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Prevalence of Nodular Regenerative Hyperplasia (Nrh) in IBD Patients Treated with Azathioprine (AZA)

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Cases of NRH in IBD patients have been reported in relation to the use of 6-thioguanine, leading its withdrawal in IBD treatment. In parallel, an increasing number of cases of NRH in patients receiving AZA have been published. The aim of this study was to evaluate the prevalence of NRH and its predictive factors in IBD patients treated with AZA. Methods: From a series of 5530 IBD patients seen consecutively (1974-2006) in the same tertiary referral center, 2269 were treated with AZA. Patients in whom AZA was stopped within the first 2 months because of intolerance (n=273) or surgery (n=83), patients with follow-up less than 2 months (n=130), and patients who developed unexplained hepatic biological abnormalities during treatment (n=29) were excluded from analysis. In the 1730 patients included, median duration of AZA treatment (target dose 2.5 mg/kg/d) was 30 mo and median follow-up after starting AZA was 50 mo. Diagnosis of NRH was based on acquired thrombopenia or portal hypertension and was proven by liver biopsy in all cases except one. The cumulative risk of NRH was estimated through Kaplan Meier method. Factors associated with NRH were analysed by using log rank method and multivariate Cox model. Data were collected when starting AZA. Variables tested were gender, age, IBD type (Crohn’s disease or UC), disease duration, disease location, disease behaviour (intestinal stricture, intestinal perforation, fistulizing perianal disease), prior intestinal surgery, extent of small bowel resection (50 cm), appendectomy, family IBD history, obesity, smoking habit, use of oral contraceptives, and prior arterial or venous thrombosis. Results: 13 patients developed NRH after a median treatment duration of 44 mo (15-214 mo). The cumulative risk of NRH was 0.7 +/- 0.2% five years after starting AZA, and 1.3 +/- 0.5% at 10 years. In univariate analysis, factors associated with NRH ($p<0.05$) were male gender, disease duration, small bowel involvement, colonic sparing, prior intestinal perforation, and prior small bowel resection > 50 cm. According to Cox model, hazard ratios (95% CI) were 8.3 (1.8-38.8) for male gender and 3.3 (1.1-9.7) for prior small bowel resection > 50 cm, respectively. Male patients with prior small bowel resection > 50 cm (n=79) had a 10-year risk of NRH of 11.4 +/- 5.1%. Conclusion: The risk of developing NRH during AZA treatment is low (0.7% at five years). However this figure should be regarded as minimal as in our cohort only cases with clinical and/or biological consequences were collected. This study suggests that male patients with prior small bowel resection > 50 cm are at higher risk of developing NRH than other patients.