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Timing of Myelosuppression During Thiopurine Therapy for Inflammatory Bowel Disease: Implications for Monitoring Recommendations

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Abstract

Background & Aims—Thiopurines (azathioprine and 6-mercaptopurine) can induce life threatening myelosuppression. To help develop rational monitoring guidelines, this study

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Dr. Lewis reports having served as a consultant to Prometheus for legal matters. Ms. Hutfless reports ownership of stock in GlaxoSmithKline. No other authors report any potential conflicts of interest with this manuscript.

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determined the frequency, timing, and outcomes of mild and severe myelosuppression following initiation of thiopurine therapy.

Methods—This retrospective cohort study of patients with inflammatory bowel disease patients who were new users of thiopurines; those tested for thiopurine methyltransferase levels before therapy were excluded. Patients were followed from their first thiopurine prescription until the earliest of severe leucopenia [white blood count $<1.0 \times 10^9/L$], severe thrombocytopenia (platelets $<20 \times 10^9/L$), the end of therapy, the first gap in therapy, disenrollment, or December 31, 2006.

Results—Among 1997 new users, the incidence of severe leucopenia per 100 person-months was 0.16 (95% CI 0.03-0.29, n=6) in weeks 0-8, 0.00 in weeks 9-24, and 0.01 (95% CI 0-0.03, n=3) after week 26 of therapy. The incidence of severe neutropenia and severe thrombocytopenia per 100 person-months during the first 8 weeks of therapy was 0.51 (95% CI 0.31 – 0.80, n=19) and 0.08 (0.02 – 0.23, n=3), respectively. During the first 8 weeks, the median duration from a normal white blood count to severe leucopenia was 13 days (range 8-26 days) and to severe neutropenia was 14 days (range 7 to 23 days).

Conclusions—The high incidence of severe myelosuppression justifies frequent monitoring (weeklyx4 then biweeklyx2) during the first 8 weeks of therapy. After 8 weeks, the rate of severe myelosuppression and the proportion of patients that progress from mild to severe myelosuppression decline, justifying less-frequent monitoring.

Background

The thiopurines, azathioprine (AZA) and 6-mercaptopurine (6-MP), are effective for inducing and maintaining remission in patients with Crohn's disease and ulcerative colitis;¹⁻³ however, they are associated with increased risk of severe myelosuppression, especially in patients with decreased thiopurine methyltransferase (TPMT) activity.⁴⁻⁹ Two strategies have been proposed to minimize this risk. The first strategy is to measure TPMT genotype or activity and withhold therapy from those who are homozygous deficient while using lower doses with those who have intermediate TPMT activity.¹⁰ The second strategy involves serially monitoring the complete blood count (CBC) with gradual titration of the drug toward a target dose. This strategy assumes that monitoring will result in early detection of myelosuppression, allowing for dose reduction before the myelosuppression becomes severe enough to cause complications. Regardless of whether or not TPMT testing is completed, serial CBC monitoring is always recommended. However, the effectiveness of serial CBC monitoring for patients with inflammatory bowel disease has not been established.^{9, 11}

Methods

Setting

Kaiser Permanente Northern California provides comprehensive healthcare services to approximately 3.2 million members, representing approximately one-third of the insured population of the geographic area. Prior research has demonstrated that 95% of Kaiser members with a pharmacy benefit fill all of their prescriptions at Kaiser pharmacies¹².

Patients with inflammatory bowel disease diagnosed in 1996 and thereafter were entered into a disease registry within Kaiser. Patients included in this study were those with two or more diagnoses for Crohn's disease (ICD-9 code 555) or ulcerative colitis (code 556) during 1996-2006 and with at least 1 year of enrollment between January 1, 1996 and December 31, 2006. A previous validation study established that 95% of patients meeting these inclusion criteria were confirmed to have inflammatory bowel disease on chart review¹³.

Cohort inclusion criteria

The study cohort was composed of patients from the inflammatory bowel disease registry who were new starters of AZA or 6-MP, defined as having at least 6 months of pharmacy benefits within Kaiser prior to filling the first prescription. No patients had prior leukemia. Patients known to have TPMT testing prior to initiation of therapy (n=18) were excluded since we were interested in the outcomes with CBC monitoring in the absence of TPMT testing. No patients included in the cohort had filled a prescription for AZA or 6-MP within Kaiser prior to the start of follow-up (defined below).

Follow-up

Patients were followed from their first prescription for AZA or 6-MP until the earliest of severe leucopenia for analyses related to leucopenia, severe thrombocytopenia for analyses related to thrombocytopenia, the end of therapy or the first gap in therapy defined by absence of a refill within 30 days after the expected end date of the most recent prescription based on the days supply of therapy dispensed, disenrollment from Kaiser, or the end of the study (December 31, 2006).

Primary exposure and outcome variables

The presence or absence of a CBC measurement was determined for each week of follow-up. If patients had more than one CBC measured within a given week, this was counted as a single measurement. This occurred primarily among patients who were hospitalized and in whom CBCs were collected on a near daily basis. Mild and severe leucopenia were defined as a WBC less than $3.0 \times 10^9/L$ and less than $1.0 \times 10^9/L$, respectively. Severe neutropenia was defined as an absolute neutrophil count (ANC) less than $1.0 \times 10^9/L$. Mild and severe thrombocytopenia was defined as a platelet count less than $100 \times 10^9/L$ and $20 \times 10^9/L$, respectively. For calculations of the incidence of myelosuppression, the lowest recorded value for the WBC and platelet count during the week was used in the calculation.

The prescribing instructions for thiopurines recommend weekly CBCs in the first 4 weeks followed by biweekly CBCs for the next 8 weeks.¹⁴ However, other position papers have recommended somewhat less frequent monitoring, particularly for patients known to have normal TPMT activity.¹⁵ Therefore, we examined the number of CBCs measured in the first 4 weeks (among those with at least one prescription during weeks 4-10), first 8 weeks (among those with at least one prescription during weeks 8-14), and between week 9 and week 26 (among those with at least one prescription during weeks 26-38).

Chart review

Available clinical charts for all patients with severe myelosuppression during follow-up and those patients with mild leucopenia during the first 8 weeks of therapy were reviewed for evidence of change in therapy, infection, hemorrhagic complications, and death.

Statistical analyses

Categorical variables were summarized using counts and percentages. Continuous variables were summarized using medians and interquartile ranges (IQR). Incidence rates were calculated as the number of events per unit of person-time with 95% confidence intervals assuming that the incidence followed a Poisson distribution. In the analysis of dose, we converted azathioprine to 6MP equivalents by dividing the azathioprine dose by 2.07. Comparison of categorical and continuous variables was completed using Chi squared test or Fisher's exact test and the Wilcoxon rank sum test, respectively.

To estimate the rapidity with which severe leucopenia and thrombocytopenia develop, we examined the interval between the last CBC measurement without leucopenia or thrombocytopenia and the first CBC with this finding. These calculations were limited to patients with severe myelosuppression that manifested in the first 12 weeks of therapy because this is a time period when frequent CBC monitoring is recommended.

To estimate the duration of leucopenia and thrombocytopenia, we examined the duration between the first and last CBC meeting the definition of severe leucopenia and severe thrombocytopenia, respectively.

Results

The study included 1997 patients who started thiopurine therapy (Table 1). Twenty-eight percent of the patients filled only a single prescription and 48% filled three or fewer prescriptions during the follow-up period.

CBC monitoring

During the first 4 weeks, first 8 weeks, and weeks 9-26 of therapy, patients completed a median of 2 CBCs (IQR 1 –2), 3 CBCs (IQR 1 –4), and 1 CBCs (IQR 1-2), respectively.

Incidence of myelosuppression

Within the first 8 weeks of therapy, leucopenia was more common than thrombocytopenia (Table 2). Of the 1997 patients who initiated therapy with a thiopurine, 6 (0.3%) developed severe leucopenia and 3 (0.15%) developed severe thrombocytopenia during the first 8 weeks of therapy, one of whom also had severe leucopenia. The incidence of severe leucopenia (0.16 cases per 100 person-months, 95% CI 0.03 to 0.29 cases per 100 person-months), severe neutropenia (0.51 cases per 100 person-months, 95% CI 0.31 to 0.80) and severe thrombocytopenia (0.08 cases per 100 person-months, 95% CI 0.02 to 0.23 cases per 100 person-months) was highest in the first 8 weeks of therapy; 3 additional cases of severe leucopenia and 2 additional cases of severe thrombocytopenia (one of whom also had late severe leucopenia) occurred during subsequent time periods, all more than 26 weeks after

the start of therapy. Thirty-six additional cases of severe neutropenia occurred, 22 of these were more than 26 weeks after the start of therapy. Seventeen of 19 (87%), 14 of 14 (100%), and 21 of 22 (95%) with severe neutropenia in weeks 0-8, 9-26, and >26, respectively also had a total WBC meeting our definition for leucopenia (i.e. $\text{WBC} < 3.0 \times 10^9 / \text{L}$).

Myelosuppression within the first 8 weeks of therapy

The median time from onset of therapy to first documentation of severe leucopenia was 24.5 days (range 15-53 days). The first documentation of severe thrombocytopenia occurred on days 22, 33, and 49 after the start of therapy.

One patient had severe leucopenia on the first CBC after the start of thiopurine therapy, which was performed 18 days after starting therapy. The remaining patients with severe leucopenia and/or thrombocytopenia during the first 8 weeks of therapy each had at least one prior CBC after the start of thiopurine therapy before the onset of severe myelosuppression.

Five of the six patients with severe leucopenia that occurred in the first 8 weeks of therapy had a prior CBC with mild leucopenia. Similarly, 13 of the 19 patients with severe neutropenia that occurred in the first 8 weeks had a prior CBC with mild leucopenia but without severe neutropenia during this time period. All of the 19 patients had a CBC with a normal WBC ($> 3.0 \times 10^9 / \text{L}$) between the start of follow-up and the first documented severe neutropenia. The median time between the first CBC with mild leucopenia and the first CBC with severe leucopenia was 5 days (range 2-22 days). All of these patients had at least one CBC after the start of therapy without leucopenia prior to the onset of mild leucopenia. The median duration from a normal WBC to mild leucopenia was 8 days (range 5 to 16 days), from a normal WBC to severe leucopenia was 13 days (range 8 to 26 days), and from a normal WBC to severe neutropenia was 14 days (range 7 to 23 days). Two of the three patients with severe thrombocytopenia in the first 8 weeks of therapy had a prior CBC with mild thrombocytopenia, at 1 and 30 days prior to the first CBC with severe thrombocytopenia. One of these had mild thrombocytopenia on their first measurement after starting therapy, but this patient also had multiple measurements with mild thrombocytopenia before initiating therapy. The other had a normal platelet count 10 days prior to developing mild thrombocytopenia and 11 days before developing severe thrombocytopenia.

The thiopurine was discontinued in all 6 patients with severe leucopenia. In 3 patients this occurred on the day that severe leucopenia was diagnosed, 2 of whom had mild leucopenia diagnosed 10 and 22 days earlier, respectively. In the remaining 3 patients, the medication was discontinued within 2 days of the diagnosis of mild leucopenia. Subsequent severe leucopenia occurred 2 days, 2 days, and 3 days after discontinuation of the thiopurine, respectively. Data on dose changes for patients with mild leucopenia who did not develop severe leucopenia were less complete. Among those for whom data were available and in whom there was a dose reduction or discontinuation, 12 of 23 patients had the drug discontinued. Of note, 1 patient had filled a prescription for allopurinol between 4 weeks prior to starting therapy and the first documentation of early myelotoxicity.

Late myelosuppression

For the three patients with severe leucopenia more than 8 weeks after the start of therapy, the most recent WBC above $3.0 \times 10^9/L$ was measured 2 days prior, 9 days prior, and 4 days prior. However, the last patient had approximately 6 weeks of mild leucopenia fluctuating with normal white blood counts prior to the onset of severe leucopenia. Of the 2 patients with late severe thrombocytopenia, 1 may have been a laboratory error, as it was repeated the next day and was within normal limits. Of note, 12 patients had filled a prescription for allopurinol within the 12 weeks prior to the first documentation of late myelotoxicity.

Characteristics of patients with and without early severe myelosuppression

Patients with myelosuppression were slightly older and were less likely to have been recently treated with infliximab. Additionally, the median starting dose of therapy was slightly higher in the group that subsequently developed myelosuppression (Table 1). Among those with early myelosuppression and in whom we could calculate the dose in terms of mg per kg body weight, the median starting dose of 6MP was 0.73 mg/kg (0.27 mg/kg – 2.46 mg/kg) in those with mild myelosuppression and 0.77 mg/kg (0.30 mg/kg – 1.47 mg/kg) in those with severe myelosuppression ($p=0.76$). Weight data were not available for those without myelosuppression.

The WBC was significantly lower ($p<0.0001$) on the first CBC measured after initiation of therapy in those with mild (median $6.0 \times 10^9/L$) and severe myelosuppression (median $5.8 \times 10^9/L$) than in those without myelosuppression (median $9.3 \times 10^9/L$) (Table 3). Similarly, there was a greater reduction in WBC from pretreatment to first on treatment assessment in those developing myelosuppression ($p<0.0001$, Table 3).

Similar results were seen when we compared patients with and without early severe neutropenia (Table 4).

Among patients who developed severe leucopenia in the first 8 weeks of therapy, the median duration with severe leucopenia was 2 days (range 1 to 11 days). Among the three patients with severe thrombocytopenia that developed in the first 8 weeks of therapy, the duration was 1, 5, and 10 days.

One of the patients with severe thrombocytopenia also carried a diagnosis of immune mediated thrombocytopenia purpura but developed pancytopenia while on azathioprine. Four other patients with mild thrombocytopenia had other potential etiologies of thrombocytopenia including immune mediated thrombocytopenia purpura (1), cirrhosis (1), heparin-induced thrombocytopenia (1), and lupus (1). For one of the patients with severe leucopenia, the myelosuppression manifested 2 days after hospitalization for sepsis. The thiopurine therapy was discontinued 2 days prior to the first CBC documenting leucopenia; thus it is not possible to know whether sepsis, thiopurine therapy, or both contributed to the myelosuppression.

Outcomes of patients with early severe myelosuppression

All patients with severe myelosuppression during the first 8 weeks of therapy were hospitalized. G-CSF or GM-CSF was given to 5 of 8 patients. No patients died within 6

weeks of the onset of severe leucopenia. Among patients with severe leucopenia, documented infections included pseudomonas sepsis (1), pneumonia (1), and rectal abscess (1). The three other patients had fever or sepsis syndrome without positive cultures. One of the patients with severe thrombocytopenia developed a fever and was found to have a urinary tract infection. Two patients who developed severe thrombocytopenia experienced gastrointestinal bleeding, while the third had bruising and limited bright red blood per rectum.

Discussion

Severe bone marrow suppression is a potentially life threatening complication of thiopurine therapy. Many physicians prescribe these medications without first measuring TPMT activity, rather relying on a strategy of gradual dose increases and serial measurement of white blood cell and platelet counts to detect myelosuppression before it becomes severe. In this study, we documented that in the absence of pre-therapy TPMT measurements, approximately 0.3% of patients develop severe leucopenia during the first 8 weeks of therapy. Severe neutropenia was more common, occurring 3 times more frequently than severe leucopenia. In addition, we documented that severe myelosuppression occurred despite use of CBC monitoring in most patients, albeit with less testing than is recommended in most guidelines, and that the onset of severe leucopenia and thrombocytopenia could occur in as little as 2 days after a CBC with mild leucopenia. Finally, a large percentage of patients with severe myelosuppression in the setting of thiopurine therapy experience infectious or bleeding complications.

The pattern of CBC monitoring in this population was heterogeneous, which allowed us to observe the timing of myelosuppression but prevented us from estimating the incidence of myelosuppression in the setting of perfect adherence to the recommended monitoring schedule. No patient had documented severe myelosuppression within the first two weeks of therapy, although one patient had severe leucopenia on their first CBC which was measured at 18 days. These data are consistent with a recent systematic review that documented the earliest occurrence of myelotoxicity 12 days after initiation of this therapy⁹. Importantly, nearly all of the patients with severe myelosuppression in our study had a prior CBC with mild myelosuppression, the median time from the last normal WBC to severe leucopenia was only 13 days, and there was a significantly greater reduction in the WBC from baseline to the first measurement on therapy among those who developed severe myelosuppression. These findings highlight the importance of frequent CBCs in the first 8 weeks of therapy. Most of the patients with mild myelosuppression did not go on to develop severe myelosuppression. In at least two patients who went on to develop severe leucopenia, it appears that the medication was continued despite mild leucopenia 10 and 22 days earlier. Thus, it is probable that some of these patients progressed to severe myelosuppression due to delays in seeing the mild myelosuppression test results, inadequate reduction in thiopurine dose, or lack of any change in therapy in response to the results (e.g. inability to reach the patient with the recommendation to discontinue therapy).

Since four of the six cases of early severe leucopenia presented within the first 4 weeks of therapy and the median interval from a normal WBC to severe leucopenia was 13 days,

weekly CBC measurement during the initial month of therapy, as is recommended on the prescribing instructions, appears to be warranted. Whether this degree of monitoring is necessary among patients with known normal TPMT activity could not be determined in this study since we excluded patients with prior TPMT testing. Likewise, we were unable to determine whether the occurrence of severe myelosuppression during the first 8 weeks correlated with planned dose escalation during this time period, as this was not clearly recorded. Thus, until further data are available, we recommend frequent CBC monitoring after dose escalation.

Severe leucopenia, thrombocytopenia, and neutropenia were 80-90% less common after 26 weeks of therapy compared to the first 8 weeks of therapy. Two of the three cases of severe leucopenia detected after the first 8 weeks occurred relatively abruptly. The third had a more gradual onset. In contrast, mild myelosuppression remained relatively common late in the course of therapy. These data suggest that the clinical implication of mild myelosuppression changes after the first few months of therapy. Immediate discontinuation of thiopurine therapy appears warranted when mild leucopenia occurs in the first few months of therapy. Reintroduction should be at a lower dose and accompanied by careful monitoring. In contrast, gradual onset of mild leucopenia later in the course of therapy may require only a prompt repeat measurement with or without discontinuation or reduction in dose, with anticipation that patients can be followed with mild leucopenia for long periods of time. Measuring thiopurine metabolites in that setting may be considered as well, with dose reduction in those with elevated 6TGN levels¹⁶. The occurrence of 2 cases of rapid onset severe leucopenia after 8 weeks suggests stable mild leucopenia (e.g. attributable to changes in adherence or body weight) is different from rapid onset severe leucopenia (e.g., attributable to drug interactions or infection).

We may have underestimated the incidence of severe myelosuppression. Myelosuppression can be identified only when a CBC is completed, and it is possible that some patients had transient episodes that went unrecorded. Because some patients may have discontinued therapy in the first two weeks due to side effects other than myelosuppression, we may have slightly underestimated the incidence of mild and severe myelosuppression during this time period. If we underestimated the incidence of myelosuppression, we may have also overestimated the percentage of patients with severe myelosuppression who experience infectious or bleeding complications.

The starting dose of those with mild or severe leucopenia was slightly higher than in those who did not develop leucopenia. Similar results were seen for analyses of neutropenia. As such, it appears that dose is at least partly responsible for leucopenia and that even with a low starting dose, early severe leucopenia is possible.

We attempted to exclude patients with prior TPMT testing, but identification of this test may be incomplete within the data source. As a result, we may have underestimated the incidence of early severe leucopenia in the absence of testing by including a small proportion of patients with known normal TPMT genotype or phenotype.

Medicaid recipients represent about 1.5% of the Kaiser population, but the study did not include the uninsured. While the biology of myelosuppression should not differ in these populations, the ability to adhere with monitoring guidelines may be even lower in those without health insurance.

Finally, it is noteworthy that most patients had less frequent monitoring than has been recommended. This could reflect lack of awareness of current guidelines, nonadherence to the guidelines by physicians¹⁷, or nonadherence to the recommendations by patients.

In conclusion, this study observed that 1 in 300 patients developed severe leucopenia and 1 in 100 developed severe neutropenia early in the course of thiopurine therapy, despite monitoring with CBCs. As such, weekly CBCs during the first month of therapy and biweekly monitoring in weeks 5-8, as is recommended in the prescribing instructions, appear to be warranted, particularly if TPMT testing is not undertaken prior to initiating thiopurine therapy. A substantial decline in total WBC from baseline to the first post-therapy CBC may be a marker of impending leucopenia and should prompt more frequent monitoring, but the absence of this does not appear to be sufficient to rule out impending myelosuppression. Mild leucopenia within the first 8 weeks of therapy should prompt immediate discontinuation of therapy, with reintroduction possible at lower doses once the blood counts have normalized. The less frequent occurrence of severe myelosuppression after the first 8 weeks of therapy justifies less frequent CBC monitoring during long term therapy, but also emphasizes the need for persistent vigilance on the part of the patient and physician for signs of myelosuppression.

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Table 1

Characteristics of 1997 patients treated with azathioprine or 6MP

	All patients (n=1997)	Patients without mild or severe myelosuppression in the first 8 weeks (n=1938)	Patients with mild but not severe myelosuppression in the first 8 weeks (n=51)	Patients with severe myelosuppression in the first 8 weeks (n=8)	P value (Mild/Severe vs. none)
Age at start of therapy (median, IQR)	48 (38, 59)	48 (38, 58)	54 (45, 70)	50 (41, 62)	0.003
Female sex (n, %)	1043 (52%)	1013 (52%)	25 (49%)	5 (63%)	0.83
IBD diagnosis (n, %)					
Crohn's diseases	803 (40%)	781 (40%)	18 (35%)	4 (50%)	Reference
Ulcerative colitis	707 (35%)	691 (36%)	14 (27%)	2 (25%)	0.56
IBD not otherwise specified	487 (24%)	466 (24%)	19 (37%)	2 (25%)	0.13
Race					
White	1500 (75%)	1456 (75%)	39 (76%)	5 (63%)	Reference
Black	149 (7%)	145 (7%)	4 (8%)	0	0.86
Asian	106 (5%)	102 (5%)	4 (8%)	0	0.62
Hispanic	104 (5%)	98 (5%)	3 (6%)	3 (38%)	0.11
American Indian	10 (0.5%)	10 (0.5%)	0	0	
Unknown	128 (6%)	127 (7%)	1 (2%)	0	0.15
Oral steroids prescription within 12 weeks prior to the start of immunomodulator	1176 (59%)	1137 (59%)	33 (65%)	6 (75%)	0.25
Oral 5-ASA prescription within 12 week prior to the start of immunomodulator	1436 (72%)	1394 (72%)	35 (69%)	7 (88%)	0.90
Anti-TNF therapy within 12 weeks prior to the start of immunomodulator	60 (3%)	55 (3%)	5 (10%)	0	0.03
Starting daily dose of immunomodulator in 6MP equivalents (median, IQR) *	48 (24, 50)	48 (24, 50)	50 (36, 50)	50 (48, 61)	0.004

* Azathioprine dose was converted to 6MP equivalents by dividing by 2.07

Table 2

Incidence of myelosuppression during first course of thiopurine therapy.

	Time since start of thiopurine (weeks)	Number of patients with onset of event*	Incidence per 100 person-months (95% CI)
Mild leucopenia	0 to 8	44	1.18 (0.83-1.53)
(WBC < 3.0×10^9 / L)	9 to 26	49	0.80 (0.58-1.02)
	> 26 weeks	100	0.38 (0.31-0.45)
Severe leucopenia	0 to 8	6	0.16 (0.03-0.29)
(WBC < 1.0×10^9 /L)	9 to 26	0	-
	> 26 weeks	3	0.01 (0-0.03)
Severe neutropenia	0 to 8	19	0.51 (0.31-0.80)
(ANC < 1.0×10^9 /L)	9 to 26	14	0.23 (0.12-0.38)
	> 26 weeks	22	0.08 (0.05-0.13)
Mild thrombocytopenia	0 to 8	26	0.70 (0.43-0.97)
(Platelets < 100×10^9 /L)	9 to 26	16	0.26 (0.13-0.39)
	> 26 weeks	27	0.10 (0.06-0.14)
Severe thrombocytopenia	0 to 8	3	0.08 (0.02-0.23)
(Platelets < 20×10^9 /L)	9 to 26	0	-
	> 26 weeks	2	0.01 (0-0.04)

* Patients can be included in the table more than once if they developed both leucopenia and thrombocytopenia. For example, the 44 patients with mild leucopenia and the 26 patients with mild thrombocytopenia during weeks 0-8 include a total of 51 unique individuals.

Table 3

Comparison of blood counts among those with and without myelosuppression

	All patients (n=1997)	Patients without myelosuppressi on in the first 8 weeks (n=1938)	Patients with mild but not severe myelosuppressi on in the first 8 weeks (n=51)	Patients with severe myelosuppressi on in the first 8 weeks (n=8)	P value (Mild/Severe vs. none)
WBC on the first CBC measured after the start of thiopurine therapy (median, IQR)	9.2 (7.1, 12.0)	9.3 (7.2, 12.0)	6.0 (3.8, 9.3)	5.8 (4.0, 9.1)	<0.0001
Platelet count on the first CBC measured after the start of thiopurine therapy (median, IQR)	333 (267, 419)	335 (271, 420)	266 (158, 373)	249 (131, 316)	<0.0001
Percent reduction in WBC from pre-therapy to first measurement after start of therapy (median, IQR)	-1 (-29 to 19)	-2 (-30, 19)	18 (-19, 40)	29 (5, 76)	0.0001
Percent reduction in platelet count from pre-therapy to first measurement after start of therapy (median, IQR)	-2 (-18, 12)	-2 (-18, 12)	4 (-12, 21)	10 (-2, 60)	0.07
Number of CBCs in the first 8 weeks (median, IQR)*	3 (2, 5)	3 (2, 5)	6 (3, 9)	14 (11, 18)	<0.0001

IQR – interquartile range

* Up to and including the first CBC with mild or severe leucopenia during the first 8 weeks of therapy. Does not include CBCs collected on the date that thiopurine therapy was initiated.

Table 4

Comparison of blood counts among those with and without early severe neutropenia

	Patients without severe neutropenia in the first 8 weeks (n=1978)	Patients with severe neutropenia in the first 8 weeks (n=19)	P value
Age at start of therapy (median, IQR)	48 (38-59)	57 (46-66)	0.04
Female sex (n, %)	1033 (52.2%)	10 (52.6%)	0.97
Starting daily dose of immunomodulator in 6MP equivalents (median, IQR)*	48.3 (24.2-50.0)	50.0 (48.3-100.0)	0.007
Oral steroids prescription within 12 weeks prior to the start of immunomodulator	1166 (59.0%)	10 (52.6%)	0.58
Oral 5-ASA prescription within 12 week prior to the start of immunomodulator	1420 (71.8%)	16 (84.2%)	0.23
Anti-TNF therapy within 12 weeks prior to the start of immunomodulator	60 (3.0%)	0	0.56
WBC on the first CBC measured after the start of thiopurine therapy (median, IQR)	9.2 (7.2-12.0)	5.1 (4.2-9.9)	0.0001
Percent reduction in WBC from pre-therapy to first measurement after start of therapy (median, IQR)	-1.5 (-29.5-19.1)	17.3 (-3.1-35.1)	0.004

* Azathioprine dose was converted to 6MP equivalents by dividing by 2.07 IQR – Interquartile range