Outcome Predictors for Thiopurine Maintenance Therapy in Patients with Crohn's Disease

Jae Jun Park

Department of Medicine

The Graduate School, Yonsei University

Outcome Predictors for Thiopurine Maintenance Therapy in Patients with Crohn's Disease

Directed by Professor Won Ho Kim

The Master's Thesis
submitted to the Department of Medicine,
the Graduate School of Yonsei University
in partial fulfillment of the requirements for the degree
of Master of Medical Science

Jae Jun Park

June 2010

This certifies that the Master's Thesis of
Jae Jun Park is approved.

_____

Thesis Supervisor: Won Ho Kim

_____

Thesis Committee Member#1: Jeon Han Park

_____

Thesis Committee Member#2: Jae Hee Cheon

The Graduate School

Yonsei University

June 2010

ACKNOWLEDGEMENTS

This page is exclusively designed to note my gratitude and respect for those who helped me to complete my thesis. I am deeply indebted to my supervisor Prof. Dr. Won Ho Kim for his kind help, guidance, support and encouragement throughout my study. Sincere gratitude goes out to my reviewers, Prof. Dr. Jeon Han Park and Prof. Dr. Jae Hee Cheon who had the patience and fortitude to read my thesis and provided constructive criticism to help me defend it. Their guidance not only improved my dissertation but also will benefit my future works. I also sincerely thank my colleagues, Jun Chul Park, Beom Kyung Kim, Minkyu Jung for their supports. Finally, this thesis would not have been possible without my family. This small thesis is devoted to God.

Jae Jun Park

<TABLE OF CONTENTS>

LIST OF FIGURES

LIST OF TABLES

ABSTRACT

Outcome Predictors for Thiopurine Maintenance Therapy in Patients with Crohn's Disease

Jae Jun Park

Department of Medicine
The Graduate School, Yonsei University

(Directed by Professor Won Ho Kim)

Little is known about the predictive factors for clinical relapse in patients with Crohn's disease receiving thiopurine therapy for maintenance of remission. The aim of this study was to investigate factors predictive of clinical relapse in these patients receiving thiopurine therapy for maintenance of remission. A total of 82 patients with CD, who received their first course of azathioprine or 6-mercaptopurine treatment at Severance Hospital from June 1996 to July 2007 were recruited. The indications of thiopurine therapy were as follows; steroid dependency in 60 cases (73.2%), draining fistula in 13 cases (15.9%), and maintenance of remission after surgery in 9 cases (11.0%). During the follow-up period of 25.5±16.6 months (range, 4.3–83.8 months), 19 patients (23.1%) discontinued medications due to significant adverse effects. Finally, 45 patients, who continually received thiopurine for maintaining medically or surgically induced remission were enrolled. After

adjustment of maintenance dose, patients in remission were followed at 2-3 months interval. Relapse was defined as a Crohn's disease activity index (CDAI) > 150. Patiens who achieved remission were followed for clinical relapse. Male to female ratio was 1.5:1 and the mean age was 26.3±7.1 year. The cumulative relapse rate was 18.0% at 1 year and 49.2% at 3 year. At multivariate Cox regression analysis, young age (<30 year) at thiopurine therapy and increased C-reactive protein level (>0.5 mg/mL) at the time of remission achievement were found to be independent predictors for relapse (hazard ratio 13.055, 95% confidence interval 1.447-117.792, P = 0.022 and hazard ratio 8.233, 95% confidence interval 1.448-46.801, P = 0.017, respectively). The results of this study suggest that thiopurine was efficacious for maintaining remission in Korean CD patients, although full dose was not administered in many cases due to leukopenia. Young age (<30 year) and increased C-reactive protein level at remission were independent predictors of relapse in patients with CD receiving thiopurines for maintenance of remission. These high risk groups warrant more close observation and might require early introduction of biologics.

Key words: Thiopurine, Crohn's disease, Relapse, Predictor

Outcome Predictors for Thiopurine Maintenance Therapy
in Patients with Crohn's Disease

Jae Jun Park

Department of Medicine
The Graduate School, Yonsei University

(Directed by Professor Won Ho Kim)

I. INTRODUCTION

Crohn's disease (CD) is an inflammatory bowel disease (IBD) that affects the gastrointestinal tract, with potential extraintestinal complications involving several organ systems.[1] There is strong evidence that the worldwide incidence of CD has been increasing over the past several decades,[2-3] which is also true in Asia including Korea.[4-5] CD is characterized by fluctuating disease course between periods of active, symptomatic disease and remission.[1,6] These clinical features necessitate appropriate maintenance therapies in patients with CD after achievement of remission. Azathioprine (AZA) and its metabolite 6-mercaptopurine (6-MP) have been reported to be effective as maintenance therapy after medically or surgically induced remission.[7-8]

Despite the effectiveness for maintaining remission with these thioprine drugs, substantial proportion, as high as more than one-half of the patients experiences clinical relapse during thiopurine maintenance treatment.[9] Thus, a recognition of high risk subgroup for relapse during thiopurine maintenance therapy is important for clinicians to plan adequate maintenance treatment. Although many investigators have

evaluated the efficacy of thiopurine for maintaining remission in CD patients, data regarding clinical predictors of relapse are still lacking. Therefore, this study aimed to investigate long-term outcomes and prognostic factors of clinical relapse in CD patients receiving AZA therapy for maintenance of remission.

II. MATERIALS AND METHODS

1. Study subjects

A retrospective observational study of a single center cohort, in which all patients were serially evaluated according to standardized evaluation protocols were performed. The medical records of all patients with CD who received thiopurine therapy with AZA or 6-MP as their first course of treatment in the Department of Gastroenterology of the Yonsei University Hospital were reviewed. The diagnosis of CD was made in accordance with previously established international criteria based on clinical, endoscopic, histopathological, and radiological findings.[10] The disease extent was determined either by endoscopic and/or radiological work-up.

2. Definition of clinical outcomes

In steroid dependent patients, remission was defined as achievement of Crohn's disease activity index (CDAI) < 150 and discontinuation of steroid at least 3 months within 1 year after initiation of thiopurine therapy[11]. On the other hand, in draining fistula patients, remission was defined as closure of individual fistulas determined as no fistula drainage despite gentle finger compression at least 4 week within 1 year after initiation of thiopurine therapy.[11] The index date of remission was defined as the date of achievement of remission in patients with medically induced remission, whereas the date of initiation of thiopurine drug in patients with post-operative maintenance remission. Relapse was defined as a CDAI > 150.[11]

3. Thiopurine dosing and follow-up protocol

The starting dose of AZA (1.0 mg/kg) was escalated upto 2.0 to 2.5 mg/kg in 1 to 4 week intervals unless adverse effects were observed. The starting dose of 6-MP (0.5 mg/kg) was escalated in the same way upto 1.0 to 1.5 mg/kg. The maintenance dose of 6-MP was converted to the equivalent dose of AZA by multiplying conversion factor (2.08). During AZA/6-MP treatment, 5-ASA was administered at a conventional dose (mesalazine 3.0 g/day). Outpatient visits were done at 1 to 2-week intervals for the first month, 1 month later, and then every 2-3 months thereafter, according to the condition of the patients.

The following parameters were routinely collected according to a standardized clinical practice protocol on each follow-up date : CDAI, hemoglobin, mean corpuscular volume, leukocyte count, neutrophil count, platelet count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP). Liver chemistry tests and serum amylase and lipase were checked at every 2-3 months interval. Leukopenia was defined as a white blood cell (WBC) count < 3000 cells/mm^3. If leukopenia occurred, AZA/6-MP treatment was withdrawn until the WBC count recovered to over 4000 cells/mm^3. For impending leukopenia, the dose of AZA/6-MP was reduced to the earlier prescribed dose. When the deterioration of liver function (AST/ALT increased over 3 times baseline) or pancreatitis (amylase/lipase increased over 2 times baseline) were observed, AZA/6-MP treatment was withdrawn. This study was approved by the Human Research Review Committee of our hospital.

4. Statistical analysis

Values were expressed as means ± standard deviation (SD) for numerical variables and as percentages for qualitative variables. Cumulative probabilities of thiopurine requirement rate and relapse free survival were estimated using the Kaplan–Meier method. Time to event was analyzed from the index date of remission to the date of relapse, or last known follow-up. To analyze the predictive factors of relapse, univariate analysis with log-rank test was used. Thereafter, these univariate predictors were integrated into Cox proportional-hazards regression for multivariate analysis. P values of <0.05 were considered significant. All statistical analyses were performed with SPSS 12.0 (SPSS Inc, Chicago, IL, USA).

III. RESULTS

1. Patients characteristics

The medical records of a total of 257 CD patients who had been followed more than 1 year in Severance Hospital, Yonsei University, Seoul, Korea between June 1996 to July 2007 were reviewed. Of these, 108 patients (42.0%) were treated with thiopurine (AZA or 6-MP). Initial thiopurine treatment was begun at the other (n=26) or Severance hospital (n=82). The cumulative rate of thiopurine requirement was 9.1% at 1 year, 32.2% at 5 year, and 51.6% at 10 years (Figure 1).

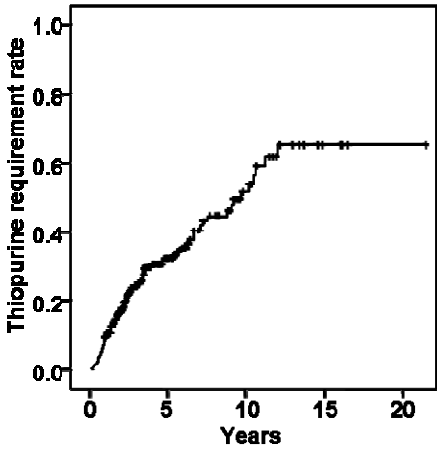

Figure 1. Cumulative rate of thiopurine requirement in Crohn's disease patients cohort

A total of 82 patients with CD who received their first course of AZA or 6-MP treatment at Severance hospital was recruited as a baseline study population for this study. The indications of AZA/6-MP therapy included steroid dependency in 60 patients (73.2%), draining fistula in 13 patients (15.9%), and maintenance of remission after surgery in 9 patients (11.0%). Most patients were treated with AZA (79 cases, 96.3%). During the follow-up period (mean, 25.5±16.6 [range, 4.3–83.8] months), 19

patients (23.2%) discontinued thiopurines due to significant adverse effects (Figure. 1). The details of adverse effects are as follows; leukopenia (53.7%, n=44), nausea/vomiting (26.8%, n=22), hepatitis (2.4%, n=2), headache (2.4%, n=2), Herpes zoster (2.4%, n=2). Patients who did not achieve a clinical remission (n=16) and those with follow-up loss (n=2) were excluded. Then finally, 45 patients who continually received AZA for maintaining medically or surgically induced remission were followed for clinical relapse (Figure 2).

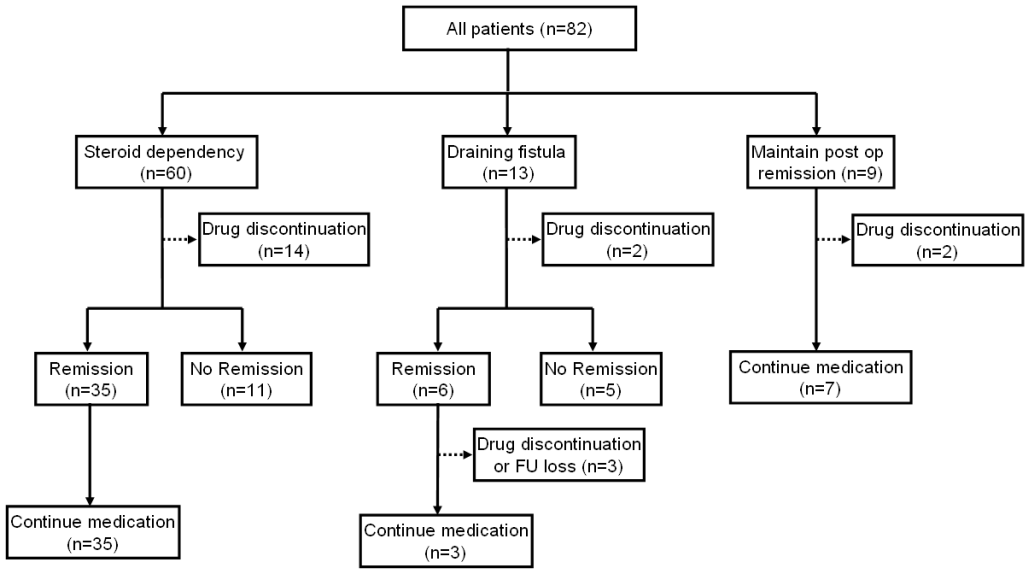

Figure 2. Recruitment of study population

OP, operation; *FU*, follow-up

The baseline characteristics of those patients are summarized in Table 1.

Table 1. Baseline characteristics of the study subjects

Characteristics	
Age at thiopurine therapy (year, mean±SD)	26.3± 7.1
Gender (%)	
Male	27 (60.0)
Female	18 (40.0)
BMI (kg/m^2, mean±SD)	18.6± 2.5
Smoking (%)	
No or Ex-smoker	42 (93.3)
Yes	3 (6.7)
Disease duration (months, mean±SD)	40.5± 36.5
Disease extent (%)	
Isolated ileal disease	12 (26.7)
Isolated colonic disease	4 (8.9)
Ileocolonic disease	29 (64.4)
Disease behavior (%)	
Non-stricturing, nonpenetrating	11 (24.4)
Stricturing	10 (22.2)
Penetrating	24 (53.3)
Method of remission induction (%)	
Medical	38 (84.4)
Surgical	7 (15.6)
Maintenance dose (mg/kg, mean±SD)	1.47 ± 0.63 (range: 0.41 – 3.05)
Type of thiopurine	
Azathioprine	45 (100)
6-Mercaptopurine	0 (0)
5-ASA co-use (%)	45 (100)
Leukocytes (10^6/l, mean±SD) [a]	4360± 1158

Neutrophil count (10^9/l, mean±SD) [a]	2766 ± 1001
Platelet count (10^9/, mean±SD)[a]	297 ± 115
Hemoglobin (g/dl, mean±SD) [a]	11.6 ± 1.5
ESR (/mh) [a]	20.7 ± 22.0
CRP (mg/l) [a]	0.95 ± 1.46

[a]Values measured at the time of remission in patients with medically induced remission or at the time of azathioprine/6-mercaptopurine initiation in patients with surgically induced remission
SD, standard deviation; BMI, body mass index; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein

The mean age of 45 patients were 26.3± 7.1 years (range, 14–45 years). Twenty seven (60.0%) patients were male. Regarding disease extent and behavior, ileocolonic disease (64.4%, 29/45) and penetrating type (53.3%, 24/45) were the most common subtype respectively. Most patients (84.4%, 38/45) achieved clinical remission through medical treatment.

2. Univariate analysis for predictor of clinical relapse during thiopurine maintenance therapy

The cumulative relapse rate was 18.0% at 12 months and 49.2% at 36 months (Figure. 3).

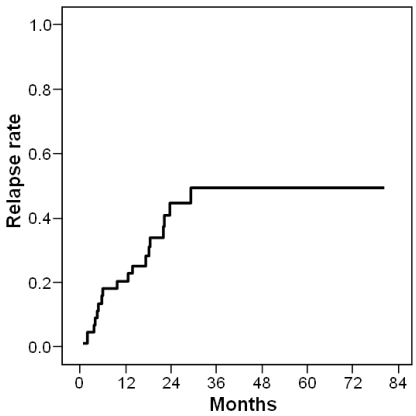

Figure 3. Cumulative relapse rate in Crohn's disease patients receiving thiopurine maintenance therapy.

In univariate analysis (log-rank test), female gender (p=0.017), young (<30 year) age (p=0.006), low (<18 kg/m2) body mass index (BMI) (p=0.026), smoking (p=0.040), high (≥250 [10^9/l]) platelet count (p=0.046), high (≥20 mm/h) ESR (p=0.023) and high (≥0.5 mg/ml) CRP level (p=0.009) were significant predictors of clinical relapse (Table 2 and Figure. 4).

Table 2 . Predictors of clinical relapse in univariate analysis

Variables	*P*-value[a]
Age (<30 year) at thiopurine therapy	0.006
Gender (Female)	0.017
BMI (<18 kg/m2)	0.026
Smoking (Yes)	0.040
Disease duration (<30 months)	0.654
Disease extent (Colon involvement)	0.361
Disease behavior (Penetrating)	0.215
Method of remission induction (medical)	0.218
Thiopurine dose for maintenance (≥2.0 mg/kg)	0.058
Leukopenia during thiopurine treatment(Yes)	0.351
Leukocytes (≥4000 [10^6/l]) [b]	0.626
Neutrophil (≥2500 [10^6/l]) [b]	0.788
Hemoglobin (≥11 g/dL) [b]	0.262
Platelet count (≥250 [10^9/l]) [b]	0.046
ESR (≥20 mm/h) [b]	0.023
CRP (≥0.5 mg/ml)[b]	0.009

[a]Log-rank test

[b]Values measured at the time of remission in patients with medically induced remission or at the time of thiopurine initiation in patients with surgically induced remission

BMI, body mass index; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein

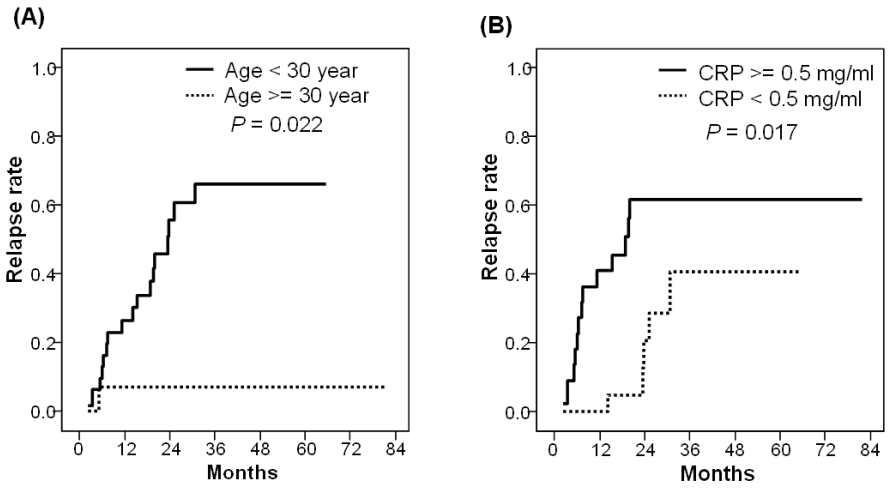

Figure 4. (A). Cumulative relapse rate according to the age. The difference between patients with age <30 year and age ≥30 year was statistically significant (P=0.022, log-rank test). (B). Cumulative relapse rate according to the value of C-reactive protein (CRP). The difference between patients with CRP ≥0.5 mg/ml and CRP <0.5 mg/ml was statistically significant (P=0.017, log-rank test).

However, disease duration, disease extent and behavior, method of remission induction, leukopenia during thiopurine treatment, thiopurine maintenance dose, leukocytes and neutrophil counts, and hemoglobin level were not associated with clinical relapse.

3. Multivariate analysis for factors predictive of clinical relapse during thiopurine maintenance therapy

The results of Cox proportional-hazard regression analysis are shown in Table 3.

Table 3 . Predictors of clinical relapse in multivariate analysis (Cox regression analysis)

Variable	*P* value	Hazard ratio	95% CI
Gender (female)	0.067	3.452	0.916-13.003
Age (<30 year) at thioprine therapy	0.022	13.055	1.447-117.792
BMI (<18 kg/m2)	0.171	2.278	0.701-7.403
Smoking (Yes)	0.080	4.572	0.833-25.101
Platelet count (≥250 [10^9/l]) [a]	0.549	1.645	0.323-8.387
ESR (≥20 mm/h)[a]	0.573	1.606	0.310-8.333
CRP (≥0.5 mg/mL)[a]	0.017	8.233	1.448-46.801

[a]Values measured at the time of remission in patients with medically induced remission or at the time of thiopurine initiation in patients with surgically induced remission.
BMI, body mass index; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein

Young age (<30 year) and increased CRP level (>0.5mg/ml) at the time of remission achievement were independent predictors for relapse (HR 13.055, 95% CI 1.447-117.792, *P* = 0.022 and HR 8.233, 95% CI 1.448-46.801, *P* = 0.017, respectively). Remaining variables including gender, BMI, smoking, platelet count and ESR which had been significant in univariate analysis were lost statistical power as a predictor in multivariate analysis.

IV. DISCUSSION

The thiopurine drugs, 6-MP and its prodrug AZA, are effective for the induction and maintenance of remission in patients with CD. Although there have been many studies that have evaluated the efficacy of thiopurine for maintenance therapy in CD, few have focused on the clinical predictors for relapse in those patients with such therapy. Accordingly, this study aimed to investigate long-term outcomes and prognostic factors of clinical relapse in CD patients receiving thiopurine therapy for maintenance of remission.

In this study, the cumulative relapse rate was 18.0% at 12 months and 49.2% at 36 months in CD patients receiving thiopurine for maintenance therapy. It was found that young age (<30 year) and increased CRP level (>0.5mg/mL) at the time of remission were independent predictors for relapse in CD patients undergoing AZA maintenance therapy.

The results of the present study show that considerable portion of the patients experience clinical relapse during thiopurine maintenance therapy after remission. The relapse rate of CD patients during thiopurine therapy has been reported 8-58%.[9,12-13] The reason for these wide range in relapse rate among studies might be due to difference in disease severity of enrolled population, the definition of relapse and follow-up durations among studies. In this study, about half of the patients with CD experienced clinical relapse during thiopurine maintenance therapy within 3 year, indicating that a substantial number of patients need additional salvage treatments such as biologics or surgery eventually. Considering these patients are steroid dependent, and previously underwent surgery for medically refractory diseases or complications, physicians should give careful attention to these subgroups. The present study is noteworthy in that early identification of high risk CD patients for relapse during thiopurine maintenance therapy could guide physicians to design appropriate follow-up plans and management including earlier implementation of biologic agent in these high risk group.

Several predictors for relapse have been investigated in quiescent CD

patients.[14-16] However these predictive factors have been found from the quiescent CD patients receiving 5-ASA alone or no medication for maintenance, therefore little is known about the predictors of relapse in patients receiving thiopurine maintenance therapy. To the best of our knowledge, this is the first study to investigate predictors for relapse in patients with CD undergoing thiopurine maintenance treatment through long-term follow-up. In the present study, young age (<30 year) was one of the independent predictors for relapse. Similar to this finding, Sahmoud et al also reported that young age (<25 year) was poor prognostic factors for relapse in untreated adult CD patients with quiescent disease after induction therapy.[14] From these results, young age CD patients undergoing thiopurine maintenance therapy should be carefully observed and more aggressive management may be required in this group.

Another prognostic factor, high CRP level (>0.5mg/ml) at the time of achievement of clinical remission was found in the present study. CRP has been widely studied and is now considered to have the best performance as a disease activity marker in CD.[17-18] Despite this background, our finding implies that even clinical remission was achieved, systemic biological inflammation process could not be fully subsided and remaining inflammatory process ultimately lead to early relapse. High CRP level as a predictor for relapse was also suggested in the study of Consigny et al in CD patients followed without maintenance therapy after remission induction.[15] Solem et al showed that active disease at ileocolonoscopy was significantly associated with an elevated CRP level.[19] From their investigation, we can infer that increased CRP level at the time of remission may reflect active mucosal inflammation even in the achievement of clinical remission. This supposition is in line with the recent studies which have demonstrated that mucosal healing is a favorable long-term predictive factor in CD patients.[20-21]

Lately, there are increasing evidences favoring early use of immunosuppressive and biologic agents, so-called top-down therapy in the management of CD.[22-23] However, this top-down therapy might preferentially be considered in the subgroup of patients who are more likely to relapse due to uncertain cost effectiveness until yet. From our results, physicians could implement early combination of biologics such as infliximab in high risk subgroup of patients for

relapse that receive thiopurine maintenance therapy, because relapse of disease potentially lead to resective surgery in these patients. Further prospective studies are needed to elucidate this issue.

Regarding optimal dose of thiopurine, there is evidence that higher doses of AZA (2.5mg/kg) are more effective than lower doses (1.0 or 2.0 mg/kg) for preventing recurrence.[7] However, a substantial portion of the patients do not tolerate with these dose due to several adverse effects especially leukopenia in our study population and therefore the mean maintenance dose was 1.47 mg/kg. Approximately over half of the patients experienced leukopenia during thiopurine therapy and most of them could not take recommended dose of thiopurine. Similar to our study, considerable incidence of leukopenia (up to 41.3%) was reported in the Korean multicenter study,[24] whereas studies from Western countries have shown leukopenia incidence of only 2% to 16.7% during thiopurine treatment.[25-28] Although the reason for this difference in leukopenia incidence among regions is not clear, the difference in thiopurine methyltransferase (TPMT) genetic polymorphisms between Asian and Western populations[5] may account for the high incidence of leukopenia during thiopurine treatment. Another presumed reason for high incidence of leukopenia is concurrent use of 5-ASA during thiopurine treatment. Previous study demonstrated that leukopenia is more likely to occur in patients with receiving both thiopurine and 5-ASA than in thiopurine without 5-ASA,[29-33] hence concurrent 5-ASA and thiopurine therapy may lead to increased 6-TGN levels through inhibition of TPMT and this interaction eventually increase the incidence of leukopenia. Correspondingly, all the patients received 5-ASA besides AZA in our study.

In this study, thiopurine was efficacious for maintaining remission in Korean CD patients, although full dose was not administered in many cases due to leukopenia. Similar to our results, several studies especially in the Asian countries suggested the efficacy of low dose thiopurine for the treatment of IBD.[34-36] However these studies including our study are not a randomized, double-blind, or controlled study. Further prospective randomized studies should be warranted for more conclusive evidences regarding the efficacy of low dose thiopurine therapy in patients with IBD

This study has several limitations. First, although patients were serially

followed according to a prospectively designed standardized evaluation carried out by experienced clinicians, it was a retrospective cohort study. Second, the number of study population was small. Further large scale prospective studies are needed to confirm our results.

V. CONCLUSION

Thiopurine was efficacious for maintaining remission in Korean CD patients, although full dose was not administered in many cases due to leukopenia. Young age (<30 year) and increased C-reactive protein level (>0.5mg/ml) at the time of remission achievement were independent predictors of relapse in patients with CD receiving thiopurine for the maintenance of remission. These high risk groups warrant more close monitoring and might require early introduction of biologic agent.

REFERENCES

1. Munkholm P, Langholz E, Davidsen M, Binder V. Disease activity courses in a regional cohort of Crohn's disease patients. Scand J Gastroenterol 1995;30:699-706.
2. Loftus EV, Jr., Sandborn WJ. Epidemiology of inflammatory bowel disease. Gastroenterol Clin North Am 2002;31:1-20.
3. Munkholm P, Langholz E, Nielsen OH, Kreiner S, Binder V. Incidence and prevalence of Crohn's disease in the county of Copenhagen, 1962-87: a sixfold increase in incidence. Scand J Gastroenterol 1992;27:609-14.
4. Yang SK, Yun S, Kim JH, Park JY, Kim HY, Kim YH, et al. Epidemiology of inflammatory bowel disease in the Songpa-Kangdong district, Seoul, Korea, 1986-2005: a KASID study. Inflamm Bowel Dis 2008;14:542-9.
5. Kim ES, Kim WH. Inflammatory Bowel Disease in Korea: Epidemiological, Genomic, Clinical, and Therapeutic Characteristics Gut and Liver 2010;4:1-14.
6. Cosnes J, Cattan S, Blain A, Beaugerie L, Carbonnel F, Parc R, et al. Long-term evolution of disease behavior of Crohn's disease. Inflamm Bowel Dis 2002;8:244-50.
7. Pearson DC, May GR, Fick G, Sutherland LR. Azathioprine for maintaining remission of Crohn's disease. Cochrane Database Syst Rev 2000:CD000067.
8. Peyrin-Biroulet L, Deltenre P, Ardizzone S, D'Haens G, Hanauer SB, Herfarth H, et al. Azathioprine and 6-mercaptopurine for the prevention of postoperative recurrence in Crohn's disease: a meta-analysis. Am J Gastroenterol 2009;104:2089-96.
9. Candy S, Wright J, Gerber M, Adams G, Gerig M, Goodman R. A controlled double blind study of azathioprine in the management of Crohn's disease. Gut 1995;37:674-8.
10. Lennard-Jones JE. Classification of inflammatory bowel disease. Scand J Gastroenterol Suppl 1989;170:2-6; discussion 16-9.
11. Sandborn WJ, Feagan BG, Hanauer SB, Lochs H, Lofberg R, Modigliani R, et al. A review of activity indices and efficacy endpoints for clinical trials of medical therapy in adults with Crohn's disease. Gastroenterology 2002;122:512-30.
12. Lemann M, Mary JY, Colombel JF, Duclos B, Soule JC, Lerebours E, et al. A randomized, double-blind, controlled withdrawal trial in Crohn's disease patients in

long-term remission on azathioprine. Gastroenterology 2005;128:1812-8.

13. Roblin X, Serre-Debeauvais F, Phelip JM, Faucheron JL, Hardy G, Chartier A, et al. 6-tioguanine monitoring in steroid-dependent patients with inflammatory bowel diseases receiving azathioprine. Aliment Pharmacol Ther 2005;21:829-39.
14. Sahmoud T, Hoctin-Boes G, Modigliani R, Bitoun A, Colombel JF, Soule JC, et al. Identifying patients with a high risk of relapse in quiescent Crohn's disease. The GETAID Group. The Groupe d'Etudes Therapeutiques des Affections Inflammatoires Digestives. Gut 1995;37:811-8.
15. Consigny Y, Modigliani R, Colombel JF, Dupas JL, Lemann M, Mary JY. A simple biological score for predicting low risk of short-term relapse in Crohn's disease. Inflamm Bowel Dis 2006;12:551-7.
16. Cosnes J, Carbonnel F, Beaugerie L, Le Quintrec Y, Gendre JP. Effects of cigarette smoking on the long-term course of Crohn's disease. Gastroenterology 1996;110:424-31.
17. Vermeire S, Van Assche G, Rutgeerts P. C-reactive protein as a marker for inflammatory bowel disease. Inflamm Bowel Dis 2004;10:661-5.
18. Desai D, Faubion WA, Sandborn WJ. Review article: biological activity markers in inflammatory bowel disease. Aliment Pharmacol Ther 2007;25:247-55.
19. Solem CA, Loftus EV, Jr., Tremaine WJ, Harmsen WS, Zinsmeister AR, Sandborn WJ. Correlation of C-reactive protein with clinical, endoscopic, histologic, and radiographic activity in inflammatory bowel disease. Inflamm Bowel Dis 2005;11:707-12.
20. Baert F, Moortgat L, Van Assche G, Caenepeel P, Vergauwe P, De Vos M, et al. Mucosal healing predicts sustained clinical remission in patients with early-stage Crohn's disease. Gastroenterology 2010;138:463-8; quiz e10-1.
21. Schnitzler F, Fidder H, Ferrante M, Noman M, Arijs I, Van Assche G, et al. Mucosal healing predicts long-term outcome of maintenance therapy with infliximab in Crohn's disease. Inflamm Bowel Dis 2009;15:1295-301.
22. Devlin SM, Panaccione R. Evolving inflammatory bowel disease treatment paradigms: top-down versus step-up. Gastroenterol Clin North Am 2009;38:577-94.
23. Colombel JF, Sandborn WJ, Reinisch W, Mantzaris GJ, Kornbluth A, Rachmilewitz D,

et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. N Engl J Med 2010;362:1383-95.

24. Kim JH, Cheon JH, Hong SS, Eun CS, Byeon JS, Hong SY, et al. Influences of Thiopurine Methyltransferase Genotype and Activity on Thiopurine-induced Leukopenia in Korean Patients With Inflammatory Bowel Disease: A Retrospective Cohort Study. J Clin Gastroenterol 2010.

25. Fraser AG, Orchard TR, Jewell DP. The efficacy of azathioprine for the treatment of inflammatory bowel disease: a 30 year review. Gut 2002;50:485-9.

26. Hindorf U, Lindqvist M, Peterson C, Soderkvist P, Strom M, Hjortswang H, et al. Pharmacogenetics during standardised initiation of thiopurine treatment in inflammatory bowel disease. Gut 2006;55:1423-31.

27. Gisbert JP, Nino P, Rodrigo L, Cara C, Guijarro LG. Thiopurine methyltransferase (TPMT) activity and adverse effects of azathioprine in inflammatory bowel disease: long-term follow-up study of 394 patients. Am J Gastroenterol 2006;101:2769-76.

28. Zelinkova Z, Derijks LJ, Stokkers PC, Vogels EW, van Kampen AH, Curvers WL, et al. Inosine triphosphate pyrophosphatase and thiopurine s-methyltransferase genotypes relationship to azathioprine-induced myelosuppression. Clin Gastroenterol Hepatol 2006;4:44-9.

29. Lowry PW, Franklin CL, Weaver AL, Szumlanski CL, Mays DC, Loftus EV, et al. Leucopenia resulting from a drug interaction between azathioprine or 6-mercaptopurine and mesalamine, sulphasalazine, or balsalazide. Gut 2001;49:656-64.

30. Gilissen LP, Bierau J, Derijks LJ, Bos LP, Hooymans PM, van Gennip A, et al. The pharmacokinetic effect of discontinuation of mesalazine on mercaptopurine metabolite levels in inflammatory bowel disease patients. Aliment Pharmacol Ther 2005;22:605-11.

31. Hande S, Wilson-Rich N, Bousvaros A, Zholudev A, Maurer R, Banks P, et al. 5-aminosalicylate therapy is associated with higher 6-thioguanine levels in adults and children with inflammatory bowel disease in remission on 6-mercaptopurine or azathioprine. Inflamm Bowel Dis 2006;12:251-7.

32. Shah JA, Edwards CM, Probert CS. Should azathioprine and 5-aminosalicylates be coprescribed in inflammatory bowel disease?: an audit of adverse events and outcome.

Eur J Gastroenterol Hepatol 2008;20:169-73.

33. Szumlanski CL, Weinshilboum RM. Sulphasalazine inhibition of thiopurine methyltransferase: possible mechanism for interaction with 6-mercaptopurine and azathioprine. Br J Clin Pharmacol 1995;39:456-9.

34. Kim DU, Kim YH, Kim BJ, Chang DK, Son HJ, Rhee PL, et al. The efficacy of low dose azathioprine/6-mercaptopurine in patients with inflammatory bowel disease. Hepatogastroenterology 2009;56:1395-402.

35. Hibi T, Naganuma M, Kitahora T, Kinjyo F, Shimoyama T. Low-dose azathioprine is effective and safe for maintenance of remission in patients with ulcerative colitis. J Gastroenterol 2003;38:740-6.

36. Andoh A, Tsujikawa T, Ban H, Hashimoto T, Bamba S, Ogawa A, et al. Monitoring 6-thioguanine nucleotide concentrations in Japanese patients with inflammatory bowel disease. J Gastroenterol Hepatol 2008;23:1373-7.

ABSTRACT (IN KOREAN)

관해유지를 위하여 Thiopurine 치료를 받는 크론병 환자의 임상결과 예측인자

<지도교수 김원호>

연세대학교 대학원 의학과

박 재 준

관해 유지를 위하여 thiopurine 치료를 받는 크론병 환자에서 임상적 재발의 예측인자에 대해서는 거의 알려져 있지 않다. 본 연구의 목적은 관해 유지의 목적으로 thiopurine 치료를 받는 크론병 환자에의 장기 임상결과와 재발의 예측인자를 알아보는 것이다. 1996년 6월부터 2007년 7월까지 세브란스병원에서 처음으로 Azathioprine 또는 6-mercaptopurine 치료를 받은 총 82명의 크론병 환자가 후향적으로 모집되었다. 면역조절제의 사용 적응증으로는 스테로이드 의존 60예(73.2%), 배농되는 누공 13예(15.9%), 그리고 수술 후의 관해 유지 9예(11.0%)였다. 평균 25.5±16.6 (범위, 4.3-83.8) 개월의 추적기간 동안 19명(23.1%)이 약제부작용으로 투약을 중단하였다. Thiopurine 치료를 지속하였던 45명의 환자가 최종적으로 분석에 포함되었다. 재발은 Crohn's disease activity index (CDAI)가 150 이상으로 증가한 경우로 정의 하였다. 약제용량을 조절한 뒤에 환자들은 2-3개월 간격으로 추적관찰 되었으며 추적기간 동안의 재발여부를 분석하였다. 남녀비는 1.5:1이었고 평균나이는 26.3±7.1세였다. 누적 재발률은 1년 18.0%, 3년 49.2%였다. 다변량 분석에서 관해 도달 당시의 젊은 연령(<30세)과 높은 C 반응 단백

수치(≥0.5mg/mL)는 재발의 독립적인 예측인자로 밝혀졌다(각각 HR 13.055, 95% CI 1.447-117.792, P = 0.022 와 HR 8.233, 95% CI 1.448-46.801, P = 0.017). 그러나 병변의 위치나 흡연 유무, 이환 기간, 백혈구 수치 등은 영향을 주지 않았다.

본 연구 결과는 상당수의 환자에서 백혈구감소증으로 인해 충분한 용량의 thiopurine이 투여되지 못했음에도 불구하고, 한국인 크론병 환자의 관해유지에 thiopurine이 효과가 있음을 보여준다. 관해 도달 당시의 젊은 연령(<30세)과 높은 C 반응 단백 수치가 thiopurine 관해 유지 치료를 받는 크론병 환자에서 재발의 독립적인 예측인자였다. 이러한 재발의 고위험군은 철저히 추적관찰 되어야 하며 생물학적 제제의 조기투여가 필요할 수 있을 것이다.

핵심되는 말 : Thiopurine, 크론병, 재발, 예측인자