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Abbreviations: AIH: autoimmune hepatitis, EASL: European association for the study of the liver, 6-TG: 6-thioguanine, IBD: inflammatory bowel disease, 6-MP: 6-mercaptopurine, 6TGN: 6 thioguanine nucleotides, NRH: nodular regenerative hyperplasia, IgG: immunoglobulin G, IQR: interquartile range, PBC: primitive biliary cirrhosis, ASAT: aspartate aminotransferases, ALAT: alanin amino transferase γ-GT: gammaglutamyl transferase, ALP: alkaline phosphatase, γ-globulins: gamma-globulins

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Introduction

Corticosteroids and azathioprine provide complete response with good tolerance in most patients for the treatment of autoimmune hepatitis (AIH).[1,2] Although some patients require second-line treatments, scarce data and side effects hamper consensus on them. Inflammatory bowel diseases (IBD) yielded increasing consideration for azathioprine metabolism and the use of 6-Mercaptopurine (6-MP) or 6-Thioguanine (6-TG), which both exhibit a more direct metabolism to the active metabolite of azathioprine: 6-thioguanine nucleotides (6-TGN).[3] Data regarding thiopurines substitution as a second-line therapy for AIH are limited and even more so regarding 6-TG. We herein report our experience with 6-TG after azathioprine failure or intolerance.

Methods

Hospital database was searched for adults patients treated with 6-TG for AIH (according to International Autoimmune Hepatitis Group simplified score ≥6). Files were reviewed to collect clinical and biological data. 6-thioguanine (20mg/day) was introduced as second or third line therapy because of failure or intolerance to azathioprine.

Because of missing data on IgG during follow-up, efficacy was evaluated on maintained biological response defined by normal serum transaminases after corticosteroids withdrawal. Relapse was defined by an increase of serum transaminases higher than 1.2 times the upper normal range, and/or reintroduction of corticosteroids.

To assess nodular regenerative hyperplasia (NRH) the initial and follow-up liver biopsies (LB) were reticulin stained and reviewed by two pathologists blinded to the patient's data.

Results

Seventeen patients were treated with 6-TG, their baseline characteristics are described in Table 1. Discontinuation of azathioprine occurred after 2[1.3-4.2] months because of intolerance (digestive: 11 patients, cutaneous: 3 patients, and haematological: 2 patients), or non-response (1 patient). Eleven patients received 6-TG as second-line therapy. For six patients second-line therapy was mycophenolate mofetil (MMF), but was afterward switched to 6-TG because of incomplete response (5 patients) or intolerance (1 patient).

The side effects for which azathioprine was discontinued regressed in all patients after initiation of 6-TG. Sixteen patients had normalization of transaminases within three months, while one patient had to disrupt 6-TG after one month because of dry-eye syndrome. Maintained biological response occurred in 11(64%) patients. One patient was lost to follow-up during corticosteroids tapering, and one although responder had anaemia prompting cessation of 6-TG after 13 months. Four patients relapsed, including the patient with previous azathioprine failure. Corticosteroids were reintroduced, with normalization of transaminases and successful tapering for one patient, whereas the 3 others did not responded leading to 6-TG cessation and switch for tacrolimus or MMF.

Beside the 2(11%) patients with dry-eye syndrome and anaemia, no clinical side effects were observed. One patient with cirrhosis had cytopenia that regressed after decreasing 6-TG to 10mg/day.

Eight patients had LB after a median 6-TG treatment time of 35[20-52] months. One patient whose LB before 6-TG treatment showed sinusoidal fibrosis and thickening of the hepatic vein wall, showed signs of NRH after 10 months of 6-TG, without clinical portal hypertension. Two patients had worsening fibrosis, one had stopped 6-TG after one month, and one had relapsed.

Discussion

Azathioprine is the treatment for which long-term data are the most available,[1,2] therefore treatments based on the same metabolic pathway have a logical relevance. Further, the direct metabolism of 6-TG to 6-TGNs avoids enzymatic variability due to genetic polymorphism, and avoids some metabolites inducing azathioprine intolerance. Moreover, similarly to azathioprine, monitoring of 6-TGN may allows treatment optimization.

MMF is a well described second-line therapy in AIH, which efficacy is 39-71% in azathioprine intolerant patients.[4,5] Although comparison is biased, our results with 6-TG show similar success rate (64%) with favourable tolerance compared to MMF which induce gastrointestinal side effects in 12-50% or leukopenia in 7% of patients.[4,5]

Safety of 6-TG is debated because of NRH. However results are discrepant and NRH even reported without azathioprine treatment.[6,7] In our study, one of eight patients with LB exhibited NRH. Interestingly some vascular changes existed before 6-TG treatment, which taking into account the short course of treatment received might suggest associated factors. Longer follow-up and larger cohort would be required to assess this issue.

Hübener *et al.* recently showed the relevance of 6-MP as a second-line treatment.[8] Although response rate was similar to our results, the initial side effects recurred in 25% of patients, whereas in our study they were rarer (11%) and differed from those experienced with azathioprine. This may be because contrary to 6-TG, 6-MP still shares metabolites with azathioprine. Interestingly and similarly to our study, non responder to azathioprine neither responded to 6-MP.

In conclusion, our results show that 6-TG could be considered as a relevant option for second-line therapy for AIH in azathioprine intolerant patients.

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Table 1: Population characteristics

Age(years)	54[46-68]
Sex(F/M)	11(64.7%) / 6(35.3%)
Follow-up time (months)	20.5[10-51]
Median AIH score	6[6-7]
Histological Fibrosis	F0: 0(0%) F1: 6(35%) F2: 3(18%) F3: 4(23.5 %) F4: 4(23.5%)
Overlap syndrome	2(12%)
AST(UI/L)	538[52-909]
ALT(UI/L)	609[285-1564]
γ-GT(g/L)	313[180-528]
ALP(UI/L)	162[128-432]
Total Bilirubin(µmol/L)	41[21.7-111]
Prothrombin Time(%)	90[86-98]
IgG(g/L)	15.3[13-21.7]
γ-globulins(g/L)	15.2[13.2-17]
Antinuclear antibody>1/80	11(64.7%)
Anti smooth muscle antibody>1/80	8(47%)

Results are expressed as median [25^{th}-75^{th} percentile] or n (percentage). IgG: immunoglobin G. ASAT: aspartate aminotransferases, ALAT: alanin amino transferase γ-GT: gammaglutamyl transferase, ALP: alkaline phosphatise.