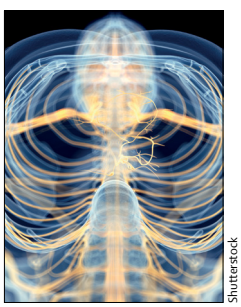
Vagus nerve stimulation for autoimmune rheumatic diseases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The vagus nerve is the primary parasympathetic nerve of the autonomic nervous system, providing an extensive network of afferent and efferent parasympathetic innervation of the viscera.[1] The vagus nerve comprises a bundle of approximately 80% afferent fibres and 20% efferent fibres, which control essential visceral functions including gastrointestinal motility, secretions, and heart rate.[1] Vagus nerve activity is also a prominent component of several homeostatic axes including the cholinergic anti-inflammatory pathway, the brain–gut axis, and the hypothalamic–pituitary–adrenergic axis.

The role of vagus nerve stimulation (VNS) has been studied in several immune-mediated inflammatory diseases, including rheumatoid arthritis,[2] primary Sjögren's syndrome,[3] and inflammatory bowel disease.[4] In mice, unilateral vagotomy[5] or genetic knockout of the nicotinic acetylcholine receptor α7nAChR[6] leads to exacerbation of arthritis. Conversely, stimulation of the α7nACh receptor either by selective or general nicotinic agonists results in clinical improvement in a collagen-induced arthritis mouse model,[5] and VNS by vagus nerve suspension leads to decreased circulating pro-inflammatory cytokines and reduced synovial inflammation and bone destruction in the same model.[7]

In humans, an open-label trial of VNS in 2016 used an implanted device in patients with rheumatoid arthritis who were unresponsive or intolerant to methotrexate or anti-tumor necrosis factor therapy, or had an insufficient response to conventional therapy and at least two different biological therapies.[2] This study showed that VNS resulted in clinical improvement and decreased concentrations of circulating inflammatory cytokines. Furthermore, worsening of disease activity was observed when VNS was suspended, and again improved when VNS recommenced.[2]

In *The Lancet Rheumatology*, Mark Genovese and colleagues[8] present a two-stage pilot study of VNS therapy in 14 patients with rheumatoid arthritis. Among the 11 patients treated in the randomised controlled part of the study (stage 2), clinical and biochemical improvements were seen among some patients in the active device groups, but no significant changes were observed versus the sham group. Although the sample size was small and the study duration short, no device or treatment-related serious adverse events were reported and no deaths occurred. Their study provides further evidence for the potential of VNS as a novel, effective, and safe non-pharmacological therapy for rheumatoid arthritis.

Targeted biological disease modifying anti-rheumatic drugs (DMARDs) have considerably improved disease outcomes in rheumatoid arthritis; however, some patients do not respond sufficiently to these treatments or have unacceptable adverse effects, and only few achieve disease remission. Furthermore, even with the introduction of biosimilars, the cost of biological DMARDs is substantial. Therefore, a large unmet need remains for additional or alternative therapies, and VNS represents an attractive therapeutic option for patients with rheumatoid arthritis and other immune-mediated inflammatory diseases because of its safety record. Additionally, the estimated cost of VNS per patient would be lower than biologic DMARDs after 1·5 years.[9]

What are the next steps from here? First and foremost, despite these promising data, larger studies are needed to confirm the efficacy of VNS in the treatment of patients with rheumatoid arthritis. Several issues should also be addressed to optimise the therapeutic potential of VNS. For instance, the optimal strength, frequency, and duration of VNS for the treatment of rheumatoid arthritis have not been fully defined. These parameters might affect the type of vagal fibres being stimulated, but also efficacy and adverse effects. In this regard, in the study by Genovese and colleagues, the efficacy of once-daily dosing appeared to be greater than a four-times-daily regimen, although the sample size was small. For an implantable device, guidance on whether the device should be removed or simply turned off if no therapeutic effect is apparent should be developed. Furthermore, identifying predictive biomarkers for use of implanted VNS devices could reduce unnecessary surgical procedures. Several non-invasive VNS devices have been developed, and non-invasive VNS has been shown to reduce inflammatory cytokine production after lipopolysaccharide stimulation.[3,10] In a pilot study of 15 patients with primary Sjogren's syndrome, 12 (80%) patients reported an improvement in patient-reported physical fatigue score within 28 days of VNS, with seven (47%) showing a 30% or greater reduction in fatigue.[3] Therefore, investigations into whether non-invasive VNS

is an effective treatment for rheumatoid arthritis might be of interest.

Mechanistically, the immune reflex is largely uncharacterised, particularly with regard to the roles of immune cells such B cells, antigen presenting cells, and regulatory cells, as well as non-immune cells such as epithelial cells and synoviocytes. Other unknown effects of VNS are the potential long-term effects of VNS on immune cell number and compartmentalisation, and the potential adaptation of neural–immune communication and desensitisation. This adaptation and desensitisation might present a limitation to the positive effects of VNS. Extended follow-up studies will help to address such issues. The broader role of VNS beyond modulation of the immune reflex in immune-mediated inflammatory diseases is also poorly understood and warrants in-depth study.

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