Zinc Treatment for Symptomatic Wilson Disease: Moving Forward by Looking Back

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Treatment with oral chelation therapy with D-penicillamine for copper accumulation in Wilson disease was first developed in the 1950s, and preemptive treatment became the standard of care for patients.[1] An alternative chelating agent, trientine, was developed more than a decade later and has gained more acceptance as first-line treatment due to its safety profile and demonstration of efficacy.[2,3] Zinc was first utilized in veterinary medicine as a treatment for copper accumulation in sheep by Dick et al.[4] in 1954. Borrowing from this experience, the first human use of zinc for patients with Wilson disease were conducted by the Dutch investigator Schouwink in 1961.[5] He recognized that zinc could block copper absorption, and later discoveries revealed that this occurred indirectly by the stimulation of a unique endogenous chelator, metallothionein (MT).[6] MT, a mainly cytosolic peptide with a ≈30% content of cysteine, binds metals such as zinc and copper avidly, and copper with a higher affinity. When present in the cytosol of enterocytes, MT binds newly absorbed copper and prevents it from passing from the gut into the circulation where it is ordinarily utilized for metabolic needs. However, in those afflicted with Wilson disease, copper that is absorbed by the gut accumulates pathologically in the liver and neurological systems due to the altered function of the copper-transporting adenosine triphosphatase, ATP7b, that is mainly expressed in the liver.[7] The shedding of enterocytes with copper still bound to MT results in a higher fecal copper content and net loss of copper from the body because copper does not undergo enterohepatic recirculation and other losses occur via secretions and cell loss.

The vast majority of early reports on the use of zinc therapy for Wilson disease focus on the role of zinc in maintenance therapy for patients treated with prior chelation therapy, or for treating asymptomatic patients. Even though this evidence base has grown over the years, many treating physicians still believe that only chelating agents can be safely used for treatment of Wilson disease. Some investigators reported over the years about many of their patients maintained on zinc, but information about how well they did and failures of treatment was not as well documented. In the United States, George Brewer at the University of Michigan performed pharmacokinetic studies of copper absorption of patients treated with zinc, demonstrating that this agent—when used in multiple daily doses and not as a single daily dose—effectively blocked copper absorption.[8] This blockage of copper absorption eventually reduced the body's copper burden over time in most patients, but in some tissue copper seemed not to change significantly despite clinical improvement. This suggested detoxification by zinc by other means than removal of copper. One such possibility is for zinc treatment to stimulate the production of MT in other cell types in addition to enterocytes. This has been shown to occur in vitro for liver cell lines,[9] but whether MT is maximally stimulated already in liver cells with high copper content and whether zinc can further protect these already copper-laden cells is uncertain. Further studies demonstrated that zinc could be used alone as a single agent to treat adults, pediatric patients, and pregnant patients with Wilson disease.[10-13] The dosage for treatment of pediatric patients was 25 mg given thrice daily, and for adults was 50 mg given with the same frequency. Although balance studies showed twice daily was adequate, many patients miss dosages and so the third dose was established mainly for safety to prevent undertreatment.

There are some reports of symptomatic patients being treated with zinc in the early stages of their disease, but these are usually after intolerance to D-penicillamine or worsening of their neurological disease on D-penicillamine. Though some clinicians report successful treatment, systematic evaluation of a cohort of symptomatic patients with Wilson disease being solely treated with zinc without chelation therapy were lacking until the report by Linn et al.[14] This unique report focuses on 17 patients followed for a median of 14 years with Wilson disease who presented with symptomatic disease, either with neurological or with hepatic disease or with both. These patients were carefully evaluated and then placed on zinc therapy. Linn et al. observed that many patients improved with this therapy alone, although this occurred more consistently for those with neurological disease without ad-

Abbreviation: MT, metallothionein.

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vanced liver disease. These results importantly show that the creation of a net negative copper balance combined with the potential for zinc to stimulate other protective peptides in cells outside the gut may be sufficient to stop and reverse cellular injury by copper. A critical question to answer is how well did these patients who improved on first-line zinc treatment do, and did their time to healing and final outcomes differ from our experience with chelating agents?

Data from patients treated with chelation with advanced liver disease suggests that improvement in biochemical parameters of synthetic function and clearance by the liver takes 3-6 months from the initiation of therapy, and may continue afterward.[15] In neurologically afflicted patients treated with chelating agents, and zinc and then zinc alone after 8 weeks, treatment responses also took weeks and months, but improvement continued for at least up to 4 years.[16] In this report by Linn et al.,[14] their patients with neurological disease were reported to have improvement over a 1-year period, although we are not told whether these patients underwent the same rigorous evaluation longitudinally beyond this initial period of recovery to see if further recovery proceeded to a later time. We are not given data to understand the rate of biochemical improvement for all of their patients' liver disease, but clearly those two that responded who had severe decompensated disease at the outset were reported to improve within a year and even afterward.

The honest report of failures of therapy in some patients in this study is of equal importance as to the success of the zinc in treating others. It is crucial to explore the reasons for failure and to determine if this could have either been predicted or discovered at a time when alternative treatment could have been chosen and disease progression prevented. Two of their patients with compensated cirrhosis worsened, after years of zinc therapy, to decompensated disease (and they mention a third excluded from the study due to lack of longitudinal follow-up) and two others with exclusively neurological presentations developed liver disease during their treatment. Many of these patients that worsened with therapy were later discovered to have nonadherence to their zinc therapy. In one in particular with initial neurological disease, the neurological deterioration due to nonadherence to treatment was later followed by hepatic deterioration; this likely contributed to the nonresponse to zinc treatment despite adherence to treatment at a later time. From the descriptions in this report, it seems nonadherence was discovered after symptom recurrence, and we can only surmise that this could have been detectable beforehand by careful biochemical monitoring and frequent clinical evaluations. Because nonadherence is clearly a problem in Wilson disease, especially in youth,[17] clinicians looking after these patients need to be hyper-vigilant and work with family and other patient caregivers to help detect this problem earlier, rather than when symptomatic disease returns. Frequent monitoring of clinical examination, liver tests, 24-hour urine copper excretion and nonceruloplasmin copper estimates, and simple pill counts all may reveal nonadherence before it becomes a clinical problem. When devastating neurological deterioration or liver failure requiring transplantation occurs, they come at great costs to the individual and their families, as well as to society as a whole.

An editorial in HEPATOLOGY by Gollan and Lipsky in 1987[18] appeared as an accompaniment to an article by Brewer et al.[8] reporting on that group's earlier experience with zinc treatment. The authors of the editorial concluded that they were not yet willing to accept zinc as a maintenance therapy for Wilson disease without longer-term data for outcome, and defended the use of D-penicillamine. This editorial, titled "Treatment of Wilson disease: in D-penicillamine we trust—what about zinc?", reflected the skepticism that existed in 1987 among practitioners about the efficacy of zinc maintenance therapy for Wilson disease. With passing time, many treating physicians have gained comfort with zinc treatment as an alternative to chelation therapy in Wilson disease, including an endorsement of zinc as one option for maintenance therapy or treatment of asymptomatic patients in the American Association for the Study of Liver Diseases treatment guidelines.[2] However, this is not universal in its acceptance, and some experts still trust only in penicillamine.[19] The data presented by Linn et al.[13] do not permit us to say that zinc is the best option for first-line treatment for patients with Wilson disease, only that zinc can be a first-line option for some individuals. As they point out, their cohort is small and the study is retrospective. Their advice is to consider zinc for neurologically impaired patients with stable liver disease, and that those with hepatic presentations undergo treatment first with chelation prior to considering zinc. With the lack of a prospective head-to-head study that would provide the evidence base to answer which therapy is best to start out with for all categories of Wilson disease presentations, we are reliant on retrospective data and clinical experience. The approved drug trientine has a better safety profile than D-penicillamine, and prospective data has been gathered on its use along with zinc as initial therapy for neurologically afflicted patients with Wilson disease.[16] Given this knowledge, are we really ready for zinc as a first-line treatment alone? For patients around the globe who lack the means to pay for chelating agents to treat their Wilson disease, the use of low-cost zinc salts as primary treatment offers

hope of effective and affordable life-saving therapy. However, when there is an option for using chelating agents as first-line therapy, these agents are preferred, at least for some initial period of time. Standardization of patient evaluation, dosing, monitoring on treatment, and the willingness of our patients to participate in clinical trials are needed to go beyond retrospective studies and provide a new evidence base for future care. Until this occurs and we have more prospective data indicating that outcomes are better or at least equivalent with zinc as a primary therapy, we will need to keep looking back from time to time at our patient experiences around the globe to help with current and future choices of treatment and treatment trials for those with Wilson disease.

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