

EDITORS

Kathleen E. Corey, *Boston, MA*
Harmeet Malhi, *Rochester, MN*

Bis-choline Tetrathiomolybdate as Old Drug in a New Design for Wilson's Disease: Good for Brain and Liver?

The article reported by Weiss et al. describes a phase II trial showing the efficacy of bis-choline tetrathiomolybdate (TTM) in 28 patients with Wilson's disease (WD).⁽¹⁾ After 24 weeks of treatment, 71% of patients met the primary endpoint of normalized non-ceruloplasmin-bound copper (NCC) (57%) or a 25% or more reduction of NCC (14%). This was accompanied by an improvement of neurological status. A reversible increase of transaminases and gamma-glutamyltransferase occurred in 39% of patients who received at least 30 mg/day. In 25% of patients, 11 serious adverse events were reported, of which 7 were unlikely to be related to the study drug.

Autosomal recessively inherited WD mutations of the responsible ATP7 β gene lead to the failure of copper translocation through the encoded carrier from cytosol to the trans Golgi network (TGN) for incorporation into apoceruloplasmin or in hepatocytes for vesicular excretion across the canaliculus into bile (Fig. 1). Consequently, apoceruloplasmin degrades and biliary excretion fades, resulting in copper overload. Accordingly, non-TGN-transported copper accumulates in cytosol, where it is bound to metallothionein (MT) serving as a cellular protective protein against cytotoxic Cu¹⁺. In later stages of WD, the binding capacity of MT is exceeded and canalization to lysosomes has been proposed (Fig. 1). They may finally burst under this copper burden, causing cell injury and the release of copper to blood, where it is loosely bound to albumin (as "free" copper or NCC). Within this NCC complex, copper can easily dissociate from albumin and is capable of entering cells through a copper transporter as well as being released in urine. The main extrahepatic organ for copper accumulation is the brain, and motoric disturbances are predominant features. The copper accumulation in neurons

may not only be due to an increased influx of NCC, but—according to the ATP7 β mutation—also due to diminished efflux. Accordingly, WD is characterized by liver cirrhosis and motoric polyneuropathy with low serum ceruloplasmin, elevated NCC, and increased urinary copper excretion.

The conventional therapy for WD uses copper chelators D-penicillamine or trientine for enhanced copper excretion in urine to achieve a negative copper balance. The source of excreted copper is NCC. An alternative therapy is to use oral zinc preparations. By zinc induction of MT synthesis in mucosal epithelial cells, the absorbed intestinal copper is trapped, and because of their rapid desquamation, a negative copper balance can be achieved. In addition, absorbed zinc induces MT synthesis in hepatocytes for neutralization of toxic copper. However, zinc therapy is not as effective as copper chelators, and indeed liver enzymes may remain elevated.⁽²⁾ On the other hand, zinc has an advantage of low adverse events with the exception of dyspepsia. Nevertheless, hepatic involvement in most cases is manageable for both therapeutic approaches.

The main challenge today is WD therapy of the neurologic manifestation. The reason is that the negatively charged chelators are unable to pass through the blood-brain barrier (BBB). At this point a medical need is defined and the therapeutic application of TTM comes into play.⁽³⁾ The mode of action is still not completely understood. TTM appears to enter cells and is capable of passing the BBB for consequent uptake into neuronal cells. Within hepatocytes it may function as a chelator that removes copper from MT for excretion in bile (negative copper balance) (Fig. 1). Furthermore, TTM can bind copper associated to albumin (NCC) in blood, and in this form, it is bound with high affinity to albumin forming a stable copper-TTM-albumin complex. In this way, NCC segregation in neurons is inhibited. A consequent achievement of a negative balance in brain may improve motoric polyneuropathy. However, previous studies using an ammonium TTM preparation were not successful and it was believed to be due to its instability.⁽³⁾

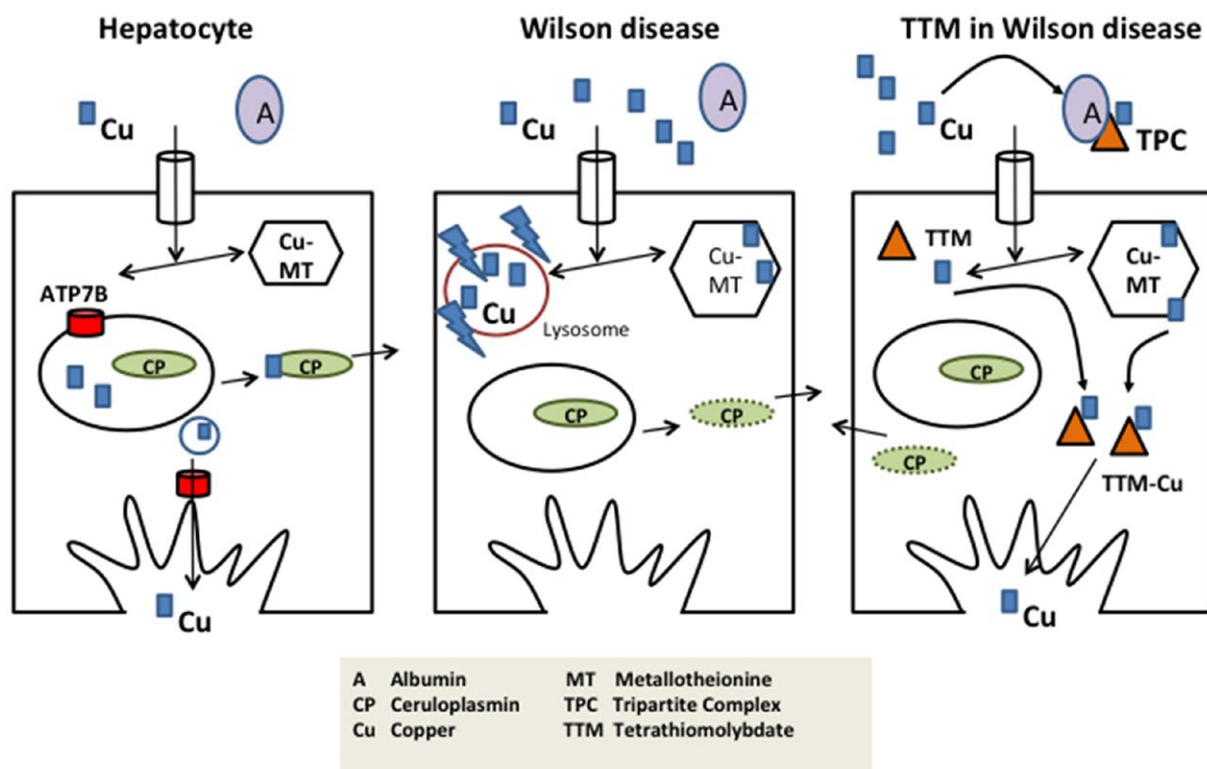


FIG. 1. Hepatocellular metabolism under control condition, Wilson's disease, and treatment with TTM.

In the present trial, a bis-choline TTM (WTX101) was examined.⁽¹⁾ The complex is more stable than TTM and has a better bioavailability. It was tested in a patient cohort with a significant neurologic burden but limited hepatic impairment. The design of this 24-week, open-label, single-arm phase II trial (NCT02273596) included 28 adult WD patients who had received either no prior treatment or a standard of care drug for up to 2 years, and they had normal or elevated NCC levels.

Patients received TTM as WTX101 monotherapy once daily at a starting dose of 15 mg to 60 mg per day with response-guided individualized dosing, depending on NCC and adverse events. The primary endpoint was defined as achieving or maintaining normal NCC levels less than or equal to 2.3 μM or a reduction of 25% or more in NCC levels from baseline. The calculated NCC levels (total serum copper minus ceruloplasmin-bound copper) were corrected for the amount of copper bound in tripartite TTM-copper-albumin complexes in blood (NCC_{corrected}), which was determined using the relationship between NCC and plasma molybdenum concentrations.⁽¹⁾

Clinical outcomes were assessed as secondary endpoints and included neurological disability and status (measured as UWDRS [Unified Wilson's Disease Rating Scale] parts II and III), liver function (modified Nazer score and MELD [Model for End-Stage Liver Disease] score), and quality of life (EQ-VAS [EuroQol-visual analog scale]).⁽¹⁾

Once-daily WTX101 dosing led to a rapid improvement in NCC_{corrected}. Mean levels were below the upper limit of normal levels at week 12 and were reduced by 72% at week 24, when 71% of patients ($P < 0.0001$) met the primary endpoints. The most striking finding was a significant improvement in neurological disability: Mean UWDRS part II scores improved from 6.6 to 4.1 (-3.7 ± 0.9 ; $P < 0.001$) and mean UWDRS part III neurological examination scores improved from 22.8 to 16.6 (-8.7 ± 1.9 ; $P < 0.0001$). These clinical improvements were reflected by a marked increase of quality of life (mean EQ-VAS scores; $+9.2 \pm 2.9$; $P = 0.0024$). International normalized ratio, albumin, modified Nazer score, and MELD score were unchanged throughout the study, indicating stable liver functions.

The observed adverse events relate to a previously treated patient who had exhibited neurological deterioration prior to enrollment with further progression after 12 weeks of treatment, which was discontinued at week 21. Two other patients were discontinued as psychiatric/behavioral symptoms led to their inability to follow the protocol.

Regarding safety, WTX101 was generally well-tolerated, which compiles with previous observations.⁽³⁾ However, 6 patients discontinued WTX101 treatment and 3 of these patients discontinued due to alanine aminotransferase elevations. Reversible elevations in liver tests were observed in 11 patients at doses greater than or equal to 30 mg/day, which usually occurred after 4-10 weeks of treatment. As this transaminase signal was considered to be dose-related, the protocol was amended, capping the maximum dose during the later recruitment period and resulting in an avoidance of dropouts showing further transaminase elevation.

Fortunately, the liver injury effects were dose-dependent and not observed at low doses, which were still sufficient to maintain positive effects on neurologic improvement. The elevation of transaminases is most likely due to the TTM uptake capability in hepatocytes, although the mechanism of injury is not known. Accordingly, when hepatic uptake of TTM is of concern, the dosage needs to be adapted to liver function in cases of cirrhosis with reduced liver cell mass. Moreover, cholestasis may represent a critical issue because TTM-bound copper released from MT may result in its hepatic accumulation.

Shortcomings of the present study are the single-arm design and a low number of patients. The determination of NCC is a suboptimal parameter to define copper burden of a patient. Moreover, it is the predefined mode of action of TTM resulting in tripartite copper complexes, which lowers NCC but not necessarily affects copper stores. Most importantly, NCC and NCC_{corrected} were only calculated based on certain physical assumptions.⁽¹⁾ This is an unreliable estimation that needs verification by direct measurement of NCC in blood. Decoppering capacity in an organism can be better evaluated by determination of low NCC in blood as well as low urinary copper

excretion after cessation of TTM therapy (e.g., over 3 days, as recommended for conventional chelating therapy).

WTX101 is a first-in-class new type of copper chelator that by forming a stable tripartite complex with albumin inhibits hepatocellular and neuronal uptake of copper as well as induces a negative copper balance by promotion of biliary excretion. It is effective in improving neurologic manifestations of WD. At present, a potential hepatotoxicity cannot be completely ruled out, but a dose adaption can overcome this adverse event. This adds to the armament for fighting WD. Thus, in the case of a phase III trial, which can confirm efficacy without severe adverse events, WTX101 may become a new therapeutic strategy, particularly for neurologic-predominant WD with an advantage of once-daily dosage.

Wolfgang Stremmel, M.D.

Department of Gastroenterology, University Hospital of Heidelberg, Heidelberg, Germany

REFERENCES

- 1) Weiss KH, Askari FK, Czlonkowska A, Ferenci P, Bronstein JM, Bega D, et al. Bis-choline tetrathiomolybdate in patients with Wilson's disease: an open-label, multicentre, phase 2 study. *Lancet Gastroenterol Hepatol*. 2017;2:869-876.
- 2) Weiss KH, Gotthardt DN, Klemm D, Merle U, Ferenci-Foerster D, Schaefer M, et al. Zinc monotherapy is not as effective as chelating agents in treatment of Wilson disease. *Gastroenterology*. 2011;140:1189-1198.
- 3) Brewer GJ, Askari F, Dick RB, Sitterly J, Fink JK, Carlson M, et al. Treatment of Wilson's disease with tetrathiomolybdate. V: Control of free copper by tetrathiomolybdate and a comparison with trientine. *Transl Res* 2009;154:70-77.

Abbreviations: MT, metallotheionine; NCC, non-ceruloplasmin-bound copper; TGN, trans Golgi network; TTM, tetrathiomolybdate; UWDRS, Unified Wilson's Disease Rating Scale; WD, Wilson's disease.

© 2018 The Authors. *HEPATOLOGY* published by Wiley Periodicals, Inc. on behalf of American Association for the Study of Liver Diseases. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

View this article online at wileyonlinelibrary.com.

DOI 10.1002/hep.30130

Potential conflict of interest: Nothing to report.