

In conclusion, we agree with Corpechot *et al.* that VCTE is a reliable predictor of clinical outcomes in individuals with PBC and that LS should be incorporated into the prognostic markers to determine the state of disease progression. Still, the differential diagnostic efficiency of LS in our study provides a hint that the prognostic value of LS in individuals with PSC, AIH or PBC-AIH overlap syndrome warrants further investigation. More importantly, studies regarding dynamic changes of LS during the follow-up of individuals with AILD are needed to further validate its prognostic impact.

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Authors' contributions

YS: data analysis and manuscript drafting. HC: data analysis and manuscript drafting. SDW: manuscript revision. WJ: study concept and manuscript revision.

Supplementary data

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B vitamins for NASH: Use methylcobalamin, not cyanocobalamin

To the Editor:

Tripathi *et al.*¹ have elegantly shown how hyperhomocysteinemia aggravates non-alcoholic steatohepatitis (NASH). Their finding that treatment with folate and B12 reduced inflammation and improved hepatic histology suggests that folate and B12 will be important therapies for this condition. However, it is crucial to recognize that the form of B12 used should be methylcobalamin or hydroxycobalamin, not cyanocobalamin, particularly in patients with impaired kidney function, including the elderly.

It is now clear that folic acid and B12 reduce the risk of stroke; however, the benefit of B vitamins was obscured in the early trials by harm from cyanocobalamin among participants

with renal failure.^{2,3} In the Vitamin Intervention for Stroke Prevention (VISP) trial, there was no benefit of B vitamins in the entire study population.⁴ However, in a subgroup from which patients with impaired kidney function (an estimated glomerular filtration rate [eGFR] <46 ml/min/1.72 m² – the 10th percentile of eGFR in the study population), there was a 34% reduction of stroke/myocardial infarction over 2 years.⁵

A trial in patients with diabetic nephropathy randomized to placebo vs. folate 2.5 mg, B6 25 mg and cyanocobalamin 1,000 µg daily showed faster decline of renal function, and a doubling of cardiovascular events, with B vitamins.⁶ All the events occurred among participants with GFR <50 ml/min/1.72 m².⁷

In contrast, folic acid improved renal function and reduced a composite outcome including cardiovascular events among participants in the China Stroke Primary Prevention trial.⁸

The greatest reduction of stroke with folate/B6/B12 was in the French Su.Fol.M3 trial, in which the renal function was much better than in the early trials, and the dose of cyanocobalamin was much lower: the mean serum creatinine was 78, vs. 99 in VISP, and the daily dose of cyanocobalamin was only 20 µg, vs. 400 µg in VISP. There was a 43% reduction of stroke in Su.Fol.OM3 over a median of 4.7 years (hazard ratio 0.57; 95% CI 0.33 to 0.97; $p = 0.04$).⁹ These issues were reviewed in 2022.³

B vitamins to lower homocysteine do reduce stroke, and seem to be beneficial in NASH, but methylcobalamin or hydroxycobalamin should be used instead of cyanocobalamin. Methylcobalamin is readily available, and not significantly more costly than cyanocobalamin. The dose of methylcobalamin would be equivalent to the dose of cyanocobalamin. A randomized controlled trial of B vitamins for NASH is needed.

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Supplementary data

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Reply to: “B vitamins for NASH: Use methylcobalamin, not cyanocobalamin”

To the Editor:

We appreciate the letter by Dr. Spence advocating the use of methylcobalamin or hydroxycobalamin rather than the cyanocobalamin form of vitamin B12 (B12) in future clinical trials investigating the efficacy of B vitamins to prevent or treat NASH.¹ This is similar to the concern that he raised previously regarding studies that employed B12 for the prevention of stroke.^{3,4} Although several large trials previously showed no benefit of folate and/or B vitamins (B6 and B12) in reducing cardiovascular events,⁴ reanalysis of data from one of them (the VISP trial) showed there was a 34% reduction in stroke/myocardial infarction events over 2 years when patients with impaired renal function were excluded.⁵ Subsequent studies using folate

supplementation of enalapril in the China Stroke Primary Prevention trial and folate, B6, and low dose B12 in the Su.Fol.M3 trial also showed beneficial stroke prevention effects.^{6,7} Almost all clinical studies for stroke prevention by B12 to date were conducted with cyanocobalamin. Dr. Spence has argued that the use of cyanocobalamin in individuals with renal impairment may have obscured the benefit of B vitamins in stroke prevention in earlier studies,^{2,3,5} since it is possible that increased cyanocobalamin leads to harmful accumulation of cyanide and thiocyanate in patients with impaired renal function.⁸

While Dr. Spence's recommendation of methylcobalamin or hydroxycobalamin makes sense based upon current available clinical data, it is noteworthy that no clinical studies