LETTER TO THE EDITOR

ECCO consensus: Evidence-based use of 6-thioguanine therapy in Crohn’s disease?

Dear Sir,

With great interest, we have read the updated ECCO consensus on the treatment of Crohn’s disease.\textsuperscript{1} Being highly interested in research on the clinical use of thiopurines, we feel that several additional comments may give opportunity to a more balanced, evidence-based conclusion on the discarded use of 6-thioguanine as an alternative thiopurine.

Firstly, the authors state that 6-thioguanine is the active metabolite of azathioprine and mercaptopurine. The drug 6-thioguanine has no pharmacological activity itself but needs to be metabolized to exert its immunomodulatory effects. The pharmacologically active anti-inflammatory metabolites of all clinically used thiopurines (azathioprine, mercaptopurine and 6-thioguanine) are believed to be the 6-thioguanine nucleotides. These endmetabolites cannot be administered as a drug itself.

Secondly, the consensus concludes that a high frequency of 6-thioguanine induced liver abnormalities has been reported, nodular regenerative hyperplasia (NRH) of the liver in particular. This holds true for a few studies using relatively high dosages (more than 25 mg of 6-thioguanine per day).\textsuperscript{2,3} Other studies, including those using approximately 20 mg daily, did not demonstrate an excessive increased risk of developing NRH.\textsuperscript{4,5} Moreover, the references used in the ECCO consensus do not provide a representative overview of the available literature. One describes a case-report, two concern data from the same research group using high-dose 6-thioguanine, another merely describes the efficacy instead of hepatotoxicity, and an additional reference provides data on the incidence of NRH during therapy with 40 mg 6-thioguanine daily. The more reassuring and encouraging data on the development of NRH during use of approximately 20 mg of 6-thioguanine per day are lacking in this consensus,\textsuperscript{4} including a series of about 100 liver biopsy specimens presented at the ECCO meeting in 2010, demonstrating a prevalence of NRH of approximately 4% during long-term 6-thioguanine therapy.\textsuperscript{6}

Finally, the authors state that NRH is an irreversible cause of portal hypertension. The reversibility of NRH and its potential complication of portal hypertension has been studied by measurement of the hepatic venous pressure gradient, but not by long-term, prospective follow-up of series of patients. It has been demonstrated that discontinuation of 6-thioguanine therapy attenuates portal hypertension, hence reducing the risk from this complication.\textsuperscript{7} As all published series describe patients with clinically apparent NRH (and thus late-stage disease), reversibility of early-stage (pathohistological) disease with or without portal hypertension remains to be elucidated. In addition, a recent retrospective study demonstrated that survival in patients with NRH is highly variable and related to age and the underlying disease process (in this series mainly malignant, prothrombotic and rheumatological conditions), however not to portal hypertension overall.\textsuperscript{8}

Based on currently available literature, we conclude that 6-thioguanine should not be discarded as a potential rescue drug when conventional thiopurines fail due to intractable adverse events.

References


LETTER TO THE EDITOR

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12 July 2010