Efficacy and Safety of Oral Chelators in Treatment of Patients With Wilson Disease

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BACKGROUND & AIMS: **Wilson disease is a genetic copper storage disorder that causes hepatic and neurologic symptoms. Chelating agents (D-penicillamine, trientine) are used as first-line therapies for symptomatic patients, but there are few data from large cohorts. We assessed the safety of D-penicillamine and trientine therapy and outcomes of patients with Wilson disease.**

METHODS: **We performed a retrospective analysis of data on 380 patients with Wilson disease from tertiary care centers in Germany and Austria, and 25 additional patients from the EUROWILSON registry. Chelator-based treatment regimens were analyzed for their effect on neurologic and hepatic symptoms and for adverse events that led to discontinuation of therapy (Kaplan–Meier estimation; data were collected for a mean of 13.3 y after therapy began).**

RESULTS: **Changes in medication were common, resulting in analysis of 471 chelator monotherapies (326 patients receiving D-penicillamine and 141 receiving trientine). Nine of 326 patients treated with D-penicillamine and 3 of 141 patients given trientine underwent liver transplantation. Adverse events leading to discontinuation of treatment were more frequent among those receiving D-penicillamine than trientine ($P = .039$). Forty-eight months after therapy, hepatic deterioration was reported in only 4 of 333 patients treated initially with a chelating agent. Hepatic improvements were observed in more than 90%, and neurologic improvements were observed in more than 55%, of therapy-naive patients, and values did not differ significantly between treatments. However, neurologic deterioration was observed less frequently in patients given D-penicillamine first (6 of 295) than those given trientine first (4 of 38; $P = .018$).**

CONCLUSIONS: **Chelating agents are effective therapies for most patients with Wilson disease; D-penicillamine and trientine produce comparable outcomes, although D-penicillamine had a higher rate of adverse events. Few patients receiving chelation therapy had neurologic deterioration, which occurred more frequently in patients who received trientine.**

Keywords: ATP7B; Metabolic Disorder; Wilsons disease; Wilson's Disease.

Wilson disease (WD) is an inborn error of copper metabolism leading to hepatic and neurologic symptoms and is caused by alterations of cellular copper processing and an impaired biliary excretion of copper.[1,2] WD is characterized by heterogeneity in clinical presentation. Hepatic and/or neurologic symptoms may be subtle. Conversely, patients also can present with acute or chronic liver failure or with immobilization, loss of speech, and complete dependency as a result of neurologic impairment.[3]

The overall therapeutic aim is the generation of a negative copper balance. This can be achieved either by liver transplantation, which phenotypically corrects the gene defect in the liver, or by medical therapy. Established scoring systems[4–6] discriminate patients in need for urgent liver transplantation as a result of fulminant hepatic disease in whom the window for

Abbreviations used in this paper: DPA, D-penicillamine; WD, Wilson disease.

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medical treatment is not wide enough. For all other WD patients, lifelong medical therapy is indicated. Current treatment regimens[7,8] include copper chelators and zinc salts. The latter reduce the intestinal uptake of copper[9,10] and act via induction of metallothionein,[11,12] a protein that acts to sequester copper in the enterocyte. Chelating agents generally are used as first-line therapy because of their distinct mode of function and higher decoppering potential.

To date, the chelator selected for therapy remains an individual decision because no head-to-head comparisons are available and costs and availability may play a role. Two chelators commonly have been used for this indication for decades: D-penicillamine (DPA) and trientine. Clinical experience with alternative experimental chelators such as tetrathiomolybdate[13–15] is limited, especially in the countries participating in the current study.

DPA was the first oral drug introduced for therapy in WD.[16] Various studies have documented its efficacy, especially in patients with liver disease.[17–20] Likewise, favorable data have been reported for the alternative chelator trientine.[17,21–23] In limited situations of unusually severe disease, reports on the use of these chelators in conjunction with zinc suggest a favorable outcome for combination therapy with DPA plus zinc[4,24] or trientine plus zinc.[25]

The safety profile of DPA is under debate because many series and case reports have reported severe adverse events under DPA such as bone marrow toxicity, elastosis cutis, nephrotoxicity, or lupus-like syndrome, leading to the discontinuation of DPA in up to 30% of patients.[26,27] Trientine is regarded to have a better safety profile, although relevant adverse events such as anemia have been observed.[28]

Given the limited outcome reports in small cohorts of patients and the lack of head-to-head comparisons based on controlled trials, the present study evaluated the efficacy and safety of DPA vs trientine therapy in terms of hepatic and neurologic outcome and adverse events leading to discontinuation to substantiate response rates and to identify medical needs in WD.

Materials and Methods

Patients

This retrospective cohort study included 380 WD patients examined at tertiary care centers in Germany (Heidelberg, Dresden, and Düsseldorf) and Austria (Vienna, Graz, and Linz) and 25 additional patients from the EUROWILSON registry under trientine monotherapy. For all cases, the diagnosis of WD was reviewed using the Leipzig score,[3] and uncertain cases of WD with a score less than 4 were excluded from further analysis. *ATP7B* mutational analysis was performed as previously described.[29,30]

Data on initial presentation and on the development of clinical and laboratory parameters under therapy were recorded. We categorized patients into subgroups on the basis of symptoms present at the time of diagnosis: asymptomatic, hepatic, neurologic, or mixed presentation. Patients with mixed presentation showed hepatic and neurologic symptoms. The presence of Kayser–Fleischer rings (slit-lamp examination) and cirrhosis were recorded. A diagnosis of cirrhosis was based on histology or on the presence of typical findings on imaging in combination with the presence of clinical signs of portal hypertension.

Approach to Monitoring and Medical Therapy

Patients with a stable course were seen in the tertiary centers approximately once a year. The patients were followed up more closely (3, 6, and 12 mo) after initiation of or a change in medical therapy. In line with current guidelines, patients generally started with chelation treatment when symptomatic. No systematic criteria were used regarding the choice of chelating agent (DPA, trientine). Patients receiving only zinc salts over the whole treatment period were excluded from the analysis.

Analysis of Treatment Changes and Adverse Events

Different treatment regimens were identified in the retrospective analysis of changes in treatment: (1) monotherapy with DPA, and (2) monotherapy with trientine. Treatments with zinc or a combination of zinc and a chelator were not analyzed.

We analyzed initial and subsequent therapies for treatment efficacy and events leading to a discontinuation of medication and categorized the reasons for discontinuation. We analyzed events leading to a change/discontinuation of treatment using Kaplan–Meier estimation. Treatment blocks with a follow-up period of less than 6 months were excluded, thus removing patients who immediately underwent liver transplantation from the analysis. We established *P* values for this calculation using the log-rank test (Mantel–Cox test). Adverse events related to discontinuation of therapy were recorded and classified.

Baseline comparison of treatments. Baseline characteristics were recorded at the time of initiation of, or change in, the chelator-based treatment regimens described earlier. Data collection included sex, presentation, genotype, age at diagnosis, presence of Kayser–Fleischer rings, presence of cirrhosis, previous therapies, body mass index, liver enzyme levels (aspartate aminotransferase, alanine aminotransferase, γ-glutamyltransferase), bilirubin level, international normalized ratio, albumin level, model for end-stage liver disease score, and serum markers of copper metabolism (serum copper, and ceruloplasmin). *P* values for comparison were calculated by the chi-square Pearson and Fisher exact tests or the Mann–Whitney *U* test where appropriate.

Outcome measures. From patient records, hepatic and neurologic outcomes were assessed at 6, 12, 24, 36, and 48 months after initiation of the current treatment regimen. The corresponding outcome measures were stratified by first- vs second-line use of the drugs. Hepatic outcome measures were based on clinical symptoms, course of liver enzymes, and liver function tests. Patients with either of these clinical or biochemical signs of liver disease were considered symptomatic. The course of neurologic disease was evaluated by the physician. Both hepatic and neurologic outcomes were scored as follows: unchanged, improved to normal, improved but not normal, deteriorated, or asymptomatic over duration. For hepatic symptoms, the classification of "improved to normal" implies normalized liver enzyme levels and liver function tests.

Based on this classification, the number of patients showing improvement or worsening of symptoms was calculated and stratified by the presence or absence of symptoms and by first- vs second-line therapies. *P* values for comparison between treatments with DPA vs trientine monotherapy were