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

KARL HEINZ WEISS,* FLORENTINE THURIK,‡ DANIEL NILS GOTTHARDT,* MARK SCHÄFER,* ULRIKE TEUFEL,§ FRANZISKA WIEGAND,* UTA MERLE,* DANIELA FERENCI–FOERSTER,‖ ANDREAS MAIERON,¶ RUDOLF STAUBER,# HEINZ ZOLLER,** HARTMUT H. SCHMIDT,‡‡ ULRIKE REUNER,§§ HARALD HEFTER,‖‖ JEAN MARC TROCELLO,¶¶ RODERICK H. J. HOUWEN,‡ PETER FERENCI,‖ and WOLFGANG STREMMEL,* for the EUROWILSON Consortium

**Department of Gastroenterology, §Department of Pediatrics, University Hospital Heidelberg, Heidelberg, Germany; ‡Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, The Netherlands; ‖Department of Gastroenterology, University Hospital Vienna, Vienna, Austria; ¶Department of Gastroenterology, Krankenhaus der Elisabethinnen, Linz, Austria; #Division of Gastroenterology and Hepatology, Department of Internal Medicine, Medical University of Graz, Graz, Austria; **Department of Gastroenterology, University Hospital Innsbruck, Innsbruck, Austria; ‡‡Clinic for Transplantation Medicine, Muenster University Clinic, Münster, Germany; §§Department of Neurology, University Hospital Dresden, Dresden, Germany; ‖‖Department of Neurology, University Hospital Duesseldorf, Duesseldorf, Germany; and the ¶¶Department of Neurology, Hospital Lariboisiere, Paris, France*

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

calculated by the Pearson chi-square and the Fisher exact tests.

Statistical methods. Calculations were performed using SPSS for Windows software version 16.0 (IBM, Chicago, IL). A *P* value less than .05 was considered significant.

Results

Initial Presentation of Study Group

A total of 405 patients (238 females) were reviewed for the analysis. Fifty-two patients (12.8%) presented with hepatic and neurologic symptoms, and 207 patients (51.1%) presented with hepatic symptoms only and 92 patients (22.7%) presented with neurologic symptoms only. Fifty-four patients (13.3%) were diagnosed as being in an asymptomatic state. At diagnosis, 21 patients (5.2%) presented with fulminant WD with hepatic failure (Supplementary Table 1).

Treatment Regimens

Changes in medical treatment were a common event within the study cohort. In summary, we identified 467 chelator-based treatments (326 DPA monotherapy, 141 trientine monotherapy) with a duration of more than 6 months that were included in the analysis (Figure 1) (Supplementary Table 2). No patients received DPA and trientine simultaneously at any time. Combination treatments (chelator + zinc salts) were not included in the statistical analysis.

Baseline Characteristics of Treatment Groups

A comparison of the baseline parameters at the start of the treatment phase between monotherapies with DPA and trientine is presented in Table 1. Laboratory parameters were available for only a subset of patients owing to the retrospective nature of the study. However, there were no statistically significant differences between groups concerning laboratory values, phenotype, predominant genotype, sex, or age. Of the 326 DPA monotherapies, 294 were actually first-line therapies, whereas the majority of trientine monotherapies (105 of 141) were second-line therapies (Table 2).

Efficacy of Chelator Therapy

Outcome measures were scored as outlined earlier and are shown in Table 2 for first- and second-line treatments for the latest available follow-up evaluation within the 6- to 48-month follow-up period. Detailed scoring of outcome measures is shown in Supplementary Table 3.

Hepatic Symptoms

In symptomatic hepatic patients, comparable rates of improvement were observed under first-line DPA therapy (185 of 204; 90.7%) and first-line trientine therapy (25 of 27; 92.6%). When chelators were given as second-line therapy, rates of improvement were generally lower, but still not statistically different between groups.

For symptomatic hepatic patients, stable hepatic disease in terms of unchanged hepatic symptoms was observed under a first-line setting in the DPA group in 15 of 204 (7.4%) treatments vs 2 of 27 (7.4%) in the trientine group. Stable hepatic disease under second-line therapy was reported for 4 of 16 (25%) DPA treatments and for 10 of 45 (22.2%) trientine treatments.

Hepatic deterioration or worsening in terms of a decline of liver functions or progression of chronic liver disease under first- or second-line chelation therapy was noted in 4 of 204 first-line treatments of symptomatic hepatic patients with DPA and in 4 of 45 second-line treatments of symptomatic hepatic patients with trientine (*P* = NS). No hepatic worsening was observed for any patient under chelation monotherapy who initially presented without hepatic symptoms.

Neurologic Symptoms

With regard to the outcome of symptomatic neurologic patients, no statistically significant differences were found concerning the rate of improvement under first-line (DPA 77 of

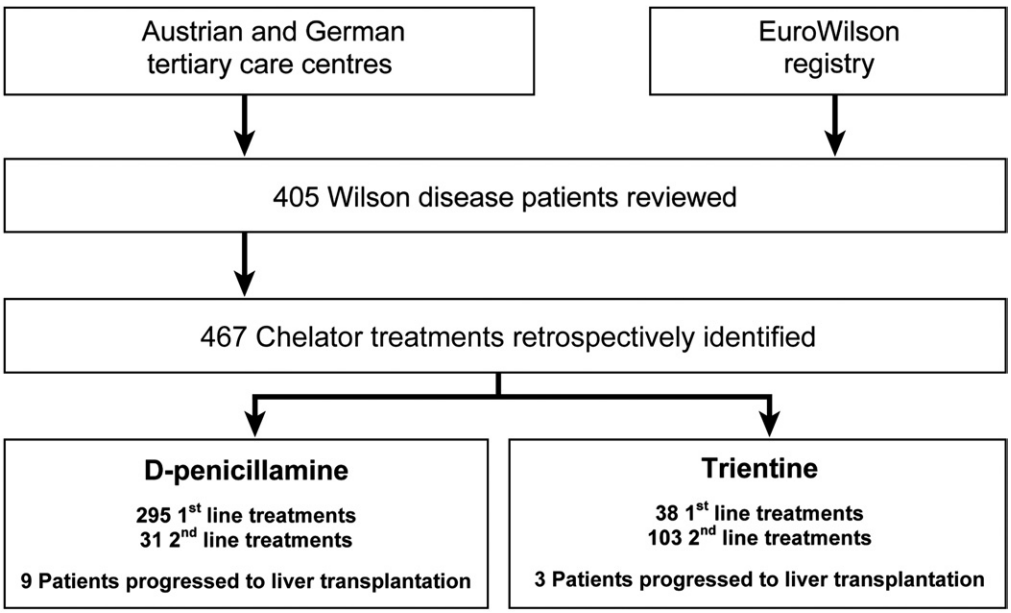


Figure 1. Number of treatments in the study cohort. Hepatic and neurologic outcomes were scored for each treatment at defined time points (6, 12, 24, 36, and 48 mo) as follows: improved to normal, improved but not normal, unchanged, worsened, or asymptomatic over duration. Combination therapies (25 treatments with DPA and zinc; 21 treatments with trientine and zinc) were not included in the numbers provided in this flow chart and were not included in the statistical analysis.

Table 1. Baseline Characteristics of Chelator Treatments

	DPA (n = 326 analyzed)	Trientine (n = 141 analyzed)	*P* value
Sex: male:female	131:195	53:88	.589
Initial presentation			
Hepatic	167/326 (51.2%)	69/141 (48.9%)	.134
Neurologic	72/326 (22.1%)	39/141 (27.7%)	
Hepatic and neurologic	35/326 (10.7%)	20/141 (14.2%)	
Asymptomatic	52/326 (16%)	13/141 (9.2%)	
ATP7B genotype: H1069Q/H1069Q	64/326 (19.6%)	26/141 (18.4%)	.764
Median age at diagnosis, y	17.51 (0.74–60.05)	19.51 (1.23–55.06)	.056
Kayser–Fleischer rings present	170/300 (56.7%)	83/135 (61.5%)	.346
Cirrhosis	92/300 (30.7%)	47/140 (33.6%)	.300
Treatment used as first-line treatment	294/326 (90.2%)	36/141 (25.5%)	< .001
Body mass index[a]	22.5 (14.8–32.4)	22.7 (17.7–27.7)	.64
AST level, U/L[b]	32 (4–2106)	34.62 (13–179)	.449
ALT level, U/L[b]	40 (4–3743)	41 (10–505)	.815
gGT level, U/L[b]	52 (6–708)	56 (12–1021)	.452
Bilirubin level, mg/dL[c]	0.8 (0.2–47)	0.7 (0.1–16.2)	.703
INR[d]	1.02 (1–3)	1.06 (1–3)	.442
Albumin level, g/L[e]	43 (23–55)	42.6 (28–58)	.571
MELD score[d]	7.5 (6.4–35.3)	7.5 (6.4–17.1)	.963
Serum copper level, μmol/L[c]	7 (1–145)	6.9 (1–24)	.652
Ceruloplasmin level, g/L[b]	0.095 (0–0.94)	0.10 (0.2–0.38)	.765

NOTE. *P* values for comparison between treatments were calculated by the chi-square Pearson or the Mann–Whitney *U* test.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; gGT, γ-glutamyltransferase; INR, international normalized ratio; MELD, model for end-stage liver disease.
[a]Data available for DPA, n = 37; trientine, n = 10.
[b]Data available for DPA, n = 184; trientine, n = 49.
[c]Data available for DPA, n = 161; trientine, n = 46.
[d]Data available for DPA, n = 71; trientine, n = 31.
[e]Data available for DPA, n = 134; trientine, n = 47.

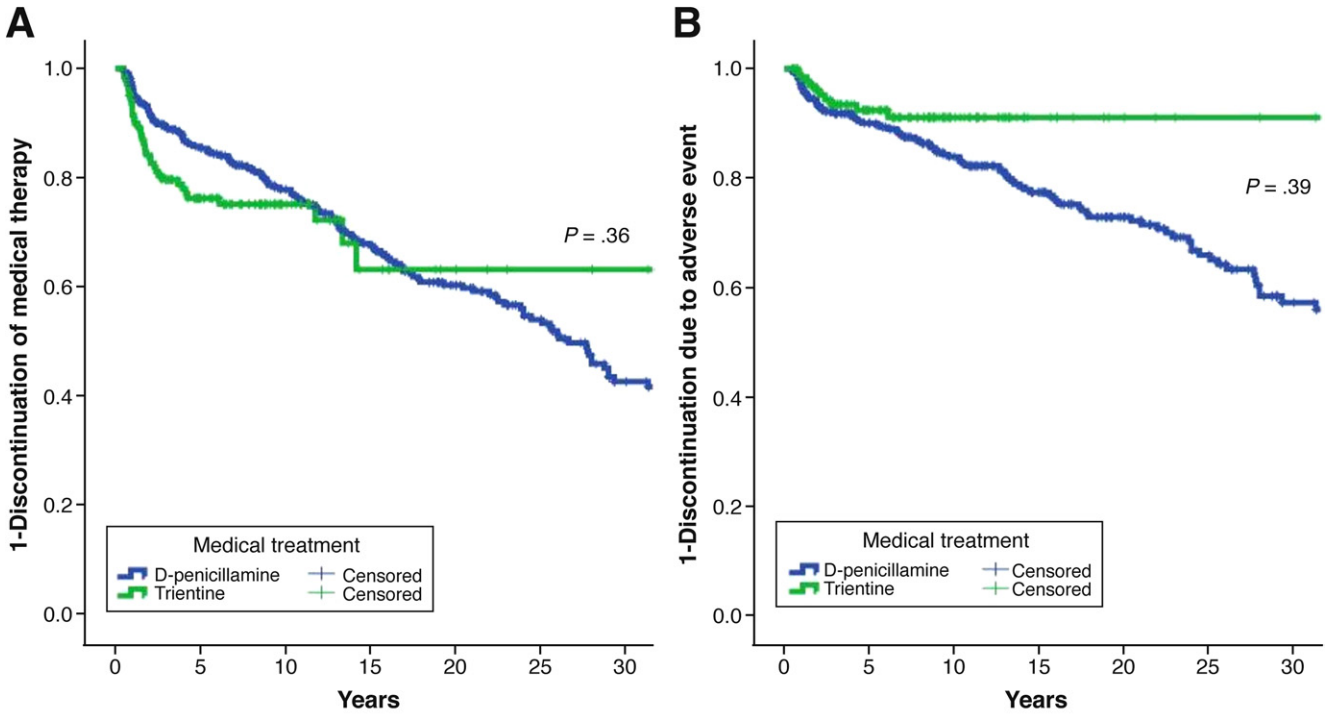
114, 67.5% vs trientine 11 of 20, 55%) or second-line (DPA 3 of 13, 23.1% vs trientine 26 of 51, 51%) chelation therapy. Stable neurologic disease was observed under a first-line setting in the DPA group in 31 of 114 (27.2%) treatments vs 5 of 20 (25%) in the trientine group. Stable neurologic disease under second-line therapy was reported for 9 of 13 (69.2%) DPA treatments and for 17 of 51 (33.3%) trientine treatments.

With second-line therapy, neurologic worsening was comparable between groups, with a trend favoring DPA (DPA: 1 of 13, 7.3%; trientine: 8 of 51, 15.7%). A significantly higher rate of neurologic worsening was reported for first-line therapies of symptomatic neurologic patients treated with trientine (4 of 20; 20%) vs DPA (6 of 114; 5.3%) ($P = .042$). No neurologic worsening under chelation therapy was reported within the fol-

Table 2. Rate of Hepatic or Neurologic Improvement and Worsening in All or Only Symptomatic Patients Stratified by First- and Second-Line Treatment

	First-line treatments			Second-line treatments		
	DPA	Trientine	*P* value	DPA	Trientine	*P* value
Hepatic improvement						
All	185/295 (62.7%)	25/38 (65.8%)	.859	12/31 (38.7%)	31/103 (30.1%)	.386
Symptomatic	185/204 (90.7%)	25/27 (92.6%)	1	12/16 (75%)	31/45 (68.9%)	.757
Hepatic worsening						
All	4/295 (1.4%)	0/38	1	0/31	4/103 (3.9%)	.573
Symptomatic	4/204 (2%)	0/27	1	0/16	4/45 (8.9%)	.565
Neurologic improvement						
All	77/295 (26.1%)	11/38 (28.9%)	.699	3/31 (9.7%)	26/103 (25.2%)	.082
Symptomatic	77/114 (67.5%)	11/20 (55%)	.312	3/13 (23.1%)	26/51 (51%)	.118
Neurologic worsening						
All	6/295 (2%)	4/38 (10.5%)	.018	1/31 (3.4%)	8/103 (7.8%)	.684
Symptomatic	6/114 (5.3%)	4/20 (20%)	.042	1/13 (7.3%)	8/51 (15.7%)	.672

NOTE. *P* values were established using the 2-tailed Fisher test.



At risk		5 years	10 years	15 years	20 years	25 years	30 years
DPA	326	254	202	150	110	79	47
Trientine	141	81	36	12	6	3	2

Figure 2. Discontinuation of treatments for (*A*) any cause or because of (B) adverse events, analyzed by Kaplan–Meier estimation.

low-up period for patients initially presenting without neurologic symptoms.

Reasons for Discontinuation of Treatment and Adverse Events

The median follow-up period for this analysis was 13.3 years. Discontinuation of treatments was analyzed using the Kaplan–Meier estimation. Overall, 142 of 326 DPA treatments and 36 of 141 trientine treatments were discontinued over time (Supplementary Table 2). The resulting Kaplan–Meier curve for adherence to treatments, regardless of the reasons for discontinuing medication, is shown in Figure 2*A*. Over the course of the observation period, 12 patients underwent liver transplantation because of hepatic failure (9 of 326 in the DPA group, 3 of 141 in the trientine group; P = NS).

However, discontinuation as a result of adverse events (Figure 2*B*) was most common in patients on DPA therapy, with 94 of 326 (28.8%) treatments stopped for this reason, compared with 10 of 141 (7.1%) trientine treatments (P = .039).

Details on the adverse events leading to the discontinuation of chelation therapies are shown in Table 3. No deaths related to adverse events were reported in any group.

Discussion

WD requires lifelong medical therapy. The chelating agents DPA and trientine have been used for this indication for many decades and are recommended by current guidelines.[7,8] In this study, we compared the treatment outcome and safety of DPA and trientine in a retrospective fashion.

Efficacy of Chelator Therapy

For WD patients with hepatic symptomatology the outcome measures showed no differences between groups. This is consistent with numerous previous reports documenting a favorable response to DPA[17–20] or trientine therapy.[17,21–23] The reasons for the lower rate of improvement of hepatic symptoms with second-line chelation therapy (70.5%) than with first-line therapy (90.9%) are not clear. This result indicates a partially unsatisfactory response in a subgroup of hepatic patients, as reflected by the percentage of patients showing no symptomatic improvement despite chelation therapy. Because the rate of progression to liver transplantation was similar in each group, this can be explained by advanced liver disease and irreversible structural liver damage, but not by the choice of chelating agent.

Compared with the overall excellent hepatic outcome, the therapeutic efficacy for neurologic WD was less satisfactory. The subgroup of neurologic patients who did not respond to therapy was considerable: nonimprovement or worsening of neurologic disease was observed in more than a third of treatments and occurred with use of both drugs. This observation suggests that, at least in part, the cerebral damage caused by copper toxicity is irreversible under chelation therapy and demands further (eg, symptomatic) medical treatment ap-

Table 3. Adverse Events Leading to Discontinuation of Medical Treatment

	DPA (n = 326 analyzed)	Trientine (n = 141 analyzed)
Death related to adverse event	0	0
Number of treatments discontinued owing to adverse events	94 (28.8%)	10 (7.1%)
Adverse events leading to discontinuation		
Sicca symptoms	7 (2.1%)	
Fatigue	3 (0.9%)	
Pruritus	2 (0.6%)	1 (0.7%)
Gastric complaints (nausea, gastric pain)	8 (2.5%)	2 (1.4%)
Arthralgia	29 (8.9%)	4 (2.8%)
Myalgia	7 (2.1%)	1 (0.7%)
Cephalgia	4 (1.2%)	
Nephropathy	3 (0.9%)	1 (0.7%)
Albuminuria/proteinuria	20 (6.1%)	
Hematuria	2 (0.6%)	
Nephrotic syndrome	4 (1.2%)	
Elastosis cutis	9 (2.8%)	
Leukopenia	6 (1.8%)	1 (0.7%)
Increase of ANA antibodies	22 (6.7%)	1 (0.7%)
Erythema	11 (3.4%)	1 (0.7%)
Alopecia	1 (0.3%)	
Lupus erythematosus	3 (0.9%)	1 (0.7%)
Hirsutism	1 (0.3%)	1 (0.7%)
Development of psychiatric symptoms	5 (1.5%)	
Optic neuritis	1 (0.3%)	
Polyneuropathy	6 (1.8%)	
Other	16 (4.9%)	4 (2.8%)

ANA, antinuclear antibody.

proaches.[31] In the group of patients with an unsatisfactory response to medical therapy in terms of nonimprovement, particular attention should be paid to the patients developing new neurologic problems, or with neurologic problems worsening in severity, because any pre-existing neurodegeneration alone cannot account for this observation. The percentage of these patients with neurologic deterioration under therapy previously has been reported to range from 3% to 30%.[20,32–37] Accordingly, the results of the current study, in which neurologic deterioration rates under first-line therapy were 4 of 20 (20%) under trientine and 6 of 114 (5.3%) under DPA, were not unexpected. In fact, the absolute deterioration rate under D-penicillamine for the defined follow-up period was quite low and significantly lower when compared with trientine. We observed a lower, but statistically insignificant, neurologic deterioration rate of 1 of 13 (7.3%) with second-line DPA therapy than the rate of 8 of 51 (15.7%) with trientine. The difficulty for interpreting this finding is the unclear mechanism underlying neurologic worsening. One possible explanation would be a lack of efficacy and progression in terms of the natural course of disease. An alternative hypothesis suggests additional toxic effects caused by a too rapid cerebral mobilization of copper by the chelating agents.[38] In clinical practice the dosage of chelators thus is escalated slowly when introduced into WD therapy. Following this line of reasoning, differences in pharmacodynamics or dosage schemes might account for the current finding of different rates of deterioration under DPA and trientine.

From a clinical point of view, this raises 2 major questions. Are there predictive factors identifying the subgroup of patients at risk for neurologic deterioration, and what is the role of other medical treatment options (ie, zinc therapy) in symptomatic neurologic WD patients? Importantly, no neurologic deterioration was observed after the initiation of chelator therapy in asymptomatic patients or those presenting with only hepatic symptoms. Other constitutional risk factors were not evident in our cohort because this event was not associated with sex, genotype, degree of liver dysfunction, or age (data not shown). Here, factors such as nutrition or compliance might play a role, but these factors could not be analyzed in detail. Additional limitations for the analysis of these findings are the relatively small number of patients in this subgroup, the nonprospective evaluation of the outcome, and the absence of a standardized or quantitative symptomatic neurologic rating scale as well as possible confounders concerning the choice of the treatment regimens including costs and drug availability.

Data comparing the therapeutic efficacy of zinc salts in neurologic patients with chelating agents are limited and were not the focus of the current study. However, in light of the current results for symptomatic neurologic patients and various previous studies showing a comparable outcome of this subgroup under zinc therapy,[20,39–41] the current study does not contradict the use of zinc in neurologic WD patients.

Safety of Chelator Therapy

We restricted the safety analysis to adverse events leading to discontinuation of the respective drug owing to study design. Our findings suggest that trientine therapy is better tolerated than DPA treatment. In line with previous reports,[26,27] in the current study the number of DPA treatments discontinued for this reason was 94 of 326 (28.8%), compared with only 10 of 141 (7.1%) in the trientine group. Notably, anemia, a previously described side effect of trientine,[7,8] was not reported to be the reason for discontinuation in any treatment group. The long-term data indicate clinically relevant adverse events under DPA therapy throughout the whole observation period, emphasizing the need for continuous monitoring. The observation that DPA was discontinued because of arthralgias 3 times more often than trientine is important in light of recent discussions about the role of joint affection in WD and clearly implies a drug-induced effect.

However, 2 considerations concerning the safety profile are important. First, no therapy-related death or any disability owing to an irreversible persistent adverse event was reported in any group. Second, clinical experience, derived from the years during which DPA was the only available oral therapy for WD, shows that most of the relevant, immune-mediated DPA–related side effects can be managed by co-administration of steroids in conditions in which DPA therapy cannot be replaced by alternative treatments. The clinical relevance of the higher rate of discontinued DPA treatments observed in the current study is obvious but should be considered in its context.

The retrospective analysis posed some limitations on our study. The study cohort consisted only of patients referred to tertiary care centers. Treatment decisions were made according to accepted standards at that time and may have been influenced by confounders, especially concerning the availability of

the drugs. This explains, at least in part, the relatively small number of patients treated with trientine as first-line therapy. Treatment assignment and outcome evaluation were performed in a nonprospective fashion. Likewise, the availability, or the nonavailability, of an alternative treatment or third-line drugs could have an impact, especially concerning the decision to maintain or change ongoing therapy.

Conclusions

In conclusion, both DPA and trientine were equally and highly effective at controlling liver disease with excellent long-term outcomes. In light of recent reports on hepatic deterioration under zinc therapy,[36] the current data emphasize the role of these chelating agents in the treatment of symptomatic hepatic patients. The experience derived from this cohort study for hepatic patients does not favor DPA over trientine or vice versa. The safety profile of both chelators was acceptable, with fewer trientine treatments discontinued because of adverse events. However, continuous monitoring for side effects even after decades of therapy is recommended for any therapy.

Although this study showed partial efficacy of chelation therapy in neurologic WD as well, the outcome of symptomatic neurologic patients is not fully satisfactory. The response and deterioration rates substantiated by the current study identify this subgroup of patients in need of further prospective evaluation of improved treatment regimens using alternative drugs, including zinc and tetrathiomolybdate. Until that goal is reached, therapy with DPA or trientine still defines the standard of care for neurologic WD.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology at* www.cghjournal.org, and at http://dx.doi.org/10.1016/j.cgh.2013.03.012.

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Reprint requests

Address requests for reprints to: Karl Heinz Weiss, MD, Department of Gastroenterology, University Hospital of Heidelberg, INF 410, D-69120 Heidelberg, Germany. fax: (49) (0) 6221-56-5255. e-mail: karl-heinz_weiss@med.uni-heidelberg.de

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Conflicts of interest

The authors disclose no conflicts.

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Supplementary Table 1. Study Collective

Characteristic	Total
Patients	405
Sex, female:male	238:167
Initial presentation	
Hepatic	207 (51.1%)
Neurologic	92 (22.7%)
Hepatic and neurologic	52 (12.8%)
Asymptomatic	54 (13.3%)
Initial presentation with fulminant liver disease (acute liver failure)	21/405 (5.2%)
Diagnosis by family screening	64/405 (15.8%)
Cirrhosis at diagnosis	120/399 (30.1%)
Kayser–Fleischer rings present at time of diagnosis	205/379 (54.1%)

Supplementary Table 2. Number of Discontinued Treatments With a Duration Greater Than 6 Months Within the Study Period Listed by Reason for Stopping or Change of Therapy

	Number of discontinued treatments		
Reasons for discontinuation	DPA (n = 326)	Trientine (n = 141)	*P* value
OLT	9	3	.360
Adverse events	94	10	.039
Pregnancy	4	0	.402
Patient request	12	5	.390
Other	23	18	< .001
Total (any reason)	142	36	.360

NOTE. *P* values for comparison between treatments were established using the Mantel–Cox test.
OLT, orthotopic liver transplantation.

Supplementary Table 3. Detailed Treatment Outcomes

	DPA (n = 326)	Trientine (n = 141)
Unchanged		
Neurologic	40/326 (12.3%)	22/141 (15.6%)
Hepatic	19/326 (5.8%)	12/141 (8.5%)
Improved but not normal		
Neurologic	58/326 (17.9%)	33/141 (23.4%)
Hepatic	58/326 (17.8%)	27/141 (19.1%)
Improved to normal		
Neurologic	22/326 (6.7%)	4/141 (2.8%)
Hepatic	139/326 (42.6%)	29/141 (20.6%)
Asymptomatic over duration		
Neurologic	199/326 (61%)	70/141 (49.6%)
Hepatic	106/326 (32.5%)	69/141 (48.9%)
Deteriorated		
Neurologic	7/326 (2.1%)	12/141 (8.5%)
Hepatic	4/326 (1.2%)	4/141 (2.8%)

NOTE. All 515 treatment outcomes as scored at the end of the follow-up period of up to 48 months.