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CLINICAL TRIAL

Experience on switching trientine formulations in Wilson disease: Efficacy and safety after initiation of TETA 4HCl as substitute for TETA 2HCl

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Abstract

Background and Aim: This retrospective, multicenter study aims to assess the efficacy and safety in Wilson disease (WD) patients treated with trientine tetrahydrochloride (TETA 4HCl) after switch from trientine dihydrochloride (TETA 2HCl).

Methods: In total, 68 WD patients with stable copper metabolism were identified to receive TETA 4HCl (Cuprior™) after previous treatment with TETA 2HCl. We analyzed biochemical markers such as urinary copper, serum copper, non-coeruloplasmin bound copper (NCC), and transaminases as well as clinical scores (APRI; FIB-4 score) at baseline with a follow-up (FU) of 12 months. Safety of TETA 4HCl treatment was based on reported adverse events (AEs).

Results: The study cohort reflects a common WD cohort with a mean age of 20.3 years at diagnosis and 38.3 years at baseline. There are no significant differences concerning serum copper, NCC, transaminases, APRI, and FIB-4 score in the 3-month FU. Six-month FU revealed a decreased AST ($P = 0.008$), APRI ($P = 0.042$), and FIB-4 score ($P = 0.039$). GGT varied only borderline significantly in the 3-month, but not in the 6-month FU. Comparison of urinary copper within the subsets did not reveal a difference to baseline in all FUs, suggesting stable control of copper metabolism. Few AEs during TETA 4HCl treatment were reported, most commonly gastrointestinal discomfort. Only three treatments with TETA 4HCl were discontinued.

Conclusion: Copper parameters and liver function were stable after treatment switch to TETA 4HCl. Treatment with TETA 4HCl was generally well tolerated. This study indicates that the switch from TETA 2HCl to TETA 4HCl is safe and viable.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional ethical committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The study was a priori approved by the local ethics committee.

Informed consent: All patients provided informed consent for the analysis of their chart data. Informed consent for the procedure and management was obtained from all individual participants included in the study.

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Introduction

Wilson disease (WD) is an autosomal recessively inherited disorder of copper metabolism caused by mutations in *ATP7B* gene.[1,2] Current guidelines[3,4] distinguish between initial decoppering treatment and long-term therapy of maintenance. D-Penicillamin (DPA) was introduced as first oral copper chelator.[5] Alternative anti-copper drugs with improved safety profile followed with zinc salts[6] and trientine.[7] Trientine was first approved in 1969 for WD patients intolerant of DPA[7,8] and today is eligible as alternative drug.[4,7,9,10] Overall, safety profile of trientine (TETA 2HCl) is more favorable than DPA: It has a few side effects, but AEs are in general fourfold less frequently reported than for DPA therapy.[4,10,11] In 2018, an alternative trientine salt to TETA 2HCl, namely, TETA 4HCl, was approved under the trade name Cuprior™. The salification of all four reactive amine groups in a scored tablet form was developed primarily for greater temperature stability. Both formulations are available in different forms with differences in PK profile: Limited clinical reports suggest further more differences in bioavailability and pharmacokinetics.[12-14] According to Summary of Product Characteristics (SmPC), TETA 4HCl needs to be individually dosed by biochemical markers of copper metabolism. PK studies in healthy volunteers conducted for TETA 4HCl suggest higher bioavailability than TETA 2HCl.[12,14,15] Therefore, a dose adjustment factor assuming that approximately 60% of TETA 4HCl relative to TETA 2HCl needs to be administered to provide the same trientine base exposure: 1 mg of TETA 2HCl base equates to 0.6 mg of TETA 4HCl base. Subsequently, dosage is titrated according to clinical response and urinary copper excretion. This study aimed to assess usage of TETA 4HCl in a real world collective and is the first report on clinical and pharmacodynamic outcomes after change from TETA 2HCl.

Methods

Study design. This retrospective, multicenter study reports the clinical course of WD patients treated with TETA 2HCl 300 mg, 200 mg of TETA 2HCl base) at baseline after switch to TETA 4HCl (150 mg TETA 4HCl base) between November 1, 2018, and January 21, 2020. In total, 68 WD patients with an established diagnosis of WD by a Leipzig score ≥ 4 (and/or genetic analysis) and a stable copper metabolism (defined by stable dose since 4 months) were included.[3] Further inclusion criteria were a previous medication with TETA 2HCl and no additional medication with zinc or previous medication with DPA. The study was a priori approved by the local ethics committee and patients provided informed consent for the analysis of their chart data. The timepoint of treatment switch was defined at baseline. Switch was necessary due to local approval status of trientine. Follow ups were performed 1, 3, 6, and 12 months counted from baseline. We analyzed biochemical markers of copper metabolism such as 24-h urinary copper, serum copper, non-coeruloplasmin bound copper (NCC), and transaminases. Prognostic scores such as APRI, CHILD, and FIB-4 score were evaluated either.[16] NCC was calculated: (Serum copper_l*63.55) − (Coeruloplasmin_l*3))/10). FIB-4 score was calculated by the formula age [years]*AST [U/L]/(Thrombocyte count [109/L]*sqrt (ALT [U/L]).[17] FU contains also measurement of weight, height, and a clinical examination with focus on neurological worsening. Safety of TETA 4HCl treatment was based on reported AEs. Discontinuation of treatment with TETA 4HCl was recorded.

Study group description. The study cohort involves two countries: Rothschild Foundation Hospital and national reference center for WD in Paris (France: n = 34); University Hospital Heidelberg and Ludwig-Maximilians University Hospital Munich (Germany: n = 34). Approach to TETA 4HCl dosing was center dependent but based on data of a randomized, open-label pharmacokinetic study (TRIUMPH), administering a single dose (600 mg trientine base) in healthy volunteers.[15] The study demonstrated higher bioavailability of TETA 4HCl than the reference product TETA 2HCl. Therefore, an adjustment factor is necessary, assuming that approximately 60% of TETA 4HCl relative to TETA 2HCl needs to be administered to provide the same trientine base exposure. In the French cohort patients were switched using the adjustment factor of 0.625: 3 capsules of Trientine™ 300 mg (Trientine 2HCl 200 mg base) were switched to 2.5 pills of Cuprior™ 150 (Trientine 4HCl 150 mg base). Maximum dose of TETA 4HCl was under 450 mg per day at baseline. FU dates for France were 2, 4 and 6 months. The dose was increased during the FUs in accordance with the urinary copper excretion and the levels of transaminases and could therefore not be matched with the German data (μmol/24 h). The French 4-month follow-up was matched to the German 3-month follow-up. Urine copper data in the French data subset were recorded in a different dimension (μmol/L). The German cohort switched patients with an adjustment factor of 0.6. Daily dose of TETA 4HCl was ≥ 450 mg in most cases. FU dates for Germany were 3, 6 and 12 months. Urinary copper results apply to the German data only.

Statistical analysis. Statistical analysis was performed by using Stata SE version 15.1. Data preparation was carried out in Excel 19. All key outcomes with the exception of the uncensored NCC and the APRI score show a left-skewed distribution. Statistical comparative calculation between the subgroups for continuous endpoints was performed using pairwise t-test. Statistical significance was set at P value < 0.05. Tests for pairwise data were applied. For the 3- and 6-month follow up periods, patients with both baseline and follow-up data were selected. Data were transformed to a logarithmic scale with the exceptions mentioned above and pairwise t-tests with the two-sided null hypothesis. Outcome differences between baseline and follow-up "equal to zero" were applied. Wilcoxon signed-rank test was performed as a secondary check whether the t-test result was influenced by outliers. As potential confounders, we defined neurologic and hepatic manifestation, pediatric *versus* adult age, time since first diagnosis (</≥ 10 years) and daily dose (< 450 mg *vs* ≥ 450 mg). In order to achieve an indication whether age or time since diagnosis had an influence, substitute threshold values (age 30 years, 10 years since diagnosis) were used. For each of the outcomes and separately for the 3- and 6-month follow-up, patients with both baseline and follow-up values were assigned to the pre-defined dichotomic groups (age ≤/> 30 years; years since first diagnosis ≤/>10 years, neurologic manifestation yes/no, hepatic manifestation yes/no, daily dosage </≥ 450 mg). For each of the outcomes and separately for the 3- and 6-month follow-up, patients with both baseline and follow-up values were assigned to the

pre-defined dichotomic groups (age ≤/> 30 years; years since first diagnosis ≤/> 10 years, neurologic manifestation yes/no, hepatic manifestation yes/no, daily dosage </≥ 450 mg). Mean values of the difference between baseline and follow-up were tested using a two-sample *t*-test, accompanied by Wilcoxon's rank-sum test as a non-parametric alternative. The influence of these effects was tested in two-level (mixed) model. Cox regression was run for all confounders of interest and added as a fixed component on the patient level, as well as age and gender as possible additional bias. The analysis plan involves repeated testing on the same data set. Correcting the significance levels was carried out by using the Bonferroni method.

Results

Patient demographics. Mean age of the patients at baseline was 38.3 years (SD 13.4 years); 55.9% of the patients were male. Mean age at first diagnosis of WD was 18.1 years (SD 11.9 years). Four patients were under the age of 18 years at diagnosis. Previous treatment was conducted with TETA 2 HCl with a range of previous treatment from 24 to 216 months (see Table 1).

Reasons for discontinuation of trientine dihydrochloride. Chart review confirmed that the discontinuation of TETA 2HCl (at baseline and similarity initiated of TETA 4HCl) was not related to TETA 2HCL associated adverse events. In almost all cases, TETA 4HCL was chosen as substitute for TETA 2HCl due to local approval, the absence of cold storage, and reimbursement status of trientine in Germany and France.

Table 1 Patient baseline characteristics

Parameter	Numbers and percentages (in %)
Number of patients	*n* = 68 (55.9% men and 44.1% women)
Median demographics at baseline:	
Age	38.00 years (range 20 to 68; 4 under 18 years)
Weight	75.0 kg (range 50 to 115)
Height	178.0 cm (range 157 to 203)
Median age at diagnosis	18.7 years (range 10 to 47)
Previous treatment	Trientine 2 HCl 300 mg
Previous treatment duration	24 to 216 months (median 120 months)
Clinical presentation of WD	*n* = 14 (21%) only hepatic *n* = 30 (44%) only neurological *n* = 22 (32%) mixed presentation (hepatic + neurological) *n* = 2 (3) asymptomatic
Liver cirrhosis	*n* = 9 (13%)
Median liver copper (µg/g dry liver weight)	516 (range 318 to 798; *n* = 8)
Neurological symptoms	*n* = 30 (44%)
- Tremor	*n* = 20 (30%)
- Ataxia	*n* = 22 (33%)
- Dysphagia	*n* = 8 (12%)
- Dystonia	*n* = 8 (12%)
- Drooling	*n* = 12 (18%)
- Dysgraphia	*n* = 12 (18%)
Kayser–Fleischer–Ring	*n* = 28 (41%)

Endpoints. For the present analysis, the research interest was focused on the biochemical markers of copper metabolism, laboratory results, and the score values.

Hepatic outcome. There are no significant differences concerning serum copper, NCC, transaminases, APRI, and FIB-4 score in the 3-month FU after exposure to TETA 4HCl. The 6-month FU revealed a slightly lower (P = AST (0.008), APRI (P = 0.042) and FIB-4 score (P = 0.039). GGT varied only borderline significantly (P = 0.037) in the 3-month FU, but not in the 6-month FU. The comparison of urinary copper within the subsets did not reveal a difference to baseline in all FUs, suggesting stable control of copper metabolism. All key outcomes with the exception of the uncensored NCC and the APRI score show a left-skewed distribution (see Tables 2 and 3). Mean coeruloplasmin is stable over the time, and serum copper rises after 6 m to 4.99 µmol/L. NCC and urinary copper are increased after 6 m. The outcome for the Child–Pugh score is limited to three integer values only (5, 6, and 7) with more than 90% of the values concentrated on the minimum value 5. In the 9 patients with preknown liver cirrhosis, liver values and Child–Pugh score remained stable. But also in early stages, patients revealed effective and safe treatment by TETA 4 HCl similar to TETA 2 HCl. APRI score acts stable during the FU period whereas the FIB-4 score is minimally elevated after 6 m. The comparisons of baseline with the 3-month follow-up values for the key outcomes does not reveal any significant differences in *t*-test. In contrast, comparisons of baseline with the 6-month follow-up values for the key outcomes yield stronger differences; *t*-tests for AST/GOT (P = 0.008; n = 27) showed a significant difference with a lower mean AST after 6 months. APRI (P = 0.042; n = 12) and FIB-4 score (P = 0.039; n = 22) reached also statistical significance in the 6-month FU (see Tables 2 and 3). Supplement figures show exemplarily the patient-specific changes of outcome values in trajectory plots for AST, ALT, and FIB-4 score between baseline and 6-month FU (Fig. S1a–c). Wilcoxon signed-rank test confirmed significant results of the parametric tests for AST and FIB-4.

Dosing. An evaluation with distinction between high (> 450 mg) and low (≤ 450 mg) dosage was performed (Table S1). Concerning dosing, the data of the complementary groups appears to be limited, as in the French cohort a daily dose of 375 mg was usually given. Comparision of copper parameters was further limited by non-uniform approaches to measuring copper in the urine and negative NCC values. In pairwise comparison of the outcomes of patients for which both baseline and follow-up data are available, no significant differences were observed. The mean values of the changes are strongly distorted by outliers. The median values for AST and ALT decrease moderately in the 3-month comparison, and more strongly in the 6-month comparison. The mixed model shows a significant influence of dosage in both AST and ALT (lowering at higher dosage). This corresponds to the (non-significant) results for the change in the median in a pairwise comparison.

Table 2 Descriptive statistics for key laboratory and score outcomes, baseline, 3-, 6-, and 12-month follow up [mean ± SD (count)]

Laboratory values	Baseline	3-month follow up	*P* (*t*-test)	6-month follow up	*P* (*t*-test)	12-month follow up	Scale
	Mean ± SD (Count)	Mean ± SD (Count)		Mean ± SD (Count)		Mean ± SD (Count)	
ALT/GPT (U/L)	54.58 ± 47.24 (*n* = 67)	54.11 ± 50.90 (*n* = 46)	0.999	59.15 ± 42.23 (*n* = 27)	0.517	56.40 ± 67.31 (*n* = 5)	Log
AST/GOT (U/L)	40.22 ± 19.91 (*n* = 67)	43.04 ± 24.27 (*n* = 46)	0.605	39.56 ± 18.60 (*n* = 27)	0.008	34.20 ± 24.01 (*n* = 5)	Log
GGT (U/L)	46.49 ± 34.32 (*n* = 67)	40.20 ± 24.11 (*n* = 44)	0.181	49.85 ± 30.89 (*n* = 27)	0.980	43.80 ± 41.12 (*n* = 5)	Log
Coeruloplasmin (g/L)	0.09 ± 0.07 (*n* = 60)	0.08 ± 0.05 (*n* = 40)	0.783	0.08 ± 0.06 (*n* = 21)	0.143	0.13 ± 0.08 (*n* = 5)	Log
Serum copper (μmol/L)	3.98 ± 3.70 (*n* = 55)	4.12 ± 3.14 (*n* = 26)	0.847	4.99 ± 3.48 (*n* = 14)	0.642	8.78 ± 5.03 (*n* = 5)	Log
NCC (μmol/L)	8.63 ± 13.51 (*n* = 24)	1.88 ± 11.34 (*n* = 17)	0.279	9.80 ± 4.76 (*n* = 10)	0.467	16.22 ± 9.16 (*n* = 5)	Log
Urine copper (μmol/day) (gathered without medication break)	3.65 ± 2.90 (*n* = 24)	7.86 ± 7.42 (*n* = 14)	0.999	4.70 ± 1.98 (*n* = 11)	0.517	5.04 ± 3.23 (*n* = 3)	Log
Scores							
CHILD	5.16 ± 0.51 (*n* = 32)	5.00 ± (0.00) (*n* = 21)	NA	5.09 ± 0.30 (*n* = 11)	NA	5.00 ± 0.0 (*n* = 1)	NA
APRI	0.58 ± 0.30 (*n* = 33)	0.61 ± 0.29 (*n* = 22)	0.364	0.57 ± 0.18 (*n* = 12)	0.042	0.27 ± 0.0 (*n* = 1)	Linear
FIB4	0.68 ± 2.69 (*n* = 67)	1.34 ± 0.83 (*n* = 31)	0.949	0.80 ± 0.94 (*n* = 22)	0.039	1.16 ± 0. 0 (*n* = 1)	Log

CHILD, Child–Pugh score; APRI, aspartate aminotransferase to platelet ratio index; AST [U/L]/(thrombocyte count [10^9/L], FIB4, fibrosis-4 (FIB-4) index for liver fibrosis; age [years]*AST [U/L]/(thrombocyte count [10^9/L]*sqrt (ALT [U/L]); Scale, set of methods underlying the statistical analysis.

Table 3 Descriptive statistics for key laboratory and score outcomes, baseline, 3-, 6-, and 12-month follow up (median; range)

Laboratory values	Baseline Median; range	3-month follow up Median; range	6-month follow up Median; range	12-month follow up Median; range
ALT/GPT (U/L)	36; 11–245 (*n* = 67)	37; 12–287 (*n* = 46)	43; 16–154 (*n* = 27)	26; 18–176 (*n* = 5)
AST/GOT (U/L)	36; 11–131 (*n* = 67)	35; 19–131 (*n* = 46)	37; 17–75 (*n* = 27)	23; 12–77 (*n* = 5)
GGT (U/L)	34; 7–150 (*n* = 67)	35; 8–106 (*n* = 44)	48; 11–143 (*n* = 27)	21; 12–107 (*n* = 5)
Coeruloplasmin (g/L)	0.07; 0.01–0.36 (*n* = 60)	0.06; 0.01–0.19 (*n* = 40)	0.06; 0.01–0.19 (*n* = 21)	0.15; 0.01–0.22 (*n* = 5)
Serum copper (μmol/L)	2.39; 1.01–20.5 (*n* = 55)	3.02; 0.7–11.9 (*n* = 26)	3.94; 1.27–11.50 (*n* = 14)	10.9; 1.7–14.5 (*n* = 5)
NCC (μmol/L)	7.07; 0.19–28.25 (*n* = 24)	4.88; 0.44–29.81 (*n* = 17)	8.71; 1.07–16.92 (*n* = 10)	15.27; 6.86–26.15 (*n* = 5)
Urine copper (μmol/day) (gathered without medication break)	2.4; 0.3–11.9 (*n* = 24)	1.68; 0.29–20.9 (*n* = 14)	3.92; 0.68–8.54 (*n* = 11)	5.85; 1.49–7.79 (*n* = 3)
Scores				
CHILD	5; 5–7 (*n* = 32)	5; 5–5 (*n* = 21)	5; 5–5 (*n* = 11)	5; 5–5 (*n* = 1)
APRI	0.48; 0.2–1.28 (*n* = 33)	0.52: 0.22–1.28 (*n* = 22)	0.59; 0.24–0.79 (*n* = 12)	0.27; 0.27–0.27 (*n* = 1)
FIB4	1.04; 0.22–11.45 (*n* = 67)	1.4; 0.26–3.91 (*n* = 31)	1.04; 0.37–3.53 (*n* = 22)	1.16; 1.16-1.16 (*n* = 1)

CHILD, Child–Pugh score; APRI, aspartate aminotransferase to platelet ratio index; AST [U/L]/(thrombocyte count [10^9/L], FIB4, fibrosis-4 (FIB-4) index for liver fibrosis; age [years]*AST [U/L]/(thrombocyte count [10^9/L]*sqrt (ALT [U/L]); Scale, set of methods underlying the statistical analysis.

Copper metabolism. In particular, the copper-related laboratory results (NCC; urinary copper excretion) were expected to vary with the factor of time. Neither NCC (P = 0.850 [3 m]; P = 0.418 [6 m]) nor urinary copper (P = 0.677 [3 m]; P = 0.169 [6 m]) revealed statistical significance at the 3- and 6-month FU (see Tables 2 and 3). Serum copper and coeruloplasmin did not differ significantly.

Neurological outcome. There was no early neurological deterioration observed during the observation phase of 12 months defined by a structured clinical examination and conducted by the treating physician.

Safety and treatment discontinuation. There were several adverse events reported as listed in Tables 4 and 5. Cumulative, 26 AE events were reported within the first 3 months and 2 during the later follow ups > 3 months. Twenty-four subjects were underdosed, due to pharmacological prescribing information. We defined discontinuation of treatment with TETA 4HCl due to AEs as of special interest. During the early observation phase of 3 months (Table 5), three subjects discontinued treatment TETA 4HCl: One subject stopped medication due to a bitter taste in the mouth after 1 week of treatment. Taste normalized after discontinuation. Two subjects stopped medication due to digestive troubles. One female subject discontinued after 13 months for progressive elevation of transaminases. This subject showed persistent elevated transaminases after change to alternative treatments and

Table 4 Listing of adverse events (AE)

Adverse events in 28 subjects	Early (≤ 3 months) *n* = 26	Late (> 3 months) *n* = 2
Diarrhea	*n* = 2	*n* = 0
Nausea	*n* = 1	*n* = 0
Vomiting	*n* = 1	*n* = 0
Stomach cramps	*n* = 1	*n* = 0
Meterorism	*n* = 2	*n* = 0
Weight loss	*n* = 3	*n* = 0
Muscle cramps	*n* = 1	*n* = 0
Bitter taste	*n* = 1	*n* = 0
Increase of antinuclear antibodies (ANA)	*n* = 1[†]	*n* = 0
Elevation of transaminases > ULN[‡]	*n* = 4	*n* = 1
Elevation of GGT/ALP > ULN	*n* = 2	*n* = 0
Elevation of bilirubin > ULN	*n* = 1	*n* = 0
Platelet count under 150/nl	*n* = 1	*n* = 0
Restlessness	*n* = 1	*n* = 0
Mentally unwell	*n* = 1	*n* = 0

[†]ANA 1: 640 compared with 1:16 UI/mL at baseline.
[‡]ULN, upper limit of normal.

was finally diagnosed with a concomitant autoimmune like hepatitis, resolved under immunosuppressive treatment.

Discussion

Trientine is recognized as alternative treatment for patients suffering from AEs under DPA.[8,18] This study provides the first real-world data for usage of TETA 4HCl as substitute for TETA 2HCl and is the first study analyzing efficacy and safety of TETA 4HCl in a real world cohort. Patient collective reflects a cross sectional maintenance cohort of WD patients. The distribution of clinical presentation is typical for WD compared with other studies with predominantly hepatic and neurological manifestation.[19,20] During the observation phase of 12 months, nine patients reported about gastrointestinal AEs, such as diarrhea, nausea/vomiting, meteorism, or gastric cramps. In two cases, these symptoms led to discontinuation of treatment with TETA 4HCl. In general, all gastrointestinal AEs were reversible within 6 months. There was no paradoxical neurological deterioration observed during the observation phase of 12 months after switching treatment to TETA 4HCl. Late neurological deterioration needs to be followed up carefully in future and was not assessed in this study. In conclusion, long-term data are needed to evaluate the continuing AEs. Efficacy assessment was focused on the biochemical markers of copper metabolism and liver parameters (transaminases and fibrosis scores). While liver parameters were stable under TETA 4HCl, the interpretation of the results for the copper parameters comes with some limitations: Urinary copper results apply to the German data only. Data of the French data subset were recorded in a different dimension (per volume and not per time) and could therefore not be matched with the German data which for sure is a limitation. Sample size in some of the tests raises some caution concerning the statistical power. There are no significant differences concerning serum copper, NCC, transaminases, APRI and FIB-4 score in the 3-month FU after exposure to TETA 4HCl. The 6-month FU revealed a slightly lower AST, APRI, and FIB-4 score. GGT varied only borderline significantly in the 3-month FU. The comparison of urinary copper within the subsets did not reveal a difference to baseline in all FUs, suggesting stable control of copper metabolism. Data are limited by the small number of patients and further loss to follow up. To confirm the observed significant changes in hepatic endpoints such as the fibrosis scores and to support their long-term reliability, a higher number of patients are required following for a longer period. Transaminases and biochemical markers of copper metabolism depend on the stability of internal copper storages. Chelating agents are dosed higher during the initial decoppering treatment and reduced during maintenance. Time of diagnosis and treatment time as well as age are important. Diagnosis > 10 years and age > 30 years were consequently defined as potential confounders. Both did not show differences in the FUs. It should be considered that the number of patients under 18 years is rather low. Further studies are needed to evaluate TETA 4HCl in this pediatric subpopulation. A similar restriction applies to the time since first diagnosis with only two patients whose initial diagnosis was less than 2 years ago with a range from 24 to 216 months of previous treatment with TETA 2 HCl due to a real world cohort of a rare disease. Knowing that long time chelating treatment leads to negative copper balance, it is per se unlikely to observe deterioration within 1 year of study observation.[8] What we did not observe in this study was an early paradoxical neurological worsening after switch between different trientine formulations, and late deterioration needs to be followed up in further studies. When comparing the stages of WD, TETA 4 HCl is safe and effective in early and advanced stages of treatment. Gender was defined as the sixth possible confounder and seems to have an effect on most of the outcome variables. Nevertheless, the grouped analysis between baseline and 3- or 6-months FU did not significantly influence the biochemical outcomes. Chelating agents affect mainly the urinary copper excretion. Here, of course, the dose of the chelator is essential. The more chelator, the higher the urinary copper excretion. We further identified two dosing groups in our cohort: Patients receiving ≥ 450 mg daily dose of TETA 4HCl and < 450 mg per day. The significant effect of the

Table 5 Treatment discontinuation

Time at discontinuation	Early (≤ 3 months)	Late (> 3 months)
N	*n* = 3	*n* = 1
Reason for discontinuation	Gastrointestinal symptoms (*n* = 2) Irritation of taste (bitter taste) (*n* = 1)	Elevation of transaminases (> 3× ULN[†] of GOT/GPT) *n* = 1

[†]ULN, upper limit of normal.

daily dose is prominent in the liver-related outcomes and some of the copper outcomes. The median values for transaminases decrease moderately in the 3-month comparison, and more strongly in the 6-month comparison. The mixed model shows a significant influence of dosage in both AST and ALT (lowering at higher dosage). This corresponds to the non-significant results for the change in the median of AST/ALT in a pairwise comparison. Nevertheless, the type of treatment, which is mainly based on center experience, and the persistence in treatment is probably most important.

Conclusion

The study cohort reflects characteristics of a WD maintenance patient cohort very well. Few AEs on TETA 4HCl were reported, and the most common were digestive troubles. Our data suggest dose dependency regarding efficacy. To preserve stability on liver enzymes, the starting dose should be at the minimum recommended dose of TETA 4HCl or greater. Trientine needs to be individually dosed among biochemical markers. TETA 4HCl appears at least to be equal to TETA 2HCl, and superiority cannot be proved due to the limitations of study design. Our data support the view, that a switch from TETA 2HCl to TETA 4HCl is safe and effective.

Data availability statement. Data are available from the authors with the permission of corresponding author. The data that support the findings of this study are available from the corresponding author [KH Weiss] upon reasonable request.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1: Comparison of daily dosage (>450 mg vs. < 450 mg / day).
Figure S1a Figures below show the patient-specific changes of outcome values in trajectory plots for AST/GOT between baseline and the 6-month follow-up:.
Figure S1b Figures below show the patient-specific changes of outcome values in trajectory plots for ALT/GPT between baseline and the 6-month follow-up:.
Figure S1c Figures below show the patient-specific changes of outcome values in trajectory plots for Fib4Score between baseline and the 6-month follow-up: