

Primary sclerosing cholangitis (PSC) is an increasingly diagnosed chronic liver disease considered to be one of the most challenging conditions in current hepatology. It leads to the progressive damage of biliary tree and its aetiology and pathomechanisms remain to be fully elucidated. Clinical symptoms of this incurable disease include chronic fatigue, intractable pruritus and recurrent episodes of cholangitis which may lead to sepsis. PSC is also associated with increased risk of cholangiocarcinoma, an aggressive tumour with a very poor prognosis.

Urosodeoxycholic acid (UDCA) remains the only drug used in PSC although its effectiveness continues to be controversial.

S-adenosylmethionine (SAME) is involved in multiple cellular reactions as a precursor of transmethylation or transsulfuration pathways facilitating elimination of endo and exotoxins. Glutathione, its main end product remains a key agent involved in antioxidant reactions. Chronic liver diseases lead to an acquired deficiency of SAME what impairs already compromised liver function. Unfortunately medical literature lacks properly designed randomized studies applying SAME in chronic cholestatic liver conditions thus the role of SAME in the therapy of liver conditions remains to be established.

Our previous works have demonstrated a beneficial additive effect of SAME in combination with UDCA in a different experimental models of cholestasis. In our more recent project we used SAME and UDCA in patients with another chronic cholestatic liver condition, namely Primary Biliary Cholangitis (PBC) and have shown that SAME not only improved liver biochemistry but also had a positive effect on patients health related quality of life including a noticeable amelioration of troublesome symptoms such as chronic fatigue and pruritus. Another interesting observation arising from our recent works was that SAME halts the autoimmune response via antioxidant and S-glutathionylation processes in cholangiocytes.

This project is going to be divided into two parts: clinical and laboratory.

In the clinical part we would assess the effect of SAME on clinical symptoms, liver biochemistry, and liver elastography in a group of 60 out-patients with a stable PSC. In this randomized study patients will receive UDCA plus SAME or UDCA plus placebo over the period of 6 months. SAME will be purchased commercially. Particular emphasis will be put on the effect of SAME on Health Related Quality of Life. This area, especially in the context of autoimmune liver diseases has been neglected for decades and requires more attention due to the devastating symptoms associated with these diseases such as chronic fatigue, intractable pruritus or depression. This issue has been of our interest for many years what is confirmed with numerous publications. Carefully selected and well validated questionnaires will be used in this part of the project. Results of the clinical part shall be instrumental in establishing the role of SAME in the treatment of chronic cholestatic conditions.

Laboratory part is aimed at getting more insight into the mechanisms of hepatoprotective properties of SAME and will be a continuation of our previous works in this area supported i.e. by NCN MAESTRO grant. Applying biochemical, molecular methods and a liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) we aim at elucidation antioxidative role of SAME and a potential benefits of its action as a sulphate and methyl donor. Both parts of the project are complementary and should contribute to our knowledge on hepatoprotection in a significant way.