

## RHEUMATOID ARTHRITIS

## Vagus nerve stimulation reduces RA severity in patients

“ improvements in [DAS28-CRP] were seen within a few days of starting treatment with VNS ”

A clinical trial published in *Proceedings of the National Academy of Sciences* reports for the first time that vagus nerve stimulation (VNS) inhibits TNF production and attenuates inflammation in humans.

“Although studied in animal models of arthritis and other inflammatory diseases, whether electrical stimulation of the vagus nerve can inhibit TNF production in humans has remained unknown,” explains Paul-Peter Tak, corresponding author of the study. The new findings support modulation of the inflammatory reflex — a neural circuit that suppresses proinflammatory cytokine production via vagus nerve signals — as a novel anti-inflammatory approach in rheumatoid arthritis (RA).

Tak and colleagues first studied the effects of inflammatory reflex activation on cytokine production in seven patients with epilepsy who underwent implantation of a VNS device. In these patients, application of a single 30s electrical pulse during

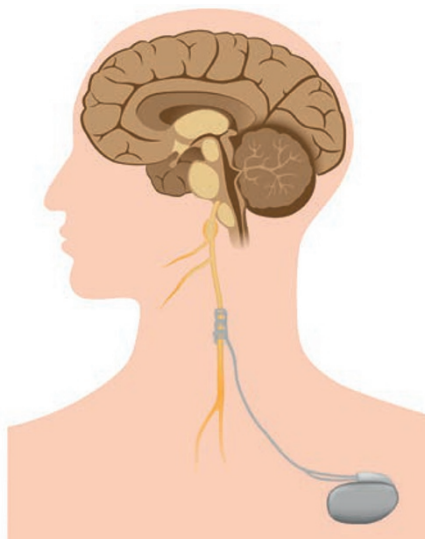
general anaesthesia reduced the LPS-induced release of TNF, IL-1 $\beta$  and IL-6 in post-VNS blood samples (versus levels in pre-VNS samples).

They next tested the device in 17 patients who had active RA at enrolment despite methotrexate therapy; some patients had also failed to respond to treatment with two or more biologic agents with differing mechanisms of action. In this RA cohort, VNS (up to four times daily) inhibited TNF production in cultured peripheral blood. Also, Tak notes, “RA disease severity improved significantly, even in some therapy-resistant patients.” Improvements in 28-joint C-reactive protein (CRP)-based disease activity score (DAS28-CRP) were seen within a few days of starting treatment with VNS in some patients.

Notably, DAS28-CRP rose significantly within a 14-day hiatus period during which the treatment was withdrawn, but clinical improvement was restored upon resuming VNS. The pattern of TNF production closely correlated with DAS28-CRP.

These results encourage further study of this approach for RA and other immune-mediated inflammatory diseases, the authors contend. “The development of therapeutic neuromodulating devices targeting inflammation will probably increase significantly,” Tak predicts.

Sarah Onuora



Ailila Medical Images/Alamy Stock Photo

**ORIGINAL ARTICLE** Koopman, F.A. et al. Vagus nerve stimulation inhibits cytokine production and attenuates disease severity in rheumatoid arthritis. *Proc. Natl Acad. Sci. USA* <http://dx.doi.org/10.1073/pnas.1605635113> (2016)

**FURTHER READING** van Maanen, M.A. et al. The cholinergic anti-inflammatory pathway: towards innovative treatment of rheumatoid arthritis. *Nat. Rev. Rheumatol.* **5**, 229–232 (2009)