SUMMARY

Background: Thioguanine derivatives, azathioprine (AZA) and 6-mercaptopurine (6-MP), have been used for many years in the treatment of inflammatory bowel disease (IBD). They represent major drugs in therapy of steroid-dependent and chronic active IBD. In 20-35% of the patients administration of AZA or 6-MP does not lead to improvement of the disease. Another limitation is the occurrence of adverse events of the therapy which can be observed in 10-15% of the patients. The metabolism of AZA/6-MP is influenced by thiopurine methyl transferase (TPMT). Since there is a significant variability in the activity of TPMP, there is an idea that monitoring the enzyme activity or the genotyping can significantly minimize the toxicity. Several studies have analysed correlation between the levels of AZA/6-MP and the efficacy or toxicity. The cut-off level corresponds to 230-250 pmol/8x10^8 RBC. High concentrations are linked with a risk of myelotoxicity. The occurrence of hepatotoxicity is dependent on the concentration of 6-methylmercaptopurine (6-MMP) in the erythrocytes. 6-thioguanine (6-TG) has been studied as an alternative therapy in patients with inflammatory bowel disease, who are resistant or intolerant to AZA/6-MP.The administration of 6-TG is effective in approximately 60% of patients. However, 6-TG related hepatotoxicity with high frequency of nodular regenerative hyperplasia (NRH) was described.

Aims:1. To evaluate the result of azathioprine/6-mercaptopurine long-term therapy
2. To assess the influence of TPMT activity on the results of azathioprine/ 6-mercaptopurine therapy and on adverse events
3. To asses the influence of 6-thioguanine and 6-methylmercaptopurine metabolite levels on the result of therapy and on adverse events
4. The efficacy and safety of 6-thioguanine therapy

Methods:The prospective trial comprised 91 patients with a chronically active course of the disease, 86 of them was used for evaluation (57 CD, 26 UC; mean age 37.7 years). The evaluation of the treatment was made after 12 month, the mean daily dose was 2.1 mg/kg for AZA and 1.1 mg/kg for 6-MP. Efficacy of therapy was assessed by means of clinical activity indexes, laboratory parameters of inflammation and the corticoid sparing effect. We observed frequency of adverse events. The TPMT activity, 6-TG and 6-MMP levels was measured.
A total of 21 patients with Crohn's disease were treated by 6-thioguanine in our centre, mean age 34.9 years. The period of the treatment was 26 weeks. 12 of the patients underwent liver biopsy. We incorporated to European multicenter study to assess hepatotoxicity of 6-TG.

Results:1. The therapy of AZA/6-MMP assessed is significant efficient.
2. No correlation was found between the TPMT activity and long-term response AZA/6-MP treatment. Adverse events were not significantly affected by TPMT activity. However, it was observed the tendency to leucopenia by pts with low TPMT activity.
3. The level of 6-TG corresponds with eficacy of AZA/6-MP therapy assessed by means of leukocyte and trombocyte decreased. The level of 6-TG is significant higher by the patiens with leucopenia.The level of 6-MP is significant higher by the patiens with hepatotoxicity.
4. The treatment with 6-TG was efficient by 63% of treated patients. 4 patients developed abnormalities in their liver tests during the 6-TG therapy. Abnormal results of liver histology occurred in 5 cases. All were assessed as liver fibrosis of different degree. However, no case of nodular regenerative hyperplasia was found by our patients. During the multicenter European study NRH was diagnosed in 8 patients (8/45), NRH could not be excluded due to pathological findings in 8 additional patients.

Conclusion: Monitoring of TPMT activity is routinely used. Measurement of 6-TG and 6-MMP metabolite is possible to use in special clinic occasions. 6-thioguanin is not recommend for treatment of inflammatory bowel disease due to hepatotoxic potential