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Original paper

The relationship between 6-thioguanine levels and remission outcomes in children with autoimmune hepatitis. Single center experience

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Abstract

Aim of the study: The treatment of autoimmune hepatitis (AIH) is based on steroids and azathioprine (AZA). AZA is a pro-drug which is converted among others into 6-thioguanine (6-TG) and 6-methylmercaptopurine (6-MMP). The aim of the study was to determine the relationship between the AZA active metabolite 6-TG and both the biochemical and histological remission outcomes.

Material and methods: The authors conducted a retrospective analysis of a single chart review. The sample size consisted of 44 pediatric patients with AIH. Biochemical remission was defined as an alanine aminotransferase (ALT) level below 40 U/l and histological remission was defined as a situation when the control biopsy revealed inflammation grade G1 (or lower) in the Batts-Ludwig score. Statistical analysis was applied to assess the difference in remission outcomes in patients with different levels of 6-TG.

Results: In the benchmark variant of our statistical analysis, we found that the correlation between 6-TG and ALT in the sample was not statistically significant. Moreover, the difference between the mean levels of ALT in the populations in and without remission was not statistically significant (the *p*-value of the *t*-test was 0.16).

Conclusions: Our results tend to support the claim that there is no statistically significant relationship between 6-TG concentration and remission (both biochemical and histological) in pediatric patients with AIH.

Key words: children, treatment, autoimmune hepatitis, remission, 6-thioguanine levels.

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Introduction

Autoimmune hepatitis (AIH) is a chronic, progressive liver disease. It may lead to liver failure requiring transplantation if not treated properly. Its incidence ranges from 0.1 to 0.23 per 100,000 children [1, 2] and the treatment recommended by ESPGHAN Hepatology Committee consists of prednisolone (or prednisone) and azathioprine (AZA) [3]. The latter medication is also used to maintain remission.

Azathioprine is a pro-drug which is converted among others into 6-thioguanine (6-TG) and 6-methylmercaptopurine (6-MMP). It is recommended to measure these metabolites in order to avoid side effects of the treatment and to estimate drug activity. 6-TG levels refer to drug activity and myelosuppression, while 6-MMP levels correlate with hepatotoxicity [4].

Despite the widespread use of AZA in AIH therapy, the appropriate 6-TG levels that can be targeted in pediatric patients with AIH have not been estab-

lished yet. To solve this problem, hepatologists apply recommendations for patients with inflammatory bowel disease, where 6-TG concentration in the range 250-450 pmol/8 × 10^8 red blood cell (RBC) is considered appropriate to maintain remission [4].

Motivated by those facts, our aim was to determine the relationship between the AZA active metabolite 6-TG and both the biochemical and histological remission outcomes.

Material and methods

Data collection

We carried out a retrospective review of 44 pediatric patients with AIH aged ≤ 18 who were diagnosed in our department between 2011 and 2018. The diagnosis was based on the clinical, biochemical, immunological and histological criteria. Other potential causes of liver disease such as Wilson disease, hepatitis B and hepatitis C were excluded during the investigation. Moreover, patients with primary sclerosing cholangitis, overlap syndrome, inflammatory bowel disease and celiac disease were excluded from the sample, too.

The following data were collected at the time of diagnosis: sex, age, comorbid diseases, weight, length, clinical symptoms, findings in physical examination and the result of liver biopsy (evaluated using the Bats-Ludwig score). On top of that, laboratory test performed upon the diagnosis included the measurement of total protein, albumin, total bilirubin, direct bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyl transferase (GGT), international normalized ratio (INR), white blood cell count (WBC), hemoglobin, hematocrit, platelet count, anti-nuclear antibody, anti-smooth muscle antibody, liver kidney microsomal type 1 antibody, antimitochondrial antibodies, anti-parietal cell antibodies, γ-globulin, and immunoglobulin G. In the course of treatment, patients regularly underwent clinical and biochemical follow-up evaluations during which data on weight, laboratory findings, medications, and biopsy result were collected.

We defined the biochemical remission as an ALT level below 40 U/l and histological remission was defined as a situation when the control biopsy revealed inflammation grade G1 (or lower) in the Bats-Ludwig score.

Statistical methods

Statistical inference was performed using the Mann-Whitney-Wilcoxon test, Kolmogorov-Smirnov test and Student's *t*-test. Correlation was measured with the Pearson correlation coefficient. We assumed that *p*-values below 0.05 were statistically significant. We estimated the logistic regression that captured the relationship between the level of 6-TG and the probability of remission and we used it to generate the ROC curve to assess how informative the 6-TG levels were in assessing the chances of remission. Statistical analysis was performed using STATA and Octave.

Results

Sample characteristics

The number of pediatric patients included in the study was 44 (68.2% girls). The mean age at the time of diagnosis was 8.2 years (with the standard deviation of 3.3 years). In the sample, 63.6% of subjects had type 1 AIH and 15.9% had type 2 AIH. The most common symptoms of AIH during the examination were jaundice, hepatomegaly and splenomegaly. Liver biopsies performed at the time of presentation revealed median inflammation of grade 3 and fibrosis at grade 2 according to the Batts-Ludwig score.

The dosage of either prednisone or azathioprine was recorded for 37 patients. The treatment of 83.8% of them started with both prednisone and azathioprine, while 16.2% started only with prednisone. Mean doses of prednisone and AZA were 1.52 mg/kg/day and 1.69 mg/kg/day, respectively. Subsequently, the dose of prednisone was gradually decreased to a maintenance dose.

The total number of 6-TG observations collected during follow-up visits was 114. For a subsample of 45 observations it was possible to calculate the correlation between the dose of AZA and 6-TG concentration.

The concentration of 6-TG was uncorrelated with the dose of AZA (the correlation coefficient was equal to 0.01 and the *p*-value was 0.93). As we discussed, the poor correlation of these two variables was documented also in the related works by Bolia *et al.* [5] and Sheiko *et al.* [4].

Sample characteristics (means and standard deviations of key variables characterizing patients in the analyzed group) are summarized in Table 1. To give an idea of what the main focus of this study looks like in our sample, Figure 1 plots the 6-TG concentration against the level of ALT.

Biochemical remission

To guarantee the comparability between our results and those documented in the related works, we used several statistical methods to assess whether the level of 6-TG affects the chances for obtaining remission.

Table 1. Patients' characteristics (N = 44)

Factor		
Demographics	**Mean ±SD or percentage (%)**	
Age (years)	8.2 ±3.3	
Female	68.2	
Type 1 AIH (ANA and/or ASMA)	63.6	
Type 2 AIH (LKM)	15.9	
Seronegative AIH	20.5	
Comorbid conditions	27.2	
Clinical signs at the time of diagnosis	**Percentage (%)**	
Yellowing of the sclera	22.7	
Yellowing of the skin	27.2	
Light stools	2.3	
Hepatomegaly	25.0	
Splenomegaly	27.2	
Petechiae	2.3	
Generalized lymphadenopathy	2.3	
Laboratory values at presentation	**Mean ±SD**	***n***
Total protein (g/l)	79.92 ±10.13	32
Albumin (g/l)	39.50 ±5.11	30
Total bilirubin (mg/dl)	2.72 ±3.68	38
Direct bilirubin (mg/dl)	2.36 ±3.60	34
AST (U/l)	719.18 ±728.28	41
ALT (U/l)	689.49 ±572.39	41
GGT (U/l)	88.88 ±66.73	39
INR	1.37 ±0.31	40
WBC (×10^3/µl)	7.66 ±4.52	41
Hgb (g/dl)	11.74 ±1.37	41
PLT (×10^3/µl)	251.17 ±129.34	41
IgG total (g/l)	26.02 ±11.68	29

ALT – alanine aminotransferase, AST – aspartate aminotransferase, GGT – γ-glutamyl transferase, INR – international normalized ratio, WBC – white blood cell count, Hgb – hemoglobin, Plt – platelet, IgG – immunoglobulin G

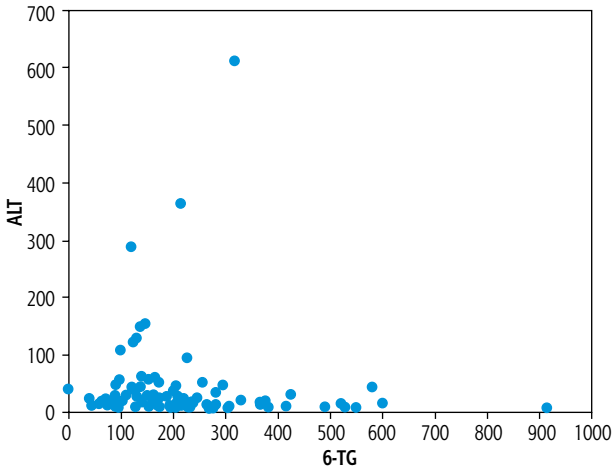

Fig. 1. Sample characteristics: 6-thioguanine (6-TG) concentration and the level of alanine aminotransferase (ALT)

Moreover, to check the robustness of our findings, we performed statistical inference for various definitions of 6-TG concentration. First, to stay in line with the literature we took the 6-TG level measured together with ALT during each follow-up visit (labeled as variant A). Second, to take into account the potential impact of past 6-TG levels on therapeutic outcomes we used the mean average of 6-TG levels recorded up to the time when the level of ALT was measured (variant B).

Variant A. The sample size in variant A was 114 (90 observations in remission and 24 without remission). The correlation of 6-TG and ALT was –0.04 but was not statistically significant (p-value of 0.68). The mean 6-TG was 174.9 pmol/8 × 10^8 RBC in the population with active disease and 218.6 pmol/8 × 10^8 RBC in the population with remission. Similarly to Sheiko *et al.* [4], we used the two-sample t-test to analyze the difference between those means and we found that the associated p-value was 0.16. As in Bolia *et al.* [5], we used the Mann-Whitney-Wilcoxon test to compare the distribution of 6-TG in populations in and with no remission. The associated p-value was 0.08 (with medians 192.5 and 139.5 for observations featuring remission and no remission, respectively). To check the robustness of those findings, we applied the Kolmogorov-Smirnov test to compare empirical cumulative distribution functions of 6-TG for observations with and without remission and the p-value was to 0.04. To illustrate the similarities between both distributions, we plot the estimated kernel densities of 6-TG in both subpopulations in the left panel of Figure 2. Furthermore, the right panel of Figure 2 plots the ROC curve associated with the logistic regression that estimates the dependency of the chances of remission on 6-TG concentration. We found that the AUC associated with the ROC curve was 0.62.

Variant B. The total number of observations in this case was 115 (with 91 classified as remission and 24 with no remission). We found no statistically significant correlation between the mean past 6-TG level and ALT (the correlation coefficient equal to –0.04 with the associated p-value at the level of 0.64). The p-value of the two sample t-test was 0.46 (with the mean past averages of 6-TG being 223.9 pmol/8 × 10^8 RBC in the population with remission and 202.5 pmol/8 × 10^8 RBC in the population with no remission). The p-value of the Mann-Whitney-Wilcoxon test was 0.26 (where the median of past mean 6-TG concentrations for the observations with remission

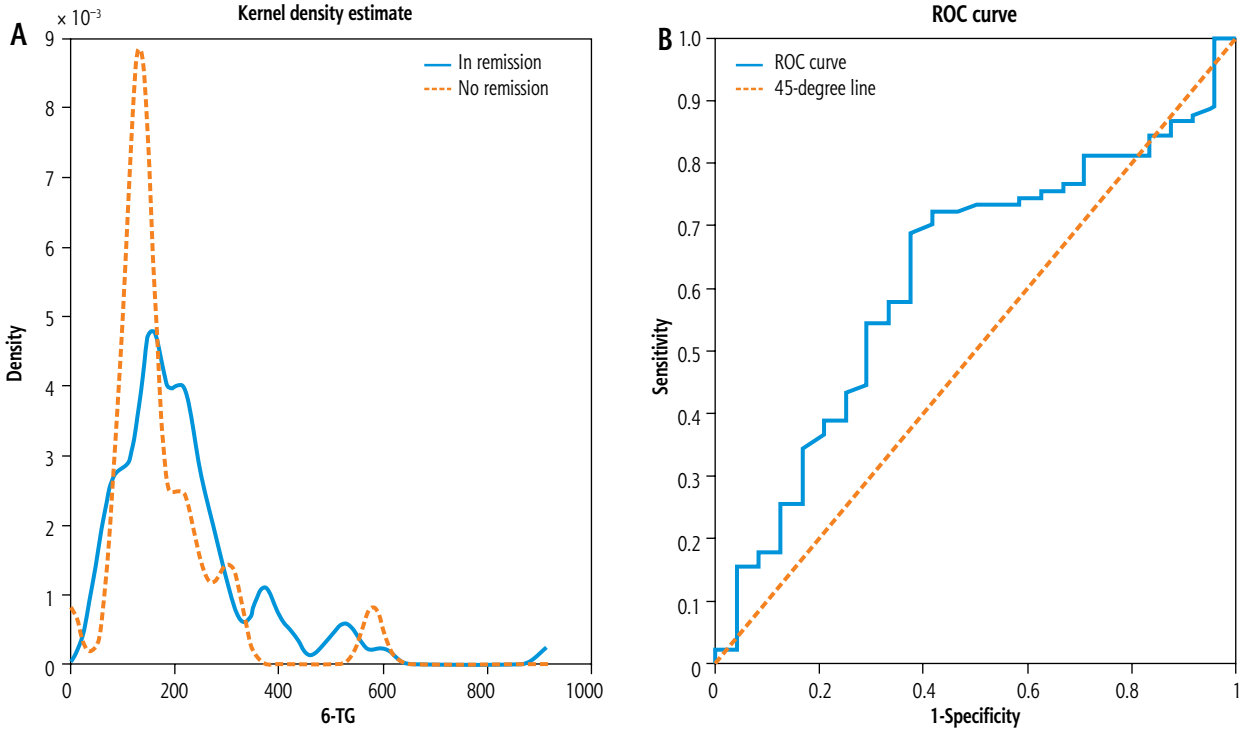

Fig. 2. Variant A – empirical densities (**A**), ROC curve (**B**)

was 194.3 pmol/8 × 10^8 RBC and for the observations with no remission was 170.5 pmol/8 × 10^8 RBC) and the *p*-value associated with the Kolmogorov-Smirnov test was 0.26. Figure 3 displays the estimated kernel densities of empirical 6-TG distributions for patients with active disease and remission (left panel) and the ROC curve based on the logistic regression estimating the impact of the mean past 6-TG concentration on the chances of remission (with the AUC of 0.57) (Table 2).

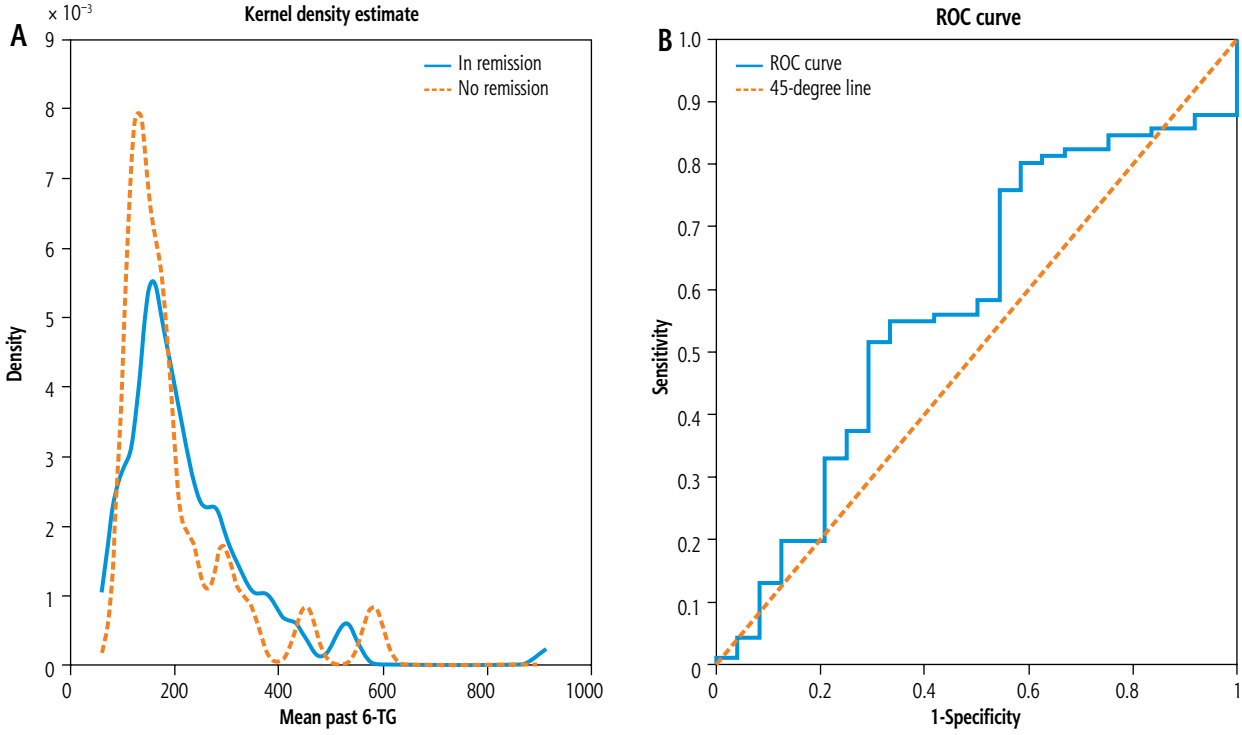

Fig. 3. Variant B – empirical densities (**A**), ROC curve (**B**)

Table 2. Results of biochemical remission

Parameter	Variant A: 6-TG level measured at the same time as the ALT level	Variant B: mean 6-TG levels recorded up to the time when the level of ALT was measured
Sample size	114	115
Observations in remission	90	91
Observations without remission	24	24
Correlation of 6-TG and ALT	−0.04 (p = 0.68)	−0.04 (p = 0.64)
Mean 6-TG in the population with active disease (Variant A)/mean past averages of 6-TG (Variant B)	174.9 pmol/8 × 10^8 RBC	202.5 pmol/8 × 10^8 RBC
Mean 6-TG in the population with remission (variant A)/mean past averages of 6-TG (variant B)	218.6 pmol/8 × 10^8 RBC	223.9 pmol/8 × 10^8 RBC
Statistically significant differences between distributions of 6-TG levels in two subgroups (patients with and without remission)	No/Yes (if Kolmogorov-Smirnov is considered) *t*-test: p = 0.16 Mann-Whitney-Wilcoxon: 0.08 Kolmogorov-Smirnov: 0.04	No *t*-test: 0.46 Mann-Whitney-Wilcoxon: 0.26 Kolmogorov-Smirnov: 0.26

6-TG – 6-thioguanine, ALT – alanine aminotransferase

Histologic remission

In our clinical practice we perform a liver biopsy approximately after two years of maintenance treatment. In this part we discuss the relationship between 6-TG concentration and the biopsy outcomes that, analogously to the presentation of results related to biochemical remission, are reported in two different variants, A and B, which correspond to various timing conventions of 6-TG measurement. The fact that biopsies are performed less frequently than the biochemical examinations severely limits the number of observations in the sample studied in this section. This also led us to constrain the set of statistical tools applied in this part to 3 tests: the *t*-test, the Mann-Whitney-Wilcoxon test and the Kolmogorov-Smirnov test.

Variant A. Number of patients: 22 (a subgroup of the sample of 44 children). The number of observations in this variant was 28. The p-value of the t-test was 0.34 (with the mean 6-TG level in the sample classified as patients in remission being 192.6 pmol/8 × 10^8 RBC and the value corresponding to those with active disease being 160.2 pmol/8 × 10^8 RBC). The p-value of the Mann-Whitney-Wilcoxon test was 0.35 (with the medians of 170.5 for patients in remission and 161.5 with no remission). Finally, the p-value of the Kolmogorov-Smirnov test was 0.58.

Variant B. Number of patients: 28. The size of the sample was 34. The p-values of Student's t, Mann-Whitney-Wilcoxon and Kolmogorov-Smirnov tests were 0.90, 0.80 and 0.99, respectively. The mean (median) past average 6-TG concentration in the subsample of patients in remission was 209.24 pmol/8 × 10^8 RBC (172.8 pmol/8 × 10^8 RBC) and for those with an active disease it was 213.6 pmol/8 × 10^8 RBC (190 pmol/8 × 10^8 RBC) (Table 3).

Table 3. Results of histologic remission

Parameter	Variant A: 6-TG level measured at the same time as liver biopsy was performed (n = 22)	Variant B: mean 6-TG levels recorded up to the time when the biopsy was performed (n = 28)
Sample size	28	34
Observations in remission	18	21
Observations without remission	10	13
Mean 6-TG in the population with active disease (Variant A)/mean past averages of 6-TG (Variant B)	160.2 pmol/8 × 10^8 RBC	213.6 pmol/8 × 10^8 RBC
Mean 6-TG in the population with remission (Variant A)/mean past averages of 6-TG (Variant B)	192.6 pmol/8 × 10^8 RBC	209.24 pmol/8 × 10^8 RBC
Statistically significant differences between distributions of 6-TG levels in two subgroups (patient with and without remission)	No *t*-test: 0.34 Mann-Whitney-Wilcoxon: 0.35 Kolmogorov-Smirnov: 0.58	No *t*-test: 0.90 Mann-Whitney-Wilcoxon: 0.80 Kolmogorov-Smirnov: 0.99

6-TG – 6-thioguanine

Discussion

Autoimmune hepatitis is a liver disease which can lead to liver failure if not treated properly. Nowadays, the standard therapy consists of either prednisolone (or prednisone) or azathioprine, and there have been only a few studies trying to answer the question of what level of 6-TG is appropriate for pediatric patients diagnosed with AIH. This is an important issue because the role of azathioprine metabolites in children suffering from AIH has not been defined yet [5]. What is also important, therapeutic drug monitoring of AZA is an important tool in patients who fail to respond to standard thiopurine doses or when patient noncompliance or toxicity is suspected [6]. Additionally, because of the differences in the disease phenotype and the AZA metabolism between pediatric patients and adult ones, the treatment of the former should not necessarily follow the guidelines formulated for the latter. In what follows, we compare our results to those discussed in the literature to argue that there is no conclusive evidence on the effective 6-TG concentration that can be targeted in the course of AIH treatment in pediatric patients.

Our analysis of biochemical remission outcomes corroborates the consensus presented in the majority of studies, which is that the difference in 6-TG levels between patients in remission and those with active disease is not statistically significant. It is worth emphasizing that there is only one meta-analysis reporting that the mean 6-TG levels were significantly higher among patients in remission than in those who were not, with a pooled difference of 15.67 pmol/8 × 10^8 RBC [6]. However, the authors also note that of the seven studies included in their meta-analysis, only 1 study had previously demonstrated such a relationship [6]. Moreover, the definition of remission was not unified, and it was based on several different threshold levels of ALT below which patients were classified as being in remission.

In our study, the results of all statistical tests – except for the Kolmogorov-Smirnov test for variant A, which referred to biochemical remission – were not statistically significant. To establish this fact, not only did we use the values of 6-TG concentration measured together with ALT (i.e., during the same follow-up visit), as described in the literature, but also, to account for the potential persistence of treatment, we documented that patients in remission and with no remission did not differ concerning either of the mean 6-TG concentrations measured up to the visit when the ALT level was assessed. Second, apart from exploring the relationship between 6-TG concentration and the biochemical remission rates, we contribute to the existing research by analyzing the relationship between 6-TG levels and histologic remission in patients with AIH.

We found no statistically significant difference in 6-TG levels between patients in remission and those not in remission, which is similar to Bolia *et al.* [5] and Sheiko *et al.* [4]. In our study, the median level of 6-TG in patients in remission was 192.5 pmol/8 × 10^8 RBC, while the level corresponding to those not in remission was 139.5 pmol/8 × 10^8 RBC. The analogous values reported by Bolia *et al.* are 271 pmol/8 × 10^8 RBC for those in remission and 224 pmol/8 × 10^8 RBC for children not in remission [5].

We documented a statistically insignificant correlation between 6-TG and ALT levels (in particular, the correlation coefficient in our study was –0.04 compared to –0.18 reported by Bolia *et al.* [5]). Similarly to Bolia *et al.* [5], we did not find any specific level of 6-TG that could be routinely targeted during the AIH treatment: the value of AUC associated with the ROC curve is relatively low both in our study (0.62) and theirs (0.61), and so are the sensitivity and the specificity of resulting optimal cut-off values. We found that the correlation between the dose of AZA and the corresponding 6-TG concentration was poor and statistically insignificant. In particular, we found that the correlation coefficient equaled 0.01 with the corresponding *p*-value of 0.93.

We found that the average rate of biochemical remission measured with ALT was higher for patients with 6-TG higher than 250 pmol/8 × 10^8 RBC compared to those with levels below that threshold, which is similar to Sheiko *et al.* [4]. More specifically, the mean remission rate for the former group was 85%, and it was 77% in the latter. It might be the case that the remission rates reported here are lower than those reported by Sheiko *et al.* because our definition of remission is more restrictive (we set the remission threshold at 40 U/l of ALT while Sheiko *et al.* used the threshold value of 50 U/l). Analogously to Sheiko *et al.*, the difference between remission rates in our analysis was not statistically significant (the *p*-values associated with the *t*-test and the Fisher exact test were 0.37 and 0.43, respectively).

Interestingly, the results of Nguyen *et al.* [7] differ substantially compared to our results. Nguyen *et al.* observed relatively high 6-TG concentrations across patients in their sample. In particular, the mean 6-TG level reported by Nguyen *et al.* was 478 pmol/8 × 10^8 RBC (with a median of 427 pmol/8 × 10^8 RBC and the corresponding range 51-1966 pmol/8 × 10^8 RBC) [7], whereas the analogous value in our sample is 209.3 pmol/8 × 10^8 RBC. Nevertheless, similarly to our study, the Mann-Whitney-Wilcoxon test showed no

significant difference between 6-TG levels in children in remission and those with active disease [7]. Another important aspect with respect to which the results of Nguyen *et al.* differ from those reported here (and from those analyzed by Bolia *et al.* [5] and Sheiko *et al.* [4]) is the statistically significant correlation between AZA dose and 6-TG level (with the coefficient of 0.31 and *p*-value equal below 0.001) [7].

We are not aware of any literature reporting levels of 6-TG that can be targeted in the course of treatment of AIH for pediatric patients. There is, however, a paper by Dhaliwal *et al.* [8] which includes both pediatric and adult patients (with a median age of 51 years and a range of 3-78), which reports the optimal cut-off for 6-TG concentration of 220 pmol/8 × 10^8 RBC based on the ROC curve featuring the AUC of 0.68 and the associated sensitivity of 83% (specificity of 62%) [8]. Moreover, in contrast to papers discussing pediatric populations, Dhaliwal *et al.* [8] observed higher 6-TG concentrations in patients in remission compared to those not maintaining remission (with the median of 237 pmol/8 × 10^8 RBC for the former and 177 pmol/8 × 10^8 RBC for the latter and with the *p*-value of the associated Mann-Whitney-Wilcoxon test equal to 0.03) [8]. Contrary to the results of Bolia *et al.* [5], Sheiko *et al.* [4] and our study, they found a negative, statistically significant correlation between ALT and 6-TG concentration of –0.32 (with the associated *p*-value of 0.007) [6]. On top of that, similarly to our analysis, Dhaliwal *et al.* [8] concluded that the correlation between the dose of AZA and 6-TG was statistically insignificant [8].

In their meta-analysis, Bolia *et al.* [6] tried to answer why Dhaliwal *et al.* [8] reached a different conclusion concerning the 6-TG levels in patients in/without remission compared to other articles. They concluded that the study by Dhaliwal *et al.* [8] was prospective and included only patients at the maintenance stage of treatment. This contrasts with other studies that included non-selected cohorts of patients receiving thiopurine therapy [6].

In an interesting study, Bąk-Drabik *et al.* [9] evaluated the usefulness of measuring thiopurine metabolites in children with inflammatory bowel disease and autoimmune hepatitis treated with azathioprine. Bąk-Drabik *et al.* [9] found that patients with 6-TG concentrations ranging from 230 to 450 pmol/8 × 10^8 RBC exhibited higher remission rates than the under- or overdosed patients. At the same time, the authors also emphasized that an optimal therapeutic 6-TG level for AIH was not determined [9].

At the same time, we are aware of two main limitations of our retrospective analysis. First, the type II error might have occurred in our study (especially in the investigation of 6-TG levels and histologic remission rates) due to the small sample size. Second, the frequency of collecting data was not equal across patients, reflecting the differences between the practice patterns of doctors employed in our department.

Conclusions

In conclusion, our results suggest that there is no relationship between 6-TG concentration and remission (both biochemical and histologic) in pediatric patients with AIH.

Disclosure

The authors declare no conflict of interest.

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