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BACKGROUND AND RATIONALE

INTRODUCTION

Alpha-1-antitrypsin (AT) deficiency is the most common genetic cause of liver disease in children. It also causes chronic liver inflammation and hepatocellular carcinoma in adults. It is the most frequent genetic liver disease necessitating liver transplantation. It is an autosomal co-dominant disorder affecting ~1 in 2000 live births in most populations (1). A point mutation alters the folding of an abundant hepatic secretory glycoprotein and renders it prone to polymerization/aggregation so that aggregated mutant protein accumulates in the endoplasmic reticulum (ER) of liver cells (2). Several lines of evidence indicate that liver injury is caused by a gain-of-toxic function mechanism. The most notable of these is the liver injury found in mice transgenic for the mutant human ATZ gene even though the endogenous anti-proteases of these mice are intact. Studies in cell line and transgenic mouse models of AT deficiency have shown that several pathways are responsible for degrading mutant ATZ when it accumulates in the ER, including the proteasomal and autophagic pathways. Furthermore, accumulation of mutant ATZ in the ER specifically activates the autophagic response (3).

The severity of the liver disease varies dramatically among AT-deficient homozygotes (1). The disease may present with prolonged jaundice in the newborn period and go onto slowly progressive liver dysfunction or may first present later in childhood, during adolescence or adulthood with portal hypertension, cirrhosis and/or hepatocellular carcinoma. In a few cases liver failure occurs in the first year of life. In many infants the jaundice will clear and later transaminases will normalize and further liver dysfunction never develops. In some cases liver injury may never be detected. Indeed, in the most important study of this disease Sveger screened all newborns in Sweden from 1972-1974 (4.5). He identified 127 with homozygous PIZZ AT deficiency and has followed that cohort over the last 30+ years. Although many had jaundice or elevated transaminases in infancy, only 8% have had clinically significant liver disease. The majority of these individuals have no clinical evidence of liver disease in their fourth decade of life. Liver biopsies were not done in this cohort and so it is not possible to tell how many of the patients have subclinical liver damage. It is well established that chronic hepatitis, cirrhosis and/or hepatocellular carcinoma can be detected incidentally in the liver in AT-deficient individuals at autopsy (6.7). It has not been possible to discern which infants who are diagnosed with AT deficiency because of prolonged jaundice or elevated transaminases will go onto severe progressive hepatic dysfunction.

The diagnosis of this deficiency is based on low serum levels of AT and altered migration of the mutant protein in isoelectric focusing gel electrophoresis, called the PI type. Although it is not pathognomonic, proteinaceous globules dilating the ER of liver cells and stained with periodic acid-Schiff after diastase treatment are a characteristic hepatic histological finding.

The only treatment currently available for severe progressive hepatic dysfunction due to AT deficiency is liver transplantation. Prior to transplantation, standard therapies (e.g. endoscopic band ligation and diuretics) for complications of portal hypertension are employed.

LIVER DISEASE IN AT DEFICIENCY

Liver involvement in AT deficiency is often first noticed at the age of 1 to 2 months because of persistent jaundice (1). Conjugated bilirubin levels in the blood and serum transaminase levels are mildly to moderately elevated. The liver may be enlarged. Infants may also be initially evaluated for AT deficiency because of an episode of gastrointestinal bleeding, bleeding from the umbilical stump, or bruising. A small number of affected infants have hepatosplenomegaly, ascites, and liver synthetic dysfunction in early infancy.

An even smaller number have severe fulminant hepatic failure in infancy. A few cases are recognized initially because of a cholestatic clinical syndrome characterized by pruritus and hypercholesterolemia. The clinical features among these infants resemble those of extrahepatic biliary atresia, but histologic examination shows a paucity of intrahepatic bile ducts (1).

Liver disease associated with AT deficiency may be discovered in late childhood or early adolescence, when the patient is seen with abdominal distension due to hepatosplenomegaly or ascites or with upper intestinal bleeding caused by esophageal variceal hemorrhage (1). In some of these cases, there is a history of unexplained prolonged obstructive jaundice during the neonatal period. In others, there is no evidence of any previous liver injury, even when the neonatal history is carefully reviewed.

AT deficiency should be considered in the differential diagnosis for any adult who has chronic hepatitis, cirrhosis, portal hypertension, or hepatocellular carcinoma of unknown origin. An autopsy study in Sweden showed a higher risk of cirrhosis among adults with AT deficiency than was previously suspected and indicated that AT deficiency has a strong association with primary liver cancer (1). This study raised the possibility that the risk of clinical liver disease is as high as 25% among AT-deficient men in the fifth and sixth decades of life. Numerous studies have indicated that AT deficiency is a more common cause of hepatic cirrhosis and hepatocellular carcinoma in adults than previously recognized.

When a patient with the typical symptoms and/or signs of liver disease is evaluated, this diagnosis is determined by low serum levels of AT (10-15% of normal levels) and a distinct migration of the serum AT protein in isoelectric focusing gel electrophoresis (Pi type Z). In addition to progressive fibrosis, the histological hallmark of the disease are intrahepatocytic deposits which stain with PAS after diastase treatment and immunostain for AT, representing the polymerized and aggregated mutant ATZ retained in the endoplasmic reticulum (1).

In the absence of a reliable test for liver function, surrogate markers of cellular injury, synthetic function, and liver fibrosis are combined with clinical measure (e.g., ascites, encephalopathy, splenomegaly, varicies, and hypersplenism) to mark severity of disease. Results from these assessments are dynamic and are impacted by conditions other than worsening liver disease (e.g., sepsis, bleeding, renal insufficiency) yet they can also precipitate acute deterioration of liver function. Two commonly used classifications of disease severity include the Child-Turcotte-Pugh (CTP) score and the Model for End-stage Liver Disease (MELD). The components of the modified CTP score include encephalopathy, ascites, bilirubin, albumin, and prothrombin time or, more recently, the international normalization ratio (INR)(8). Cut-off values and clinical assessments are weighted for severity from 1 (least) to 3 (worse) and the sum of the component points determines the CTP score: A (5-6 points), B (7-9 points), and C (10-15 points). The components of the MELD score, used in patients 12 years of age and older, include the total bilirubin, serum creatinine,

and INR. The MELD score was developed to assess prognosis for patients undergoing a transjugular portosystemic intrahepatic shunt and represents a continuous variable from 6-40 (9). It has been adapted for use in determining the listing status for liver transplantation. While both CTP and MELD have their limitations, they are used to reflect disease severity in patients with chronic liver disease.

Hepatic venous pressure gradient (HVPG) measurements have been integrated into routine clinical practice in the assessment of adults with cirrhosis (10, 11) During this procedure transvenous liver biopsies (typically 2 to 4 samples from different segments of the liver) can be obtained thus providing additional clinical and research information from the same procedure. The procedure can be performed with local anesthesia but usually is done with sedation or low levels of general anesthesia (12, 13). In the study by Manolakopoulos, HVPG dropped significantly in 19 subjects after a 12-month course of lamivudine therapy for chronic hepatitis B (14.4 $\pm$ 3.9 vs 12.4 $\pm$ 3.3 mmHg, p =0.007) (12). In the study by Roberts, of the 10 subjects with chronic hepatitis C with a sustained viral response to pegylated interferon and ribavirin, there was a significant drop in HVPG (9.0 $\pm$ 4.0 vs 6.9 $\pm$ 3.4 mmHg, p =.05) (13).This procedure provides an outstanding global assessment of the degree of fibrosis by assessing overall resistance to portal flow via the calculated portal pressure. The global nature of the measurement avoids problems related to sampling errors from non-homogeneous patterns of fibrosis.

AUTOPHAGY

Because liver damage is caused by intracellular accumulation of the mutant ATZ, the pathways by which this mutant protein is degraded within liver cells have been the subject of a number of investigations. Indeed, one of the major hypotheses about this disease is that pathways for intracellular degradation of mutant ATZ play a role in protecting some deficient individuals from liver disease or in decreasing the severity of the liver disease phenotype (2). The studies in this area have shown that at least 2 major cellular disposal pathways are involved, the proteasome and autophagy (3). Autophagy is a tightly regulated process by which cells consume unwanted cytoplasmic macromolecular constituents and recycle nutrients for cellular remodeling. During autophagy, a double membrane known as the isolation membrane wraps around portions of the cytoplasm to form a double-membrane vesicle, the autophagosome. The engulfed cargo, including organelles and damaged proteins, is degraded upon autophagosome fusion with late endosomes or lysosomes. Autophagy appears to be particularly important for disposal of polymerized and/or aggregated mutant ATZ and the pathway is specifically activated when ATZ accumulates in the endoplasmic reticulum of liver cells (3).

CARBAMAZEPINE AMELIORATES LIVER INJURY IN MOUSE MODELS OF AT DEFICIENCY BY ENHANCING INTRACELLULAR DISPOSAL OF MUTANT ATZ

Because autophagy plays an important role in intracellular disposal of ATZ, particularly aggregated ATZ that accumulates when there are high levels of expression, we recently tested the possibility that drugs which enhance autophagy could reduce the hepatic load of ATZ and reduce hepatic fibrosis in mouse models of AT deficiency. From a list of FDA-approved drugs that have been shown to enhance autophagic disposal of aggregation-prone polyQ proteins, we selected carbamazepine (CBZ) because it has a long

history of safe use in children with seizures. We found that administration of CBZ to PiZ mice by orogastric gavage for 2 weeks resulted in a marked decrease in hepatic ATZ load, as measured by number and size of AT-containing intrahepatocytic globules in liver sections and by hepatic ATZ levels on immunoblots (14). Furthermore, there was a significant reduction in hepatic fibrosis, as measured by Sirius red staining and by quantification of hepatic hydroxyproline concentration. Studies in cell line models of AT deficiency indicate that CBZ mediates increased intracellular degradation of ATZ by several mechanisms including autophagy. Taken together, these results provide a basis for testing the possibility that CBZ will reduce the hepatic load of ATZ and hepatic fibrosis in patients with AT deficiency.

CARBAMAZEPINE (CBZ)

Clinical uses

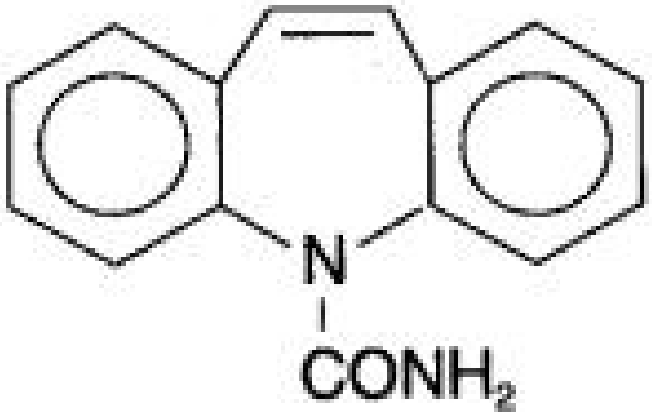
CBZ is a drug that has been used for many years as an anticonvulsant and mood stabilizer. Its chemical name is 5*H*-dibenz [*b, f*] azepine-5-carboxamide and its structural formula is shown below. The FDA-approved product insert that includes detailed chemical data, active and inactive ingredients and labeling information is included with this protocol as Attachment 1.

CBZ is effective in preventing partial (focal) seizures, especially complex partial (psychomotor) seizures and generalized tonic-clonic (grand mal) seizures (15). It is also used for treatment of chronic neurogenic pain and in hemifacial spasm. CBZ also has psychotropic actions and has been used in affective disorders. It has had beneficial effects in depression and mania, both alone and together with lithium. CBZ also has beneficial effects in the dyscontrol syndrome, a disorder characterized by episodes of aggressive outbursts.

The mechanism of action of CBZ on neurons is thought to be similar to that of lithium and valproic acid and to involve depletion of cellular inositol (16). Interestingly, this is thought to be the mechanism by which these 3 drugs enhance autophagic activity (17).

Chemistry and Metabolism

CBZ is a tricyclic compound related to iminostilbene. It is a hydroscopic, neutral, lipophilic chemical that is soluble in organic solvents but has low solubility in water. Its limited aqueous solubility has made formulation difficult. Furthermore it tends to form insoluble crystals when its hydration increases in humid conditions. CBZ is eliminated predominantly by hepatic conjugation and hydroxylation. A stable epoxide accumulates in serum. This epoxide has activities that are similar to those of CBZ but lower in potency. The epoxide is eliminated in the urine after hydrolysis of the epoxide. CBZ is also inactivated by conjugation and hydroxylation. A minor metabolic pathway involves aromatic hydroxylation of the lateral rings. CBZ is known to induce hepatic drug-metabolizing enzymes CYP2C and CYP3A as well as UDP-glucuronosyltransferase (18).



Pharmacokinetics

CBZ has linear and predictable elimination kinetics. The relationship between dose and concentration in the blood is predictable within individuals but not within groups and this is why measurement of blood levels is important in determining the appropriate dose in any single subject. CBZ induces its own metabolism. This autoinduction causes the elimination rate to increase when doses of CBZ are initiated or modified. This process takes several weeks to evolve so that the half-life of the drug decreases by ~50% within several weeks. CBZ elimination rate also declines with age.

CBZ is absorbed slowly after oral administration with peak concentrations reached within 4-8 hours. This is mostly due to the time it takes for dissolution of CBZ tablets. The bioavailability is estimated at 75-85% and variably affected by food intake (19). CBZ is distributed throughout the body and ~75% is bound to albumin. It passes the blood-brain barrier, placenta and penetrates breast milk.

Safety

CBZ is a very safe drug with minimal side effects noted after extensive use (15). Side effects have led to reduction of dosage in only 3% of patients receiving the drug and to discontinuation of the drug in another 3%. Dose dependent side effects include drowsiness, sedation, vertigo and opthalmoplegia. These tend to occur early in treatment and dissipate with chronic treatment in an overwhelming number of cases. Use of a dose escalation schedule also reduces the incidence of these side effects. Hyponatremia has been noted, especially in elderly patients. It is usually mild and asymptomatic. It may lower plasma concentrations of thyroid binding globulin, bound and unbound T4 and T3 but clinical hypothyroidism is rare. CBZ treatment may be associated with elevated serum transaminase levels in 5-10% of cases. In the vast majority of these cases CBZ can be continued without dose reduction. On rare occasions when evidence for hepatic dysfunction develops, CBZ must be discontinued.

Severe idiosyncratic reactions are rare. Hematological toxicity with aplastic anemia, agranulocytosis and or thrombocytopenia has been estimated to occur in less than 1 in 50,000 individuals treated with CBZ. A dose-dependent reduction in neutrophil count occurs in 10-20% of patients. However, the neutrophil count rarely goes below 1,200 per mm^3 and CBZ administration has not been associated with an increase in infections. Allergic rash occurs in 4 to 10% of patients and is the most common reason for intolerance to CBZ. Allergic reactions with fever, renal and hepatic toxicity are very rare.

They usually occur in the first month of treatment. These generalized hypersensitivity reactions are almost always self-limited with discontinuation of drug. Serious, sometimes fatal reactions, including toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS) have been reported; with a risk of these events estimated to be 1-6 per 10,000 new users. The risk is higher for individuals of Han Chinese ancestry with the genetic marker HLA-B*1502 (20, 21) and individuals of European ancestry with HLA-A*3101 (22). The liver histology can look like a chemical hepatitis, sometimes with granulomas. In recent work, screening for HLA-B*1502 in Taiwan significantly reduced the incidence of Stevens-Johnson syndrome/toxic epidermal necrolysis in people taking CBZ (23). Presence of HLA-A*3101 was found to increase the incidence of CBZ hypersensitivity syndrome and also the mild maculopapular exanthema associated with CBZ treatment (22) Idiosyncratic neurological reactions including tics, asterixis and dystonia are rare. Moreover these reactions often occur in patients with neurobehavioral diagnosis and so are difficult to completely attribute to CBZ.

CBZ treatment has been associated with AV block. Other cardiovascular events that have been reported include congestive heart failure, edema, aggravation of hypertension, hypotension, syncope and collapse, aggravation of coronary artery disease, thrombophlebitis, and thromboembolism. Other side effects that have been reported in limited numbers include urinary frequency and urinary retention.

A recent study reported an increase in suicide caused by CBZ, particularly in patients who are on this medication for indications other than epilepsy (24). However, these patients were probably receiving CBZ for indications such as refractory depression, refractory neurogenic pain or agitation associated with severe dementia that can be independently highly associated with suicide. This study did not have the appropriate control groups for these indications. Furthermore, an extensive series of studies do not show an increase in suicide in patients taking CBZ for epilepsy or any of these other clinical indications (25-29). Nevertheless, the FDA continues to include this drug as a cause of suicidal ideation. We will evaluate and monitor subjects for suicide potential as described below and exclude or remove them from the trial based on previously established guidelines.

CBZ can cause damage to the fetus when administered to women during pregnancy. Congenital anomalies, especially spina bifida, have been reported. It is considered class D for low but increased risk during pregnancy by FDA.

Use of CBZ in Children and Adolescents

CBZ has been used safely in children and adolescents for many years. In most cases, CBZ is used to manage chronic seizure disorders. Side effects are similar to what is described in adults. There are no pediatric-specific adverse events or precautions.

Interaction with other medications

CBZ induces hepatic microsomal enzymes which can alter CBZ metabolism as well as other medications that include: other anticonvulsants (phenytonin, phenobarbital, primidone, and valproic acid), barbiturates, clozapine, corticosteroids, cyclosporine, dacarbazine, doxycycline, estrogens and oral contraceptives, fleodipine, haloperidol, levothyroxine, quinidine, tricyclic antidepressants, warfarin, xanthines (e.g.,

caffeine, theophylline). Drugs that can inhibit metabolism of CBZ and increase plasma concentrations include: cimetidine, clarithromycin, diltiazem, erythromycin, troleandomycin, verapamil, and metronidazole. Monamine oxidate inhibitors cannot be used concurrently with CBZ. Increased CNS depressant effects can occur with CBZ plus lixapine, maprotiline, molindone, phenothiazines, pimozide or thioxanthenes.

NON-EPILEPTIC USES OF CBZ

CBZ appears to have benefits as adjunctive treatment in major depressive disorders, including bipolar disorder (24). Mostly it is used to treat irritability or agitation in patients who are already on conventional antidepressants. CBZ is used for aggression and impulsive behavior. In one study it was superior to placebo in reducing self-aggressive activity of women with borderline personality disorder but in other studies it was not different from placebo (25). CBZ treatment improved mood and overall functioning in short-term trials for patients with agitation/aggression associated with Alzheimer's disease.
Although several studies suggest that CBZ is more effective than benzodiazepines in treating alcohol withdrawal symptoms, the evidence for use of CBZ for this indication is not compelling (26). CBZ is the first line treatment for trigeminal and glossopharyngeal neuralgia (27).

USE OF CBZ IN PATIENTS WITH LIVER DISEASE

CBZ has been in clinical use for over 40 years, yet clinical studies relating to the use of CBZ in patients with known liver disease are not available (28). In fact, the presence of chronic liver disease has been an exclusion criteria for drug studies, including CBZ (29). As chronic elevation of serum aminotransferase levels is present in up to 8% of adults (30), the importance of targeting patients with chronic liver disease to assess safety and efficacy of medications in this population is now recognized (31).

Pathophysiologic changes associated with chronic liver disease and cirrhosis can impact drug absorption, metabolism, bioavailability, and elimination. Portal hypertensive gastropathy, delayed gastric emptying (32), and altered intestinal permeability (33) can alter the expected absorption kinetics of an orally administrated medication. An increased volume of distribution may increase drug elimination half-life (34). Hepatic extraction of the absorbed medication as well as elimination through conjugation, hydroxylation and biliary excretion will be highly individualized depending upon the severity of the liver disease (35). Renal function can also be impaired (36).

CBZ has a low hepatic extraction (<30%) and low protein binding (75%)[18, 35]. With this pharmacodynamic profile, peak CBZ levels would be expected to be similar to patients without liver disease, but elimination of CBZ may be slowed (37). Cholestasis can impair the activity of CYP2C which would also decrease hepatic clearance of CBZ (38). Therefore, the maintenance dose may be lower than expected in subjects with liver disease as compared to those without liver disease. While careful attention to CBZ serum levels will minimize dose-dependent adverse effects, idiosyncratic reactions may not be

avoidable with dose reduction. We find no evidence that patients with compensated cirrhosis are at any greater risk of developing an idiosyncratic reaction than patients without liver disease.

OBJECTIVES

1. Determine whether CBZ treatment reduces hepatic ATZ load in AT-deficient patients with severe liver disease
2. Determine whether CBZ treatment reduces hepatic fibrosis in AT-deficient patients with severe liver disease
3. Determine whether CBZ treatment reduces portal pressure in AT-deficient patients with severe liver disease as assessed by serial hepatic venous pressure gradient measurements
4. Determine whether CBZ treatment is safe and tolerated by patients with severe liver disease caused by AT deficiency
5. Determine whether CBZ treatment leads to stabilization in disease severity as measured by the MELD scores

STUDY DESIGN (See also Study Flow Chart in Attachment 2)

This is a Phase II prospective study of the use of CBZ in adolescents and adults with AT deficiency and compensated cirrhosis. It is a randomized, double-blinded, placebo-controlled study in which 20 subjects will receive drug and 10 subjects will receive placebo. Eligible patients will take CBZ or placebo for 12 months. Transvenous catheterization of the hepatic vein for measurement of hepatic venous pressure gradient will be carried out before and after the treatment period. Liver biopsies will be carried out through the transvenous catheterization at the same time to obtain liver tissue for measurement of hepatic ATZ load and hepatic fibrosis. These studies are often done as a part of standard of care for adults with cirrhosis. Clinical and biochemical follow-up will be undertaken to assess safety and tolerability of CBZ in these patients. After 12 months of therapy, HVPG and transvenous biopsies will be repeated permitting a formal assessment of effects on ATZ load (by PAS staining, immunostaining, and immunoblot analysis) and fibrosis (by quantitative Sirius red staining and by examination of changes in HVPG).This approach has been effectively utilized to demonstrate efficacy of antiviral therapy in both Hepatitis C and Hepatitis B in reducing portal pressure.

The primary efficacy outcome will be to determine the effect of CBZ on hepatic ATZ load. This will be based on the number of hepatocytes with PAS+/diastase-resistant globules. Secondary measures will include the area of a liver section occupied by these globules. If there is enough tissue available for immunoblot analysis we will also use the steady state level of ATZ as a measure of hepatic ATZ load. For the secondary efficacy outcomes we will determine the effect of CBZ treatment on hepatic fibrosis on the basis of Sirius red staining and hydroxyproline concentration and whether CBZ treatment changes portal pressure as determined by HVPG. We will also determine if CBZ treatment reduces the MELD score by monitoring it at the beginning and end of the 12-month treatment period, including measuring at 7 follow-up visits while on active medication or placebo. The differences in the change in MELD score for subjects on active medication will be compared to that in subjects on placebo. Safety and tolerability will be investigated by close observation and routine laboratory testing of the 30 subjects.

STUDY POPULATION

Potential subjects for the study will be identified from the clinical practices of the pediatric and adult hepatology programs in the UPMC system and via outside referrals. The typical potentially eligible subject will have AT deficiency (ZZ and SZ phenotypes and low serum level) and clinical evidence of cirrhosis complicated by portal hypertension (e.g. splenomegaly or thrombocytopenia [platelet count <150,000 or a complication of portal hypertension (e.g. varices or ascites)]. HVPG measurement will be used as a screening procedure to determine if the potential study subject has documented significant portal hypertension (HVPG greater than or equal to 10 mm Hg or as indicated in inclusion criteria below). The research program will be advertised in relevant specialty journals and through the Alpha-1 Association. Interested individuals would need to be seen in the aforementioned clinical programs. Eligible subjects will be approached by one of the study investigators so that the study can be explained and inclusion/exclusion criteria can be reviewed.

SCREENING

Following a signed assent/consent, patients with AT deficiency will undergo a screening assessment to determine their eligibility for the interventional study.

Entry criteria for the screening assessment include:

1. Age $\geq$ 14 years to $\leq$to 80 years of age.
2. AT deficiency confirmed by ZZ or SZ phenotype and serum level < 83 mg/dl (in subjects who are receiving AT replacement therapy at the time of enrollment, AT deficiency will be confirmed by ZZ or SZ phenotype and serum levels <83 mg/dl at the time of initial diagnosis and/or prior to the initiation of AT replacement therapy).
3. Clinical evidence of portal hypertension
    a. History of endoscopically confirmed esophageal or gastric varicies, or
    b. Hypersplenism, or
    c. Splenomegally and
        a. Platelet count <150,000
        b. History of sonographic or
        c. Clinically evident ascites requiring on-going diuretic therapy

Exclusion criteria for the screening assessment include:

1. Child Pugh Score $\geq$ 12
2. Serum total bilirubin > 5 mg/dl
3. INR > 2.2
4. Hepatic encephalopathy uncontrolled with outpatient medical therapy
5. Serum creatinine > 1.5 mg/dl
6. History of bone marrow depression (independent of hypersplenism associated with cirrhosis), hypersensitivity to carbamazepine or any of the tricyclic compounds such as amitriptyline, desipramine, imipramine, protiptyline or nortriptyline.
7. Evidence of a known secondary process leading to active liver disease, and for which there is compelling evidence, including but not limited to Hepatitis B, Hepatitis C, alcohol related liver disease, Wilson disease, sclerosing cholangitis, primary biliary cirrhosis
8. Alcohol intake > 30 gm/day (average from total intake over a week)

9. Evidence or history of hepatobiliary malignancy, e.g. hepatocellular carcinoma
10. Pregnancy, lactation
11. Severe cardiac or pulmonary disease felt to be a contraindication to CBZ therapy
12. History of suicide attempt
13. Potential for suicide behavior based on pre-treatment screening tools (PHQ-9 score greater than or equal to 10)
14. WBC <1,500
15. Platelets <25,000
16. Inability to take oral medication
17. Status post Transjugular Intrahepatic Portosystemic Shunt (TIPS) or scheduled to undergo procedure during trial participation

Screening visits:

At the screening visits a complete history and physical examination will be performed. Screening blood tests will be obtained to assess liver function and to verify the Child Pugh status. A pregnancy test will be done. AT phenotyping and absence of the genetic markers HLA-A*3101 and HLA-B*1502 will be confirmed. Potential subjects will be screened with the Personal Health Questionnaire-9 (PHQ-9). The PHQ-9 has been used successfully to screen adolescents over 13 years of age and adults (39). Subjects will be excluded if scoring 10 or higher on PHQ-9. An abdominal sonogram with Doppler will be performed to assess patency and directional flow of the portal and hepatic veins. Once these studies are confirmed as being consistent with the eligibility criteria arrangements will be made for the pre-treatment HVPG measurement (see below). The hepatic venous pressure gradient measurement and liver biopsy are done together as a single procedure using the transvenous route. Intravenous conscious sedation is used to carry out the procedure. Subjects will receive fresh frozen plasma if the INR >1.6 and platelet transfusion if the platelet count is <50,000 prior to the procedure to prevent bleeding as per usual clinical practice. Subjects will be carefully monitored during the procedure and in the recovery room after the procedure.

Screening Hepatic venous pressure gradient:

HVPG measurements will be obtained at the screening visits and at the 12-month follow up visit to determine the effect of the treatment. After anesthesia a venous introducer is placed in the right femoral vein or internal jugular vein by the Seldinger technique. Under fluoroscopy a 7-F balloon-tipped catheter (Boston Scientific Medi-Tech, Natick, MA) is guided into one of the major veins that drain blood from the liver into the inferior vena cava. An FDA-approved radiopaque contrast agent is infused into the catheter to be assured that it is located within the main right hepatic vein. The free hepatic vein pressure (FHVP) is then measured by recording for 60 seconds. This is done two to three times to assure that the mean pressure is reproducible. The balloon is then inflated and gently wedged so that it totally occludes the hepatic vein for the wedged hepatic vein pressure (WHVP). Once the pressure reading stabilizes the tracing is recorded for 60 seconds. This is repeated three times to assure that the mean pressure is reproducible. At the end of the measurement, contrast is injected while the balloon is inflated to check for total occlusion. The HVPG is then determined by calculating the difference between the WHVP and FHVP.

Screening Liver biopsy:
Liver biopsy provides detailed additional information regarding fibrosis and accumulation of abnormal AT in liver cells and ATZ globules.
The advantage of the current protocol, which includes HVPG measurement, is the ability to obtain 2 to 4 transvenous biopsies at the same procedure with no incremental increase in risk to the subjects (40-42). The results of the liver biopsy will in no way determine whether the subject is eligible for the trial. However, it is necessary to carry it out at the same time as the screening HVPG measurement because otherwise the subject would have to undergo 2 separate procedures (including anesthesia and transvenous catheter insertion) in the screening phase of the study

TREATMENT TRIAL

Patients who have completed the screening phase and meet the following inclusion and exclusion criteria will be eligible for the proposed interventional study. For the convenience of the study subjects, if it is verified per protocol that they do meet full inclusion criteria, the subject may be enrolled to the study and initiate therapy on the same day.

Those who completed the screening phase and are found not to be eligible will be given the option to be reevaluated in the future to determine eligibility for future studies of CBZ or other potential therapeutic agents. Patients will be eligible for the proposed CBZ trial and will be approached for informed consent to participate in the full clinical trial if following inclusion and exclusion criteria are met. They will be provided with the Carbamazepine medication guide before they give informed consent.

Inclusion criteria:

1. Met criteria for entry into the treatment trial from screening protocol
2. Age $\geq$ 14 years to $\leq$80 years of age
3. AT deficiency confirmed by ZZ or SZ phenotype and serum level < 83 mg/dl (in subjects who are receiving AT replacement therapy at the time of enrollment, AT deficiency will be confirmed by ZZ or SZ phenotype and serum levels <83 mg/dl at the time of initial diagnosis and/or prior to the initiation of AT replacement therapy).
4. Subjects must have HVPG greater than or equal to 10 mm Hg unless collateral intrahepatic vessels are visualized via fluoroscopy, in which case the subject must meet all other criteria to participate in the trial.

Exclusion criteria;

1. Child Pugh Score $\geq$ 12
2. Serum total bilirubin > 5 mg/dl
3. INR > 2.2
4. Hepatic encephalopathy uncontrolled with outpatient medical therapy
5. Serum creatinine > 1.5 mg/dl
6. History of bone marrow depression (independent of hypersplenism associated with cirrhosis), hypersensitivity to carbamazepine or any of the tricyclic compounds such as amitriptyline, desipramine, imipramine, protiptyline or nortriptyline.

7. Evidence of a known secondary process leading to active liver disease including but not limited to Hepatitis B, Hepatitis C, alcohol related liver disease, Wilson disease, sclerosing cholangitis, primary biliary cirrhosis
8. Alcohol intake > 30 gm/day (average from total intake over a week)
9. Evidence or history of hepatobiliary malignancy, e.g. hepatocellular carcinoma
10. Pregnancy, lactation
11. Severe cardiac or pulmonary disease felt to be a contraindication to CBZ therapy
12. HLA-B*1502 positive
13. HLA-A*3101 positive
14. History of suicide attempt
15. Potential for suicide behavior based on pre-treatment screening tools (PHQ-9 score greater than or equal to 10)
16. WBC <1,500
17. Platelets <25,000
18. Inability to take oral medication
19. Status post Transjugular Intrahepatic Portosystemic Shunt (TIPS) or scheduled to undergo during trial participation

STUDY DRUG AND DRUG MANAGEMENT:

Rationale for Placebo Control:

The placebo group is designed to provide control for the effects of sample error and variability. This variability could affect liver biopsy as well as HVPG measurements and the placebo control is particularly important because of the relatively small number of subjects in the trial. In addition, the placebo control may provide insight into the tolerability of CBZ by providing natural history data for complications of AT deficiency-associated cirrhosis. Placebo will be prepared by the UPMC Investigational Drug Service (IDS) in capsules that are identical to those of the active compound CBZ.

Randomization:

Once it is determined the patient is eligible for the clinical trial, the patient will be randomized to receive a study medication that will be CBZ, the active medication, or a placebo that will appear similar to but not contain the active medication. Patients will be randomized 2:1 (CBZ: Placebo) with two patients receiving CBZ for every one patient receiving placebo. Patients will be further stratified by ongoing treatment with non-selective beta-blockers used for portal hypertension (e.g. propranolol, nadolol or carvedilol). If the patient is receiving any dose of nonselective beta-blocker prior to study entry, this may decrease portal hypertension which in turn should be associated with decreased HVPG. We want to ensure that both treatment and placebo arms have an equal number of patients receiving nonselective beta-blocker and do not plan to alter this therapy during this investigation.

The Investigational Drug Service will provide subjects with study medication sufficient to last until the next visit + 5 days extra. The UPMC Investigational Drug Service (IDS) will use Medi-dose cups for dispensing CBZ/placebo capsules, depositing one dose of medication/placebo (two capsules) in each Medi-dose cup. UPMC Investigational Drug Service (IDS) will seal and then label the Medi-dose cup with the subject's ID number and the dose of medication (or placebo). IDS will be responsible for delivering the

Medi-dose cups to subject's home address via UPS overnight shipping, and storing the remaining of the Medi-dose cups.

A Study Monitor (see below) will be the only members of the investigative team that is not blinded because the Study Monitor will be responsible for adjustments in CBZ dosage based on drug levels. The Study Monitor will consult with the sponsor-investigator and/or physician sub-investigators to determine exactly how to adjust the dosage but these consultations will be carried out without revealing the identity of the patient.

Administration and Drug Accountability:

CBZ/placebo will be administered at a maximum dose of 1200 mg/day orally for 12 months for subjects over 15 years of age and at a maximum dose of 1000 mg/day for subjects less than 15 years of age. This will involve twice daily dosing with a combination of 100 mg-extended release tablets. Extended release tablets are better tolerated, have a narrow fluctuation in drug concentration, and fewer central nervous system complications than immediate-release formulations (43). To reduce the likelihood of hypersensitivity reactions the subjects will be started on 400 mg/day in 2 doses and the dose will be increased weekly by 200 mg per day until reaching a dose of 1200 mg/day (or 1000 mg/day in subjects less than 15 years of age). A subject's dose escalation may be adjusted if deemed appropriate by the sponsor-investigator or principal investigator but it will not exceed a weekly 200 mg per day increase. Drug levels will be monitored beginning at the 4 week visit, then at each study visit to ensure that the therapeutic concentration of 4-12 ug/ml is reached but not exceeded and then maintained. CBZ will be administered orally twice a day using extended release tablets. The Study Monitor will review the results of the blood level measurements following each visit and use that information for adjustment of the dose of CBZ to maintain the therapeutic drug level. The Study Monitor will not be a member of the investigative team involved with direct patient management. The Study Monitor will not be blinded. To maintain the blinding that is essential to the study design, the Study Monitor will not communicate the actual blood level result to the subject, the subject's physician or to the sponsor-investigator team.

The Study Monitor may increase or reduce the dose of CBZ based upon the drug level, but will not increase the dose of the study drug above 1200 mg/day (or 1000 mg/day in subjects less than 15 years of age). We will only be using trough blood levels. Subjects will have to return for repeat testing if it is discovered that a determination was not done at the trough. The Study Monitor may also elect to repeat the trough blood level determination if needed to have 2 determinations before deciding on a dose adjustment. The formulation of the extended release CBZ tablets approved for commercial marketing will be supplied by Novartis and dispensed by the UPMC IDS. Patient-subjects will not be charged for CBZ or placebo.

Study Monitor

The Study Monitor will be a physician who is familiar with the side effects of CBZ. The Study Monitor will receive and review each CBZ blood level determination. Other members of the research team will monitor the clinical status and physical examination of the patients and will receive the results of the monitoring laboratory values (with the exception of CBZ levels). The Study Monitor will not communicate the actual blood level of the study medication to the patient, family, or the research team

involved with day to day management of patient-subjects participating in the clinical study. However, the Study Monitor will release the identity of the subject's study group to the Sponsor-investigator or physician sub-investigators if that information is needed for the patient's safety. The Study Monitor will recommend adjustment of the CBZ dosing based upon the blood level of CBZ.

On-treatment assessments:
During therapy, study subjects will be seen on a regular basis to assess their clinical status and to obtain standard biochemical measures of liver and renal function, cell counts, etc. Visits will also include a full history and physical examination. Specific assessments and queries will be made for any signs or symptoms of liver disease. Child-Pugh (CP) score and MELD score will be calculated at each study visit. Other than blood collection during study visits, no additional invasive testing is proposed until the week 52b visit when a repeat liver biopsy and HVPG will be obtained. The procedure for the liver biopsy and HVPG will be identical to the procedure used in the screening visit. Data will be collected from procedures undertaken as part of clinical follow up (e.g. endoscopy reports, imaging studies, etc.).

If the study subject undergoes liver transplantation during the study period, samples will be obtained at the time of surgery to provide follow up data. If a subject dies during the study period and the family consents to an autopsy, samples of liver tissue will be obtained at autopsy to provide follow up data. In these cases, follow up HVPG measurements will not be available.

Potential for suicide attempts will be monitored with the Columbia Suicide Severity Rating Scale (C-SSRS) at study visits the week of enrollment through week 52a. It is a semi-structured, clinician-administered instrument to track severity of both suicidal behavior and ideation. This measure is reliable and valid and has been used in previous clinical trials (44, 45). Patients will be withdrawn from the trial if the C-SSRS identifies suicidal ideation or behavior and then the patient will then be referred for mental health evaluation and treatment.

Study visits will be scheduled at weeks 4 (+/- 1 week), 8 (+/- 2 weeks), 18 (+/- 2 weeks), 36 (+/- 2 weeks), and 52a (+ 3 weeks) for a history and physical examination, assessment for depression and suicide behavior, biochemistry measures, and measurement of the blood level of the CBZ. Blood will also be collected at the time of enrollment and at week 52 visit for Fibrotest analysis. All female subjects of child-bearing age will undergo a urine pregnancy test on visit S2, enrollment, and at each follow up visit during the trial. The effect of CBZ treatment will also be assessed by a novel investigative test, a hepatic biomarker assay using samples that are obtained pre- and post-treatment as well as once during treatment. Study subjects may undergo MRI using Elastography within the first six months of study enrollment and at week 52 visit.

Additional visits may be scheduled, at the discretion of the Investigator, to ensure the safety and well-being of subjects. These will include a history, assessment for depression and suicide behavior, biochemistry measures, and measurement of the blood level of the CBZ. A physical exam may also be performed at the discretion of the investigator. Full list of assessments can be found on the schedule of events flow sheet.

Assessment of adherence:
Adherence will be assessed at each of the follow up visits by pill counts and patient medication diaries. Medications will only be available from the Investigational Drug Service (IDS), thus an accurate assessment of medication dispensed will be available. Subjects will be instructed to return unused medications at each visit. By pill count, medication adherence will be assessed. Adherence will be defined as intake of > 80% of the prescribed CBZ or placebo – persistent nonadherence to the study regimen may lead to discontinuation of the study for those subjects. For patients receiving CBZ, adherence will also be assessed by measuring trough CBZ levels at each visit. It is expected that the levels will be between 4 and 12 μg/ml. Standard deviations of sequential levels will also be used as a measure of adherence (46).

End of treatment assessment (week 52 visit + 1 wk):

Hepatic venous pressure gradient – see above

Liver biopsy – see above

Concomitant Medications:
CBZ may interact with other anticonvulsants, including half-life shortening when given with phenobarbital, phenytoin and primidone and half-life prolongation with valproate. Several drugs inhibit the elimination of CBZ and therefore elevate its serum levels, including erythromycin, isoniazid, triacetyloleandomycin, destropropoxyphene, viloxazine, nicotinamide, verapamil and diltiazem. CBZ itself can affect the serum concentrations of other drugs, including valproate, ethosuximide, doxycycline, clonazepam, haloperidol, phenytoin and warfarin.

These drug interactions may necessitate changes in dose of CBZ or other drugs but do not prohibit the use of CBZ or other drugs while administering CBZ. These changes will be directed by the Sponsor-Investigator or sub-investigators.

ADVERSE EVENTS AND TOXICITY MANAGEMENT

Subjects will be closely monitored for the major side effects of CBZ, including allergic reaction, sedation, and bone marrow depression as well as for hepatotoxicity that could worsen the liver disease. This will include history, clinical examination and laboratory testing. Monitoring will be carried out at each study visit. In general it will not be necessary to reduce the dose of CBZ or discontinue CBZ unless there is an obvious allergic reaction, progressive hematological toxicity that includes aplastic anemia, neutropenia and/or thrombocytopenia, progressive hepatic toxicity with rising transaminases, decreasing albumin levels or prolongation of the prothrombin time, unremitting sedative effect, or CBZ levels in the toxic range.

In the event that a subject temporarily discontinues drug for any reason OR an investigator determines the a subject should temporarily hold study drug due to a clinical reason, we will reinitiate therapy based upon the following parameters;

-If study drug has been stopped for less than or equal to 5 days the subject will resume taking the previous dose.

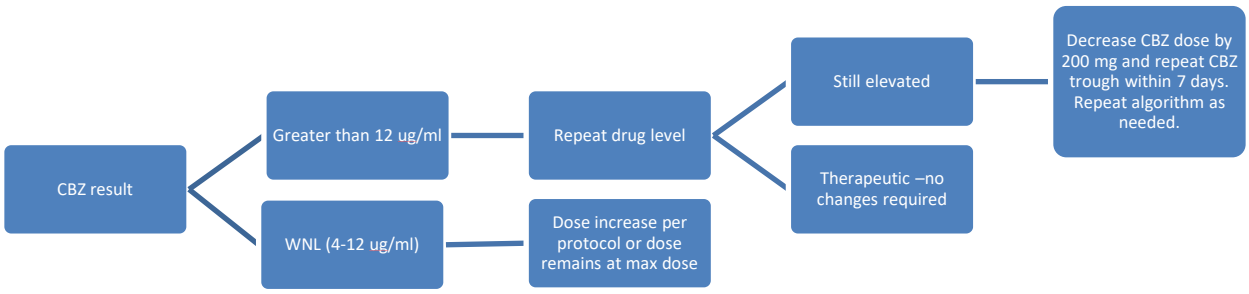
-If study drug has been stopped for more than 5 days but less than or equal to two weeks, the subject will resume half of the previously assigned dose (if half the previous dose is unavailable, the next available formulation close to but less than half the previous dose is acceptable) for one week and return to the full previous dose 7 days later.

-If study drug has been stopped for more than 2 weeks, the sponsor-investigator along with principal investigator will determine both the dose with which the subject restarts and the appropriate dose escalation schedule.

Carbamazepine (study drug) or placebo dose alteration:

The dose of the study drug will be altered based upon the schedule below. Only the study monitor will know the serum trough level and only the study monitor will make dose adjustments for changes in the blood level. The Sponsor-Investigator and/or sub-investigators will be responsible for making adjustments in the dose of Study Medication based upon the clinical and biochemical results outlined below. If these individuals determine that the dose of study drug needs to be adjusted, the request will be made to the Study Monitor who will in turn contact the IDS to carry out the change in dose. When a dose alteration is made based on findings other than the trough blood level, comparable dose reductions will not occur in patients receiving placebo.

1. Serum trough level ≥ 12 µg/ml (to be performed ONLY by the study monitor) See algorithm.



2. (Serum trough level ≤ 4 µg/ml (to be performed ONLY by the study monitor)(study monitor may elect to order a repeat trough level before making a change in dosage)
    a. No change in protocol unless prior dose reduction.

   b. If a prior dose reduction has been made by the study monitor based upon clinical or biochemical abnormality, the dose of the study medication will not be increased unless there is resolution of the clinical or biochemical finding. Increase in dose cannot be made if subject is already on dose of 1200 mg/day or, if less than 15 years of age, on a dose of 1000 mg/day
   c. Continue "b" until trough level is in the therapeutic range
2. WBC <1,000
   a. Decrease dose by 50%
3. Neutrophil count <500
   a. Decrease dose by 50%
4. Platelets < 20,000
   a. Decrease dose by 50%
5. ALT > 500 IU/dl
   a. Decrease dose by 50%
6. INR $\geq$ 1.8 not corrected by 5 mg of vitamin K
   a. Decrease dose by 50%

Guidelines for subsequent Study drug dose adjustments

Indications to discontinue CBZ

1. Child-Pugh score > 12
2. Hepatic encephalopathy uncontrolled with outpatient medical therapy
3. Total bilirubin > 7 mg/dL
4. Evidence of anticonvulsant hypersensitivity syndrome
   a. Fever > 38.5 and
   b. Lymphadenopathy, and
   c. Erythematous, maculopapular, pruritic, or exfoliating rash
5. WBC <1,000 despite 2 weeks of Carbamazepine dose reduction, may resume therapy at 50% of starting dose when WBC > 3,000
6. Neutrophil count <500 despite 2 weeks of Carbamazepine dose reduction, may resume therapy at 50% of starting dose when ANC > 1,500
7. Platelet count <20,000 despite 2 weeks of Carbamazepine dose reduction, may resume therapy at 50% of starting dose when plt > 40,000
8. Hgb <8.5 mg/dl
9. INR $\geq$ 2.5 not corrected by 5 mg of Vitamin K
10. ALT > 750 IU/L
    a. May resume previous dose when ALT < 500
11. Pregnancy
12. Liver transplantation
13. Signs or symptoms of TEN or SJS.
14. Breast feeding.
15. Allergic reaction of Grade 3 or Grade 4.
16. Evidence for behavior or ideation predisposing to suicide (increase in C-SSRS score of 1 from previous test score).

SCREENING AND MANAGEMENT FOR SPECIFIC ADVERSE EVENTS

Patients entering the study will have evidence of chronic liver disease from AT deficiency. At entry into the study, patients may have one or more of the following: elevated serum aminotransferase levels, jaundice, elevated total and direct bilirubin, medically treated ascites, esophageal and/or gastric and/or hemorrhoidal varicies, biochemical evidence of hypersplenism with a white blood count (WBC) and platelet count (PLT) below the normal range, and a prolonged prothrombin time (PT) or International Normalized Ratio (INR). Adverse events will be assessed using the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. Baseline laboratory values for patients entering the study will likely be above the normal range in the case of ALT, AST, total bilirubin, and INR and below the normal range for hemoglobin, WBC, platelets and neutrophils count. Therefore, changes in laboratory values after initiation of the study drug will need to be assessed within the context of the patient's baseline laboratory tests. We will not be reporting every variation in subject lab results as an adverse event. Small deltas from within normal limits to just outside the normal range are not clinically significant in the care of patients and should not be used to define AEs. The investigative team will use standards that define a minimum delta that determines when a change becomes an AE, either as a discrete value change or a percentage change. These can be used in combination with claims of clinical significance by the site investigator.

An increase of CP score to > 12, development of Grade III-IV encephalopathy, or total bilirubin > 7 mg/dl will be considered a treatment failure and therapy will be discontinued. Therapy will not be restarted in these subjects even if there is an improvement in clinical status.

Alterations in liver function:
Markers of liver injury and dysfunction that will be monitored include: PT, INR, AST, ALT, GGTP, total and direct bilirubin, WBC, platelet count, hemoglobin, absolute neutrophils count, and lymphocyte count. These tests will be monitored regularly during the course of treatment, with more frequent measurements occurring in the first four months of treatment. It is anticipated that there will be fluctuations in liver biochemistries (especially ALT, AST, GGTP and alkaline phosphatase) as part of the expected clinical course of AT deficiency. It is anticipated that study subjects will have some element of hypersplenism and associated cell line reductions.

Dermatologic reactions:
Patients will be counseled regarding dermatologic signs that should be reported to a study investigator or study coordinator immediately, these include redness of the skin, blister formation, pealing, itching or oral ulceration. If these signs or symptoms occur, the study medication would be discontinued immediately and the patient would be seen within 24 hours. If the skin lesions are felt to be consistent with Stevens-Johnson syndrome (SJS) or Toxic Epidermal Necrolysis (TEN), then appropriate treatment will be initiated and the study medication will be permanently discontinued. The risk of developing SJS or TEN will be decreased as patients who carry the HLA-B*1502 and/or HLA-A*3101 gene will be excluded from the study. In addition, other less serious dermatologic changes will be assessed at each visit. The presence of mild dermatologic changes such as photosensitivity, non-specific erythema, or mild pruritus, can be observed without dose modification.

Nervous system

Mild symptoms of dizziness, drowsiness, confusion or headache have been described with CBZ. Beginning with a low dose with an incremental increase in medication on a weekly basis has been shown to reduce these side effects. It is possible these symptoms may be more pronounced when CBZ is given to patients with chronic liver disease. Patients will be monitored carefully for evidence of these symptoms.

Metabolism:

Hyponatremia can occur in patients with chronic liver disease and chronic diuretic use in the management of ascites. Therefore, its presence may reflect the natural course of liver disease. On rare occasion, inappropriate antidiuretic hormone (ADH) secretion has been associated with CBZ. Serum electrolytes will be monitored regularly as well as a "first void" urinalysis to assess specific gravity (see appended Study Flow Chart). Alterations or thyroid function studies have been reported with CBZ treatment, but they have not been associated with clinical evidence of hypothyroidism. T4 and TSH will be monitored periodically (see Study Flow Chart in Appendix 2).

Suicide

An increase in suicide in patients taking CBZ has been reported in one study (24) but numerous other studies provide strong evidence against this potential risk (25-29). Nevertheless we will monitor for suicidal tendencies very assiduously and patients will be withdrawn based on well-established guidelines (see above).

Pregnancy

Transplacental passage of CBZ to the fetus is rapid and associated with congenital malformations, including spina bifida, cardiovascular malformations, and developmental disorders.

Patients will be asked to practice effective birth control while they are taking CBZ in this study. However, given the long duration of therapy and the number of female subjects in the child-bearing age, the following precautions will be taken:

1. All female subjects of child-bearing age will undergo urine pregnancy test on enrollment, prior to starting therapy, and monthly during the trial.
2. All female subjects of child-bearing age will need to use a barrier method of contraception as CBZ has the potential to interfere with oral contraceptives
3. All female subjects of child-bearing age will be counseled monthly during the treatment portion of the trial on barrier methods of birth control.
4. If a subject is found to be pregnant, CBZ will be immediately discontinued and permanently stopped and the subject will be referred to an obstetrician for advice and consultation
5. The study will collect data on the outcomes of any pregnancies that occur in women who conceived while taking the study medication.
6. The study will collect data on the outcome of liver disease for those women whose medication was immediately discontinued.

Breast feeding

CBZ and its metabolites are transferred to breast milk and can result in transient cholestatic hepatitis[45]. The estimated dose given to a breast feeding infant is 2-5 mg/kg/day. Breast feeding will not be allowed while the mother is receiving CBZ.

Adverse events

Definition

An adverse event (AEs) is any adverse change from the patient's baseline (pre-treatment) condition, including intercurrent illness which occurs during the course of the trial, after the consent form has been signed, whether the event is considered related to treatment or not.

A serious adverse event (SAE) is an untoward medical occurrence that results in any of the following: Death, or an event that is either life-threatening (risk of death at the time of the event) requires in-patient hospitalization or prolongation of existing hospitalization, or results in persistent or significant disability/incapacity or congenital abnormality or birth defect. Important medical events that do not result in one of the events listed above may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

A SAE which is unexpected and is drug related (even remotely) will require expedited reporting to the FDA and the University of Pittsburgh IRB in accordance with respective timeline requirements. The following events are disease outcomes and will not be considered to be serious adverse events as they can occur in the usual course of patients with AT deficiency.

1. Development of hepatocellular carcinoma
2. Complications associated with chronic liver disease which include, but not limited to
    a. Worsening ascites
    b. Bleeding from esophageal, gastric, or hemorrhoidal varicies
    c. Worsening hypersplenism (hard to differentiate from bone marrow toxicity)
    d. Hepatic encephalopathy
    e. Hepatopulmonary syndrome
    f. Portopulmonary hypertension
3. Extra-hepatic conditions related to alpha-1 antitrypsin deficiency which include, but not limited to
    a. Chronic obstructive pulmonary disease
    b. Hypoxia

Data collection procedures for adverse events

Patients will be interviewed regarding medical conditions, medication changes, and symptoms that have occurred at each study visit. An AE form will be completed if any adverse event is reported.

If a study coordinator or investigator learns of any hospitalizations or other adverse events between study visits, an AE form will be completed. All AEs and SAEs from time of study entry (consent) up to the end of follow-up will be reported to the Sponsor-Investigator. A SAE form will be completed for all adverse events rated as serious. Patients will be followed for all ongoing unresolved adverse events until they are either resolved, or in the opinion of the Sponsor-Investigator or treating sub-investigator, the patient is medically stable.

The Sponsor-Investigator will assess the relationship of each adverse event to the use of study drug, based on available information, using the following as guidelines:

1. Unlikely related: No temporal association, or the cause of the event has been identified; or the drug cannot be implicated.
2. Possible related: Temporal association is present, but other etiologies are likely to be the cause; however, involvement of the drug cannot be excluded.
3. Probably related: Temporal association is present; other etiologies are possible, but unlikely.

Reporting procedures

All SAEs that are unexpected and related to study drug will be reported to the Sponsor-Investigator within 72 hours by telephone. This reporting includes serious adverse events that occur from the time the patient has signed the clinical trial consent. The Sponsor-Investigator will promptly review all SAEs and will notify the reviewing IRB and FDA within requisite time frames if an event is considered to be unexpected and possibly or definitely related to the study drug (e.g., *serious, unexpected adverse events related to the investigational drug to the agency within 15 days of the Sponsor becoming aware of such; deaths and life-threatening reactions reported to the agency within 7 days of the Sponsor's awareness).* The Sponsor-Investigator will notify all sub-investigators of unexpected SAEs related to the CBZ. Status reports on all adverse events will be generated under the direction of the Sponsor-Investigator and sent to the DSMB every month and will include the relationship of the AE to trial medication, the severity of the event and if the event is resolved or ongoing. All AEs will be reported annually to the FDA and reviewing IRB, as required

Statistical considerations

Analysis

Objective 1. Determine whether CBZ treatment reduces hepatic ATZ load in AT-deficient patients with severe liver disease.

The primary analysis will test for differences between the treated and placebo groups in the change from baseline to follow-up in the number of hepatocytes with PAS+/diastase-resistant globules using an unpaired t-test (or nonparametric equivalent if appropriate). Given the small sample size, we do not assume that randomization will balance treated and placebo groups at baseline with respect to outcome variables. Therefore, we will compare changes over the course of the treatment rather than differences at the end of the treatment. Secondary analyses will look at the area of a liver section occupied by these globules and the

steady state level of ATZ by immunoblot again using an unpaired t-test (or nonparametric equivalents if appropriate) of the differences between the treated and placebo groups in changes from baseline to follow-up.

Given that the sample is small, randomization may not balance the groups with respect to important covariates, though our ability to detect statistically significant differences is likewise limited to relatively large effect sizes. Furthermore, the number of variables that could be adjusted for in a regression model is also limited by the sample size, as is our ability to do subgroup analyses. However, as exploratory analyses, we will compare the distributions of important confounders between treated and placebo groups and fit multiple linear regression models that include independent variables, in addition to treatment group and baseline values of outcome measures, with variables whose distributions are markedly imbalanced between treatment groups.

Objective 2. Determine whether CBZ treatment reduces hepatic fibrosis in AT-deficient patients with severe liver disease.

Analysis will proceed as in objective 1; however, the outcome will be hepatic fibrosis. The primary analysis will compare treatment group differences in baseline to follow-up changes in hepatic hydroxyproline concentration using an unpaired t-test (or nonparametric equivalent if appropriate). Secondary outcome measures will include Sirius red staining of the liver. Exploratory analyses using multiple regression models will proceed as described above.

Objective 3. Determine whether CBZ treatment reduces portal pressure in AT-deficient patients with severe liver disease as assessed by serial hepatic venous pressure gradient measurements.

Analysis will proceed as in objective 1; however, the outcome will be portal pressure. The analysis will compare treatment group differences in baseline to follow-up changes in hepatic wedge pressure gradient as the outcome. An unpaired t-test (or nonparametric equivalent if appropriate) will be the primary analysis and we will conduct exploratory multiple regression analyses to adjust for the possibility of covariate imbalances as described above.

In subjects with intrahepatic collateral vessels (visualized radiologically) together with HVPG less than 10 at baseline, we will assess the outcomes in all categories other than objective 3

It is possible that we will not see a difference in hepatic ATZ load or fibrosis because of variability and heterogeneity within the liver but that the drug will produce a stabilization or improvement in overall clinical status. Therefore, as an exploratory analysis we will assess whether CBZ treatment will lead to stabilization or improvement in disease severity as measured by the MELD score. The analysis will compare treatment group differences in baseline to follow-up changes.
Analysis will proceed as above; however, the outcome will be the MELD score. Unpaired t-tests (or nonparametric equivalent if appropriate) will be the primary analysis and we will conduct exploratory multiple regression analyses to adjust for the possibility of covariate imbalances.

Power calculations

Resources limited the sample size, so we performed power calculations with an effect size estimated from prior work on the primary outcome for this study – the number of hepatocytes with PAS+/diastase-resistant globules.

The only available data come from studies we have carried out in mice. We found statistically significant differences between 18 treated and 11 placebo mice in the number of globule-containing hepatocytes after CBZ treatment. At the end of the study there were an average of 1088 (sd=260) globule-containing hepatocytes among control and 323 (sd=179) globule-containing hepatocytes among treated mice (14). Assuming that the average number of globule-containing hepatocytes at baseline was the same in the two groups of mice, then the group difference at follow-up (765 globule-containing hepatocytes) reflects the group difference in changes. Assuming equal standard deviation (sd) in the two groups, the effect size was 3.5. Then, for the proposed sample size (20 treated:10 controls) and a two-sided type I error of 5% there would be 80% power even if the effect is 1.1, about 1/3 of what was found in mice. This translates to being able to detect a drop in the treated group of 765 globule-containing hepatocytes compared to a drop in the controls of 514 (rather than 0).

For the second objective of fibrosis the only relevant data come from hepatic hydroxyproline concentrations in mice after CBZ treatment. There were statistically significant differences between the treated and placebo groups in hepatic hydroxyproline concentrations after CBZ treatment with values of 2.27 (sd=1.02) in 24 control mice and 1.21 (sd=0.70) in 25 CBZ-treated mice (14). Assuming that the hepatic hydroxyproline concentrations at baseline were the same in the two groups of mice, then the group difference at follow-up (1.06) reflects the group difference in changes. Assuming equal standard deviation (sd) in the two groups, the effect size was 1.2. Then, for the proposed sample size (20 treated:10 controls) and a two-sided type I error of 5% there would be 80% power even if the effect is 1.1, about 1/10 of what was found in mice. This translates to being able to detect a drop in the treated group of 1.06 compared to a drop in the controls of 0.106 (rather than 0).

For the third objective of portal pressure, power calculations utilized information from 3 studies in which statistically significant and clinically relevant changes in HVPG were demonstrated in small numbers of individuals treated with antiviral drugs. A drop of ~2 mm Hg, or 20%, was found in response to drug treatment (26-28). With 20 patients treated with drug and 10 treated with placebo, there would be 80% power, assuming an average drop in portal pressure of 3.4 or more mm Hg in the treated group compared with no change in the placebo group, with a standard deviation of 3 mm Hg for the measurements.

To increase recruitment, subjects in which an HPVG cannot be measured but have collateral intrahepatic vessels visualized via fluoroscopy, may be enrolled if they meet all other criteria. We expect the possibility of a loss of 20% of the patients for the primary aim due to no HVPG measurement. We expect the loss to be balanced in the intervention and placebo group. With 16 intervention/8 placebo as a sample size, we would have power to find an effect size of 1.2 demonstrating that we have adequate power.

Statistical Support, Data Management and Quality Control

The study administrator will prepare data collection forms and manuals of operations and will monitor study adherence to the trial protocol.

Safety analysis of this limited group of study subjects will be descriptive and will indicate tolerability of carbamazepine by individuals with compensated cirrhosis. Descriptive statistics of laboratory parameters at the end of therapy and at the time point of largest deviation from normal will be compiled.
The prevalence of other potential toxicities (e.g. dermatologic reactions) will also be compiled. Limited comparisons to the control group will be performed, although the study is not powered to identify relatively rare toxicities.

Approach to safety/tolerability

Clinical adverse events or laboratory value abnormalities requiring treatment reduction or discontinuation will be recorded. Particular attention will be placed upon potential serious adverse events known or believed to be related to CBZ that are fatal, potentially life threatening, significantly or permanently disabling, or require hospitalization.

Safety analysis

Adverse events. Summaries of adverse events (number adverse events, number and percentage of subjects with adverse events, rates per person-months) will be provided. Events will be summarized based on the date of onset for the event. A treatment emergent adverse event will be defined as an adverse event that begins on or after the date of first dose of study drug. Events that occur prior to the first dose of study medication or after the last dose of study medication will be summarized separately.

Summaries of the following are planned:

1. All adverse events recorded between screening and first dose of study medication.
2. All treatment emergent adverse events.
3. All emergent and related adverse events.
4. All treatment emergent hepatic adverse events.
5. All treatment emergent hematologic adverse events.
6. All adverse events that caused permanent discontinuation of study drug.
7. All adverse events that caused temporary interruption of study drug.
8. All serious adverse events and.
9. All serious and related adverse events.

Annual safety analysis will be reported to DSMB.
Laboratory abnormalities.
Laboratory results will be presented as both actual value as well as a function of normal range. Selected data (using conventional units) will be summarized by the change from baseline in laboratory test. If baseline data are missing, then any graded abnormality is considered treatment emergent.
Interim analysis.

Interim analysis of safety data will be performed after all subjects have completed 24 weeks of therapy. Interim analysis of adverse events will be made quarterly throughout the study.
Additional analyses will be performed at the request of the DSMB, if there are any concerns raised by adverse events or serious adverse events reported.

EFFORTS TO ENSURE ADHERENCE TO THE PROTOCOL

Every effort will be made to ensure adherence by patients, their family and study personnel. This includes inclusion of all eligible patients, accession of initial data in a timely fashion and prompt institution of CBZ treatment. Data sheets will be used to record every step in the protocol including enrollment, collection of initial clinical and lab data, data transmission and initiation of CBZ treatment. Patients will be seen at 4 weeks (+/- 1 week) following initiation of study product and then again at 8 weeks (+/-2 weeks), 18 weeks (+/- 2 weeks), 36 weeks (+/-2 weeks) and finally at the week 52 visit(+3 weeks), which will include the repeat HVPG measurement and liver biopsy.
These visits will involve history, physical exam, pill counts and lab tests to monitor each of the clinical and biochemical parameters mentioned above (refer to Study Flow Chart in Appendix 2). In addition serum levels of CBZ will be measured at each follow- up visit. All data will be recorded on the patient flow log.

OVERALL PATIENT MANAGEMENT
This study will generally not affect patient management, although there will be minor modifications made related to the HVPG measurements. Medications known to influence HVPG measurements (e.g. nonspecific beta blockers) will be discontinued for 3 days prior to HVPG measurements. Each of the subjects is being followed for supportive management of severe liver disease. This will include careful monitoring and medical therapy as indicated by the responsible physician team. At the end of the study period a follow-up HVPG measurement will be performed accompanied by transvenous liver biopsy. As with the first procedure, medications known to influence HVPG measurements will be discontinued for 3 days prior to the procedure. If the subject undergoes liver transplantation during the study period, tissue from the native liver will be collected immediately upon its removal for the analyses proposed above. Follow up HVPG measurements will not be performed in these patients.

PATIENT WITHDRAWAL

It is the right of the patient, the patient's parents or legal guardians, or the physicians caring for the patient to discontinue study medication at any time during the study. Medical care and transplantation will proceed in a manner that is unaffected by study participation.

COMPLETE LIST OF WITHDRAWAL CRITERIA

1. Child-Pugh score >12.
2. Hepatic encephalopathy uncontrolled with outpatient medical therapy.
3. Total bilirubin >7 mg/dl.

4. Evidence of anticonvulsant hypersensitivity syndrome.
5. Leukocyte count <1,000 despite 2 weeks of CBZ dose reduction.
6. Neutrophil count <500 despite 2 weeks of CBZ dose reduction.
7. Platelet count <20,000 despite 2 weeks of CBZ dose reduction.
8. Hemoglobin <8.5 mg/dl.
9. INR greater than or equal to 2.5 not corrected by vitamin K 5 mg.
10. ALT >750 IU/L.
11. Pregnancy.
12. Breast feeding.
13. Evidence for behavior or ideation predisposing to suicide or increase in C-SSRS score of 1 from previous test score.
14. Persistent non-adherence to medication study regimen.

DATA RETRIEVAL AND STORAGE

A data repository in the University of Pittsburgh computing facility has been established to accept all information about subjects including; demographics, history, physical exam, labs and a tracking/event file. The tracking/event file is designed for important events: study entry; study completion; adverse events; treatment failures; exits; dropouts; protocol violations; etc. Security of the deposited data will be maintained through the use of unique patient identifier numbers and passwords to enter the repository. Data can be exported from the repository for reporting and statistical analysis.

Data quality and accuracy will be audited annually by comparing what is in the database with the medical records of the patients.

The electronic data storage and retrieval system used for the purpose of this clinical investigation has not been fully validated for compliance with the FDA regulations at 21 CFR Part 11 taking into account the limited size and scope of the investigation.

DATA AND SAFETY MONITORING PLAN

The Data and Safety Monitoring Board (DSMB) will consist of individuals who are independent of the institutions and investigators participating in the CBZ study, and who have no financial ties to the outcome of the trial. The ongoing review of the data by this independent committee assures the investigators and the study sponsor that the trial can continue without jeopardizing patient safety. Individuals on the DSMB will be responsible for monitoring data and safety during the course of this study.

The DSMB will review the study protocol, recommend recruitment continuation, monitor all aspects of the study (e.g., recruitment, protocol deviations, adverse events, site visit summaries, data quality, attrition, descriptive characteristics), and recommend protocol modifications, which may include early study termination. Annual reports will be prepared by the study investigators including tables showing study progress overall and including recruitment, protocol deviations, attrition, adverse events, and data quality. There will also be a table providing descriptive characteristics of the study sample. The study investigators

will maintain a cumulative summary of adverse events overall and stratified by serious/non-serious status to be forwarded to the DSMB biannually. The DSMB will meet at least once per year in person or via internet conferencing. A closed session will be held to review safety, efficacy, and data quality. Based on the data presented, the DSMB will recommend continuation, changes, or termination of the study. A summary of the DSMB findings will be forwarded to all investigators for submission to the IRB.

The DSMB will meet at least annually in person or via internet conferencing to evaluate the following issues:

1. Progress of the study, including assessment of data quality and timeliness.
2. Subject recruitment, accrual and retention.
3. Review of outcomes and adverse events to determine whether there has been a change in the risk-benefit ratio of the study and whether the study should continue as originally planned, should be changed or terminated.
4. Assessment of external factors such as relevant information from the current literature, including therapeutic developments and results of related studies, that could have an impact on safety of participation in the study or ethics of the study.
5. Review of study procedures to protect the privacy of the research subjects and confidentiality of their research data.

The following information will be reported by the DSMB to the investigators for submission to the IRB at regular annual intervals:

1. The date(s) and frequency of the DSMB meetings.
2. Summary of cumulative adverse event data including a respective assessment of whether the events were caused by the experimental intervention.
3. Summary of the assessment of relevant information from the current literature that could have an impact on safety of participation in the study or ethics of the study.
4. Summary of the outcome of procedural reviews carried out to ensure subject privacy and confidentiality of research data.
5. Final conclusions regarding changes to the benefit-to-risk ratio of study participation and final recommendations related to continuing, changing or terminating the study.
6. Rationale for any recommended changes in the research study protocol.
7. The study investigators are committed to comply with IRB policies for reporting of serious and unexpected adverse events, disputes between investigators and research subjects, and disputes between investigators as articulated in chapters 3.0, 3.4 and 3.5 of the IRB Reference Manual. The study investigators are also committed to monitoring of data for accuracy and protection of subject confidentiality. This monitoring will be carried out by the study coordinator. The study coordinator will also audit all regulatory documents. The investigators and study coordinator will conduct quarterly meetings to review study data and confidentiality. Minutes from these meetings will be kept in the study regulatory binder.

INSTITUTIONAL REVIEW BOARD REQUIREMENTS

The protocol will be approved by the University of Pittsburgh IRB.

INFORMED CONSENT

Written informed consent from the patient, parent or legal guardian is required for any part of this study. The consent form will embody the legally required elements of informed consent. The investigative team shall give the patient or his/her representative adequate time to read the form prior to signing. A copy shall be given to the person signing the form. The patient, parent or legal guardian can withdraw from the study at any time and this decision will not influence the treatment otherwise offered. The NIH guidelines on inclusion of females and minorities as subjects in clinical research will be followed.

CONTRACTUAL ARRANGEMENTS
None yet.

REIMBURSEMENT OF SUBJECTS
If subjects need financial assistance to cover travel expenses for participation in the study, funds will be provided in the following amounts: up to $500 if they live within 100 miles of Pittsburgh; up to $3,000 if they live 100-500 miles away from Pittsburgh; up to $5,000 if they live 500-1,000 miles away from Pittsburgh; up to $7,000 if they live more than 1,000 miles from Pittsburgh, and up to $10,000 if they live more than 1,300 miles from Pittsburgh. When airfare from certain locations exceeds these amounts, we may provide an amount of funding that covers the airfare and other travel costs for the subject and an accompanying adult (parent(s), spouse, etc.) even if it exceeds the amounts mentioned above.

SUMMARY

A Preliminary Study of the Efficacy and Safety of Carbamazepine in Severe Liver Disease Due to Alpha-1-Antitrypsin Deficiency

Aim of project: The primary objective is to determine if CBZ therapy in patients with severe liver disease due to AT deficiency leads to a significant reduction in the hepatic accumulation of ATZ globules

1. **Criteria for Inclusion:** Subjects must have clinical or histologic evidence of compensated cirrhosis secondary to a diagnosis of homozygous PIZZ or PISZ AT deficiency confirmed by PI typing and serum AT levels (in subjects who are receiving AT replacement therapy at the time of enrollment, AT deficiency will be confirmed by ZZ or SZ phenotype and serum levels <83 mg/dl at the time of initial diagnosis and/or prior to the initiation of AT replacement therapy). Subjects must be able to tolerate oral medication. Age ≥14 to <or equal to 80 years of age. Inclusion of nonpregnant females and minorities will follow NIH guidelines.

Criteria for Exclusion: Subjects will not be excluded on the basis of gender, race or ethnic group. Subjects will be excluded if they have a history of bone marrow depression, hypersensitivity to carbamazepine or any of the tricyclic compounds such as amitriptyline, desipramine, imipramine, protiptyline or nortriptyline.

Subjects will be excluded if they have evidence of an additional potential cause of active liver disease (e.g. infectious hepatitis, alcohol related liver disease, Wilson disease, sclerosing cholangitis, primary biliary cirrhosis). Subjects will also be excluded if they have very severe liver disease (Child-Pugh score greater than or equal to12; serum bilirubin>5; INR>2.2; hepatic encephalopathy uncontrolled with outpatient medical therapy), severe renal disease (serum creatinine >1.5 mg/dl), alcohol intake >30 gms/day, evidence of hepatobiliary malignancy, pregnancy/lactation, portal vein or splenic vein thrombosis, severe cardiac or pulmonary disease felt to be a contraindication to CBZ therapy, HLA-B*1502-positivity, HLA-A*3101-positivity, history of suicide attempt, potential for suicide behavior based on pre-treatment screening test, severe leucopenia (wbc count<1,500) or thrombocytopenia (platelet count<25,000).

Total Duration of Therapy: 12 months

Forms to Complete: Informed consent signed by patient and or parent/legal guardian; entry data; visit follow up data; final report

Endpoints of the study:

1. Change in hepatic load of ATZ.
2. Change in degree of hepatic fibrosis.
3. Change in HVPG.
4. Ability to tolerate long-term course of CBZ without adverse events.

Reimbursement for study participation: Only financial assistance to cover travel related expenses.

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