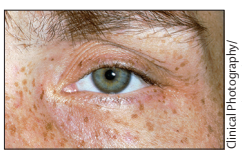
Monitoring and treatment of Wilson disease: progress and challenges



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In *The Lancet Gastroenterology & Hepatology*, Michael L Schilsky and colleagues report the results of a multicentre, randomised, open-label, non-inferiority, phase 3 trial on the copper chelator trientine tetrahydrochloride (TETA4),[1] a new trientine formulation that is stable at room temperature, compared with penicillamine in patients with Wilson disease. The study included 53 patients with Wilson disease with both hepatic and neuropsychiatric manifestations who were considered to be stable according to clinical presentation and copper metabolism parameters, particularly 24 h urinary copper excretion and non-caeruloplasmin-bound copper (NCC) serum levels. Patients either continued on penicillamine, the first-line copper chelator, or were switched to TETA4 using a mg-for-mg dose conversion strategy. Patients were assessed for copper metabolism and clinical stability at 24 weeks and 48 weeks, with the primary outcome being NCC levels at 24 weeks. The study showed that TETA4 is non-inferior to penicillamine in maintaining NCC levels as a reflection of efficacy of copper balance control (mean difference in serum NCC by speciation assay between the penicillamine group and TETA4 group was −9·1 µg/L [95% CI −24·2 to 6·1], with the lower limit of the 95% CI within the defined non-inferiority margin). This finding is important because, although drug regulatory agencies are still indicating penicillamine as first-line treatment for patients with Wilson disease, many, if not most, clinicians will actually prescribe trientine formulations at the time of diagnosis or switch from penicillamine to trientine to prevent or limit side-effects. Numerous reports indicate that penicillamine is associated with side-effects in up to 40% of patients, and side-effects can be observed even after years of treatment, particularly nephropathy, autoimmune conditions, and interference with collagen metabolism with consequent skin changes.[2,3]

This clinical trial was challenging in its execution due to technical issues associated with the method initially used to measure serum NCC. Traditionally, NCC is measured by a combination of total copper quantification and immunological assays for caeruloplasmin concentration alongside an averaged number of copper ions (3·15 µg copper per mg caeruloplasmin) bound to the protein.[4] However, the immunological assays do not differentiate between metal-bound and metal-free caeruloplasmin, frequently leading to inaccurate NCC values.[5] This challenge was in part addressed by introducing a parameter called exchangeable copper, as measured by copper in the filtrate of a molecular-weight cutoff filter upon treatment of a sample with a low-molecular-weight copper chelator.[6] As the copper ions within caeruloplasmin are tightly bound, the assumption with this method was that the chelator only captures the NCC population. However, the method showed inaccuracies due to the ability of the chelator to still remove a portion of caeruloplasmin-bound copper from the protein. Therefore, this method was replaced during the course of the study by a new parameter, termed speciated copper (NCC-Sp), in which copper was measured directly alongside protein separation. The parameter is measured by liquid chromatography inductively coupled plasma mass spectroscopy, allowing for direct online measurement of copper speciated into caeruloplasmin versus other serum components.[5] This method overcomes the challenges associated with the indirect measurements of NCC based on estimations or on its ability to be chelated. This method has promise to provide reliable and reproducible quantification due to its direct read-out of copper components excluding that bound to caeruloplasmin. Although it relies on specialised instrumentation, the authors show its unprecedented reliability in clinical samples. The method lends itself to further analysis of copper-containing species within the NCC population. Should these proteins be identified in healthy and diseased conditions, such information could bring to light specific copper-containing species that might be valuable new copper biomarkers in patients with Wilson disease and could be measured with more widely accessible methods. Certainly, the issue of the method to measure copper balance is not just a mere technicality but instead it reflects the common challenge of practising clinicians with defining clinically and metabolically stable Wilson disease and with having the technical tools to assess and measure copper balance stability. The key questions regard the validation of this tool, the correlation between NCC-Sp and clinical

manifestations, the potential of NCC-Sp to predict worsening clinical manifestations, and ultimately how and when NCC-Sp will be available to clinicians.

Future studies should include a larger number of patients, evaluated over a longer follow-up period, and the primary outcomes would ideally include clinical signs and symptoms and not only biochemical clinical parameters. Importantly, participants' ethnic and racial diversity cannot be further ignored in clinical research for rare diseases. The CHELATE trial, as a multicentre study on patients with Wilson disease, includes participants with minimal diversity, and, consequently, it cannot compare copper metabolism in different ethnicities. Given the progress that clinical research has made in Wilson disease and knowing that ethnicity has a substantial effect on metabolic liver disease outcomes,[7] it is crucial to expand the focus to broader populations of patients with rare diseases.

In summary, the key messages for gastroenterologists, hepatologists, and any clinician following patients with Wilson disease are that penicillamine can safely be switched to trientine formulations and that there is hope to have a tool to measure and monitor copper metabolism stability.

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