Targeting GM-CSF in rheumatoid arthritis

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ABSTRACT

Granulocyte-macrophage colony-stimulating factor (GM-CSF) is well-known as a haemopoietic growth factor. However, it is also essential in regulating functions of mature myeloid cells such as macrophages. Preclinical studies and observations of flares of arthritis in patients following GM-CSF treatment supported its important contribution to the pathogenesis of rheumatoid arthritis (RA). As the most advanced compound, mavrilimumab, a monoclonal antibody against GM-CSF receptor, has already completed phase II trials with a long term of follow-up period of 74 weeks. During this exposure period, an acceptable sustained safety and tolerability profile has been observed addressing the concerns of development of cytopenias or pulmonary alveolar proteinosis. Of note, a rapid and sustained efficacy and normalisation of acute phase reactants were consistently shown in studies both targeting GM-CSF and its receptor. Its tumour necrosis factor (TNF) independent mode of action with concurrent blockade of GM-CSF as well as IL-17 signalling reported from preclinical studies supports the assumption that it can be a useful biologic and an alternative agent in TNF inhibitor resistant patients with RA. Therefore, subsequent studies are warranted to investigate the safety and efficacy of GM-CSF blocking agents in different subgroups of RA.

Introduction

Although treatment of rheumatoid arthritis (RA) has evolved tremendously in recent years, still an important number of patients fail to reach the target, disease remission or low disease activity (LDA) (1). Blockade of any single cytokine or cellular subset cannot control the disease in all patients, which necessitates investigations of other cytokines or cellular mechanisms responsible from RA pathogenesis. To most clinicians, granulocyte-macrophage colony-stimulating factor (GM-CSF) is well-known as a haemopoietic growth factor used to treat neutropenia following chemotherapy. It was a long-time concern that targeted therapies against this cytokine could cause severe side effects such as neutropenia or pulmonary alveolar proteinosis. Therefore, during the early development phase of compounds targeting GM-CSF or its receptor special attention was paid to this potential adverse event revealing no evidence for such an associated risk profile. On the other hand the so far available results clearly showed rapid and sustained effects on disease activity and patient reported outcomes in RA (2).

GM-CSF

GM-CSF, a small secreted cytokine is a haemopoietic growth factor responsible for proliferation and differentiation of myeloid cells from bone marrow progenitors. Besides myeloid cells, T and B cells and tissue resident cells including chondrocytes, fibroblasts, osteoblasts, microglia, endothelial and epithelial cells can secrete GM-CSF (3-5). GM-CSF binds to a heterodimeric GM-CSF receptor (GM-CSFR) composed of a specific-ligand binding α-chain (GM-CSFRα) and a signal-transducing β-chain (GM-CSFRβ), which is shared with IL-3 and IL-5 receptors (6, 7). GM-CSFR activation leads to downstream signalling pathways of Janus kinase-signal transducer and activator of transcription-suppressor of cytokine signalling (JAK-STAT-SOCS) as well as other pathways including mitogen-activated protein kinases (MAPK), phosphatidylinositol 3 kinase (PI3K), and NFκB (7-11). The cytoplasmic tail of GM-CSFRα has also the capacity to interact with signalling pathways (12). GM-CSF is not solely a growth factor responsible for proliferation of myeloid cells, but also essential in regulating functions of mature myeloid cells such as chemotaxis and cell adhesion, dendritic cell function, expression of

pro-inflammatory cytokines, phagocytosis, and microbial killing (6, 13, 14). It has a central role in regulating innate immunity. Regarding *in vitro* studies, GM-CSF can polarise macrophages into M1-like macrophages producing inflammatory cytokines instead of M2-like macrophages which in contrast produce an anti-inflammatory medium (15, 16). However, *in vivo* studies suggested also association with M2 polarisation in the lung and collaboration of other immune factors such as interferon-gamma (IFNγ), interferon regulatory factor 5 (IRF-5) or transforming growth factor-β (TGFβ) family member activin A (17-20). In the pulmonary mucosa, the epithelium is a major producer of GM-CSF. This GM-CSF plays a critical role locally in regulating microbial defense and surfactant clearance by alveolar macrophage population. Defects in GM-CSF or its receptor led to death of mice causing pulmonary disease characterised by accumulation of surfactant-like proteins and increased susceptibility to microbial infection (21). However, a surprising finding in this study was a relatively normal myelopoiesis.

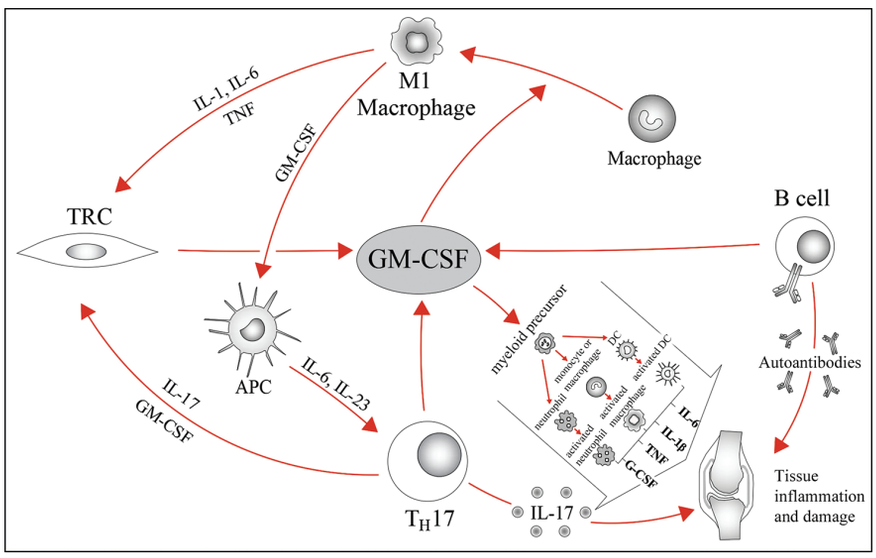

Fig. 1. GM-CSF as a therapeutic target for inflammation. GM-CSF, is a haemopoietic growth factor responsible for proliferation and differentiation of myeloid cells from bone marrow progenitors. Myeloid cells, T and B cells and tissue resident cells can secrete GM-CSF. GM-CSF can polarise macrophages into M1-like macrophages producing inflammatory cytokines. These cytokines induce the recruitment of inflammatory cells and activation of tissue resident cells. GM-CSF secreted by M1 macrophages induces antigen presenting cells to produce IL-6 and IL-23. IL6 and IL-23 causes again activation of T cells and differentiation to TH17 cells which in turn secrete GM-CSF and IL-17 maintaining the circle. GM-CSF produced by TH17cells also induce inflammation by activating monocyte-macrophage system and neutrophils.
APC: antigen presenting cell; DC: dendritic cell; IL: interleukin; G-CSF: granulocyte colony-stimulating factor; GM-CSF: granulocyte-macrophage colony-stimulating factor; T_H17: T-helper-17cell; TNF: tumour necrosis factor; TRC: tissue resident cell.

GM-CSF and RA

GM-CSF is expressed in the synovial membrane and levels of GM-CSF are elevated in synovial fluid of RA patients (22, 23). The GM-CSFRα is also up-regulated in synovial tissue and on circulating mononuclear cells from RA subjects (24, 25). Synovial tissue macrophage populations are associated with articular damage and decrease in numbers of macrophages is a sensitive biomarker for response to treatment in patients with RA (26-28). Since GM-CSF plays a central role in macrophage differentiation, survival and activation, inhibiting GM-CSF activity can affect macrophage function and may provide clinical benefit in RA. Th17 cells have an important place also in RA pathogenesis and GM-CSF contributes to the differentiation and pathogenicity of these cells (29, 30). Figure 1 provides a schematic representation summarising the association of GM-CSF with cells and cytokines important in RA pathogenesis.

In animal models of arthritis, while deficiency and blockade of GM-CSF is protective, overexpression or injection of GM-CSF is associated with flares of arthritis (31-35). Other *in vitro* studies suggest a role for GM-CSF pathway blockade in tumour necrosis factor (TNF) inhibitor resistant situations and as a part of combinations strategies *e.g.* with IL-17 or p38 inhibitors (32, 36-39). Finally, the observation of flares of arthritis following administration of recombinant GM-CSF to treat neutropenia in patients with Felty's syndrome or after chemotherapy suggested a potential role for targeting GM-CSF and its receptors in RA (40-42).

Clinical studies

GM-CSFR inhibition

Phase I. Mavrilimumab (CAM-3001) is a high-affinity human monoclonal antibody to the GM-CSFRα chain with competitive antagonistic effect on GM-CSF signalling. The first in-human study targeting the innate arm of the immune system via the GM-CSF pathway was performed with mavrilimumab in adult onset RA patients with a Disease Activity Score 28-joint assessment (DAS28) ≤4.8 (mild to moderate RA) under a stable dosage of methotrexate (MTX) for ≥3 months (43). This was a double-blind placebo-controlled study with a 5:1 randomisation (mavrilimumab:placebo) where patients received single escalating intravenous (IV) doses of mavrilimumab (0.01, 0.03, 0.1, 0.3, 1.0, 3.0 and 10.0 mg/kg) or placebo on study Day 0 and were followed up for 24 weeks. Overall, 32 patients were enrolled and completed the planned evaluations including safety analysis. The primary objective was safety of the compound, while secondary objectives included pharmacokinetics and effect on disease activity. As a surrogate marker for biologic activity, inhibition of the induction of SOCS3 mRNA by GM-CSF was shown with doses of 1.0 mg/kg just after 4 hours of dosing and this effect was sustained over 2 weeks. Of note, the study population had LDA at baseline and 63% of patients had normal acute phase reactants at the study entry.

Of the n=10 out of 27 subjects treated with mavrilimumab who had elevated erythrocyte sedimentation rate (ESR) (≥ 20 mm/hr) at baseline, normalised values were measured in n=9 of them after treatment. None of the patients had significant haematological changes or deterioration of lung functions. Of note, adverse events (AEs) were similar between placebo and mavrilimumab-treated groups, mostly mild and not related to the drug dosage.

Phase II trials. The phase 2A multicentre, randomised, double-blind, placebo-controlled study (EARTH) of mavrilimumab included 233 adult European subjects with moderate-to-severely active seropositive and MTX-resistant RA (DAS28 ≥3.2) on a stable MTX dose over at least 4 weeks prior to screening (44). Patients with active or latent tuberculosis (TB), clinically significant chronic or recurrent infections including hepatitis C or chronic active hepatitis B were excluded. Furthermore, a history of previous treatment with more than one biologic therapy for RA that was discontinued for lack of efficacy was also an exclusion criteria. Subjects received 10, 30, 50 or 100mg of mavrilimumab subcutaneous (SC) or placebo every other week (eow) for 12 weeks and patients were followed-up for additional 12 weeks. The primary endpoint defined as an improvement in DAS28-CRP of at least 1.2 at Week 12 was significantly more frequently achieved in the mavrilimumab-treated group compared to placebo (55.7% *vs*. 34.7%; p=0.003). Of note, differences in response rates were observed already by Week 2, increased throughout the study period and were dose related with best improvement in the 100 mg group. Additionally, all categories of the American College of Rheumatology (ACR) criteria (ACR20: 69.2% *vs*. 40.0%, p=0.005; ACR50: 30.8% *vs*. 12.0%, p=0.021; ACR70: 17.9% *vs*. 4.0%, p=0.030), as well as the Health Assessment Questionnaire Disability Index (HAQ-DI) (-0.48 *vs*. -0.25, p=0.005) were significantly improved. The proportion of patients achieving a moderate or good European League Against Rheumatism (EULAR) response was significantly higher compared to placebo (67.7 *vs*. 50.7%; p=0.025) with the highest proportion of moderate or good EULAR responders in the 100 mg group (46.2% and 30.8%, respectively). AEs were generally mild or moderate and no relevant hypersensitivity reactions, serious infections or clinically significant deterioration of lung functions were noted. As add-on to the EARTH study, the same protocol was performed in 51 Japanese patients (45). With the exception of ACR70, the 100mg dose showed a high degree of consistency in almost all efficacy endpoints with comparable safety profile to the European patients.

A phase IIb study of mavrilimumab (EARTH EXPLORER 1) enrolled 326 patients with moderate to severe adult onset RA (DAS28–CRP ≥3.2; ≥4 swollen joint; mean DAS28-CRP at baseline: 5.77) from Europe and South America with an inadequate response to at least one of disease-modifying anti-rheumatic drugs (DMARDs) (46-52). Patients were randomised to receive 1 of 3 SC mavrilimumab dosages (150, 100, 30 mg eow) or placebo plus MTX (7.5–25.0 mg/week). At Week 12, a statistically significant difference (p<0.001) in DAS28-CRP as the primary endpoint was seen for all dosages of mavrilimumab vs. placebo and this effect was sustained until Week 24 (p<0.001). Furthermore, a significantly greater percentage of mavrilimumab-treated patients met the ACR20 co-primary endpoint *vs*. placebo for all dosages at Week 24 (p<0.001). In summary, mavrilimumab (particularly 150 mg eow) showed rapid and clinically meaningful effects across a number of disease activity parameters with an acceptable safety and tolerability profile over the 24-week study period.

In another phase II study of mavrilimumab (EARTH EXPLORER 2), moderate-to-severe active RA patients who have had an inadequate response to one or two anti-TNF agents were randomised to SC mavrilimumab 100 mg (eow) or golimumab 50 mg (monthly) for 24 weeks (53). The study has been completed, however, results have not been published so far.

An open label extension study was performed in adult RA patients who had completed EARTH Explorer 1 and 2 Phase IIb studies or were rescued as inadequate responders at Week 12 (54). The aim of the study was to evaluate the long-term safety and efficacy of mavrilimumab 100 mg eow through 74 weeks of treatment in patients with moderate to severe RA. Primary endpoint was to assess the long-term risk benefit ratio of mavrilimumab 100 mg eow via evaluation of treatment-emergent adverse events (TEAEs), treatment-emergent serious adverse events (TESAEs), laboratory parameters and pulmonary function tests. Exploratory endpoints included DAS28–CRP LDA (<3.2), DAS28–CRP remission rate (<2.6), ACR20/50/70 response rates and change in modified Total Sharp Score (mTSS) erosion/narrowing scores. Among the 440 patients receiving mavrilimumab in this study, the most common TESAEs (n[rate/100 patient years]) were arthritis symptoms (coded as "osteoarthritis") (4[0,7]) and bronchitis (3[0,5]). The most common TEAEs of special interest were bronchitis (29[4,8]) and respiratory tract infection(12[2,0]). Within the clinical programme, no monocytopenia was reported and there were no cases of pulmonary alveolar proteinosis. Overall, also no other pulmonary safety concerns were identified, and pulmonary function tests demonstrated a generally transient 20% reduction to <80% of predicted values in a few patients. With respect to efficacy, mavrilimumab demonstrated sustained efficacy with DAS28-CRP <3.2 and <2.6 rates of 57.3% and 38.5%, respectively. After 74 weeks of treatment, 68% of patients showed no radiographic progression (<0.5 change in mTSS vs. baseline). In conclusion, all performed clinical trials reached their primary outcome and demonstrated the benefit of inhibiting the GM-CSFR-α pathway on RA disease activity. Importantly, mavrilimumab showed an acceptable sustained safety and tolerability profile, with no significant pulmonary findings over the 74-week treatment duration. Since mavrilimumab produced sustained and clinically meaningful effects across a number of disease activity parameters

Table I. Clinical trials of agents targeting GM-CSF pathway in rheumatoid arthritis.

Drug/ ClinicalTrials.gov Identifier	Target	Drug regime	Primary outcome measures	Trial status
Mavrilimumab NCT00771420 (43)	GM-CSFR	a single, escalating IV doses of mavrilimumab (0.01, 0.03, 0.1, 0.3, 1.0, 3.0 and 10.0mg/kg) or placebo, plus MTX	Incidence and severity of AEs	Phase I published
Mavrilimumab NCT01050998 (44)	GM-CSFR	10mg, 30mg, 50mg, or 100mg SC mavrilimumab eow or placebo, plus MTX	Improvement in DAS28-CRP	Phase II published
Mavrilimumab NCT01050998 (Japanese patients) (45)	GM-CSFR	10mg, 30mg, 50mg, or 100mg SC mavrilimumab eow or placebo, plus MTX	Improvement in DAS28-CRP	Phase II published
Mavrilimumab NCT01706926 (46-52)	GM-CSFR	150, 100, 30mg SC mavrilimumab eow or placebo, plus MTX	Improvement in DAS28-CRP and ACR20	Phase IIb abstracts presented
Mavrilimumab NCT01715896 (53)	GM-CSFR	Mavrilimumab 100mg SC eow or golimumab 50mg SC monthly alternating with placebo, plus MTX	ACR20, 50, 70 responses, DAS-28<2,6, HAQ-DI improvement>0,25	Phase II completed, no results posted
Mavrilimumab NCT01712399 (54)	GM-CSFR	Mavrilimumab 100 mg SC eow plus MTX	Incidence and severity of AEs	Phase II abstract presented
MOR103 NCT01023256 (55)	GM-CSF	Weekly escalating IV doses of MOR103 (0.3, 1.0 and 1.5mg/kg) or placebo	Incidence and severity of AEs	Phase Ib/IIa published
Namilumab NCT01317797 (56)	GM-CSF	Weekly escalating SC doses of namilumab (150mg and 300mg) or placebo, plus MTX	Incidence and severity of AEs	Phase I abstract presented
Namilumab NCT02354599 (57)	GM-CSF	Single SC doses of namilumab (80mg, 150mg and 300mg) or placebo	Incidence and severity of AEs	Phase I recruiting
Namilumab NCT02379091 (58)	GM-CSF	SC doses of namilumab (20mg, 80mg and 150mg) or placebo, plus MTX	DAS28-CRP response	Phase II recruiting
Namilumab NCT02393378 (59)	GM-CSF	Namilumab 300mg SC at Week 0 followed by 150mg eow or adalimumab 40mg eow, plus MTX	Change in synovitis, erosion and bone marrow edema (osteitis) based on OMERACT RAMRIS	Phase II recruiting
MORAb-002 NCT01357759 (60)	GM-CSF	A single, escalating IV doses of MORAb-002 or placebo	Incidence and severity of AEs	Phase I completed, no results posted
KB003 NCT00995449 (61)	GM-CSF	70mg, 200mg, or 600mg KB003 IVx5doses or placebo IVx5doses	Incidence and severity of AEs	Phase II terminated (program refocus)

ACR: American College of Rheumatology; AE: adverse event; CRP: C-reactive protein; DAS28: Disease Activity Score-28; eow: every other week; G-CSF: granulocyte colony-stimulating factor; GM-CSF: granulocyte-macrophage colony-stimulating factor; HAQ-DI: Health Assessment Questionnaire Disability Index; IV: intravenous; MTX: methotrexate; OMERACT: Outcome measures in Rheumatology; RAMRIS: rheumatoid arthritis magnetic resonance imaging studies; SC: subcutaneous.

(DAS28-CRP <3.2, DAS28–CRP <2.6, ACR20/50/70), further studies are warranted to confirm the promising results in larger cohorts and to find an optimal positioning for mavrilimumab in the treatment algorithm in patients with RA.

GM-CSF inhibition

MOR103. An alternative approach to interfere with GM-CSF signalling would be the direct neutralisation of the cytokine. The first in patient Study of an anti-GM-CSF monoclonal antibody (MOR103) in RA included 96 patients with active RA (DAS28≤5.1) (55). The primary outcome measure was the adverse event rate and safety profile, while secondary endpoints included DAS28, ACR core set measures, EULAR response criteria and magnetic resonance imaging of synovitis (MRI synovitis). By using three different dosages of MOR103 (0.3, 1.0 and 1.5 mg/kg) compared to placebo, a rapid and significant clinical improvement was demonstrated compared to placebo, most pronounced at the 1.0 mg/kg dosage in this study. Short-term safety and tolerability remained in the range of placebo. AEs were generally mild or moderate and the most common AE was nasopharyngitis.

Namilumab. Namilumab (MT203) is another monoclonal antibody targeting GM-CSF and has been evaluated in patients with mild to moderate RA in a phase Ib study, PRIORA (56). Patients were on stable MTX doses and received three single injections of namilumab 150 or 300mg or placebo on days 0, 15 and 29 with a follow-up period of 12 weeks. Namilumab was generally well tolerated with a similar safety outcome across the treatment groups. By Day 29, greater improvements in DAS28 (ESR and CRP) and joint counts could be observed in namilumab-treated patients compared to placebo. Additionally, DAS28-ESR response rates were higher in namilumab group than placebo at Day 56 (71.4% *vs*. 28.6%). Currently, another phase I and two phase II trials of namilumab

are recruiting patients (57-59). Current status and characteristics of the studies targeting GM-CSF pathway are summarised in Table I.

Discussion and conclusion

Data from both preclinical and clinical studies suggest that targeting GM-CSF and its receptor is a reasonable treatment option in RA. The favourable safety together with early and sustained efficacy and consistency of results in patients from different continents support the initiation of worldwide phase III studies. Although the obtained ACR20 and ACR50 responses are comparable to marketed biologic agents, the TNF-independent mode of action of GM-CSF blockade may provide an alternative treatment option in patients resistant to other biologics. Moreover, data from preclinical studies support the hypothesis that targeting GM-CSF can be a part of possible future combination therapies especially with concurrent blockade of IL-17. Finally, the introduction of new therapies with novel targets has the potential to decrease the proportion of refractory patients in RA. The most important issue in the near future will be the selection of right biological DMARD on an individual basis.

References

1. SMOLEN JS, ALETAHA D: Rheumatoid arthritis therapy reappraisal: strategies, opportunities and challenges. *Nat Rev Rheumatol* 2015; 11: 276-89.
2. AVCI AB, FEIST E, BURMESTER GR: A Promising Target in Rheumatoid Arthritis Treatment: Granulocyte-Macrophage Colony-Stimulating Factor. Curr Treat Options in Rheum 2015; 1: 320-33.
3. LEIZER T, CEBON J, LAYTON JE, HAMILTON JA: Cytokine regulation of colony-stimulating factor production in cultured human synovial fibroblasts: I. Induction of GM-CSF and G-CSF production by interleukin-1 and tumor necrosis factor. *Blood* 1990; 76: 1989-96.
4. CAMPBELL IK, NOVAK U, CEBON J, LAYTON JE, HAMILTON JA: Human articular cartilage and chondrocytes produce hemopoietic colony-stimulating factors in culture in response to IL-1. *J Immunol* 1991; 147: 1238-46.
5. HAMILTON JA: Colony-stimulating factors in inflammation and autoimmunity. *Nat Rev Immunol* 2008; 8: 533-44.
6. FLEETWOOD AJ, COOK AD, HAMILTON JA: Functions of granulocyte-macrophage colony-stimulating factor. *Crit Rev Immunol* 2005; 25: 405-28.
7. HANSEN G, HERCUS TR, MCCLURE BJ *et al*.: The structure of the GM-CSF receptor complex reveals a distinct mode of cytokine receptor activation. *Cell* 2008; 134: 496-507.
8. JENKINS BJ, BLAKE TJ, GONDA TJ: Saturation mutagenesis of the beta subunit of the human granulocyte-macrophage colony-stimulating factor receptor shows clustering of constitutive mutations, activation of ERK MAP kinase and STAT pathways, and differential beta subunit tyrosine phosphorylation. *Blood* 1998; 92: 1989-2002.
9. SATO N, SAKAMAKI K, TERADA N, ARAI K, MIYAJIMA A: Signal transduction by the high-affinity GM-CSF receptor: two distinct cytoplasmic regions of the common beta subunit responsible for different signaling. *EMBO J* 1993; 12: 4181-9.
10. BROUGHTON SE, NERO TL, DHAGAT U *et al*.: The betac receptor family - Structural insights and their functional implications. *Cytokine* 2015; 74: 247-58.
11. HERCUS TR, DHAGAT U, KAN WL *et al*.: Signalling by the betac family of cytokines. *Cytokine Growth Factor Rev* 2013; 24: 189-201.
12. HERCUS TR, BARRY EF, DOTTORE M, *et al*.: High yield production of a soluble human interleukin-3 variant from E. coli with wild-type bioactivity and improved radiolabeling properties. *PLoS One* 2013; 8: e74376.
13. COOK AD, BRAINE EL, HAMILTON JA: Stimulus-dependent requirement for granulocyte-macrophage colony-stimulating factor in inflammation. *J Immunol* 2004; 173: 4643-51.
14. WICKS IP, ROBERTS AW: Targeting GM-CSF in inflammatory diseases. *Nat Rev Rheumatol* 2016; 12: 37-48.
15. FLEETWOOD AJ, LAWRENCE T, HAMILTON JA, COOK AD: Granulocyte-macrophage colony-stimulating factor (CSF) and macrophage CSF-dependent macrophage phenotypes display differences in cytokine profiles and transcription factor activities: implications for CSF blockade in inflammation. *J Immunol* 2007; 178: 5245-52.
16. MANTOVANI A, SOZZANI S, LOCATI M, ALLAVENA P, SICA A: Macrophage polarization: tumor-associated macrophages as a paradigm for polarized M2 mononuclear phagocytes. *Trends Immunol* 2002; 23: 549-55.
17. CATES AM, HOLDEN VI, MYERS EM, SMITH CK, KAPLAN MJ, KAHLENBERG JM: Interleukin 10 hampers endothelial cell differentiation and enhances the effects of interferon alpha on lupus endothelial cell progenitors. *Rheumatology* 2015; 54: 1114-23.
18. WILLART MA, DESWARTE K, POULIOT P *et al*.: Interleukin-1alpha controls allergic sensitization to inhaled house dust mite via the epithelial release of GM-CSF and IL-33. *J Exp Med* 2012; 209: 1505-17.
19. KRAUSGRUBER T, BLAZEK K, SMALLIE T *et al*.: IRF5 promotes inflammatory macrophage polarization and TH1-TH17 responses. *Nat Immunol* 2011; 12: 231-8.
20. SIERRA-FILARDI E, PUIG-KROGER A, BLANCO FJ *et al*.: Activin A skews macrophage polarization by promoting a proinflammatory phenotype and inhibiting the acquisition of anti-inflammatory macrophage markers. *Blood* 2011; 117: 5092-101.
21. STANLEY E, LIESCHKE GJ, GRAIL D *et al*.: Granulocyte/macrophage colony-stimulating factor-deficient mice show no major perturbation of hematopoiesis but develop a characteristic pulmonary pathology. *Proc Natl Acad Sci USA* 1994; 91: 5592-6.
22. FARAHAT MN, YANNI G, POSTON R, PANAYI GS: Cytokine expression in synovial membranes of patients with rheumatoid arthritis and osteoarthritis. *Ann Rheum Dis* 1993; 52: 870-5.
23. BELL AL, MAGILL MK, MCKANE WR, KIRK F, IRVINE AE: Measurement of colony-stimulating factors in synovial fluid: potential clinical value. *Rheumatol Int* 1995; 14: 177-82.
24. FIELD M, CLINTON L: Expression of GM-CSF receptor in rheumatoid arthritis. *Lancet* 1993; 342: 1244.
25. BERENBAUM F, RAJZBAUM G, AMOR B, TOUBERT A: Evidence for GM-CSF receptor expression in synovial tissue. An analysis by semi-quantitative polymerase chain reaction on rheumatoid arthritis and osteoarthritis synovial biopsies. *Eur cytokine Netw* 1994; 5: 43-6.
26. MULHERIN D, FITZGERALD O, BRESNIHAN B: Synovial tissue macrophage populations and articular damage in rheumatoid arthritis. *Arthritis Rheum* 1996; 39: 115-24.
27. HARINGMAN JJ, GERLAG DM, ZWINDERMAN AH *et al*.: Synovial tissue macrophages: a sensitive biomarker for response to treatment in patients with rheumatoid arthritis. *Ann Rheum Dis* 2005; 64: 834-8.
28. WIJBRANDTS CA, VERGUNST CE, HARINGMAN JJ, GERLAG DM, SMEETS TJ, TAK PP: Absence of changes in the number of synovial sublining macrophages after ineffective treatment for rheumatoid arthritis: Implications for use of synovial sublining macrophages as a biomarker. *Arthritis Rheum* 2007; 56: 3869-71.
29. CODARRI L, GYULVESZI G, TOSEVSKI V *et al*.: RORgammat drives production of the cytokine GM-CSF in helper T cells, which is essential for the effector phase of autoimmune neuroinflammation. *Nat Immunol* 2011; 12: 560-7.
30. EL-BEHI M, CIRIC B, DAI H *et al*.: The encephalitogenicity of T(H)17 cells is dependent on IL-1- and IL-23-induced production of the cytokine GM-CSF. *Nat Immunol* 2011; 12: 568-75.
31. COOK AD, BRAINE EL, CAMPBELL IK, RICH MJ, HAMILTON JA: Blockade of collagen-induced arthritis post-onset by antibody to granulocyte-macrophage colony-stimulating factor (GM-CSF): requirement for GM-CSF in the effector phase of disease. *Arthritis Res* 2001; 3: 293-8.
32. PLATER-ZYBERK C, JOOSTEN LA, HELSEN MM, HEPP J, BAEUERLE PA, VAN DEN BERG WB: GM-CSF neutralisation suppresses inflammation and protects cartilage in acute streptococcal cell wall arthritis of mice. *Ann Rheum Dis* 2007; 66: 452-7.
33. CAMPBELL IK, BENDELE A, SMITH DA, HAMILTON JA: Granulocyte-macrophage colony stimulating factor exacerbates collagen induced arthritis in mice. *Ann Rheum Dis* 1997;56 : 364-8.
34. LANG RA, METCALF D, CUTHBERTSON RA *et al*.: Transgenic mice expressing a hemopoietic growth factor gene (GM-CSF) de-

velop accumulations of macrophages, blindness, and a fatal syndrome of tissue damage. *Cell* 1987; 51: 675-86.
35. CAMPBELL IK, RICH MJ, BISCHOF RJ, DUNN AR, GRAIL D, HAMILTON JA: Protection from collagen-induced arthritis in granulocyte-macrophage colony-stimulating factor-deficient mice. *J Immunol* 1998; 161: 3639-44.
36. HUA F, HENSTOCK PV, TANG B: ERK activation by GM-CSF reduces effectiveness of p38 inhibitor on inhibiting TNFalpha release. *Int Immunopharmacol* 2010; 10: 730-7.
37. ESPELIN CW, GOLDSIPE A, SORGER PK, LAUFFENBURGER DA, DE GRAAF D, HENDRIKS BS: Elevated GM-CSF and IL-1beta levels compromise the ability of p38 MAPK inhibitors to modulate TNFalpha levels in the human monocytic/macrophage U937 cell line. *Mol Biosyst* 2010; 6: 1956-72.
38. VAN NIEUWENHUIJZE AE, VAN DE LOO FA, WALGREEN B *et al*.: Complementary action of granulocyte-macrophage colony-stimulating factor and interleukin-17A induces interleukin-23, receptor activator of nuclear factor-kappaB ligand and matrix metalloproteinases and drives bone and cartilage pathology in experimental arthritis: rationale for combination therapy in rheumatoid arthritis. *Arthritis Res Ther* 2015; 17: 163.
39. PLATER-ZYBERK C, JOOSTEN LA, HELSEN MM, KOENDERS MI, BAEUERLE PA, VAN DEN BERG WB: Combined blockade of granulocyte-macrophage colony stimulating factor and interleukin 17 pathways potently suppresses chronic destructive arthritis in a tumour necrosis factor alpha-independent mouse model. *Ann Rheum Dis* 2009; 68: 721-8.
40. PEREIRA J, VELLOSO ED, LOTERIO HA, LAURINDO IM, CHAMONE DA: Long-term remission of neutropenia in Felty's syndrome after a short GM-CSF treatment. *Acta Haematol* 1994; 92: 154-6.
41. HAZENBERG BP, VAN LEEUWEN MA, VAN RIJSWIJK MH, STERN AC, VELLENGA E: Correction of granulocytopenia in Felty's syndrome by granulocyte-macrophage colony-stimulating factor. Simultaneous induction of interleukin-6 release and flare-up of the arthritis. *Blood* 1989; 74: 2769-70.
42. DE VRIES EG, WILLEMSE PH, BIESMA B, STERN AC, LIMBURG PC, VELLENGA E: Flare-up of rheumatoid arthritis during GM-CSF treatment after chemotherapy. *Lancet* 1991; 338: 517-8.
43. BURMESTER GR, FEIST E, SLEEMAN MA, WANG B, WHITE B, MAGRINI F: Mavrilimumab, a human monoclonal antibody targeting GM-CSF receptor-alpha, in subjects with rheumatoid arthritis: a randomised, double-blind, placebo-controlled, phase I, first-in-human study. *Ann Rheum Dis* 2011; 70: 1542-9.
44. BURMESTER GR, WEINBLATT ME, MCINNES IB *et al*.: Efficacy and safety of mavrilimumab in subjects with rheumatoid arthritis. *Ann Rheum Dis* 2013; 72: 1445-52.
45. TAKEUCHI T, TANAKA Y, CLOSE D, GODWOOD A, WU CY, SAURIGNY D: Efficacy and safety of mavrilimumab in Japanese subjects with rheumatoid arthritis: findings from a Phase IIa study. *Mod Rheumatol* 2015; 25: 21-30.
46. BURMESTER GR, McINNES IB, KREMER JM *et al*.: Efficacy and safety of mavrilimumab, a fully human GM–CSFR-alpha monoclonal antibody in patients with rheumatoid arthritis: primary results from the EARTH EXPLORER 1 study [abstract]. EULAR 2015: *Ann Rheum Dis* 2015; 74 (Suppl. 2): 78.
47. KREMER JM, BURMESTER GR, WEINBLATT M *et al*.: Patient-reported outcomes (PROS) during treatment with mavrilimumab, a fully human monoclonal antibody targeting GM–CSFR-alpha, in the phase IIb EARTH EXPLORER 1 study [abstract]. EULAR 2015. *Ann Rheum Dis* 2015; 74 (Suppl. 2): 483.
48. MCINNES IB, BURMESTER GR, KREMER JM *et al*.: Rapid Onset of Clinical Benefit Is Associated with a Reduction in Validated Biomarkers of Disease in Patients with Rheumatoid Arthritis Treated with Mavrilimumab, a Human Monoclonal Antibody Targeting GM-CSFR [abstract]. ACR 2014.
49. GUO X, SINIBALDI D, KUZIORA M *et al*.: Sustained response to mavrilimumab in rheumatoid arthritis patients via suppression of macrophage and T cells [abstract]. EULAR 2015. *Ann Rheum Dis* 2015; 74 (Suppl. 2): 734.
50. JIN DC, WU CY, ROSKOS LK, GODWOOD A, CLOSE D, WANG B: Exposure–efficacy analysis of mavrilimumab in rheumatoid arthritis: modeling and simulation of phase II clinical data [abstract]. EULAR 2015. *Ann Rheum Dis* 2015; 74 (Suppl. 2): 1043.
51. KREMER JM, BURMESTER GR, WEINBLATT M *et al*.: Analysis of Patient-Reported Outcomes during Treatment with Mavrilimumab, a Human Monoclonal Antibody Targeting GM-CSFRá, in the Randomized Phase 2b Earth Explorer 1 Study [abstract]. ACR 2014.
52. MCINNES IB, BURMESTER GR, KREMER JM *et al*.: Rapid onset of clinical benefit in patients with RA treated with mavrilimumab, a fully human monoclonal antibody targeting GM–CSFR-alpha: subanalysis of the phase IIb EARTH EXPLORER 1 study [abstract]. EULAR 2015. *Ann Rheum Dis* 2015; 74 (Suppl. 2): 723.
53. A study of Mavrilimumab versus anti tumor necrosis factor in subjects with rheumatoid arthritis. ClinicalTrials.gov [Access date: May 15, 2016]; Available from: https://clinicaltrials.gov/ct2/show/study/NCT01715896
54. BURMESTER GR, MCINNES I, KREMER J *et al*.: Long-term Safety and Efficacy of Mavrilimumab, a Fully Human Granulocyte-Macrophage Colony-Stimulating Factor Receptor-α (GM–CSFR-α) Monoclonal Antibody, in Patients with Rheumatoid Arthritis (RA) [abstract]. ACR 2015. *Arthritis Rheumatol* 2015; 67 (Suppl. 10).
55. BEHRENS F, TAK PP, OSTERGAARD M *et al*.: MOR103, a human monoclonal antibody to granulocyte-macrophage colony-stimulating factor, in the treatment of patients with moderate rheumatoid arthritis: results of a phase Ib/IIa randomised, double-blind, placebo-controlled, dose-escalation trial. *Ann Rheum Dis* 2015; 74: 1058-64.
56. HUIZINGA TWJ, BATALOV A, YABLANSKI K *et al*.: First-in-patient study of namilumab, an anti-GM-CSF monoclonal antibody, in active rheumatoid arthritis: results of the PRIORA phase Ib study [abstract]. EULAR 2015. *Ann Rheum Dis* 2015; 74 (Suppl. 2): 733.
57. A Phase 1 MT203 Single-dose Study to Evaluate Safety, PK and PD. ClinicalTrials.gov [Access date: May 15, 2016]; Available from: https://clinicaltrials.gov/ct2/show/NCT02354599.
58. Dose Finding Study of Namilumab in Combination With Methotrexate in Participants With Moderate to Severe Rheumatoid Arthritis (RA). ClinicalTrials.gov [Access date: May 15, 2016]; Available from: https://clinicaltrials.gov/ct2/show/NCT02379091.
59. Namilumab vs Adalimumab in Participants With Moderate to Severe Early Rheumatoid Arthritis Inadequately Responding to Methotrexate (TELLUS). ClinicalTrials.gov [Access date: May 15, 2016]; Available from: https://clinicaltrials.gov/ct2/show/NCT02393378.
60. Safety and Tolerability of MORAb-022 in Healthy and Rheumatoid Arthritis Subjects. ClinicalTrials.gov [Access date: May 15, 2016]; Available from: https://clinicaltrials.gov/ct2/results?term=NCT01357759.
61. Study of KB003 In Biologics-Inadequate Rheumatoid Arthritis. ClinicalTrials.gov [Access date: May 15, 2016]; Available from: https://clinicaltrials.gov/ct2/results?term=NCT00995449.