Official title: Combination of Danazole With Berberine in the Treatment of ITP

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Study Protocol and Statistical Analysis Plan

Background:

Immune thrombocytopenia (ITP) is an autoimmune bleeding disorder characterized by antibody-induced destruction of platelets and decreased production of platelets due to impaired thrombopoiesis. Berberine (BBR), an isoquinoline alkaloid derived from plants, is widely used as a nonprescription drug to treat diarrhea. Our previous data demonstrated that gut microbiota dysbiosis may contribute to the development of steroid-resistant ITP (Sci China Life Sci, 2020). BBR may correct steroid-resistance by modulating the gut microbiota structure, representing a novel potential second-line candidate to treat ITP. Danazol is an attenuated androgen that has successfully been used in the treatment of ITP. Considering the side effects of a regular dose of danazol and that BBR and danazol share disparate mechanisms in the treatment of ITP, we hypothesized that combination of these two agents might be a promising option to maximize efficacy, while minimizing adverse effects.

Objectives:

To evaluate the long-term efficacy and safety of berberine plus danazol in patients with corticosteroid-resistant or relapsed ITP.

Design and methods:

The trial is an open-label, single-arm, phase 2 trial. The trial will be performed on nonsplenectomized patients with steroid-resistant or relapsed ITP from the Peking University People's Hospital and other 5 large medical hematological centers in China. Eligible patients are 18 years to 80 years with a platelet (PLT) count of $<30\times10^9$/L on two occasions or a PLT of no less than 30×10^9/L combined with bleeding manifestation. Patients who are receiving other maintenance regimens (primarily corticosteroids, mycophenolate mofetil, cyclosporine, or intravenous immunoglobulin) are also eligible if the dose has been stable in the past month and the dose is expected to be stable after enrolment and remains unchanged at least for the first 4 weeks of the study until initial response is assessed, unless severe adverse events are suspected. Participants will be excluded if they have malignant diseases, hepatitis B or C, positive serology for HIV, other active infections, drug-associated thrombocytopenia, or are pregnant. Each patient will sign and date the written informed consent. Our primary outcome is a 6-month sustained response rate defined as PLT counts maintained $> 50\times10^9$/L without any additional ITP-modifying therapy at 6-month follow up. Secondary outcome measures include response at day 28 (partial response: PLT of 30×10^9/L or more and at least a doubling of baseline platelet count; complete response: PLT of 100×10^9/L or more and the absence of bleeding without rescue medication), duration of response (DOR), adverse events and cumulative rate of bleeding. Treatment consists of oral BBR (300 mg three times daily) plus oral danazol (200 mg twice daily). Treatment period will last for 16 weeks unless otherwise specifies. Patients will not be withdrawn from the study unless severe adverse events occur. Treatment will be interrupted if PLT count is more than $300*10^9$ per L in two consecutive tests with a minimal interval of 2 weeks.

The follow-up period will last until the required number of events have occurred or 2 years after the last patient enrolment, whichever comes first. Complete blood count is assessed at baseline, weekly for 28 days, monthly until month 6, and three months a time after then. In addition, we will do clinical examination, and record bleeding score, liver enzyme and creatinine concentrations, concomitant medications given, and adverse events.

Statistical analysis plan:
Patient characteristics will be reported as numbers (%) or medians (IQR, expressed as: first; third quartiles). The 6-month sustained-response-rate estimates (95% confidence interval [CI]) will be reported. Analyses of secondary end points used point estimates. Treatment safety profiles and side effects were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. The analysis was performed with SPSS software version 24.0.