17 progeny cells in humans [51]. A recent study reported that IL-23 drives switch of surface signature from CCR6 to CCR2 which defines GM-CSF/IFNγ-producing inflammatory Th17 cells and that CCR2 drives these cells to the central nervous system (CNS) in experimental autoimmune encephalomyelitis (EAE) [52]. The pathway to induce GM-CSF production in Th cells has not been clarified well yet. T-bet was reported to drive $CCR6^{-}CCR2^{+}$ GM-CSF/IFNγ-producing Th17

cell formation [52]. On the other hand, T-bet-deficient Th17 cells are reported to have normal GM-CSF production [3]. Ectopic RORγt expression showed that RORγt drove GM-CSF production in Th cells [4]. Conversely, RORγt-deficient CD4 T cells were also able to produce GM-CSF [3]. These reports indicate the existence of additional pathways.

GM-CSF is also reported to be produced by Th1 cells and is crucial for their encephalitogenicity [4]. It was reported that STAT4 regulated GM-CSF production in Th1 cells but not in Th17 cells [53]. On the other hand, the other report indicated that STAT4 regulated GM-CSF production in both Th1 and Th17 cells by directly binding to the Csf2 promoter [54]. Recent findings on Th17 plasticity and heterogeneity indicate that it is necessary to re-examine previous studies in this field.

In addition to these cells, recent studies reported the existence of an IL-2- or IL-7-activated STAT5-dependent novel subset of GM-CSF-producing Th cells (Th-GM) which express low or undetectable T-bet, GATA-3, or RORγt [55, 56] and that Th-GM cells were able to induce more severe EAE than Th17 or Th1 cells [55]. In humans, the $CCR10^{+}CCR4^{+}CXCR3^{-}CCR6^{-}$ signature was reported to define Th-GM [56]. It is possible that Th-GM cooperate with Th1/17 cells or Th1 cells to exacerbate the development of inflammation.

Th2 cells are also reported as one of the GM-CSF-producing cells [57]. A positive correlation between $GATA\text{-}3^{+}$ cells and $GM\text{-}CSF^{+}$ cells in the nasal mucosa of allergic rhinitis patients is reported [58]; however, the precise mechanism of GM-CSF production in Th2 cells has not been analyzed yet.

GM-CSF in autoimmune disease

Recent evidence revealed that GM-CSF played critical roles in the development of many autoimmune diseases. GM-CSF depletion or neutralization suppresses many autoimmune disease models, including EAE [3, 4], arthritis [59–61], arthritis-related interstitial lung disease [60], nephritis [62], or psoriasis [63]. On the other hand, GM-CSF administration is reported to improve the models of myasthenia gravis [64], type 1 diabetes [65], or colitis [66].

GM-CSF in the CNS

IL-17-producing Th17 cells have been reported as central mediators of CNS inflammation in both EAE and multiple sclerosis (MS) [67, 68]. However, recent studies reported that GM-CSF was essential for the encephalitogenicity of CD4 T cells in EAE and that IL-17 was dispensable for the development of EAE [3, 4]. The concentrations of GM-CSF and the number of GM-CSF-producing CD4 T cells in the cerebrospinal fluid were reported to be elevated in MS patients [56, 69]. GM-CSF deficiency or neutralization was reported to prevent the onset of EAE [70, 71]. In contrast, the administration of recombinant GM-CSF exacerbated EAE [70].

GM-CSF induces the proliferation and activation of microglial cells which produce highly neurotoxic substances such as ROS, nitrogen species, and glutamate [71, 72]. GM-CSF-producing CD4 T cells also induce the polarization of neurotoxic M1-like phenotype of microglia and promote the production of pro-inflammatory cytokines such as IL-1β, IL-6, and TNFα, which also contribute to myelin sheath damage [72, 73]. GM-CSF is also required for the recruitment of peripheral myeloid cells that contribute to blood-brain barrier and blood-spinal cord barrier disruption and demyelization into the CNS [74, 75]. These resident and infiltrating antigen-presenting cells (APCs) re-stimulate T cells and lead to further APC activation [76].

GM-CSF in arthritis

In the models of arthritis, IL-17 has been reported as a main pathogenic cytokine as in EAE [77, 78]. IL-17 deficiency ameliorated collagen-induced arthritis (CIA) but did not completely inhibit it [78]. IL-17 inhibition was also reported to be an unsatisfactory method for the treatment of rheumatoid arthritis (RA) [79]. These reports indicated the existence of the other critical factors in the development of arthritis.

In RA patients, the concentration of GM-CSF in the synovial fluid and plasma was elevated [80, 81] and the administration of recombinant GM-CSF exacerbated the disease activity [82]. Bone marrow adjacent to the RA joints contains an increased number of granulocyte-macrophage progenitors, colony-forming unit granulocyte-macrophages (CFU-GM), which can differentiate into granulocytes or macrophages with GM-CSF stimulation [83] and also into osteoclasts with M-CSF and RANKL stimulation [84]. The frequency of GM-CSF-producing T helper cells in synovial fluid cells was also significantly increased compared to peripheral blood mononuclear cells (PBMCs) and correlated with erythrocyte sedimentation rate (ESR) levels in juvenile idiopathic arthritis (JIA) [85].

In mouse models of arthritis, GM-CSF deficiency or neutralization prevented the development of arthritis [59–61] and reduced the concentrations of TNF and IL-1 in joints [59]. Conversely, GM-CSF administration exacerbated arthritis [86]. In arthritis of SKG mice, GM-CSF secreted by T cells upregulated the production of pro-inflammatory cytokines such as IL-6 or IL-1β from macrophages [60, 87]. This in turn induced further differentiation and expansion of IL-17-producing and GM-CSF-producing CD4 T cells [60] and exacerbated arthritis.

GM-CSF in arthritis-related interstitial lung disease

SKG arthritis model develops chronic-progressive interstitial lung disease (ILD) which histologically resembles connective tissue disease-associated ILD (CTD-ILD) [60, 88]. This model was characterized with massive infiltration of Th17 cells, GM-CSF-producing CD4 T cells, and neutrophils with fibrosis in the lungs [60]. The overexpression of GM-CSF was reported to induce severe neutrophil, eosinophil, and macrophage infiltration with fibrosis in the lungs [89, 90]. GM-CSF promotes macrophages to produce IL-6 and IL-1β and enhances differentiation of IL-17A and/or GM-CSF-producing T cells and therefore infiltration of neutrophils into the lungs [60]. Neutrophils were reported to produce ROS, MMPs, neutrophil elastase, or myeloperoxidase and cause parenchymal and stromal cell injury in the lungs [91–93]. GM-CSF also stimulates macrophages to release profibrotic cytokines and induces fibrosis by direct stimulation of airway smooth muscle cells [90, 94]. GM-CSF neutralization completely blocked the development of ILD in SKG mice but IL-17A neutralization did not, indicating that GM-CSF played a more critical role than IL-17A in this ILD [60].

The contribution of GM-CSF in human ILD has not been analyzed well yet. In patients with pulmonary fibrosis, the concentration of GM-CSF in the bronchoalveolar lavage fluid (BALF) was reported to be elevated [95, 96]. A recent report also reported that serum concentration of GM-CSF was associated with ILD in patients with RA [97]. Further studies to clarify the contribution of GM-CSF in CTD-ILD are awaited.

GM-CSF in the intestine

In the intestine, GM-CSF contributes to mucosal barrier function and resistance to bacterial translocation by promoting the recruitment and activation of myeloid cells. GM-CSF also promotes tissue repair via acceleration of epithelial cell proliferation and macrophages as effectors of wound healing [98–100].

Recent studies suggested that mucosal innate immunodeficiency caused by a variety of genetic defects contributed the susceptibility of Crohn's disease (CD) and increased the translocation of pathogens to the bowel tissue [101]. Higher levels of GM-CSF secretion have been detected in mucosal lesions of inflammatory bowel disease (IBD) compared with normal mucosa [102, 103] and also in the colon lesions of dextran sodium (DSS)-induced colitis mice model [104]. On the other hand, in CD, the increased levels of GM-CSF autoantibodies have been reported [105]. The levels of GM-CSF autoantibodies correlated with the disease activity and inversely correlated with the neutrophil phagocytic activity in CD patients [105]. GM-CSF-deficient mice were reported to be more susceptible to acute DSS-induced colitis [106], and the severity of this colitis was largely prevented by GM-CSF administration [66, 107]. Conversely, GM-CSF neutralization was reported to ameliorate 2,4,6-trinitrobenzene sulfonic acid (TNBS)-induced colitis [108] and IL-23-driven colitis [109]. The overexpression of GM-CSF in the stomach was reported to lead to autoimmune gastritis [110]. These data indicated the possibilities that both relative shortage and excessive amount of GM-CSF could induce colitis. Further studies are also needed to clarify whether GM-CSF autoantibodies in CD patients are pathogenic or not pathogenic and produced just as a result of elevated GM-CSF.

There are some trials of GM-CSF administration for the treatment of CD patients. Initial reports indicated a high rate of clinical response and remission with minimal adverse effects [111–113]. However, a recent large randomized trial reported that it is not effective for induction of clinical remission or improvement in active CD [114]. The pathogenic mechanism of CD patients is considered to be heterogeneous. Therefore, GM-CSF administration might be effective only in some subgroups of patients.

GM-CSF target therapy

There are several ongoing or completed clinical trials targeting GM-CSF or GM-CSF receptor (Table 1). Detailed information is available at ClinicalTrials.gov. Although GM-CSF inhibition showed rapid clinical response with no serious adverse reactions so far [115–117], there are some potential side effects which need to be monitored. The existence of GM-CSF autoantibodies or the mutations of GM-CSF receptor are reported to cause PAP [6]. On the other hand, healthy individuals also have GM-CSF autoantibodies [118], suggesting that the risk of PAP is increased only when GM-CSF autoantibody levels are increased above a critical threshold [119]. In addition, GM-CSF inhibition might exacerbate the existing Crohn's disease as mentioned above. An increased susceptibility to infections in GM-CSF-deficient mice [5, 120] also indicates the risk of infection in GM-CSF target therapy.

Mavrilimumab

Mavrilimumab is a human monoclonal antibody against GM-CSF receptor α. In the first phase 1 study, 32 subjects with mild RA received single intravenous escalating doses of mavrilimumab and showed its safety and tolerability. Reductions of acute-phase reactants and disease activity score (DAS) 28 was also observed [121].

A phase 2a randomized, double-blind, placebo-controlled, ascending-dose study in subjects with moderate to severe active RA (EARTH study) reported significant efficacy with no serious adverse

Table 1 Clinical trials targeting GM-CSF

Target	Drug	Indication	Trial	Phase	Regimen	Status	
GM-CSFR	Mavrilimumab (CAM-3001)	RA	NCT00771420	I	MTX + 0.01, 0.03, 0.1, 0.3, 1.0, 3.0, and 10.0 mg/kg or placebo, single dose	Completed	[121]
		RA	NCT01050998 (EARTH study)	IIa	MTX + 10, 30, 50, and 100 mg or placebo biweekly for 12 weeks	Completed	[117]
		RA	NCT01706926 (EARTH EXPLORER 1)	IIb	MTX + 30, 100, and 150 mg or placebo biweekly for 24 weeks	Completed	[122–125]
		RA	NCT01712399	IIb	Long time safety study (5 years) MTX + 100 mg biweekly	Active, not recruiting	[126, 127]
		RA	NCT01715896 (EARTH EXPLORER 2)	II	MTX + mavrilimumab biweekly or golimumab alternating with placebo	Completed	[128]
GM-CSF	MOR103	RA	NCT01023256	Ib/IIa	0.3, 1.0, and 1.5 mg/kg or placebo weekly for 4 weeks	Completed	[116]
		MS	NCT01517282	Ib	0.5, 1.0, and 2.0 mg/kg or placebo biweekly for 10 weeks	Completed	[115]
GM-CSF	Namilumab (MT203)	RA	NCT01317797	Ib	150 and 300 mg or placebo biweekly, 3 times	Completed	[129]
		RA	NCT02393378	II	MTX + namilumab or adalimumab for 24 weeks	Recruiting	[131]
		RA	NCT02379091	II	MTX + 20, 80, and 150 mg or placebo for 24 weeks	Recruiting	[130]
		Psoriasis	NCT02129777	II	40, 100, 160, and 300 mg or placebo on day 1; 20, 50, 80, and 150 mg or placebo on days 15, 43, and 71 (followed by open-label extension study)	Recruiting	[132]
GM-CSF	KB003	RA	NCT00995449	II	600 mg or placebo at weeks 0, 2, 4, 8, and 12	Terminated	[133]
		Asthma	NCT01603277	II	400 mg or placebo	Completed	
GM-CSF	MORAb-022	RA	NCT01357759	I	Escalating doses of MORAb-022 or placebo	Completed	[134]

Abbreviations: *GM-CSFR* GM-CSF receptor, *RA* rheumatoid arthritis, *MS* multiple sclerosis, *MTX* methotrexate

events [117]. In this study, 239 patients with active RA despite methotrexate (MTX) treatment received subcutaneous mavrilimumab or placebo every other week for 12 weeks on stable-background MTX therapy and 55.7 % of all mavrilimumab-treated participants met the primary end point of achieving a ≥1.2 decrease from baseline in the DAS (DAS28-CRP) vs 34.7 % of placebo-treated participants at week 12. All mavrilimumab-treated patients showed a response by week 2. The 100 mg dose of mavrilimumab demonstrated a significant effect vs placebo on DAS28-CRP <2.6, all categories of the American College of Rheumatology (ACR) criteria, and the Health Assessment Questionnaire Disability Index.

In a subsequent phase 2b study (EARTH EXPLORER 1) [122–125], 326 patients with moderate to severe RA received an ascending dose of mavrilimumab or placebo every 2 weeks plus MTX for 24 weeks and showed an acceptable safety and tolerability. A statistically significant difference in DAS28-CRP was observed in all doses of mavrilimumab vs placebo at week 12, and a significantly higher ACR response rate of mavrilimumab-treated subjects than that of placebo was observed at week 24. Particularly, the 150 mg dose showed a significant difference vs placebo for these parameters as early as week 1.

A nonrandomized, open-label phase 2 study to evaluate the long-term safety and tolerability from day 1 through to approximately 5 years is ongoing (NCT01712399) [126]. This study enrolled RA patients who had completed the EARTH EXPLORER 1 and 2 studies or were rescued as inadequate responders at a predefined time point, and they received 100 mg of mavrilimumab every other week. At week 74, mavrilimumab demonstrated sustained safety and efficacy with DAS28-CRP <3.2 and <2.5 rates of 57.3 and 38.5 %, respectively, and 68 % of patients showed no radiographic progression [127].

A randomized, double-blind, placebo-controlled phase 2 study (EARTH EXPLORER 2) to compare the safety and efficacy of mavrilimumab with those of golimumab, an anti-TNF antibody in 120 patients with moderate to severe RA who had an inadequate response to one or two anti-TNF agents, was completed [128].

MOR103

MOR103, which is a fully human monoclonal antibody against GM-CSF, has shown preliminary evidence of safety and rapid efficacy (within 2 weeks) in a randomized, double-blind, placebo-controlled, dose-escalating phase 1b/2a trial for patients with moderate RA ($n = 96$) [116]. Patients received four times of weekly intravenous MOR103 or placebo, and subjects receiving higher doses of MOR103 (1.0 and 1.5 mg/kg) showed significant improvement in DAS28 scores and joint counts and significantly higher European League Against Rheumatism response rates than subjects receiving placebo.

MOR103 was also tested in a randomized, double-blind, placebo-controlled phase 1b trial for patients with relapsing-remitting MS or secondary progressive MS. Patients received placebo or an escalating dose of MOR103 every 2 weeks for 10 weeks and showed acceptable tolerability of MOR103 [115].

Namilumab (MT203)

Namilumab is a human monoclonal antibody against GM-CSF. In a randomized, double-blind, dose-escalating phase 1b study, mild to moderate RA patients received three times of every 2-week injection of namilumab and showed its safety and tolerability [129]. The other trials testing namilumab is ongoing: a dose-finding phase 2 study of namilumab in combination with MTX in moderate to severe RA patients with inadequate response to MTX or one TNF inhibitor [130] and a phase 2 trial to evaluate the efficacy and safety of the combination of the existing MTX and namilumab vs adalimumab, an anti-TNF antibody in patients with moderate to severe early RA inadequately responding to MTX [131].

It is also being tested in a randomized double-blind phase 2 trial for moderate to severe plaque psoriasis [132].

KB003

KB003 is a humanized monoclonal antibody targeting GM-CSF. A randomized phase 2 study in RA patients showed safety and tolerability in 3 months of repeated dosing [133].

MORAb-002

MORAb-002 is a human monoclonal antibody against GM-CSF. A randomized, double-blind phase 1 trial in RA was completed recently [134].

Conclusions

Recent studies clarified the pivotal roles of GM-CSF in the development of many autoimmune diseases. Much attention has been focused on the inhibition of GM-CSF as an attractive approach for the treatment of these diseases. Further studies to clarify the molecular mechanism of GM-CSF production and precise role of GM-CSF in the development of autoimmune disease are awaited with interest.

Abbreviations

APC: antigen-presenting cell; CIA: collagen-induced arthritis; CTD-ILD: connective tissue disease-associated interstitial lung disease; DAS: disease activity score; DC: dendritic cell; EAE: experimental autoimmune encephalomyelitis; GM-CSF: granulocyte-macrophage colony-stimulating factor; ILD: interstitial lung disease; MS: multiple sclerosis; MTX: methotrexate; PAP: pulmonary alveolar proteinosis; RA: rheumatoid arthritis.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

AS drafted the manuscript. TU helped to draft the manuscript. TM gave the final approval of the version to be submitted and any revised version. All authors read and approved the final manuscript.

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