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Effect of Combination Therapy of Allopurinol and Reduced Dose of Azathioprine on Inflammatory Bowel Disease (IBD)

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ABSTRACT

Background: Thiopurine, Azathioprine and 6–Mercaptopurine are the maintenance therapies for inflammatory bowel disease (IBD); however, treatment frequently fails due to adverse drug reactions. This study is aimed at conducting combination therapy of allopurinol and reduced dose of Azathioprine in order to study the complications and treatment effect in IBD patients.
Method: Some IBD patients with indication for treatment using Azathioprine were divided into two groups, each including 32 patients: (1) Group A in which patients received the combination therapy of allopurinol (100 mg/d) and reduced dose of Imuran down to 50% daily; and (2) Group B in which patients received standard therapy. The patients were evaluated for 24 weeks in terms of complications and response to treatment.
Results: Among patients who received polytherapy, i.e. Group A, 12.5% of them suffered some complications such as neutropenia as the most common one (6.2%), and then nausea and loss of appetite. From those treated with standard therapy, i.e. Group B, 34.4% suffered some complications such as gastrointestinal intolerance as the most common one (18.9%), neutropenia (6.2%) and increased liver enzymes (6.2%). There was a significant relationship between the complications and type of the treatment ($p = 0.039$), however, remission rate in Group A was 87.5% and the same rate in Group B was 81.2% which showed no significant difference.
Conclusions: In patients with stable IBD, the combination therapy of allopurinol and Azathioprine is effective in reducing drug complications of Azathioprine, especially for hepatic and gastrointestinal complications. Nevertheless, the remission level in polytherapy was not greater than that of standard therapy. In patients with combination therapy, routine monitoring of hematologic complications (neutropenia) is of vital importance.
KEYWORDS: Azathioprine, Imuran, Allopurinol, IBD.

1. INTRODUCTION

Inflammatory bowel diseases include two important forms: Crohn's disease and ulcerative colitis, and various reports indicate their increase in our country; (1) unfortunately, however, few studies have been conducted regarding such diseases in Iran.(1-2) Both of these forms are characterized with being chronic, and undesirable gastrointestinal symptoms such as rectal bleeding, dysentery, bloody, chronic and diarrhea periodic diarrhea, constipation, abdominal pain and some extraintestinal manifestations such as skin involvement, rheumatology, eye-related, hepatic or metabolic symptoms, intestinal cancer including Colon cancer and sclerosing cholangitis.(1)

Azathioprine (Imuran) and 6–Mercaptopurine (Azathioprine's active metabolite) are the effective medications for resistant and corticosteroid-dependent cases, also as a maintenance therapy in ulcerative colitis and Crohn's disease as well as for acute phase of fistula and Crohn's rectal pain. (3)

Despite effectiveness of thiopurines, 30-50% of the patients have some limitations for using these drugs, either because of the drug complications and/or lack of effective clinical response due to insufficient drug metabolism.(4) Drug complications and poor response of thiopurines happen in 15-40% of the cases.(5, 17) Neutropenia, nausea and vomiting (even after 3 months) are the most common complications of azathioprine in inflammatory bowel diseases,(18) among which neutropenia is dose-dependent and delayed (third week), but is reversible with drug discontinuation.(15) Hepatic complications occurs in 10% of cases (7) and the hepatotoxicity risk increases up to 24% due to drug effectiveness in high doses.(8) Therefore treatment with higher doses and also long and continuous treatment results in drug toxicity and limits the usage of these medications.

The drug complications can be decreased and its efficacy can be improved by understanding Azathioprine metabolism pathway and the effective active metabolite for treatment. Azathioprine is converted to 6-mercaptoperin (6-MP)'s active metabolite by glutathione S-transferase in liver. Its further metabolisms occur in liver and gastrointestinal tract via three main pathways: first, it is converted by hypoxanthine-guanine phosphoribosyltrans ferase (HGPRT) to 6-

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thioguanine nucleotide (6-TGN), then it is converted by xanthine oxidase to 6-thiouric acid (6-TU) and finally thiopurine methyltransferase (TPMT) converts it to 6-methyl mercaptopurine (6-MMP).(9-11) If 6-thioguanine nucleotide level may not reach to the desirable one, no satisfactory response to Azathioprine will be observed, or if there would be no thiopurine methyl transferase or it would have low enzyme activity, greater hepatic complications will be suffered due to increased methyl mercaptopurine.(10)

Thus, it seems that using a combination of drugs that may alter its metabolism and reduce its complications will be a suitable solution. Given the inhibition of xanthine oxidase by allopurinol in drug combination of allopurinol and Azathioprine that increases Azathioprine's inactive metabolite and leads the metabolic pathway to Azathioprine's active metabolite, (18-11) although the actual mechanism of Azathioprine and allopurinol co-therapy is unknown, a combination of Azathioprine and allopurinol and reducing the dose of Azathioprine, not only decrease hepatic complications of Azathioprine but also increase effectiveness of the drug.

In 1993, it was for the first time reported that combination therapy with allopurinol and azathioprine in renal transplant patients reduced the rate of acute renal rejection.(19) Further researches indicated the increased Azathioprine's active metabolite as the cause for the effectiveness of polytherapy.(20)

In 2007, White and Ginsberg at Gastroenterology Research Center, George Washington University treated 4 IBD patients who did not respond to any treatment using a combination therapy of allopurinol and Azathioprine.(21) Several other studies also used combination therapy of allopurinol and Azathioprine for reducing complications and improving responses and reported it to be effective.

Due to limited number of the researches in this regard in Iran, this research is important concerning the response levels of patients to Azathioprine, the incidence of complications of azathioprine and their types, as well as the dose required to control the disease.

METHOD

This is an experimental study. The study population included all patients with inflammatory bowel diseases (Crohn's or ulcerative colitis) who were referred to gastroenterology clinic of Imam Reza Hospital, Tabriz and Vali Asr Hospital, Zanjan during the period of this study as well as the admitted patients in gastroenterology department of these hospitals. Data was collected by interviewing patients, the test results and pathology (biopsy during colonoscopy). The study was conducted during the years 2008-2011. Patients were randomly divided into two groups of 32 people. The first group received combination therapy of azathioprine with reduced dose down to 50% along with 100 mg allopurinol daily (group A), while the next group was given the standard therapy of azathioprine, i.e. 1.5 to 2.5 mg per kg of body weight, (Group B).

Remission or exacerbation of the diseases was determined based on clinical and laboratory symptoms and colonoscopy, when needed. For the final stage of the research, remission was considered to be realized in those patients who went into remission phase. Crohn's disease was quantified using Adult CDAI, while ulcerative colitis using SCCAI. For patients with Crohn's disease, the score of less than 97 was considered to be as remission phase, 97-150 as mild phase, 150-450 as moderate and over 450 as severe phases. For patients with ulcerative colitis, the score of less than four was considered to be as remission phase, 4-7 as mild phase, 7-9 as moderate and over 9 as severe phases.

Prior to treatment, all patients were tested for CBC, BUN, Cr, ESR, CRP, LFT and Pt, and colonoscopy was conducted for all of them. Patients were checked every week during the first month, every two weeks during the second month and then monthly for CBC, LFT and Pt, and complications and clinical signs and symptoms were followed-up for 24 weeks. BUN, Cr, ESR, CRP were checked monthly.

Patients who were treated with Azathioprine (with fixed dose), or those with indication for treatment with Azathioprine (for Crohn's disease as: a new case or maintenance treatment, post-operative for prevention, acute phase of fistula and rectal pain; and in ulcerative colitis as: maintenance treatment, resistant and corticosteroid-dependent) were included in the study. In the event of drug allergy to allopurinol or azathioprine, existence of certain chronic diseases or consumption of amoxicillin, diuretics, and angiotensin-converting-enzyme (ACE) inhibitors, patients were not included.

In case of hematologic complications, i.e. platelet count < 100,000 and white blood cell count < 3,000, hepatic complication of total bilirubin > 3, elevated liver enzymes up to 2 times than normal or more, prothrombin time > 5 seconds above the normal, psoriasis or recurrence or worsening of symptoms, the patients were excluded and received necessary treatment.

After 24 weeks, the collected data was analyzed using SPSS Ver.17 software program and using chi-square and T-test, and the two groups were compared in terms of complications and remission.

RESULTS

In this study, 64 IBD patients were included in two groups, A and B. Two patients of Group A who were received combination therapy of Azathioprine and Allopurinol were excluded due to drug side effects such as gastrointestinal intolerance and neutropenia, and were provided with the standard therapy. Three patients among those who received the standard therapy of Azathioprine (group B) also were excluded due to gastrointestinal side effects, increased liver enzymes and neutropenia. Patients who did not respond to standard therapy protocols were treated using IBD treatment protocol and received other medications (e.g. Infliximab (Anti-TNF) or cyclosporine).

The patients included 30 males (46.9%) and 34 females (53.1%); the group who received the standard therapy of Azathioprine included 15 males (23.4%) and 17 females (26.5%), where 18 patients were affected by Crohn's disease (28.1%) and 14 patients by ulcerative colitis (21.9%). The mean and standard deviation of age for polytherapy and standard therapy groups were 35.2±5.7 and 38.2±6.6 years, respectively. There was no significant difference between the groups in terms of age. The mean and standard deviation of disease duration among patients was 8.1±2.7 years for polytherapy group and 8.9±3.4 years for standard therapy group that showed no significant difference.

The laboratory results showed the Hb mean of the patients receiving polytherapy to be 13.1g/dl, while this was 12.7 g/dl in patients who received standard therapy, and no significant difference was observed in this regard (Table 4.6). For other blood tests and renal tests, no significant difference was observed between polytherapy and standard therapy (Table 4.6).

After combination therapy, the mean of ESR in patients was 21.8mm/h, while it was further reduced in those patients receiving standard therapy of Azathioprine (18.5mm/h), although this difference was not significant. Concerning hepatic tests, the mean of ALT for polytherapy was 22.5 u/l, which was higher than the rate in standard therapy (27 u/l); moreover, the mean value of AST for polytherapy was lower (27.3u/l), meanwhile it was 32.7 in standard therapy ($p < 0.05$). For CRP, its level in standard therapy was higher than the level in combination therapy; however, no significant difference was found.

Regarding the frequency and types of drug side effects in polytherapy group, neutropenia was the most common complication of IBD patients as it was seen in 2 patients (6.2%), and nausea and loss of appetite affected only one patient (3.1%) in this group. In the standard therapy group, the most common complication type was gastrointestinal complications as nausea, vomiting and gastrointestinal intolerance (as a series of GI symptoms) as they was observed in two patients (6.2%), and neutropenia and elevated liver enzymes also observed in two patients; furthermore, one case of thrombocytopenia (3.1%) was also observed (Table 4.8). Generally speaking, the most common side effects included gastrointestinal complications and neutropenia in both groups, with higher frequency in the standard therapy group than polytherapy group. Frequency of hematologic complications, i.e. neutropenia, thrombocytopenia and increased liver enzymes was higher for standard therapy (Table 4.8). A significant difference in complication rates was observed for two treatment groups ($p = 0.039$).

Severity of the disease was determined using Adult CDAI and SCCAI, and in group A, 13 patients (40.6%) were in mild phase, 11 patients (34.4%) in moderate phase and 8 patients (25%) were in severe phase; meanwhile, for group B, 10 patients (31.2%) were in mild phase, 12 patients (37.5%) in moderate phase and 10 patients (31.2%) in sever phase. Disease severity was not significantly different between the two groups. After completion of standard therapy, four patients (12.4%) were still in the mild phase of the disease and two patients (6.2%) in the moderate phase and were regarded as the patients who did not respond to treatment in this group. Generally speaking, after completion of treatment, 28 patients (87.5%) in patients who received polytherapy and 26 patients (81.2%) who received standard therapy went into remission; so the remission level was not significantly different between the two groups.

Table 1: Details of the studied patients before combination therapy

variable	Mean±SD	p-value
age	36.7±6.3	0/06
Duration of disease	8.5±3.1	0/32
HB (g/dl)	12.9±1.05	0/65
WBC (count/mm3)	44251±1862	0/053
Plt(count/mm3)	2816257±79392	0/95
Cr (mg/dl)	0.91±0.14	0/055
ALT (U/L)	24.8±9.7	0/77
AST (U/L)	30±10.6	0/51
ESR (mm/h)	20.2±9.6	0/14

Table 2: Comparison of (post-treatment) laboratory data for both groups

Test	Combunational tratment mean±SD	Standard treatment mean±SD	p-value
HB(g/dl)	13.1±1.05	12.7 ± 1/03	0.13
WBC (count/mm3)	4253 ±868	4596±2497	0.46
Cr(mg/dl)	0.93±0.13	0.9±1.01	0.057
ALT(U/L)	22.5±8.8	27.1 ± 1/05	0.139
AST(U/L)	27.3±9.2	32.7±11/2	0.038
ALP(U/L)	275.1±43.7	282.7± 44/2	0.12
ESR(mm/h)	21.8±8.6	18.5±1/05	0.174

Table 3: Frequency distribution of drug complications for both groups

Complication	Combination N (%)	Standard N (%)	Total N (%)
Complication	28 (87.5)	21(65.6)	49(76.6)
Nausea	1(3.1)	2(6.2)	3(4.7)
Vomiting	0(0)	2(6.2)	2(3.1)
Loss of appetite	1(3.1)	0(0)	1(1.6)
Thrombocytopenia	0(0)	1(3.1)	1(1.6)
Gastrointestinal intolerance	0(0)	2(6.2)	2(3.1)
Neutropenia	2(6.2)	2(6.2)	4(6.2)
Abnormal liver enzyme	0(0)	2(6.2)	2(3.1)
Total	**32(100)**	**32(100)**	**32(100)**

DISCUSSION

In this study, 64 patients with diagnosed Crohn's disease or ulcerative colitis were treated by standard therapy, i.e. normal dose of Azathioprine, and combination therapy, i.e. reduced dose of Azathioprine and allopurinol. Drug side effects including gastrointestinal and hepatic complications were reduced and liver enzymes were decreased dramatically in polytherapy comparing the standard therapy. Hematologic complications including neutropenia were the main side effects of combination therapy, but these were not of higher intensity than those of standard therapy. The remission rate in patients who received combination therapy was not better than those who treated by standard therapy.

Drug complications for azathioprine in IBD patients can be observed in 15-40% of cases, with leukopenia, and particularly neutropenia as the most common one, as well as gastrointestinal complications of nausea and vomiting.(7) Hepatic complications are other significant side effects of azathioprine which have been observed in 10% of IDB patients and often disrupts continuation of therapy (7); in doses well above normal which are used for greater effectiveness and resistance to disease, hepatotoxicity risk increases up to 24%.(8) Such side effects caused Azathioprine to be effective only as much as 55% in cases of deficiency of metabolizing enzyme.(15-20)

In this study, the patients who were given the standard dose of Azathioprine in 6.2% cases were faced with hepatotoxicity that is lower than other studies. Such reduction in hepatotoxicity in our study could be due to the metabolic differences of Azathioprine in liver in terms of genetic metabolism in TPMT activity enzyme that ultimately led to producing less 6-MMP, i.e. hepatotoxicity agent. In those patients who received standard therapy, gastrointestinal complications were the most frequent complications and occurred in 18.6% of the cases; then hematologic complications such as neutropenia (6.2%) and thrombocytopenia (1.6%) were observed and these results are consistent with prior studies. Therefore, given the immunosupression caused by these medications in patients, the follow-up of the hematologic complications is necessary for them.

A study in Australia found that combination therapy of Azathioprine and allopurinol in IBD patients not only reduces hepatic complications in these patients, but also mitigates other side effects of Azathioprine. (12) In another study, long-term use of combination therapy with Azathioprine and allopurinol decreased hepatotoxicity risk in patients who had liver problems, and relapse rate was lower.(15) In this study, the amount of the combination of the drugs were adjusted regarding the metabolizing enzyme for Azathioprine, i.e. red cell TPMT activity, and Azathioprine was given in the high doses for patients when needed. In another study which used polytherapy for the patients who had hepatic complications due to standard therapy of Azathioprine, 8 out of 11 patients showed remission and 3 patients were affected by leucopenia, which in turn disappeared by reducing the dose.(25)

In our study, gastrointestinal complications and neutropenia were the most common side effects in both groups, with higher frequency in standard therapy group than polytherapy one. The most common side effects in combination therapy were the hematologic ones (neutropenia), while in the standard therapy these were gastrointestinal complications. Furthermore, laboratory results indicated that the mean of ALT for polytherapy was 22.5 u/l, which was higher than the rate in standard therapy (27 u/l); the mean values of AST for polytherapy was lower (27.3u/l), meanwhile it was 32.7 in standard therapy. Therefore, ALT values were reduced considerably and AST values significantly in patients who received combination therapy of allopurinol and Azathioprine and who had no hepatic disease or drug complications. In addition to improvement in liver enzymes, hepatic, hematologic and gastrointestinal complications were significantly lower in the patients receiving combination therapy of allopurinol and Azathioprine, comparing those who only received Azathioprine from standard therapy ($p < 0.05$). This is due to effective production of desired level of Azathioprine's active metabolite (6-TGN) given the inhibition of xanthine oxidase by allopurinol and changes in metabolism pathway for producing 6-TGN and subsequent inhibition of hepatotoxic metabolite (6-MMP); where 6-TGN causes the bone marrow to be suppressed. Change of metabolism pathway for production of 6-TGN is the reason for more common hematologic complications (neutropenia) found in combination therapy with allopurinol and Azathioprine.

Thus, given the immunosuppression due to Azathioprine and despite reduced complications in patients receiving the combination therapy, regular monitoring of medication side effects including hematologic complications (neutropenia) which can cause a serious infection or severe hemorrhage is necessary.

In a previous study, 4 patients with IBD who did not respond to any treatment, were treated with a combination therapy of allopurinol and Azathioprine, and the metabolizing enzyme for azathioprine, i.e. red cell TPMT activity was

measured so that before starting polytherapy with azathioprine and high dose of allopurinol, complications can be controlled.(21) In another study in London, long term use of allopurinol along with Azathioprine in patients who poorly responded to Azathioprine and had hepatic complications, such complications mitigated and patients went into remission.(8) Sparrow et al demonstrated that the score of active patients decreased due to combination therapy, especially in patients with Crohn's disease.(25) In our study, such decrease can be observed in combination therapy where remission rate in polytherapy (i.e. 87.5%) was higher than the standard therapy (i.e. 81.2%), but it was not significantly different ($p = 0.49$).

It seems that in other studies, the patients has had a significantly greater improvement, were those who have been treated by polytherapy because of numerous complications and organ dysfunctions such as liver, and poor response to treatment; so better remission was due to reduced complications and effective response to therapy. In our study, however, the combination therapy was conducted for uncomplicated patients with stable symptoms, most of who could recover without combination therapy. In this study, given the previous stable conditions of the patients for taking Azathioprine (lack of complications and organ dysfunction) there was no need to measure serum level for TPMT, and reduced side effects in these patients ($p = 0.39$) compared to the patients taking the standard dose of Azathioprine showed the effectiveness of combination therapy.

The results showed that in stable IBD patients, combination therapy with allopurinol and Azathioprine is effective in reducing the side effects of Azathioprine particularly hepatic and gastrointestinal complications, but further remission is not observed due to combination therapy compared with standard therapy. In patients who receive combination therapy, regular monitoring of hematologic complications (neutropenia) is necessary. Further studies in different communities are needed for results that are more accurate.

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