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AZATHIOPRINE (AZA) AND MERCAPTOPURINE (MP)-INDUCED MYELOTOXICITY IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE (IBD): A SYSTEMATIC REVIEW
J.P. Gisbert 1, F. Gomollon 2. 1La Princesa Hospital, Madrid, Spain; 2Clínico Hospital, Zaragoza, Spain
Aim: Probably the most important and potentially lethal adverse event of AZA and MP is myelosuppression. Our aim was to conduct a systematic review of studies evaluating incidence of AZA/MP-induced myelotoxicity in IBD patients.
Methods: Bibliographical searches were performed in MEDLINE up to 2007 looking for the following words: (“inflammatory bowel disease” OR “Crohn’s disease” OR “ulcerative colitis”) AND (azathioprine or mercaptopurine) AND (pancytopenia OR “bone marrow” OR myelotoxicity OR myelosuppression OR leucopenia OR leucopenia). Studies evaluating incidence of thiopurine-induced myelotoxicity in patients with IBD were specifically reviewed. The weighted mean percentage of patients with myelotoxicity was calculated; the risk of myelotoxicity was expressed as the incidence of myelotoxicity per patient-years of follow-up.
Results: 67 studies, including a total of 8,302 patients, evaluated the incidence of thiopurine-induced myelotoxicity in IBD patients. Definition of drug-induced leucopenia markedly varied but the cut-off point for the number of leucocytes was generally set at 3-4 x 10^9/l, and the number of neutrophils at 1.5 x 10^9/l. The mean overall incidence of AZA/MP-induced myelotoxicity was 6.4% (95%CI, 5.9-7%). Patients received AZA/MP treatment during a total of 9,103 years of follow-up, and mean annual drug-induced myelotoxicity rate was only 3.8% (95% CI, 3.4-4.2%). The risk was roughly similar with AZA and with MP (6.3% vs. 8.2%). The incidence of myelotoxicity was similar for studies prescribing standard dose (AZA at 2-2.5 mg/kg or MP at 1-1.5 mg) than for those using low doses of these drugs (6.3% vs 7.1%). Duration of AZA/MP treatment in patients with myelotoxicity ranged form 12 days to 27 years. The incidence of infections among those patients suffering AZA/MP-induced myelotoxicity was 6.5%. The incidence of severe myelotoxicity was only 1.1% (mean annual severe drug-induced myelotoxicity rate was 0.9%). Three deaths were reported due to myelotoxicity. The mortality rate due to AZA-induced myelotoxicity was 0.06% (95%CI, 0.02-0.17%), and the risk of death among IBD patients who developed myelotoxicity was 0.94% (95%CI, 0.32-2.7%).
Conclusion: The incidence of myelotoxicity in IBD patients receiving AZA/MP is of approximately 4% per patient and year of treatment. Bone marrow toxicity from AZA/MP treatment may develop at any time after starting therapy. The incidence of severe myelotoxicity in IBD patients receiving AZA/MP is of less than 1% per patient and year of treatment, and the mortality rate is less than 0.1% (which means that the risk of death among IBD patients who develop myelotoxicity is approximately 1%).

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USEFULNESS OF FIBROSCAN FOR THE FOLLOW UP OF PATIENTS TREATED WITH METHOTREXATE
D. Laharie 1, E. Chabrun 1, T. Schaeverbeke 1, T. Hubiche 1, M. Douitre 1, M. Longy-Boursier 2, J. Pellegrin 3, J. Foucher 4, S. Villars 5, F. Zerbib 6, V. de Ledinghen 1. 1Hôpital Haut-Leveque, Pessac, France; 2Hospital Pellegrin, Bordeaux, France; 3Hôpital Saint-Andre, Bordeaux, France
Introduction: Liver stiffness measurement using FibroScan allows evaluating liver fibrosis. Recently, it has been shown that FibroScan could be useful for the follow-up of patients with Crohn’s disease treated with Methotrexate (MTX) and that significant fibrosis was rare in these patients (Laharie et al., 2006). The aim of this prospective study was to evaluate significant fibrosis using FibroScan in a large cohort of patients with various diseases treated with MTX compared to patients without MTX.
Methods: From January 2005 to October 2007, all consecutive patients treated with more than 1500 mg of MTX (group I, n=129) were compared to controls who never received MTX or received MTX ≤1500 mg (group II, n=279). In all patients, liver fibrosis was evaluated using FibroScan. For the diagnosis of significant fibrosis, published cut-off (> 8.7 kPa) was used (Ziol et al. Hepatology 2005).
Results: A total of 408 patients (165 males, mean age 50.6 years, mean BMI 24.6 kg/m², Crohn’s disease (n=109), psoriasis (n=103), rheumatoid arthritis (n=91), other inflammatory diseases (n=105), mean total dose of MTX in group I 3773 mg for 275 weeks) were included. Liver stiffness values ranged from 1.8 to 25.7 kPa (median: 4.6 kPa). For all patients, no correlation was observed between the total dose of MTX and FibroScan (Kendall Tau-b=0.034). Between group I and II, no difference was observed for liver fibrosis assessment. In group I, patients with liver stiffness measurement > 8.7 kPa had a total dose of MTX between 2220 and 3240 mg; 1 patient had cirrhosis on liver biopsy and 4/5 others had BMI > 25 kg/m² with or without fibrosis using Fibrotest. In group II, 5/12 patients with liver stiffness measurement > 8.7 kPa had never received MTX. For others (mean cumulative dose: 890 mg), 1 alcoholic patient had cirrhosis on liver biopsy and others 6 had BMI > 25 kg/m² with or without fibrosis using Fibrotest. In both groups, no correlation between the underlying disease and FibroScan values was observed.
Conclusion: There is no increased risk of significant fibrosis in patients treated with MTX, whatever indication, cumulative dose or treatment duration. According to these results, liver biopsy could be avoided during the follow-up of patients treated with MTX. A liver biopsy should be performed only in patients with persistent liver enzyme abnormalities or elevated liver stiffness measurement.

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IRON DEFICIENCY ANAEMIA IN INFLAMMATORY BOWEL DISEASE (IBD): PREVALENCE AND RESPONSE TO INTRAVENOUS (I.V.) IRON
J.P. Gisbert 1, F. Gomollon 2. 1La Princesa Hospital, Madrid, Spain; 2Clínico Hospital, Zaragoza, Spain
Background: Anaemia is very common in IBD patients, although the reported prevalence of this condition has been markedly varying, depending both on the definition and on the patient population considered (hospitalized vs. out-patients). The anaemia in IBD is likely to be multifactorial in origin, frequently being due to a combination of iron deficiency (the first cause) and anaemia of chronic disease (the second major cause). Oral iron supplementation has relevant limitations, such as its low efficacy, slow response, and intolerance. Therefore, i.v. iron formulations have recently been used. Aim: To systematically review the prevalence of anaemia and ferropenia, and the efficacy of i.v. iron administration, in IBD patients.
Methods: Bibliographical searches were performed in MEDLINE electronic database up to September 2007 looking for the following words (all fields): (“inflammatory bowel disease” OR “Crohn’s disease” OR “ulcerative colitis”) AND (anaemia OR iron OR ferritin). Weighted mean (and corresponding 95% confidence interval; 95% CI) were calculated, to make sure allowance for the number of patients included in each study.
Results: 1) Anaemia: Twenty-two studies evaluating the prevalence of anaemia in IBD, summing a total of 12,544 patients, were included. Mean prevalence of anaemia (weighted mean) calculated from those studies was 17% (95% CI, 16-18%). However, the prevalence was 16% in out-patients, while this figure increased up to 68% when only hospitalized patients were included. 2) Ferropenia: Five studies, including a total of 364 patients, evaluated the prevalence of ferropenia in IBD patients, reporting a mean figure of 45% (95% CI, 40-50%). 3) Treatment with i.v. Iron: Eleven studies, including a total of 362 patients, evaluated the efficacy of i.v. iron for the treatment of anaemia in IBD patients. Iron sucrose was prescribed in most cases (in all but 2 studies). Response was defined, in almost all the studies, as increase of haemoglobin of ≥ 2 g/dL. A single infusion of i.v. iron was prescribed in one study, and therefore it was excluded from the calculation of the weighted mean. Iron sucrose was effective in 50-91% of the patients (depending on the criteria used for efficacy definition), with a mean response (weighted mean) of 73% (95% CI, 68-79%).
Conclusion: The prevalence of anaemia in IBD patients is very high (17%). This figure increases to more than 50% in hospitalized patients. Ferropenia is present in almost half of IBD patients. The i.v. iron formulation (sucrose) represents an effective and safe alternative for the treatment of iron deficiency anaemia in IBD patients.