for the treatment of NMOSD, done at six hospitals in China. Azathioprine was the first therapy observed to reduce the risk of relapses in patients with NMOSD, and although all studies supporting its use are based on class 4 evidence from observational studies, azathioprine is the most widely used current therapy, partly due to the low cost and high availability. Therefore, the comparison of tocilizumab with azathioprine provides a realistic appraisal of IL-6 receptor blockade in NMOSD.

In the trial by Zhang and colleagues, 118 patients were enrolled (87% of whom were AQP4-IgG seropositive) and randomly assigned (1:1) to intravenous tocilizumab (8 mg/kg every 4 weeks; n=59) or oral azathioprine (2–3 mg/kg per day; n=59) for up to 60 weeks. Eight (14%) of 59 patients in the tocilizumab group had relapsed compared with 28 (47%) of 59 patients in the azathioprine group (HR 0.236, 95% CI 0.107–0.518; p<0.0001), equating to a risk reduction of 76%. The participants who had the best response were those with other concurrent autoimmune diseases. The main differences between this trial of tocilizumab and the two satralizumab trials are that the tocilizumab was administered intravenously, rather than subcutaneously, the study duration was approximately 1 year, and the investigators were not masked to the treatment allocation. Similar to satralizumab, adverse effects with tocilizumab were mild, including asymptomatic elevations in liver enzymes and an increased incidence of respiratory and urinary infections, with no significant differences identified between the tocilizumab and azathioprine groups.

The results of these three large trials of IL-6 blockade for the prevention of relapses in patients with NMOSD demonstrate a benefit of reduced hazard of relapse of between 55% and 74%. Two additional placebo-controlled trials in patients with NMOSD were published in 2019 using drugs that target different immunopathological mechanisms: the first was eculizumab, a C5 complement inhibitor, which reduced the risk of relapse by 94%, and the second was inebilizumab, a CD19 B-cell depleting monoclonal antibody that reduced the risk of relapse by 73%. The safety concerns regarding these approaches are all substantially outweighed by the benefit of preventing NMOSD relapses.

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role of intensive medical management over stenting, irrespective of age.

SAMMPRIS\(^5\) and VISSIT\(^6\) showed that stenting was not superior to intensive medical management in patients with intracranial arterial stenosis. However, the lower than expected rates of stroke recurrence in the intensive medical management groups were controversial because of the recruitment of patients younger than 60 years in these trials. Thus, stenting is still commonly done in many countries without clear evidence of its superiority. OXVASC reported an even lower rate of stroke than those in the intensive medical management groups of the SAMMPRIS and VISSIT trials (1-year risk 5.6% vs 9.4% in VISSIT; 2-year risk 5.6% vs 14.1% in SAMMPRIS), despite including patients older than 60 years, which supports the generalisability of the trial results to routine clinical practice for a wide age range of patients. Patients in OXVASC received intensive medical management similar to that of SAMMPRIS and VISSIT, which consisted of dual antiplatelet therapy with aspirin and clopidogrel for the first month, followed by monotherapy with aspirin or clopidogrel thereafter. Medical management also included aggressive statin treatment, strict blood pressure control (<130/80 mmHg), smoking cessation, and exercise and dietary advice. These multiple interventions might have contributed to the reduced risk of recurrent stroke in patients in the OXVASC cohort.

However, the WEAVE trial\(^7\) has shown a low rate of periprocedural stroke, bleeding, and death in patients with symptomatic intracranial arterial stenosis. The WEAVE trial is a post-market surveillance trial mandated by the US Food and Drug Administration (FDA) to assess the periprocedural safety of the Wingspan Stent system in patients who met the FDA on-label usage criteria, which included age 22–80 years, stenosis of 70–99%, modified Rankin Scale score of 3 or less, and two or more strokes in the vascular territory of the stenotic lesion with at least one stroke while on medical therapy, and stenting of the lesion 8 days or more after the last stroke. SAMMPRIS, however, included patients who did not meet the FDA on-label usage criteria for stenting.

Stroke due to intracranial arterial stenosis or carotid stenosis is classified as large artery atherosclerosis in the subtypes of ischaemic stroke. Data from TIAregestry.org, an international observational registry of patients with acute transient ischaemic attack or minor stroke, showed that the rate of recurrent stroke is higher in patients with large artery atherosclerosis (atherothrombotic stroke and transient ischaemic attack) than in those with other stroke subtypes.\(^3\) This registry-based analysis also showed a sustained risk of cardiovascular events over a period of 5 years, with half of the events occurring during years 2–5, despite adherence to current guidelines.\(^1\) Overall, this evidence suggests that the frequency of recurrent strokes needs to be reduced through more intensive secondary prevention strategies.

Atherothrombosis is a polyvascular disease, which includes atherothrombotic stroke, transient ischaemic attack, coronary artery disease, and peripheral artery disease. The risk of vascular events in patients with atherothrombosis increases as the number of involved vascular beds increases.\(^3\) In the OXVASC cohort, any vascular disease, history of stroke or transient ischaemic attack, peripheral vascular disease, and ischaemic heart disease were more common in patients with intracranial arterial stenosis than in those without.\(^4\) In a subgroup analysis of TIAregestry.org,\(^3\) the risk of vascular events remained high after carotid endarterectomy or stenting in patients with symptomatic carotid stenosis. Thus, the risk of vascular events in vascular beds might not be reduced by local stenting in patients with symptomatic intracranial arterial stenosis. Taken together, to reduce the residual risk of composite vascular events in patients with intracranial arterial stenosis, more intensive antiplatelet therapy and total risk management are needed regardless of concomitant stenting.

I declare no competing interests.

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The transformative potential of plasma phosphorylated tau

Various diseases underlie age-related cognitive decline at the population level and any combination of these diseases can exist in an individual. The phenotype of cognitive impairment is not specific to any one disease; therefore, biomarkers have been pursued as indicators of specific diseases that can account for age-related cognitive decline. The two proteinopathies that define Alzheimer’s disease—deposits of aggregated amyloid β and deposits that contain a mixture of three-repeat (3R) and four-repeat (4R) tau isoforms—can be detected in vivo. Until recently, however, the detection of these biomarkers has been either expensive, in the case of PET imaging, or invasive, in the case of CSF sampling, which requires a lumbar puncture.

A potential solution is the development of plasma-based biomarker assays. In The Lancet Neurology, Thomas K Karikari and colleagues report results from the application of a new ultrasensitive blood immunoassay for tau phosphorylated at threonine 181 (p-tau181), for the detection of Alzheimer’s disease pathology. The immunoassay was evaluated in four independent samples: a discovery cohort (n=37); two observational research cohorts (TRIAD, n=226, and BioFINDER-2, n=763); and a primary care cohort (n=105). Concentrations of plasma p-tau181 increased progressively from levels in amyloid β-negative young adults to those in amyloid β-positive cognitively unimpaired older adults to those in amyloid β-positive patients with dementia. This finding suggests that the assay is sensitive along the entire Alzheimer’s disease continuum. The assay distinguished patients with Alzheimer’s disease from those with other neurodegenerative disorders, including frontotemporal dementia, which supports the specificity of the measure for the tauopathy of Alzheimer’s disease. After autopsy, tau PET is the next best available source of pathological validation, and plasma p-tau181 was significantly associated with tau PET measures. High correlation with CSF p-tau181 provided further validation that plasma p-tau181 reflects the CNS molecular environment. In the primary care cohort, the assay distinguished patients with clinically defined probable Alzheimer’s disease from young adults and cognitively unimpaired older adults, which indicates applicability in a general medical setting. In summary, Karikari and colleagues have shown the validity of their plasma p-tau181 assay in a rigorous and convincing manner.

The investigators also found that plasma p-tau181 was highly correlated with tau PET and amyloid PET. They suggest that increased production of p-tau181 represents a neuronal response to amyloid β aggregation, a conclusion supported by in vivo isotope labelling studies. The close relationship between plasma p-tau181 and both tau PET and amyloid PET is consistent with evidence from PET studies showing that significant neocortical tau deposition occurs (with very rare exceptions) only if amyloidosis is present. This collective evidence suggests that plasma p-tau181 is an indicator of the pathophysiological state leading to both of the defining proteinopathies of Alzheimer’s disease, amyloid β deposition and deposits that contain a mixture of 3R and 4R tau isoforms.

The report from Karikari and colleagues adds to other recent studies that support the use of plasma p-tau181 (but not plasma total tau) as an indicator of the Alzheimer’s disease pathophysiological state. A CSF-based study indicated that other pathological phosphorylation sites might also be diagnostically useful, particularly tau phosphorylated at threonine 217 (p-tau217), and studies comparing the diagnostic performance of plasma p-tau181 and p-tau217 will be important.

One of several clear potential uses for plasma p-tau181 is in clinical trials. Because plasma p-tau181 seems to indicate occurrence of both amyloid β deposition and tauopathy in Alzheimer’s disease, it could be used in trials that target amyloid β or tau or both. Plasma p-tau181 could be used to select potential participants for amyloid and tau PET screening, or to establish that an individual is on the Alzheimer’s disease pathway as a standalone study entry criterion. This approach could substantially...