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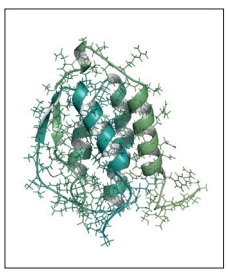
The efficacy and safety of targeting GM-CSF in arthritis



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Three randomised controlled trials published in *The Lancet Rheumatology* evaluate the biology, clinical efficacy, and safety of otilimab, in patients with rheumatoid arthritis[1,2] and hand osteoarthritis.[3] Otilimab is a monoclonal antibody that binds to and blocks granulocyte-macrophage colony-stimulating factor (GM-CSF) from connecting with its receptors that is being developed for treatment of rheumatoid arthritis. It is one of four GM-CSF inhibitors undergoing clinical trials in humans; all are humanised monoclonal antibodies. Mavrilimumab targets the GM-CSF α receptor; whereas otilimab, namilumab, and lenzilumab bind directly to GM-CSF. Lenzilumab is being studied in asthma; whereas, the other three GM-CSF inhibitors have shown efficacy in reducing disease activity and improving pain in patients with rheumatoid arthritis.[4]

Targeting GM-CSF is a novel therapeutic approach in rheumatoid arthritis, with all available therapies acting to reduce activity of haematopoietic cells.[5,6] By contrast, GM-CSF mediates the differentiation of macrophages and granulocytes from myeloid cells and, in turn, dendritic cells. Myeloid cells promote cytokine production, tissue damage, and upregulate chemokine (C-C motif) ligand 17 (CCL17)—a mediator of peripheral nerve sensitisation thus far only seen in animal models.[4] These three proof-of-concept trials[1–3] are an exciting advance in the field.

Christopher Buckley and colleagues[1] did a phase 2b dose finding study evaluating the clinical effects of five doses of otilimab (22·5 mg, 45 mg, 90 mg, 135 mg, or 180 mg) versus placebo. Patients with active rheumatoid arthritis and an inadequate response to at least 12 weeks of methotrexate (222 patients, 37 per group) received weekly subcutaneous injections for 5 weeks, which was reduced to every other week until week 50. Standardised otilimab dosing frequencies were used in all three trials. Patients who did not have the prespecified improvements in disease activity at week 12 or 24 were transferred to otilimab 180 mg. The primary endpoint of Disease Activity Score-28 for Rheumatoid Arthritis with C-reactive protein (DAS28-CRP) remission at week 24 was not achieved. However, this goal was unrealistic in the patient population assessed, given that the study was powered to detect a large 30% difference between otilimab and placebo. Patients were also assessed for a range of other clinical outcomes, including 20%, 50%, or 70% improvement in American College of Rheumatology (ACR) core domains, including function, and pain. ACR20 responses were reported in 51%, ACR50 responses in 30%, and ACR70 in 19% of patients.

DAS28-CRP 24-week remission rates ranged from 14% to 19% in patients receiving otilimab, similar to those in other trials of advanced therapies studied in patients with an inadequate response to methotrexate. A high number of patients escaped to the 180 mg dose at 12 and 24 weeks—more so in the 135 mg group—resulting in missing data at weeks 16, 20, and 24, and leaving an apparent efficacy advantage of the 90 mg over 135 mg dosage. Dose response relationships across most dosage groups were as expected. Clinically meaningful, dose-responsive improvements in single, core, composite, and patient reported measures support the efficacy of otilimab in rheumatoid arthritis, warranting further study in phase 3 trials.

Mark Genovese and colleagues[2] did a 22-week mechanistic phase 2a proof-of-concept study of otilimab in 39 patients with rheumatoid arthritis, who met the same eligibility criteria as those included in the study by Buckley and colleagues,[1] to evaluate the effect of 180 mg of otilimab (n=28) versus placebo (n=11) on molecular and cellular biomarkers in GM-CSF signalling pathways and on MRI measured synovitis, erosions, osteitis and oedema, and cartilage loss. Groups were imbalanced in terms of DMARD exposure. During the 10-week treatment period, the only meaningful change was reduced serum concentrations of CCL17 in the otilumab group compared with the placebo group. A clinically meaningful reduction in pain severity scores was also reported with otilumab but not with placebo. Differences in MRI outcomes were minimal with overlapping CIs. A trend for reduced synovitis and osteitis was seen early during active treatment but not at 12 weeks after stopping of treatment. The direction of change in outcomes in this study were consistent with what would be expected given preclinical models of GM-CSF effects but need to be confirmed in larger trials.

The third study by Georg Schett and colleagues[3] was a 22-week, phase 2a exploratory study of pain and hand function in 44 patients with hand osteoarthritis randomly assigned (22 per group) to receive either otilimab 180 mg or placebo. More patients receiving otilimab had numerical clinically meaningful improvement of

maximal pain and pain severity over time; the proportion of patients achieving a 30% or higher reduction in pain was numerically (although not statistically) higher in the otilimab group than the placebo group. Hand function also improved more in the otilimab compared with the placebo group. No change in MRI synovitis scores were observed between the groups. More patients withdrew in the otilimab group; two patients receiving otilimab had a herpes zoster infection and one withdrew because of an unrelated humoral fracture. Of note, in the trial by Buckley and colleagues,[1] three fractures were described in patients receiving otilimab suggesting that GM-CSF might have a role in supporting bone health. GM-CSF inhibitors affect the JAK/STAT pathway, thus additional vigilance regarding herpes zoster events is needed.

Because GM-CSF promotes inflammation, tissue destruction, and inflammatory cytokine production, and also activates and promotes the survival of mature myeloid cells (including macrophages, neutrophils, and dendritic cells) in autoimmune inflammatory diseases driven by T-helper-1 and T-helper-17 pathways, reducing its concentrations is expected to do more good than harm. However, GM-CSF might be protective in the gut, it improves myasthenia gravis, and it is used to augment antitumour vaccines. Thus, safety concerns remain regarding the risk of impairing immunological responses to vaccines and causing colitis or type I diabetes. Alternatively, GM-CSF might have off target benefits in the lung by slowing the progression of interstitial fibrosis, as suggested by preclinical data.[5,6]

Reassuringly, a review of cumulative safety data from mavrilimumab randomised controlled trials did not reveal safety signals in terms of infection, malignancy, pulmonary disease, pulmonary alveolar proteinosis, or cardiovascular events attributable to the study drug. However, decreases in neutrophil counts below 3000 per mm^3 did occur, but no associated adverse safety events were reported.[7] Efficacy waned in the long-term extension groups from those trials indicating that a higher maintenance dose was needed. Will this be the case for otilimab? Calculated pharmacokinetic and pharmacodynamic models described linear pharmacokinetic trends over tested doses.[8] Of concern, antibody clearance was significantly higher and bioavailability was lower than expected of a typical monoclonal antibody, resulting in lower trough concentrations at steady-state and an elimination half-life of 10 days. For clinically meaningful responses, higher trough concentrations using 150 mg of weekly subcutaneous otilimab would be required to maintain DAS28-CRP low disease activity or remission states.[8] Even higher doses would be required to support every other week maintenance schedules.

Factors affecting peak and trough concentrations and durability of response have implications on efficacy and safety. GM-CSF protects against the development of pulmonary alveolar proteinosis, a rare lung disease. Concerns about pulmonary alveolar proteinosis have been high during development of GM-CSF inhibitors, with attempts to offset this risk by excluding patients with low pulmonary reserve by early intensive pulmonary screening. Fortunately, no cases of pulmonary alveolar proteinosis have yet occurred in any of the trials of otilumab or trials of other GM-CSF targeting drugs.[7]

Practical issues have emerged from these trials. Will screening with pulmonary function tests be a requirement before using otilimab in future? In these studies, participants were excluded if their diffusing capacity for carbon monoxide was less than 60% and forced expiratory volume in 1 second was less than 70% of predicted, but the lung diseases of concern were not specified. One patient did have a clinically meaningful decline in pulmonary function, not due to pulmonary alveolar proteinosis, but associated with upper lung fibrosis. All patients with a positive tuberculosis test were also excluded from the trials and no cases of tuberculosis were reported, as such these trials cannot inform the risk of GM-CSF inhibitor exacerbation of latent tuberculosis.

In rheumatoid arthritis it remains unknown whether these drugs are best combined with methotrexate or other conventional synthetic DMARDs, and whether they will be effective in patients with late rheumatoid arthritis who have been unresponsive to multiple previous therapies or in those with pauci-immune synovial phenotypes.[9] Incorporating synovial tissue biomarker research could greatly enhance the understanding of who might best respond to GM-CSF inhibitors. There is more to come not only in rheumatoid arthritis and osteoarthritis but from trials of GM-CSF inhibitors being done in COVID-19, asthma, psoriatic arthritis, and ankylosing spondylitis.[10]

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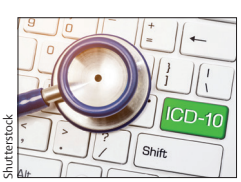
The contribution of the observational research design to COVID-19 research



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As the COVID-19 pandemic continues to influence global health, the search for effective therapies has been vigorous. An analysis published early during the pandemic suggested that hydroxychloroquine, with or without azithromycin, might improve nasopharyngeal viral clearance of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of COVID-19.[1] Despite the low quality of this study due to poor handling of confounders and participants lost to follow-up who had poor outcomes, a surge of prescriptions for the therapeutic and prophylactic use of hydroxychloroquine created shortages for patients with systemic lupus erythematosus and other rheumatic diseases who rely on this medication to treat their disease. Subsequently, an increased incidence of cardiac arrhythmias was observed in patients with COVID-19 treated with hydroxychloroquine. Thus, there is a need to determine whether the benefits of hydroxychloroquine for COVID-19 outweigh the risk of harms.

Randomised controlled trials (RCTs) are the gold standard by which the efficacy of an intervention is evaluated. Several RCTs have been published that largely demonstrated no benefit when hydroxychloroquine was used for COVID-19.[2-6] An alternative research design, the retrospective observational study, can usually be carried out relatively quickly and at comparatively low cost, but is limited by numerous potential sources of bias. The appropriate scientific contribution of observational studies, it is argued, is to provide estimates of disease outcomes in real-world patient populations and to generate hypotheses to support further research. Improving the validity of the results of observational studies requires construction of comprehensive models that identify all potential confounding and modulating variables that could link the intervention to the outcome. So far, validated measures of important variables are not routinely available.

In *The Lancet Rheumatology*, Chris Gentry and colleagues[7] leveraged a large dataset derived from the electronic health record of the US Veterans Health Administration (VHA) to carry out a retrospective, observational, propensity-matched analysis comparing the rate of laboratory-confirmed COVID-19 in adults with rheumatic diseases prescribed hydroxychloroquine with patients treated with other rheumatic disease medications. From 70 270 patients with an International Classification of Diseases (10th revision; ICD-10) diagnosis of rheumatic disease, the authors compared 10 703 patients treated with hydroxychloroquine who demonstrated satisfactory hydroxychloroquine adherence to 21 406 patients not treated with hydroxychloroquine. Commendably, the two groups were propensity matched for several dozen variables, including zip code of residence, comorbidities, laboratory test results, emergency or urgent care