

Thiopurine treatment in inflammatory bowel disease: Response predictors, safety, and withdrawal in follow-up

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Safety

Abstract

Background and aims: Thiopurines represent the mainstay of immunosuppressive therapy in inflammatory bowel diseases. Since it is likely that response to therapy and adverse events depends on the genetic background of patients our study aimed to evaluate retrospectively response to therapy and safety in a mixed IBD population in Southern Europe.

Methods: We evaluated demographic and clinical data of our patients treated with thiopurines. after 6 months in responders and non-responders to therapy. Moreover the likelihood to remain in thiopurine monotherapy was evaluated in responders, whereas adverse events were investigated in all patients.

Results: Among disease- and patient-related parameters a shorter disease duration, female gender and ileal disease in Crohn's patients were associated with better response. By ROC analysis, the best predictors of response were decreasing values of C-reactive protein and erythrocyte sedimentation rate. In the long-term more than half of IBD patients who responded at 6 months remained on monotherapy at 42 months. Flu-like syndrome represented the most frequent adverse event followed by abnormalities of liver function tests and myelotoxicity. Adverse events did occur at any time and were frequently unpredictable.

Conclusions: In this retrospective study, thiopurines showed a good clinical efficacy, especially in patients with short duration of disease. Normalization of markers of systemic inflammation

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represents the most useful tool to assess response. Careful monitoring of patients is required during the whole duration of treatment although it may not prevent all severe complications. © 2011 European Crohn's and Colitis Organisation. Published by Elsevier B.V. All rights reserved.

1. Introduction

Thiopurines, azathioprine (AZA) and its metabolite 6-mercaptopurine (6-MP), are widely used in the management of inflammatory bowel disease (IBD). AZA and 6-MP, alone or in combination with other drugs, are effective in maintaining remission and as steroid-sparing drugs in patients with frequent flare-ups and in steroid-dependent or -refractory patients^{1,2}, although their capacity of inducing remission has been questioned in a recent metaanalysis³. From recent data it appears that AZA reduces the surgery rate in Crohn's disease and, thus, it is able to change the natural history of disease⁴. Furthermore thiopurine therapy impacts positively on health-related quality of life⁵.

Unfortunately, thiopurine therapy is frequently hampered by adverse events (AE) which occur in approximately 15–40% of patients leading to dose reduction or drug withdrawal⁶. AE due to AZA and 6-MP are classified as dose-independent or dose-dependent. The former non-dose related, or "allergic", include fever, malaise, nausea, abdominal pain, diarrhoea, arthralgia and pancreatitis and usually occur early (within days or weeks). The latter dose-related or "non allergic", like myelotoxicity and liver toxicity usually develop later (months or years)^{7–10}, but may also occur very early.

Another drawback of thiopurine therapy is represented by the difficulty to evaluate the entity of clinical response to therapy, i.e. in the absence of specific response markers, efficacy of thiopurine therapy is defined for Crohn's disease (CD) as a Crohn's disease activity index (CDAI) below 150 points (or Harvey–Bradshaw index, HBI, below 4 points) and for ulcerative colitis (UC) a partial Mayo-score (pMS) below 3 points at 4–6 months after introduction of thiopurines, in the absence of concomitant steroids or need for surgery. The identification of partial responders is more difficult, i.e. patients with symptom improvement and steroid reduction but not complete withdrawal, which may benefit from dose escalation or an association with additional therapies.

Some parameters, like white blood cell count, neutrophil count, mean corpuscular volume increase and red blood cell 6-thioguanine nucleotides (6-TGN) concentrations, have been proposed as surrogate markers for the assessment of correct dosing and, thus, for clinical response^{11–14}. Whereas the former tests are available everywhere, the latter is limited to specialised laboratories and is often used only for research purposes.

Both, AZA and 6-MP are inactive prodrugs. In order to get activated, they must undergo a very complex metabolism that leads to the formation of active metabolites represented by 6-TGN and toxic metabolites like 6-methylmercaptopurine ribonucleotides (6-MMP). The former metabolites are known to be involved in myelosuppression whereas the latter in liver toxicity^{15,16}. One of the key enzymes of thiopurine metabolism is thiopurinomethyltransferase (TPMT)^{17,18}. The TPMT activity is genetically determined and 89% of Caucasian

subjects present the wild-type gene with high enzyme activity. Cases of severe myelosuppression are related to the presence of mutant alleles of TPMT¹⁹.

Therefore, it has been proposed to screen genetically patients before thiopurine treatment. But, Colombel et al. showed that only 27% of severe myelosuppression in patients with CD during AZA treatment is related with mutant alleles of the TPMT gene making genetic screening questionable¹⁹. Moreover, genetic testing seems not to represent a reliable predictor of response²⁰.

Interestingly, in a recent survey less than half of the interviewed physicians identified as experts in the field of IBD did determine TPMT genotype or phenotype prior to the introduction of AZA and roughly 50% did determine 6-TGN levels in patients on treatment²¹.

According to the most recent guidelines of the British Society of Gastroenterology (BSG)²² and of the American College of Gastroenterology (ACG)²³, the regular assessment of complete blood cell counts is important to prevent or timely recognize side effects, optimize therapy and evaluate the clinical response, but routine control of transaminases and serum amylase is not recommended.

Since response to and toxicity of any pharmacological treatment are partly based on the genetic background of the population, we retrospectively assessed efficacy of treatment, frequency and type of side effects leading to dose adjustment or withdrawal and the usefulness of surrogate predictors of response in an IBD population of Southern Italy followed at our outpatient clinic.

2. Material and methods

2.1. Study population

We retrospectively reviewed the medical records of IBD patients followed in our IBD-Unit from 1998 to 2010 in order to identify patients who were exposed to AZA or 6MP. We collected: demographic data, Body Mass Index (BMI), smoking status and clinical phenotype according to the Montreal classification²⁴. Other registered data were the indication and duration of treatment, duration of disease before the therapy started and thiopurine dose.

According to the major available guidelines^{22,23,25,26} AZA dose was targeted at 2.0–2.5 mg/kg body weight and 6-MP at 1.0–1.5 mg/kg body weight. Since TPMT testing is not available routinely, we start treatment in our clinical practice with a low dose and then gradually increase it up to the target dose.

2.2. Assessment of response to therapy

In order to assess response to thiopurine treatment and to evaluate the validity of proposed surrogate markers, a subset of patients with available data for C-reactive protein (CRP),

erythrocyte sedimentation rate (ESR), white blood cells (WBC), neutrophils (NC), red blood cells (RBC), mean corpuscular volume (MCV) and platelets (PLTs) at the start of therapy and after 6 months was analyzed. Responders (R) were compared to non-responders (NR) with respect to the above parameters.

R were defined as subjects who were in clinical remission (HBI < 4 points for CD and pMS < 3 points for UC), off corticosteroids, with no need for biologic therapies or surgery after 6 months of treatment. NR were considered patients who were unable to discontinue corticosteroids and/or needed biologic therapies at 6 months. Receiver Operator Characteristic (ROC) curves were generated to assess sensibility and specificity of surrogate markers in response to thiopurines.

2.3. Long-term response

For the long-term evaluation HBI and pMS were collected prior and after 6 months and over time. The chance of remaining on thiopurine monotherapy was evaluated by means of Kaplan–Meier analysis.

2.4. Toxicity and withdrawal of thiopurine

Adverse events were recorded in order to identify the type of AE, the daily dose of the drug at the moment of onset of AE and the time elapsing between start of therapy and the occurrence of AE. AE were divided into early (within 6 months) or late (beyond 6 months of continuative therapy). Early AE were further subdivided in very early, i.e. within 4 weeks, or intermediate, from the 2nd to the 6th months of treatment. The reason for drug discontinuation was investigated separately.

2.5. Statistical analysis

Statistical analyses were performed using SPSS 11.0 for Window package and Med Calc 11.5.1.0 for Receiver Operating Characteristic (ROC) analysis. $P < 0.05$ was considered to be statistically significant.

The numerical data are expressed as mean \pm standard deviation (SD) and the categorical variables as number and percentages. For examined variables that did not present normal distribution as verified by the Kolmogorov Smirnov test, a non-parametric approach was used. With reference to laboratory tests (CRP, ESR, WBC, NC, RBC, and MCV) we performed the two-by-two comparisons between times (basal and six months) by means of the Wilcoxon test.

The non-parametric Spearman correlation test was applied in order to assess the existence of any significant interdependence between numerical parameters. In order to assess the association between categorical variables, the Log-likelihood Ratio test was used. Finally, univariate and multivariate logistic regression models were employed to identify the most important variables of response evaluation.

Kaplan–Meier survival curves were constructed to assess the likelihood to remain on thiopurine monotherapy for CD and UC and comparison was done with the Log-Rank test.

3. Results

3.1. General data

Data from 837 patients followed at our outpatient clinic between 1998 and 2010 were reviewed. Of these, 266 (31.8%) were treated with AZA or 6MP at some time during their evolution; 141 (53%) were male, 157 (59%) were diagnosed with CD and 109 (41%) were diagnosed with UC according to established criteria. According to the Montreal classification most of CD patients had an ileo-colonic disease (82/157) while the majority of UC patients had extensive colitis (68/109). Steroid dependency/refractoriness was the indication for treatment in 190 (71%) patients, other indications were extensive disease in 38 (14%) patients, post-surgical recurrence in 23 (9%) patients, perianal fistulas in 12 patients (5%) and other indications in 3 (1%) patients. Active smokers were a minority (60/266; 22.5%) and the mean BMI was 23 ± 4 kg/m². The mean age of our population was 42.6 ± 14.8 years (range 15–78 years), while the mean age at diagnosis was 31.6 ± 13.8 years (range 10–69 years). Mean duration of disease before thiopurine treatment was 63.7 ± 76.4 months (range 0–348 months). Thiopurine treatment duration was 33.5 ± 36.3 months (range 0–240). AZA was given to 228 patients and 6-MP to 48 patients. Ten patients out of the 48 patients on 6-MP have been treated before with AZA. No patient has been treated before by biologics or methotrexate.

3.2. Response evaluation

For the evaluation of predictors of response to treatment, parameters from 139/266 (52%) patients were available at the start and after 6 months of therapy (exclusion of other patients was due to primary failure of therapy and switch to biologics, early occurrence of side effects, patients already on immunomodulator therapy at their first visit in our clinic, and patients lost on follow-up). According to the definition of response we identified 96 R (54 CD, 42 UC; 46 male) and 43 NR (21 CD, 22 UC; 28 male). Patients' characteristics are summarized in Table 1.

Clinical activity indexes decreased significantly in R in both diseases, CD and UC (HBI dropped from 6.5 ± 3.5 to 2.6 ± 1.4 , $p < 0.001$; pMS from 5.4 ± 2.9 to 1.1 ± 1.0 , $p < 0.001$) while this did not occur in NR (HBI from 8.3 ± 4.1 to 8.5 ± 4.9 , $p = 0.836$; pMS from 5.3 ± 3.0 to 4.5 ± 3.8 , $p = 0.243$).

Monitoring laboratory parameters over the first 6 months of therapy revealed (Table 2) a significant decrease of WBC, NC, CRP, and ESR ($p < 0.0001$, all) and a significant increase of MCV in R, whereas in the NR group RBC decreased significantly ($p < 0.02$) as well as WBC and NC ($p < 0.001$), whereas CRP and ESR remained unchanged. Of note, MCV increased significantly also in the NR group ($p < 0.001$) (Fig. 1). The results for MCV did not change when subjects with heterozygosity for thalassemia were eliminated from calculation (data not shown). The numerical increase of MCV was 6 fl in R and 4 fl in NR.

Statistical analysis revealed among disease- and patient-related predictors of response in CD a significant better response to therapy ($p = 0.003$) in patients with ileal disease

Table 1 Patients' characteristics in responders (R) and non-responders (NR) to thiopurine treatment; p values assessed with the Log-likelihood ratio test.

	R	NR	p-value
M/F (n)	46/50	28/15	0.044
Age at diagnosis, y	31.9±1.4	31.4±1.9	ns
Smoking status (n) yes/no	29/67	13/30	ns
BMI (kg/m ²)	23.0±0.5	23.1±0.7	ns
Duration of disease (months)	47.4±6.6	85.4±14.6	0.007
Crohn's disease; Montreal classification			
Ileal (L1) (n)	27	2	0.003
Colonic (L2) (n)	9	3	ns
Ileo-colonic (L3) (n)	18	16	ns
Ulcerative colitis			
Distal colitis (n)	4	6	ns
Left colitis (n)	8	4	ns
Pancolitis (n)	30	12	ns
AZA; daily dose mg/kg	1.98±0.45	2.00±0.48	ns
6-MP daily dose; mg/kg	1.08±0.24	1.56±0.95	ns

than those with other localizations. No difference was seen for disease extension in UC patients. Disease duration prior to treatment with thiopurines was significantly lower in R than in NR (p=0.007), suggesting that an early aggressive approach did better in terms of clinical response.

Female gender was positively associated with response to therapy (p=0.04) independently from duration of disease.

Neither BMI (p=0.888) nor smoking status (p=0.866) did influence response to therapy.

Interestingly, the daily dose of thiopurines was not associated with response to therapy (p=0.931). The mean daily dose of AZA/6-MP was not statistically different in R and NR and both groups were within the recommended range (Fig. 2).

Univariate analysis showed that treatment response at T6 was significantly associated to CRP (p=0.002), ESR (p=0.001) and NC (p=0.007) variations. Multivariate logistic

Table 2 Laboratory parameters before and after 6 months of therapy with AZA/6-MP in responders and non-responders. ^ap<0.001, ^bp<0.02, vs corresponding basal value; mean values±SD. CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, RBC: red blood cells, MCV: mean corpuscular volume, WBS, white blood cells, NC: neutrophil cells.

	Responders (n=96)		Non-responders (n=43)	
	Basal	6 months	Basal	6 months
CRP; mg/l	17.4±2.1	3.1±0.3 ^a	16.5±2.7	14.9±2.9
ESR; mm/h	35.2±2.4	16.6±1.2 ^a	31.7±3.3	35.2±4.0
RBC; 10 ⁶ /ml	4.46±0.59	4.35±0.61	4.51±0.93	4.25±1.0 ^b
MCV; fl	83.3±0.7	89.5±0.8 ^a	84.2±1.3	88.5±1.6 ^a
WBC; 10 ³ /ml	9.05±0.3	5.77±0.2 ^a	9.14±0.4	7.08±0.5 ^a
NC; 10 ³ /ml	6.07±0.2	3.56±0.1 ^a	6.07±0.3	4.74±0.3 ^a

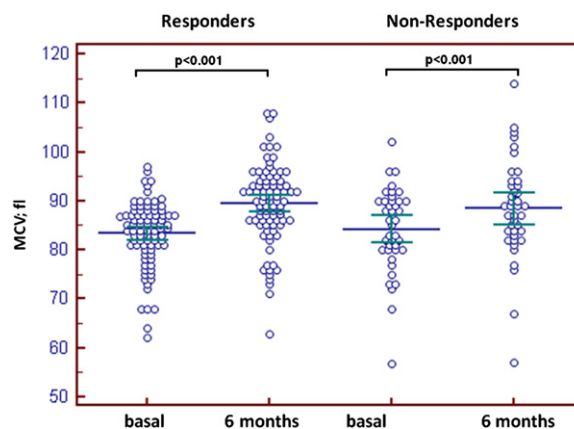


Figure 1 Single values for MCV before and 6 months after start of thiopurines in responders and non-responders. Within the groups there is a statistically significant increase between basal and 6 months; there is no difference when comparing the mean values of the two groups.

regression showed a significant relation of treatment response at T6 only on ESR (p=0.001).

Constructing Receiver Operating Characteristic curves (ROC) (Fig. 3) the worst predictor of response in our cohort resulted to be the recommended MCV (AUC 0.55±0.06), whereas the best in terms of sensibility and specificity were CRP (AUC 0.77±0.05) and ESR (AUC 0.72±0.05).

3.3. Long-term treatment efficacy

Data from 89 R were available for the analysis of long-term efficacy. Kaplan–Meier analysis (Fig. 4) showed no difference between CD and UC. Once remission was achieved, at 42 months approximately 50% of patients were still in remission with THIO monotherapy. In patients responding to therapy at 6 months, the estimated chances to remain on THIO monotherapy without need for steroids or other additional therapy were 24 months for CD and 25 months for UC (difference not statistically significant).

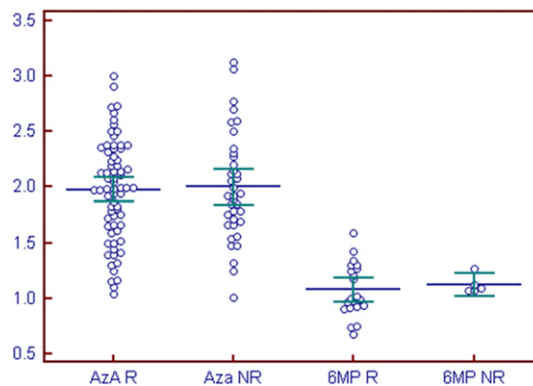


Figure 2 Single values for daily dosing of azathioprine (AZA) and of 6-mercaptopurine (6-MP) in responders (R) and non-responders (NR) to therapy showing a comparable dosing regimens for both patient groups.

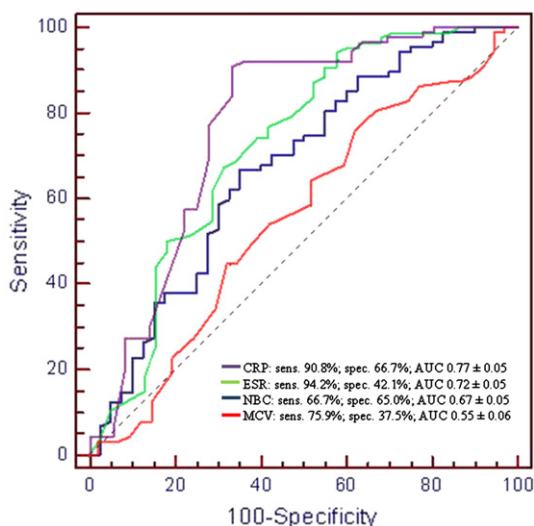


Figure 3 ROC curve analysis for 4 surrogate markers of clinical response to thiopurines in IBD patients. The best marker appears to be CRP followed by ESR. Neutrophil count (NC) and MCV did show low sensibility and specificity for the prediction of response.

3.4. Side effect analysis

Analysis of AE was carried out on 733 patient-years. Altogether we observed 115 adverse events in 87/266 (32.5%) of our patients treated with AZA or 6-MP. In 73/266 patients (27.4%) therapy was discontinued, whereas in 14/266

patients (5.2%) the daily dose was reduced to the maximal tolerated daily dosing. All AE are summarized in Table 3.

Very early AE occurred in 55 patients and represented almost half of all AE. The most frequent was represented by flu-like syndrome, observed in 21 patients (7.9%). Other AE were represented by gastrointestinal symptoms (nausea, vomiting or non-specific abdominal pain) in 10 patients (3.8%), pancreatic hyperenzymemia (defined as twofold increase of serum amylase or lipase) without clinical signs of pancreatitis in 9 patients (3.4%) and clinical pancreatitis in 4 patients (1.5%). All pancreatic events had a favourable non-surgical outcome. The mean time from start therapy to early AE was 14.7 ± 9.8 days (range 3–30 days).

Intermediate AE occurred in 26 patients (12.8%). The most frequent was represented by liver toxicity, observed in 12 patients (4.5%). The mean time from start therapy to intermediate AE was 86 ± 49 days (range 32–180 days). Compared to very early AE liver toxicity was statistically significantly more frequent ($p < 0.001$) in the time range from 2 to 6 months.

Late AE occurred in 34 patients (12.8%). Leucopenia and major infections are the most frequent, observed respectively in 12 patients (4.5%) and 8 patients (3.0%). Infections were: *Listeria* meningitis (1), mycoplasma pneumonia (2), CMV-related pneumonia (1), herpetic keratitis (1), herpes zoster (2) and herpetic vaginitis (1). The mean time from start of therapy to late AE was 36 ± 28 months (range 8–120 months). AZA mean cumulative dose at the moment of onset of AE was 48.9 ± 96.5 g. 6MP cumulative dose at the moment of onset of AE was 26.9 ± 40.6 g. Leukopenia developed gradually in uncomplicated cases, but sudden in CMV-related pneumonia. No predictive marker for leukopenia was identified.

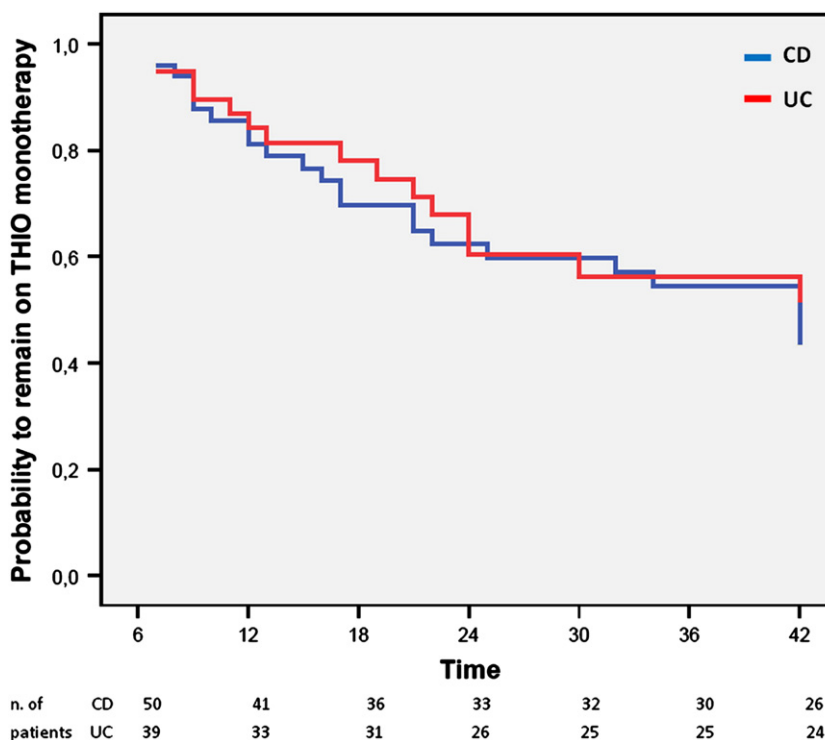


Figure 4 Kaplan–Meier survival curves for the chance of remaining on thiopurine monotherapy after reaching clinical response at 6 months in CD and UC.

Table 3 Adverse events in our patient population divided in very early, early, and late events; percentage of AE in parenthesis relative to the total events of each column, except for first row where percentages are given for the total of 115 events.

Type of AE	Early AE first 6 months		Late AE over 6 months	No AE total
	Very early (0–4 weeks)	Intermediate (2–6 months)		
Total	55 (47.%)	26 (22.6%)	34 (29.6%)	115
Leucopenia	2 (3.6%)	1 (3.8%)	12 (35.3%)	15 (13.0%)
Pancreatitis	4 (7.7%)	–	1 (2.9%)	5 (4.35%)
Pancreatic hyperenzymemia	9 (16.4%)	4 (15.4%)	1 (2.9%)	14 (12.2%)
Liver toxicity	5 (9.1%)	12 (46.2%)	6 (17.6%)	23 (20.0%)
Infections	–	2 (7.7%)	8 (23.5%)	10 (8.7%)
Flu-like syndrome	21 (38.2%)	2 (7.7%)	1 (2.9%)	24 (20.9%)
GI symptoms	10 (18.2%)	3 (11.5%)	1 (2.9%)	14 (12.2%)
Skin disorders	2 (3.6%)	1 (3.8%)	–	3 (2.6%)
Anemia	2 (3.6%)	1 (3.8%)	3 (8.8%)	6 (5.2%)
Death	–	–	1 (2.9%)	1 (0.9%)

One therapy-related death, probably due to the hemophagocytic lymphohistiocytic syndrome complicated by liver failure, occurred in a female patient after 8 years of therapy. No case of neoplasia was observed.

3.5. Discontinuation of therapy

In the whole study population the reason for thiopurine-therapy discontinuation at any time was: 74 patients because of AE, 35 patients because of inefficacy, and 26 patients because of reaching the 5 years therapy limit. Thirty three patients stopped arbitrary therapy (safety concerns, pregnancy, etc.).

4. Discussion

In the present retrospective analysis we evaluated efficacy and safety in an IBD population from Sicily. From the IBD population followed in our centre 32% needs treatment with immunosuppressors during the course of disease.

Concerning efficacy, in the subgroup with 139 patients without early AE leading to thiopurine withdrawal, 69% achieved remission without steroids at 6 months. In other studies achievement of remission ranges from 69 to 75%^{6,27,28}. Following the patients over time, more than half of these patients did not need any therapy intensification over the following 3 years. In accordance with Gisbert et al.²⁹, there was no difference between CD and UC patients.

For the assessment of response to therapy we investigated several surrogate markers. The most important finding is the poor quality of MCV as predictive marker. Similar to the findings of Thia et al.³⁰, MCV did increase significantly in both, R and NR, although the degree of increase in our analysis was somewhat inferior in NR. In Fig. 1 the wide overlap of MCV values in both groups is evident. It has been suggested that an increase of 6 fl is associated with therapeutic 6-TGN levels²⁸, this holds true also in our population, but it is questionable if this is applicable to single patients. The correlation between 6-TGN and MCV is well known³¹, but it has to be kept in mind that erythrocyte 6-TGN concentrations are not associated with disease activity³²⁻³⁴, are not

predictive for clinical response³⁵, nor distinguish between R and NR^{30,36}, except in one study in a mixed IBD population¹¹. In only one prospective study on steroid-dependent UC patients MCV was found to be predictive for treatment success³⁷. However, we agree with the importance of 6-TGN and 6-MMP levels in order to identify refractory, resistant, non-adherent, and/or underdosed patients⁶.

For other variables like WBC and NC a significant reduction was found in both, R and NR, also a greater decrease was observed in R. Univariate analysis showed statistical significance for NC in our study. In our ROC analysis we included NC but it shows a low sensitivity and specificity. In another study a relative leucopenia was not found to be associated with clinical response¹¹, whereas in the analysis of Fraser et al. lower WBC and NC were associated with response⁷.

Finally, when comparing the different surrogate parameters by ROC analysis, reduction of CRP and ESR yielded the best results confirming the validity of CRP in the assessment of clinical (and also endoscopic) activity³⁸ confirming that the achievement of a complete absence of systemic inflammation is mandatory in IBD. Surprisingly, multivariate analysis showed significance at 6 months only for the non-specific ESR. In a recent investigation in pediatric UC both parameters, CRP and ESR, reflected disease activity to a similar degree at least in 2/3 of patients³⁹.

Concerning disease- or patient-related parameters, we cannot confirm the finding of Holtmann et al.⁴⁰ since in the present investigation the BMI was not related to a poor response to thiopurine therapy even when UC and CD were analyzed separately.

According to a former study³⁷ extension of disease was not predictive of response in UC, but in CD ileal localization was more likely to respond in our patients. Similar results were found recently in a pediatric population⁴¹. In a retrospective Italian study thiopurine efficacy was independent from disease localization⁴².

In the present study a short duration of disease was strongly predictive to response emphasizing the importance of an early aggressive approach. This is in line with the paper of Markowitz et al. in a pediatric population where an early introduction (within 8 weeks from diagnosis) of

6-MP was associated with a 89% response rate maintained in nearly all over the following 18 months⁴³. No influence of disease duration was found in the Italian study⁴², but this may be due to the stratification in three categories (<12 months, 1–5 years, over 5 years) used in this study, whereas in our analysis duration was evaluated as continuous variable.

Although no dose–response trial for thiopurines has ever been conducted, the daily dose for AZA is fixed at 2–2.5 mg/kg and for 6-MP at 1–1.5 mg/kg by most gastroenterologists⁴⁴. There is a strong convergence of our results with those of Fraser et al.⁷. In both analyses the daily dose of thiopurines did not correlate with response. In Fig. 2 a perfect match of thiopurine doses between R and NR is clearly visible. This finds confirmation in a recent paper of Komiyama et al. who found that half of the usually employed dose did achieve therapeutic 6-TGN concentrations in Japanese patients. Again, therapeutic 6-TGN levels were not different in R compared with NR in this latter paper²⁸. As possible explanation genetics have been advocated.

Considering a withdrawal rate of 27% in our patients from Southern Europe, our data are in the lower part of the range of studies from Northern European areas where withdrawal was indicated from 28 to 60%^{6,7,45}. The distribution of AE was roughly comparable with previous reports. Analyzing the data with respect to therapy duration the most frequent AE within 4 weeks of therapy were flu-like syndrome and GI symptoms. The frequency of the former was somewhat higher than previously reported from a study from Northern Italy⁴² and reasons for this may be sought in data collection (multicentre retrospective study) or in genetic differences. In frequency the third AE were represented by pancreatic hyperenzymemia (defined as 2 fold increase of amylase or lipase) which represents 16% of very early AE. To our opinion pancreatic hyperenzymemia represents an entity distinct from pancreatitis since it responds to dose reduction, whereas pancreatitis is considered an allergic event. Jharap et al.⁶ reported that only 6/16 (37.5%) IBD patients treated with thiopurines, classified as having pancreatitis (defined as increase of amylase/lipase and CRP), had also clinical signs of pancreatitis (pain). Since pancreatitis occurs early, when CRP levels may still be high due to the underlying intestinal disease, it is likely that the remaining 10 patients in this report had pancreatic hyperenzymemia. In our patients with clinical pancreatitis the clinical picture was not preceded by a rise of enzymes but presented in an unpredictable manner. Since asymptomatic pancreatic hyperenzymemia has never been addressed in guidelines and since evolution of such hyperenzymemia is unknown, in our practice we prefer to reduce dosing, or stop treatment in case of lack of biochemical response.

Close routine surveillance for blood cells in the most recent guidelines is recommended for the first months of treatment (ACG²³: every 1–2 weeks, later every 3 months after dose achievement; BSG²²: every 2–4 weeks for 2 months and then every 4–8 weeks; ECCO: undefined). In a recent paper on myelosuppression with thiopurine therapy, weekly monitoring in the first 4 weeks and biweekly monitoring from week 4 through week 8 was advocated⁴⁶. Most physicians practice blood controls every 3 months once target dose is achieved⁴⁴. In our clinical practice bimonthly monitoring after the first 3 months is performed,

but such approach could not prevent a very severe CMV-related pneumonia⁴⁷, but minor variations could be resolved with dose adjustments. The one therapy-related death occurred in a 38-year old woman with UC in perfect remission who assumed therapy over 8 years, the last 3 of them without any medical surveillance. Other AE like liver toxicity represented 20% of all AE and occurred early or late during maintenance therapy in nearly 9% of our patients. Only, the AGA guidelines from 2006 recommended periodic measurements of liver-associated chemistries⁴⁸, whereas the most recent BSG guidelines²² did not mention such recommendation assuming an incidence of liver toxicity of less than 5%. Conversely to Aberra and Lichtenstein, we feel that monitoring of hepatic enzymes once a year is not enough⁴⁹. Pancreatitis is unpredictable, but pancreatic hyperenzymemia occurs throughout the whole treatment duration and monitoring at least one enzyme may be useful.

In conclusion, with the limitations due to the retrospective nature of the study, thiopurines have a good clinical efficacy, especially in patients with short duration of disease. Normalization of markers of systemic inflammation represents the most useful tool to assess response, whereas other surrogate markers like MCV increase or the reduction of leukocyte/neutrophil count were less sensible markers. The identification of partial responders still remains problematic and other markers have to be sought. Careful monitoring of patients is required during the whole duration of treatment although it may not prevent all severe complications.

Since the increase of liver- and pancreas-related enzymes is more frequent than otherwise reported, the recommendation for monitoring of these parameters should be included in upcoming guidelines.

Conflict of interest

None.

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