

Summary

Crohn disease (CD) treatment in children doesn't differ from adults today. The main role in management of disease play systemic corticosteroids (CS) and immunosuppressants.

Aims: 1) evaluate efficacy and hepatotoxicity of 6-thioguanine (6-TG) on mice model of experimental colitis. 2) evaluate time to steady state of 6-thioguanine nucleotides after azathioprine (AZA) treatment initiation in children with inflammatory bowel disease (IBD). 3) evaluate dose (incl. cumulative dose) of CS applied through the first year after diagnosis according to disease activity. 4) AZA steroid sparing effect analysis in week 52 of follow up.

Methods: 1) Dextran sodium sulfate colitis was induced in 50 mice (BALB/c F) for 9 days, treatment with placebo, AZA and 6-TG started at once. Study was terminated on day 14. 2) inclusion criteria: new IBD diagnosis, AZA treatment. Steady state analysis was performed by high performance liquid chromatography. 3-4) inclusion criteria: age 0-19, CD (according to Porto criteria), prospective disease activity assessment, follow-up at least 52 weeks.

Results: 1) 6-TG is highly effective in acute phase of experimental colitis ($p < 0.01$), liver toxicity was not ascertained. 2) Median time to steady state of 6-TG nucleotides was 29.7 days (8.4-156), 75.4 days represented time to steady state on 75th percentile. 3-4) 48 patients matched inclusion criteria, median age at diagnosis was 15 years and pediatric Crohn disease activity index (PCDAI) was 27.5 points. Median of follow-up was 42 months. CS started in 35 (72.9%) patients in week 0, 32 (91.4%) of them with prednisone or methylprednisolone, 3 (8.6%) with budesonide. Median dose of prednisone equivalent was 1 mg/kg/day (0.8-2). Prednisone equivalent dose dropped to 0.21 mg/kg/day in week 12, median cumulative dose 46.6 mg/kg. Remission was achieved in 33 (86.8%) patients, partial therapeutic response was achieved in 4 (10.5%). 20 patients received CS in week 52; 16 in prednisone group, 4 in budesonide group. 11 (68.8%) patients from the first group received < 0.09 mg/kg/day of prednisone equivalent. Median of year's cumulative dose ($n=40$) was 70.1 mg/kg/year (15.0-159.6), that's 0.19 mg/kg/day. Remission was stated in 35 (87.5%) patients. Six patients (12.5% from $n=48$) became CS dependent. Relapse was recorded in 7 (20%) patients treated with prednisone or methylprednisolone, and in 3 (60%) patients treated with budesonide. Surgery was performed in 6 (12.5%) patients from the whole group. Prednisone cumulative dose of children treated with AZA early was 66.3 mg/kg/year. Patients who didn't received AZA early or at all, have the year's cumulative dose of prednisone equivalent 102.8 mg/kg/year ($p=0.089$).

Conclusions: 6-TG is effective in the treatment of experimental mice colitis, it's liver toxicity assessment requires further studies (e.g. high-dose, long-term). 6-TG nucleotides accumulation is highly variable. Approximately one fourth of patients may demonstrate time to steady state longer than 75 days. CS are very efficacious in reaching remission and management of relapse in paediatric Crohn disease. Cumulative dose of CS during the first year after diagnosis didn't reached values, that are (according to known data) linked to growth failure. AZA treatment contributes to lower exposition to CS, decreases frequency of CS dependence, and helps to maintain long-term remission.