ALZHEIMER DISEASE

In search of an anti-inflammatory drug for Alzheimer disease

Erika Gyengesi and Gerald Münch

Evidence suggests that chronic neuroinflammation has an important role in the pathogenesis of Alzheimer disease. However, in a new clinical trial, the tetracycline antibiotic minocycline, which has anti-inflammatory properties, failed to delay disease progression in individuals with mild Alzheimer disease.

Chronic microglial activation occurs in many neurodegenerative diseases, including chronic traumatic encephalopathy, amyotrophic lateral sclerosis, Parkinson disease (PD) and Alzheimer disease (AD). In the brains of patients with AD, this microglial activation is observed at all stages of the disease and is accompanied by increased levels of pro-inflammatory mediators, such as tumour necrosis factor (TNF), IL-1β, IL-6, prostaglandins, reactive oxygen species and reactive nitrogen species. Furthermore, genome-wide association studies (GWAS) have identified associations between variants in inflammation-related genes, including the gene that encodes triggering receptor expressed on myeloid cells 2 (TREM2) and the risk of developing AD. TREM2 is present on the surface of microglial cells and responds to damage-associated molecular patterns (DAMPs) and bacterial lipopolysaccharides by activating phagocytosis and promoting microglial survival; the link between TREM2 and AD is considered to be one of the strongest arguments for a role of neuroinflammation in the disease. These genetic and histological findings suggest that progression of AD is driven — at least partly — by a self-perpetuating cycle of inflammatory neurotoxicity. In this cycle, injured neurons release DAMPs, which activate microglia. The activated microglia then secrete neurotoxic cytokines (for example, TNF) and free radicals (for example, superoxide and nitric oxide), which damage neurons, thus beginning the cycle again. Consequently, treatments that target chronic neuroinflammation might be able to modify the course of AD.

In a new clinical trial published in JAMA Neurology, Howard et al. tested the efficacy of the tetracycline antibiotic minocycline for the treatment of mild AD. Minocycline was chosen for the trial on the basis of two systematic reviews that identified the drug as a high-priority candidate for repurposing as a treatment for AD. The drug has a variety of off-target effects, including immunosuppression, and is therefore already used as a second-line agent for the management of rheumatoid arthritis. Evidence from animal studies indicates that minocycline reduces neutrophil-mediated tissue injury via inhibition of neutrophil migration and degranulation, as well as suppression of oxygen radical formation. In animal models of familial AD, minocycline has anti-inflammatory properties; for example, it reduces levels of IL-1β, TNF, IL-4 and IL-10. In the preclinical studies, minocycline has been tested at a daily dose of ~50 mg/kg. This translates into a dose of 400 mg for the average person, which is considerably higher than the 200 mg that is given to treat infections.

In the trial by Howard et al., participants received a daily dose of either 200 mg minocycline, 400 mg minocycline or placebo. Cognitive performance was measured with the Standardized Mini-Mental State Examination (sMMSE), and patients’ ability to carry out basic activities of daily life, such as eating, dressing or taking medication, was assessed with the Bristol Activities of Daily Living Scale (BADLS). No statistically significant differences were seen between participants receiving minocycline and those receiving placebo. However, a closer look at the data reveals that the mean change in sMMSE score over 24 months was 4.1 points in the group that received placebo and 3.3 points in the group that received 400 mg of minocycline, which suggests that deterioration was ~20% slower among participants who received 400 mg minocycline than among those who received placebo (FIG. 1). However, at the 400 mg dose, the adverse effects of minocycline were severe and only 28% of participants in this group completed the study.

Howard and colleagues did a diligent job of discussing possible explanations for the negative outcome. The first explanation given in the paper is that neuroinflammation “may be a reaction to pathologic characteristics of the disease rather than an important factor in neurodegeneration”. However, results of GWAS indicate that >60% of the genes linked to late-onset sporadic AD are inflammation-related, which strongly...
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suggests a role for inflammation in AD pathogenesis. Furthermore, a large, retrospective case–control study of the electronic health records of 56 million individuals indicated that TNF-blocking agents reduce the risk of AD in patients with rheumatoid arthritis and psoriasis. For example, patients with rheumatoid arthritis who were being treated with etanercept, adalimumab or infliximab were less likely to be diagnosed with AD than patients with untreated rheumatoid arthritis.

The second potential explanation for the failure of the trial is that, because the association between microglial activation and neurodegeneration is complex, minocycline might be having unexpected effects and could even interfere with the supportive function of microglia. One of the biggest problems with minocycline is that it was not designed to be an anti-inflammatory drug, and its exact target and mode of action are not entirely clear. Whether the doses of minocycline given in the trial by Howard et al. can decrease levels of the relevant pro-inflammatory cytokines, radicals and neurotoxins is not yet known.

As a third explanation for the negative results, the investigators hypothesized that “minocycline did have some efficacy against AD, but treatment effects were too small to be detectable”. Small effect sizes could reflect the contribution of processes other than neuro-inflammation to disease progression. For example, if neuroinflammation was responsible for only 50% of the cognitive and functional decline seen in patients with AD, and minocycline decreased neuroinflammation by 50%, then the observed effect size of minocycline treatment would only be ~25%.

In future trials, use of anti-inflammatory drugs with known targets, such as the cytokine-suppressive anti-inflammatory drugs (CSAIDs), would be preferable. CSAIDs target pro-inflammatory signal transduction pathways in microglia and astroglia, and thus they decrease the production of cytotoxic cytokines, such as TNF, and free radicals, such as nitric oxide. Future trials could also monitor the anti-inflammatory effects of candidate drugs with PET imaging of translocator protein, which is a marker of activated microglia and astroglia in the brain.

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Competing interests
The authors declare no competing interests.