Expert Opinion on Orphan Drugs

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Treatment of Wilson's disease: our patients deserve better

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EXPERT OPINION

Treatment of Wilson's disease: our patients deserve better

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This editorial represents my opinion on the best management of treatment for Wilson's disease (WD) following 40 years of experience.

Unlike many rare inherited diseases, there are multiple effective drugs available for the treatment of WD. However, there are various presentations and stages of WD that have different optimal therapies in my opinion, thus leading to a certain amount of complexity in treating the disease. This complexity is not understood by many physicians treating WD patients. It is my view that currently some patients are being inappropriately treated, leading to unnecessary patient damage and even death. I have spent the last 40 years of my career developing new treatments, and evaluating old treatments, for WD, and claim considerable expertise in this area. I believe there are two situations where treatment is mismanaged. It is my intention in this editorial to point out what I consider to be the two treatment errors harmful to patients, and to discuss misunderstood aspects of the various drugs.

First, I shall give a quick primer on WD for those not familiar with the disease [1]. It is inherited as an autosomal recessive, and is rare, occurring in about 1 in 40,000 births in most populations, with probably around 10,000 patients in the U.S. It is therefore, an orphan disease. The gene that produces ATP7B is mutated in this disease. ATP7B is an ATPase enzyme that is a critical part of the path that causes excretion of copper from the liver into the bile for loss in the stool, thereby keeping copper excretion in balance with copper absorption. With their copper excretory path crippled, WD patients accumulate a little copper every day of their lives. The extra copper is stored in the liver for a time, but eventually the liver storage capacity is exceeded. The liver becomes damaged, and about half the patients present with liver disease, such as hepatitis and/or cirrhosis, and occasionally, acute liver failure. The liver damage may be subclinical, and copper accumulates in other organs, with certain areas of the brain being most sensitive. These are areas of the brain that coordinate movement, and about half the patients (the half that doesn't present with liver disease) present with a movement disorder, with tremor, dystonia and coordination problems, becoming progressively severe if not treated. As the disease progresses these patients have increasing difficulty with speech, sometimes swallowing, eventually develop abnormal body positions, and have difficulty in walking. Both the liver presentation and the neurologic presentation tend to occur in the second and third decades of life, although the age of presentation can be quite broad for occasional patients.

Walshe introduced the first orally effective anticopper drug, penicillamine, for the treatment of WD in 1956 [2]. This drug revolutionized the treatment of WD and a generation of WD patients owed their survival to this drug. Penicillamine acts by chelating and mobilizing copper and causing its excretion in the urine. Because some patients couldn't take penicillamine due to severe side effects, later Walshe [3] introduced trientine as another chelator, which like penicillamine, bound copper and caused its excretion in the urine. It too has some serious side effects, but at a lower frequency than penicillamine.

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My group observed that zinc, used as a therapy for sickle cell anemia, caused copper deficiency [4]. Because of the significant side effects of penicillamine and trientine, I decided to turn this side effect of zinc into a therapy for WD. Our first paper on zinc therapy for WD was published in 1983 [5]. Schouwink had given zinc to WD patients earlier but his work was never published, and confined to a thesis [6]. Because WD was an orphan disease, there was no pharmaceutical company interest, so my group had to do all the studies that a company would normally do to develop the drug, and most of the 18 papers detailing this work can be found referred to in reference [7]. Zinc was approved for the maintenance therapy of WD by the U.S. FDA in 1997, based on my data. It was later approved in Europe and in Japan. Zinc acts differently than the chelators. It blocks the intestinal absorption of copper.

As we began publishing on the efficacy of zinc therapy in WD, patients, who had presented with the neurological manifestations of WD and who had then had serious additional neurological worsening when treated with penicillamine, were coming to us in the hope that zinc therapy could benefit them. Unfortunately it could not, their neurologic damage was permanent. But this caused us to ask how often this worsening from penicillamine occurs. With the cooperation of the Wilson's Disease Association, we did a retrospective survey of neurologically presenting patients who had been treated with penicillamine. We found that half of such patients worsened, and in half of those that worsened, the additional damage was permanent, that is, they didn't recover to their pre-penicillamine baseline. We published these results in 1987 [8]. As a result of this study, I believe penicillamine is contraindicated in neurologically presenting patients.

Since zinc is slow acting and it take 6 – 12 months to control copper toxicity in acutely ill patients, and penicillamine is contraindicated in neurologically presenting patients, we decided to developed a new drug, tetrathiomolybdate (TM), specifically for neurologically presenting patients. This drug is a very potent and fast acting anticopper agent. It forms a tight three-way complex with serum-free copper (the toxic copper) and serum albumin, and quickly (in a week or two) stops further copper toxicity. We did a 55 patients open-label study in neurologically presenting WD patients [9]. TM was given for 8 weeks, during which neurological status was assessed weekly by neurologists using a special evaluation instrument. We found that only two (3.6%) patients reached criteria for neurological deterioration, which was a fantastic result compared to the 50% value we had earlier found for penicillamine [8].

Since there was little information on trientine use in neurologically presenting patients, we did a randomized double-blind clinical trial (an RCT) comparing a standard dose of trientine with TM in neurologically presenting patients [10]. Using our neurologic evaluation instrument, 1 of 25 (4%) patients on TM reached criteria for worsening, while 6 of 23 (26%) patients on trientine worsened. Results with the two drugs were statistically significantly different at $p = 0.05$. Three of the six trientine patients who worsened died, and two others did not do well [10]. These results indicate to us that trientine is also contraindicated for neurologically presenting patients. Further, these results support the concept that penicillamine, whose 50% worsening rate is softer, based upon a retrospective survey, has a worsening rate > 26%, since it acts in a similar manner to trientine, but is a more aggressive, more robust, mobilizer of copper then trientine. We believe the mechanism of neurologic worsening induced by penicillamine and trientine is that the mobilization of copper into the bloodstream for excretion in the urine, with additional elevation of free copper in the blood, causes a further elevation of copper in the brain, and further damage to the brain. In summary, the data are strong that both these drugs should be contraindicated for the initial treatment of neurologically presenting patients.

About half of all WD patients initially present neurologically. Based on the above, if initially treated with a chelator (penicillamine or trientine) a large proportion of them, at least one in four, suffer disastrous consequences, dying or ending up severely neurologically impaired. I have personally seen and cared for many of these badly disabled patients, many of them coming to me after their initial therapy and worsening, in the mistaken belief that zinc, and later TM could somehow help them. However, the damage is permanent, and no drug can help them at that point. Each one represents a terrible and unnecessary tragedy. They are the victims of iatrogenic disease.

Given the above, what is the stated standard of care for initial treatment of neurologically presenting WD patients? Both the American Association for the Study of the Liver (ASSLD) [11] and the European Association for the Study of the Liver (EASL) [12] present guidelines for the treatment of WD. Both recommend initial use of a chelator (penicillamine or trientine) for symptomatically presenting patients, not differentiating neurologic or hepatic presentations.

So why do these guidelines ignore the data about the high risk of treating neurologically presenting patients with chelators? Possibly because they are written by hepatologists who aren't adequately informed about neurological patients, although the guidelines supposedly pertain to all patients.

And treating physicians, whether because of these guidelines or because penicillamine has been used for WD for decades and many physicians know nothing else, routinely treat their neurologically presenting patients with chelators, usually penicillamine. I had one physician say to me, "There is no problem with neurologic patients and penicillamine, I have many WD patients, and I started them all out on penicillamine. The neurologic patients did fine". The problem is, doctors who have much experience with WD are rare, usually at a few medical centers. Patients have to travel long distances to get to the clinic. When these physicians start neurologically presenting patients on penicillamine, those patients who have significant neurologic worsening can't

talk, often can't swallow and need a feeding tube, often can't ambulate, and never make it back to the WD clinic. The doctor only sees those patients who return, who of course are doing well, and those who don't return are just assumed to be dropouts. The doctor remains unaware of the extensive damage that penicillamine has caused in a portion of the patients being treated.

Based on my research and published work [8,10], my first strong recommendation is that neurologically presenting patients should not be treated with a chelator. TM isn't approved as yet although it is in clinical trials. It can be obtained by purchase of bulk product from the manufacturer, and a compounding pharmacist can put it into capsules. But this is more hassle than most will accept for a single patient. In the meantime, the best way to treat neurologically presenting patients is with zinc. The downside of zinc in these patients is that it is slow acting, and the disease may progress a little on its own during the 6 – 9 months it takes zinc to fully suppress copper toxicity. But this mild, often temporary, worsening is nothing compared to the disastrous drug catalyzed worsening caused by the chelators.

My second area of concern with current WD treatment is that some authors have been making certain incorrect assumptions about zinc maintenance therapy. For example, Weiss *et al.* [13], reporting for two large WD centers in Heidelberg, Germany and Vienna, Austria, reported on 288 patients examined between 1954 and 2008 at these two centers. They titled their paper, "Zinc monotherapy is not as effective as chelating agents in treatment of Wilson's disease". Another example is Gunther *et al.* [14] who used an oral radiocopper test to evaluate whether zinc therapy was effective, and found that in 43% of zinc-treated patients, suppression of radiocopper intake was insufficient. These two papers are example of authors claiming that there is a relatively high incidence of 'zinc failures' in the zinc maintenance therapy of WD.

Unfortunately, these papers ignore the original literature characterizing various properties of zinc during its development as an FDA-approved therapy. In that development work, we carefully established that zinc worked in all patients, there were no 'zinc failures,' and we published these findings. It was important in our presentation to the FDA in 1997 that we document the rate of zinc failures. We did, and it was zero. Papers by Weiss *et al.* [13], Gunther *et al.* [14], as well as other such papers were obviously written without the realization that in 40 straight WD patients, zinc therapy produced a negative copper balance, and complete blockage of radiocopper uptake [15]. These patients were in hospital, nurses were giving them their medication, and there was no noncompliance. This is the major difference between our work and that of Weiss *et al.* [13] and Gunther *et al.* [14]. In other words, when the patients are known to take their zinc medicine, there are no, zero, nil, nada, zinc failures.

In both the Weiss *et al.* [13] and Gunther *et al.* [14] papers, and other papers reporting zinc failures (such as reference [16]), there was no adequate evaluating of compliance, that is, knowledge of whether the patients were actually taking their medicine was inadequate. Zinc is known to have a higher rate of noncompliance than chelators, because it must be taken on an empty stomach, and zinc salts under those conditions cause stomach irritation, severe in about 10%, but bothersome in upward of 30%. We reported this level of noncompliance in the paper we published on long-term follow-up in zinc-treated patients [7]. In this paper, and others, we urge regular monitoring for compliance in zinc-treated patients. And monitoring methodology for compliance is straightforward, and doesn't require the expensive, hard-to-use, radiocopper system urged by Gunther *et al.* [14]. Twenty-four hours urine copper and zinc should be monitored every 3 months at first, then if the patient is complying well, every 6 months, and eventually annually. Twenty-four hours urine copper should not increase over 125 μg, and 24 h urine zinc should be at least 2 mg in well-complying patients.

So, my second strong recommendation is, physicians, if you put patients on maintenance zinc therapy, and you should because it is an excellent maintenance therapy, monitor them for compliance. When you don't monitor your patients for compliance, those who don't comply will have recurrence of their disease and suffer additional damage, potentially irreversible, to liver and/or brain, and may die. These are the bad outcomes Weiss *et al.* [13] reported, more common with zinc than with chelators, all because patients didn't take their zinc. Doctors, if you start patients on a medication that is critical to their survival, you have a responsibility to see that they take it adequately.

So, in summary, first don't use chelators for initial treatment of neurologically presenting patients, and second, monitor your patients on zinc therapy for compliance. An improved, once a day, zinc product, which because of its slow release doesn't cause stomach irritation, is in the works [17]. Until then, if monitoring reveals a patient can't take zinc properly, switch them to trientine.

Declaration of interest

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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