World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/esps/
wjg@wjgnet.com
doi:10.3748/wjg.v19.i20.2979

World J Gastroenterol 2013 May 28; 19(20): 2979-2984
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

FRONTIER

Expert opinion: Experience with 6-mercaptopurine in the treatment of inflammatory bowel disease

Burton I Korelitz

Burton I Korelitz, Clinical Research in Gastroenterology, Division of Gastroenterology, Department of Medicine, Lenox Hill Hospital, New York, NY 10075, United States
Author contributions: Korelitz BI solely contributed to this paper.
Correspondence to: Burton I Korelitz, MD, Chief Emeritus, Director of Clinical Research in Gastroenterology, Division of Gastroenterology, Department of Medicine, Lenox Hill Hospital, New York, NY 10075, United States. bkorelitz@nshs.edu
Telephone: +1-212-4342063 Fax: +1-212-4342446
Received: December 26, 2012 Revised: April 9, 2013
Accepted: April 17, 2013
Published online: May 28, 2013

Abstract

Arbitrarily, modern day treatment of inflammatory bowel disease begins with the introduction of immunosuppressives for ulcerative colitis. Clinical improvement with sulfasalazine had been meaningful but modest. Treatment with adrenocorticotropic hormone and corticosteroids led to clinical responses never before realized but it took much too long to recognize that they were not capable of maintaining remission, that adverse reactions were subtle but potentially devastating and that some other agent would be necessary to capitalize on their transient advantage. This of course was true in the treatment of Crohn's disease as well. Not much was ever made of the role of sulfasalazine for Crohn's disease, but with the severing of the diazobond and the elimination of the sulphur component, the 5-aminosalacylic acid (5-ASA) products clearly led to clinical improvement, especially in cases of Crohn's colitis and those with ileitis where the 5-ASA product was released in the terminal ileum and more proximal in the small bowel as well as in ulcerative colitis. The induction of remission was first demonstrated by 6-mercaptopurine (6-MP) with case reports and uncontrolled trials in patients with ulcerative colitis, but its placebo controlled trial for Crohn's disease firmly established its role in inducing remission. No subsequent trial has confirmed its similar role for ulcerative colitis, but nevertheless clinicians know well that 6-MP works at least as well and probably more effectively for ulcerative colitis than for Crohn's disease. What changes have taken place utilizing 6-MP in the management of inflammatory bowel disease since its introduction in the 1960's and 1970's and its trial for Crohn's disease published in the *New England Journal of Medicine* in 1980?

Key words: 6-Mercaptopurine; Crohn's disease; Ulcerative colitis

Core tip: Calculation of dose, utilization of serological tests, maintenance therapy, desensitization to 6-mercaptopurine (6-MP), toxicity to 6-MP, post-operative prevention, extraintestinal manifestations, perirectal fistulas and other fistulas, pregnancy, role of biologicals in management, brand name *vs* generic 6-MP and azathioprine.

Korelitz BI. Expert opinion: Experience with 6-mercaptopurine in the treatment of inflammatory bowel disease. *World J Gastroenterol* 2013; 19(20): 2979-2984 Available from: URL: http://www.wjgnet.com/1007-9327/full/v19/i20/2979.htm DOI: http://dx.doi.org/10.3748/wjg.v19.i20.2979

CALCULATION OF DOSE

In the original controlled study, the dose of 6-mercaptopurine (6-MP) chosen by Present and myself was based on weight at 1 ½ mg per kilogram. This precedent has subsequently been used in almost all other studies around the world when the immunosuppressive of choice was 6-MP rather than Azathioprine. Despite this and due to my own experience based on the wide range of leukopenia as influenced by dose, I changed my preference from dose by weight and started all patients at 50 mg/d. Since

in both cases my policy was to have blood drawn for a complete blood count (CBC), at one, two and three weeks, a rapid fall in the white blood cell count (WBC) would be recognized early and the drug could be reduced or stopped accordingly. On the contrary should there be no fall in the WBC and there also be no clinical improvement in the inflammatory bowel disease (IBD), ulcerative colitis (UC) and Crohn's disease (CD), I would have the opportunity to increase the dose within the 3 wk period[1-5].

If the patient were still on steroids when the 6-MP was started and there was clinical improvement, I have reduced the steroid dose early to minimize its duration, also keeping in mind that the WBC was elevated because of the steroids and their reduction might accelerate the leukopenia. Reintroduction of 6-MP after stabilization on recovery from the leukopenia would be by 25-50 mg less than before. Some patients tolerate only as little as ½ tablet or 25 mg/wk while others require an increase up to 300 mg/d, the low and the high doses being equally effective for the individual case.

This exercise has been modified by the availability of biologicals since the severity of disease and lack of response to early doses of 6-MP will serve to accelerate the decision to add the biological to the therapy[6-8].

UTILIZATION OF SEROLOGICAL TESTS TO INFLUENCE THE DOSE OF 6-MP

Since these tests were not available in the 1960's and 1970's, we were permitted a prolonged period of experience without them and then later learned that I never had to utilize them. By the time I would decide to start 6-MP the first CBC was drawn and interpreted before there was even time to receive a report on thiopurine methyltransferase, TGN or TPPT. Furthermore, a favorable clinical response was documented as early as possible since the blood counts were entered on a monitor sheet followed by directions by me when the patient called as told to do so. If the patient did not call on time, it was the practice of my office to call them should a change in dose be warranted. With increased experience, I would also get liver function tests including a GGTP early on and then periodically to recognize mild abnormalities consistent with an acceptable "transaminitis" versus a progressive abnormality of true liver damage. One monitor sheet included a column for WBC, Hb, Hct, and platelets and another for bilirubin, serum glutamic oxaloacetic transaminase, serum glutamic pyruvate transaminase, alkaline phosphatase, GGTP and Amylase[9-12].

MAINTENANCE THERAPY WITH 6-MP FOLLOWING SUCCESSFUL INDUCTION

As an outcome of the original controlled trial, we learned that the mean time to induction of remission was three months. Even then, however, it was clear that some patients responded faster, even as little as three weeks, and others might take up to a year and still be successful. The differences were modified by recognizing the success of a small dose of 6-MP leading to that dose becoming the maintenance dose, and the failure of the initial dose leading to a relatively rapid increase until the maintenance dose was found without requiring a whole year or even six months. Again, should the patient be on steroids when the 6-MP was started, tapering and elimination of the steroids was part of the goal, always mindful that any reduction of steroids increased the risk for leukopenia.

The role of immunosuppressives in top down *vs* bottom up straddles these two approaches to therapy. This is because 6-MP has maintenance as well as induction value as opposed to steroids which work quickly but have no maintenance value and infliximab which also works quickly and does have maintenance value. The 6-MP, however, is slower in its action than both of the above in most cases. Therefore 6-MP will be more appropriate as a Step Up drug unless used from the outset as a Top Down in conjunction with infliximab as done in the Sonic Trial.

At the other end of the spectrum, after prolonged remission on 6-MP [± a 5-aminosalacylic acid (5-ASA) product but no biological as yet], some patients wanted to stop the drug, others refused to stop it remembering the severity of their disease before its introduction, and others accepted my recommendation based on clinical judgment. The time between CBC's and LFT's was already extended due to persistence of normality, so that some patients reached an interval of three months. I have chosen not to extend the interval beyond this period. If I then chose to reduce the dose on clinical grounds (usually because of patients' persistent fear of toxicity), I would deduct 25-50 mg. from the daily dose and keep that level for a trial of one year before considering a further reduction. This means that some patients would be maintained on one tablet/day (reduced from 2/d or 1 ½/d) and others on ½ every other day reduced from ½/d or ½ on two out of three days.

At this time I will add that in a few cases I eventually stopped the 6-MP entirely. I have not yet analyzed the results but have witnessed many examples of recurrence on both stopping and reducing the dose of the 6-MP[13-16].

DESENSITIZATION TO 6-MP IN THE COURSE OF TREATMENT OF IBD

Next to leukopenia, allergic reactions to 6-MP are the next most common adverse effects. Whether nausea and malaise are also on an allergic basis has not been clear. In my own experience, the most common allergic reactions are fever, skin rash, joint pains and back pain. Unfortunately, the 6-MP has often been terminated on this basis and both CD and UC have frequently progressed in severity thereafter, leading to surgical resections which might not have been necessary. Just as we have found earlier that desensitization to sulfasalazine not only is frequently successful, and treatment with that drug resulted in remissions of IBD, particularly UC, desensitization has been fruitful for 6-MP. This has been done by starting

with as little as 1/8 tablet and increasing the dose every few days or switching to Azathioprine at either full dose or the same fractions. In my experience the only allergic reaction to which desensitization has rarely been successful has been pancreatitis. Once desensitization to 6-MP has been accomplished, remission has been maintained on this drug for many years[17,18].

TOXICITY TO 6-MP IN THE COURSE OF TREATMENT OF IBD

Other than leukopenia and allergic reactions to 6-MP, concern about neoplasm has prevailed. After many years of experience, I am convinced that malignant tumors such as breast, lung, liver, pancreas, kidney, prostate and brain are not more common in those treated with 6-MP than in the entire IBD population or the general population. The problem of lymphoma has warranted intense observation and it is statistically significantly increased but still rare. I accept the conclusion that a lymphoma occurs in somewhere between 1:2000 and 1:4000 cases. If it occurs its prognosis is no different than lymphomas in IBD patients not treated with 6-MP or Azathioprine or no IBD. The exception to this rule is the hepato-splenic lymphoma which carries the worst prognosis of the lymphomas and it occurs in children, particularly male children who have the most virulent IBD, so that even in this group of patients it is challenging not to use 6-MP as well as to using it. Most patients with this type of lymphoma have been on combination therapy (6-MP or Azathioprine plus IV infliximab) but the onus is on the immunosuppressive since the lymphoma rarely occurs with infliximab alone. The one neoplasm which theoretically might be increased with immunosuppressive therapy is colon cancer superimposed on ulcerative or Crohn's colitis. My own studies and those of others have shown that this is not the case. If anything, treatment with immunosuppressives has reduced the risk of colon cancer, probably as a result of eliminating inflammation due to successful therapy.

Unfortunately, skin cancers are common in IBD patients treated with immunosuppressives. While basal cells can be successfully resected and don't often lead to terminating 6-MP, this is not so true of squamous cell carcinomas which I see fairly commonly in patients who have received the drug for many years. I have rarely seen a melanoma in patients on 6-MP.

Opportunistic infections are rare. When they occur they correlate best with situations when the disease is not controlled by the immunosuppressive drug and usually when the patient is still being treated with steroids.

Pancreatitis usually occurs within three weeks of onset of treatment with 6-MP. In our original studies, we encountered pancreatitis in 3% of patients. I rarely see it anymore.

Thrombocytopenia is fairly common in patients on 6-MP and if it occurs it is usually in conjunction with leukopenia. Anemia due to 6-MP is rare and if it occurs is most likely accompanied by a pancytopenia and requires stopping the immunosuppressive therapy[19-26].

POST OPERATIVE PREVENTION WITH 6-MP

Trials of available drugs for prevention of recurrent ileitis after ileo-colic resection have been disappointing. My own study of 6-MP for this indication showed statistically significant but not impressive results. Nevertheless, I have had many patients who started 6-MP following surgery who have remained without clinical recurrence for many years. It is my impression that endoscopic recurrence may occur despite taking the 6-MP, but its progress to a point of clinical recurrence is extremely retarded. I have also reassessed the results of my own study and learned that when the 6-MP is started in the immediate peri-operative period, protection against the recurrence is far more effective. This is an area where infliximab is proving to be more effective than immunosuppressives, again best when started immediately postoperatively. More studies in the area of which drug, both, and when are needed to resolve this question[27-29].

THE ROLE OF IMMUNOSUPPRESSIVES FOR EXTRAINTESTINAL MANIFESTATIONS

Before the advent of biologicals, treatment of pyoderma gangrenosum, erythema nodosum, arthritic manifestations and uveitis were often successful with the introduction of 6-MP. If however, the extraintestinal manifestation occurs while the patient is already taking an immunosuppressive, the need to introduce a biological is clear.

PERIRECTAL FISTULAS AND OTHER FISTULAS

Many of my own studies have demonstrated the favorable effect on all fistulas with 6-MP treatment. Perirectal fistulas and abscesses often require incision and drainage in conjunction with 6-MP but are more likely to be recurrent without immunosuppressive therapy at the same time. Infliximab also has been very effective in closing fistulas. Nevertheless, it is fairly common to see persistent drainage from fistulas despite treatment with either drug alone and even with the combination. Fortunately, the severity of the residual fistula is not great and if the primary CD has been brought into remission, the patient tolerates the drainage well[30,31].

PREGNANCY AND IMMUNOSUPPRESSIVES

The issue of 6-MP and AZA before and during pregnancy prevails since the most common years of onset

of Crohn's disease and ulcerative colitis are during the ages of greatest fertility and Crohn's disease occurs more often in females than males. Furthermore, consideration of continuing immunosuppressives during pregnancy is markedly diluted as an issue since pregnancy usually takes emotional priority over treatment of the disease in female IBD patients who want to stop all medications and so often the obstetrician is encouraging them to do so.

The evidence favoring continuing 6-MP/AZA during the pregnancy is based on the following: (1) The largest reported study on pregnancy and adverse outcomes possibly attributed to 6-MP from Mount Sinai has concluded that these drugs are safe; (2) Most adverse reactions to 6-MP/AZA occur early, soon after the drug is started. Therefore, the coincidence of any other toxicity to 6-MP in pregnancy most likely must be attributed to active disease; and (3) If the most virulent factor with toxic complications during pregnancy is active Crohn's disease and if the patient is in a remission just achieved by the drug, it should not be stopped. On the other hand, in a study from Lenox Hill Hospital there was a 23% incidence of spontaneous abortions (*vs* 13% in IBD controls), a 3% incidence of ectopic pregnancies (compared with none in IBD controls) and finally an abnormal amniocentesis in 2 patients (and none in the IBD controls).

Statistically speaking, no one is yet certain of the risk or the safety of immunosuppressives taken before or during pregnancy and therefore no conclusion should yet be drawn. Logically there must be a compromise solution: (1) Given that the most important issue is active Crohn's disease at conception, if the patient has already been started on the immunosuppressive drug it should be continued and the dose even increased if the clinical severity of the disease warrants it; (2) If the IBD is in remission and has been for months or for years, I find no contraindication to stopping the drug at or before the diagnosis of pregnancy since our experience has shown that any exacerbation is not likely to occur immediately or for that matter even for months, by which time the pregnancy may be ended or at least the fetus is protected through the first trimester when theoretically it would be most susceptible to any danger. Should an exacerbation occur earlier in the pregnancy, the choice may be made to reintroduce the drug; (3) The risk of toxicity to the pregnancy when the father is the one who has the IBD and is taking 6-MP/AZA raises a special consideration. If the male has been in remission, it might be prudent to stop the drug for 1 to 3 mo before conception. Since the timing of the pregnancy is so infrequently controlled, this opportunity does not occur often; and (4) Decisions whether to continue 6-MP/AZA in pregnant women and their husbands who are taking the drug for IBD require rigorous clinical judgement. For example, if the woman has been in remission for a long time, it seems reasonable to stop the drug until delivery since recurrence is very unlikely. If recurrence does develop, then the drug can be restarted at that time. If either the pregnant female patient or the husband with IBD have active Crohn's disease or have been in remission only briefly following a severe attack, I recommend continuing the drug. This is an area where rules should not be rigid[32-36].

THE ROLE OF 6-MP SINCE THE AVAILABILITY OF BIOLOGICALS; WHEN TO ADD ONE TO THE OTHER, WHEN TO TERMINATE ONE OR THE OTHER AND WHICH ONE

Some of the most challenging therapeutic decisions have been raised since the publication of articles suggesting that once a patient with Crohn's disease is in clinical remission while being treated with both infliximab and 6-MP/AZA, there is no advantage to continuing the immunosuppressive drug. These studies do not adequately allow for the duration of treatment with the 6-MP, when it was started in reference to infliximab, or the duration and dose of infliximab required to bring the patient into remission. Furthermore, it does not allow for the conclusions of the Study of Immunomodulator Naïve Patients in Crohn's Disease which demonstrated that the therapeutic efficacy of the combination of infliximab and 6-MP/AZA is greater than either drug alone.

The following are the my suggested options for changing therapy for Crohn's disease and ulcerative colitis in regard to either 6-MP or AZA alone, infliximab or other biological alone, and 6-MP/AZA and a biological together.

No response or beginning failure with 6-MP/AZA alone

Increase the dose if WBC or platelets permit; add a biological; add a 5-ASA product (this is a particularly good opportunity to add a once daily dose product for compliance reasons.); surgery, usually the last resort, but influenced by location and specific complication of Crohn's disease.

No response or failure with a biological

Increase the dose, decrease the interval between infusions or injections; add 6-MP or AZA; add a 5-ASA product; change the biological; Measure serum infliximab and antibody levels for guidance; brief rescue therapy with intravenous corticosteroids; Surgery, usually the last resort, but influenced too by location and specific complication of the Crohn's disease.

Failure with combined therapy of immunosuppressive and biological

Increase the dose of the immunosuppressive if WBC or platelet counts permit; decrease the interval between infusions or injections; add a 5-ASA product; brief rescue therapy with intravenous corticosteroids; measure serum infliximab and antibody levels for guidance; stop biological if degree of immunogenicity is high and accompanied by allergic symptoms such as joint pains; stop 6-MP or

AZA if complications suspected of being attributed to these drugs are evident, such as nausea, malaise, fever, and worsening liver or pancreatic function tests; surgery.

Eliminating 6-MP/AZA after remission with combined therapy of immunosuppressives and biologicals

Complications of drug or disease; reduce the dose - especially for persistent leukopenia; patients' fear of late complications; in some cases of pregnancy or anticipated pregnancy; continuation influenced by earlier severity of the disease.

Eliminating biologicals (when used alone) after remission

Fear of complications of the drug; lack of compliance; now substitute 6-MP/AZA; first extend interval for infusion or injection; first reduce the dose; add a 5-ASA product if not already done.

Eliminating the biological or immunosuppressive after remission with both

To be considered preferably only after 1 full year of maintenance therapy and full dose of both after remission achieved; first reduce dose of the immunosuppressives; eventually eliminate the 6-MP/AZA or the biological; the author's preference is to eliminate the 6-MP/AZA and continue the biological; later reduce the dose of the biological as well.

Once remission of the IBD has been maintained for at least a year, there are many considerations. While some patients do not wish to change the therapeutic program because of its success, others are fearful of complications of either or both drugs and are anxious to eliminate or reduce. In some cases the specific indication for starting the program remains tolerable but not eliminated, in which case I encourage the patient to persist. In other cases where the indication for starting one or both drugs is gone and indeed mucosal healing has been accomplished as well (mucosal healing to me requires histological healing), I undertake a dose reduction.

Despite the efforts made in rationalizing the reduction of 6-MP *vs* infliximab, the subsequent management is currently influenced by the subsequent course of the primary disease rather than patient hardships or drug complications. I have witnessed exacerbations of Crohn's disease and ulcerative colitis following elimination or reduction of both drugs. The course of management is then clear by reinstituting the appropriate drug, preferably to the dose of 6-MP at which the longest remission was maintained or the infliximab at the dose and frequency of infusions in which remission was achieved.

One other option for failure or intolerance to 6-MP or lack of response to Remicade is the substitution of a different biological. My experience is biased by the long period of time with the availability of only the Remicade. With the subsequent introduction of Adalimumab and Certolizumab pegol, I had already learned how to use the inflximab well and had no need to change, or if the infliximab had failed so then did the other biological that I then tried. Furthermore, I don't consider self administration of the biological an advantage since the patient has been known to alter the dose or the frequency for whatever the rationale whenever the guidance of the managing gastroenterologist is reduced or otherwise modified. Rapport between patient and doctor remains an influential factor in successful therapy even though the scientific evidence for this might be lacking[37-39].

BRAND NAME *VS* GENERIC 6-MP AND AZATHIOPRINE

While there are no controlled trials to resolve this issue, I have seen more recurrences of IBD after switching to the generic than when continuing with the brand (Purinethol or Imuran). Therefore, I continue using the brand name when feasible.

REFERENCES

1 **Korelitz BI**, Wisch N. Long term therapy of ulcerative colitis with 6-mercaptopurine: a personal series. *Am J Dig Dis* 1972; **17**: 111-118 [PMID: 4401205 DOI: 10.1007/BF02232730]
2 **Present DH**, Korelitz BI, Wisch N, Glass JL, Sachar DB, Pasternack BS. Treatment of Crohn's disease with 6-mercaptopurine. A long-term, randomized, double-blind study. *N Engl J Med* 1980; **302**: 981-987 [PMID: 6102739 DOI: 10.1056/NEJM198005013021801]
3 **Adler DJ**, Korelitz BI. The therapeutic efficacy of 6-mercaptopurine in refractory ulcerative colitis. *Am J Gastroenterol* 1990; **85**: 717-722 [PMID: 1972315]
4 **Korelitz BI**. Antimetabolites in inflammatory bowel disease: long-term experience. *Mt Sinai J Med* 1990; **57**: 297-304 [PMID: 2096276]
5 **Markowitz J**, Grancher K, Kohn N, Lesser M, Daum F. A multicenter trial of 6-mercaptopurine and prednisone in children with newly diagnosed Crohn's disease. *Gastroenterology* 2000; **119**: 895-902 [PMID: 11040176 DOI: 10.1053/gast.2000.18144]
6 **Korelitz BI**, Adler DJ, Mendelsohn RA, Sacknoff AL. Long-term experience with 6-mercaptopurine in the treatment of Crohn's disease. *Am J Gastroenterol* 1993; **88**: 1198-1205 [PMID: 8338087]
7 **Colonna T**, Korelitz BI. The role of leukopenia in the 6-mercaptopurine-induced remission of refractory Crohn's disease. *Am J Gastroenterol* 1994; **89**: 362-366 [PMID: 8122645]
8 **Korelitz BI**. What are the rules when treatment with 6-MP/AZA is started? *Inflamm Bowel Dis* 2008; **14** Suppl 2: S262-S263 [PMID: 18816727]
9 **Dubinsky MC**, Lamothe S, Yang HY, Targan SR, Sinnett D, Théorêt Y, Seidman EG. Pharmacogenomics and metabolite measurement for 6-mercaptopurine therapy in inflammatory bowel disease. *Gastroenterology* 2000; **118**: 705-713 [PMID: 10734022 DOI: 10.1016/S0016-5085(00)70140-5]
10 **Korelitz BI**. A history of immunosuppressive drugs in the treatment of inflammatory bowel disease: origins at The Mount Sinai Hospital. *Mt Sinai J Med* 2000; **67**: 214-226 [PMID: 10828907]
11 **Kornbluth A**, Sachar DB. Ulcerative colitis practice guidelines in adults: American College Of Gastroenterology, Practice Parameters Committee. *Am J Gastroenterol* 2010; **105**: 501-523; quiz 524 [PMID: 20068560 DOI: 10.1038/ajg.2010.52]
12 **Cuffari C**. Optimizing Azathioprine Therapy in IBD Patients. In: Bayless TM, Hanauer SB. Advanced Therapy of Inflammatory Bowel Disease. 3rd ed. Shelton: PMPH-USA, 2010

13 **Korelitz BI**. Immunosuppressive Therapy. In: Bayless TM, editor. Current Management of Inflammatory Bowel Disease. Toronto: M.C. Decker, Inc., 1989: 252-256
14 **Sutherland LR**, Hanauer S, Scholmerich J. Standards for trials of therapy in inflammatory bowel disease. *Inflamm Bowel Dis* 1997; **3**: 277-283 [PMID: 23282874]
15 **D'Haens G**, Baert F, van Assche G, Caenepeel P, Vergauwe P, Tuynman H, De Vos M, van Deventer S, Stitt L, Donner A, Vermeire S, Van de Mierop FJ, Coche JC, van der Woude J, Ochsenkühn T, van Bodegraven AA, Van Hootegem PP, Lambrecht GL, Mana F, Rutgeerts P, Feagan BG, Hommes D. Early combined immunosuppression or conventional management in patients with newly diagnosed Crohn's disease: an open randomised trial. *Lancet* 2008; **371**: 660-667 [PMID: 18295023 DOI: 10.1016/S0140-6736(08)60304-9]
16 **Korelitz BI**. Azathioprine and 6-Mercaptopurine for treatment of Crohn's Disease. In: Bayless TM, Hanauer SB. Advanced Therapy of Inflammatory Bowel Disease. 3rd ed. Shelton: PMPH-USA, 2010
17 **Korelitz BI**, Present DH, Rubin PH, Fochios SE. Desensitization to sulfasalazine after hypersensitivity reactions in patients with inflammatory bowel disease. *J Clin Gastroenterol* 1984; **6**: 27-31 [PMID: 6142067]
18 **Korelitz BI**, Zlatanic J, Goel F, Fuller S. Allergic reactions to 6-mercaptopurine during treatment of inflammatory bowel disease. *J Clin Gastroenterol* 1999; **28**: 341-344 [PMID: 10372932 DOI: 10.1097/00004836-199906000-00011]
19 **Present DH**, Meltzer SJ, Krumholz MP, Wolke A, Korelitz BI. 6-Mercaptopurine in the management of inflammatory bowel disease: short- and long-term toxicity. *Ann Intern Med* 1989; **111**: 641-649 [PMID: 2802419]
20 **Farrell RJ**, Ang Y, Kileen P, O'Briain DS, Kelleher D, Keeling PW, Weir DG. Increased incidence of non-Hodgkin's lymphoma in inflammatory bowel disease patients on immunosuppressive therapy but overall risk is low. *Gut* 2000; **47**: 514-519 [PMID: 10986211 DOI: 10.1136/gut.47.4.514]
21 **Korelitz BI**, Mirsky FJ, Fleisher MR, Warman JI, Wisch N, Gleim GW. Malignant neoplasms subsequent to treatment of inflammatory bowel disease with 6-mercaptopurine. *Am J Gastroenterol* 1999; **94**: 3248-3253 [PMID: 10566724 DOI: 10.1111/j.1572-0241.1999.01530.x]
22 **Warman JI**, Korelitz BI, Fleisher MR, Janardhanam R. Cumulative experience with short- and long-term toxicity to 6-mercaptopurine in the treatment of Crohn's disease and ulcerative colitis. *J Clin Gastroenterol* 2003; **37**: 220-225 [PMID: 12960720 DOI: 10.1097/00004836-200309000-00006]
23 **Kandiel A**, Fraser AG, Korelitz BI, Brensinger C, Lewis JD. Increased risk of lymphoma among inflammatory bowel disease patients treated with azathioprine and 6-mercaptopurine. *Gut* 2005; **54**: 1121-1125 [PMID: 16009685 DOI: 10.1136/gut.2004.049460]
24 **Peyrin-Biroulet L**, Khosrotehrani K, Carrat F, Bouvier AM, Chevaux JB, Simon T, Carbonnel F, Colombel JF, Dupas JL, Godeberge P, Hugot JP, Lémann M, Nahon S, Sabaté JM, Tucat G, Beaugerie L. Increased risk for nonmelanoma skin cancers in patients who receive thiopurines for inflammatory bowel disease. *Gastroenterology* 2011; **141**: 1621-1628.e1-5 [PMID: 21708105 DOI: 10.1053/j.gastro.2011.06.050]
25 **Sultan K**, Korelitz BI, Present D, Katz S, Sunday S, Shapira I. Prognosis of lymphoma in patients following treatment with 6-mercaptopurine/azathioprine for inflammatory bowel disease. *Inflamm Bowel Dis* 2012; **18**: 1855-1858 [PMID: 22241664 DOI: 10.1002/ibd.22866]
26 **Satchi M**, Korelitz BI, Panagopoulos G, Bratcher J, Yu C, Atallah-Vinograd J, Schneider J. Is treatment with 6-mercaptopurine for colitis associated with the development of colorectal cancer? *Inflamm Bowel Dis* 2013; **19**: 785-788 [PMID: 23392347 DOI: 10.1097/MIB.0b013e318289664c]
27 **Hanauer SB**, Korelitz BI, Rutgeerts P, Peppercorn MA, Thisted RA, Cohen RD, Present DH. Postoperative maintenance of Crohn's disease remission with 6-mercaptopurine, mesalamine, or placebo: a 2-year trial. *Gastroenterology* 2004; **127**: 723-729 [PMID: 15362027 DOI: 10.1053/j.gastro.2004.06.002]
28 **Regueiro M**, Schraut W, Baidoo L, Kip KE, Sepulveda AR, Pesci M, Harrison J, Plevy SE. Infliximab prevents Crohn's disease recurrence after ileal resection. *Gastroenterology* 2009; **136**: 441-450.e1; quiz 716 [PMID: 19109962 DOI: 10.1053/j.gastro.2008.10.051]
29 **Peyrin-Biroulet L**, Deltenre P, Ardizzone S, D'Haens G, Hanauer SB, Herfarth H, Lémann M, Colombel JF. Azathioprine and 6-mercaptopurine for the prevention of postoperative recurrence in Crohn's disease: a meta-analysis. *Am J Gastroenterol* 2009; **104**: 2089-2096 [PMID: 19568226 DOI: 10.1038/ajg.2009.301]
30 **Sohn N**, Korelitz BI, Weinstein MA. Anorectal Crohn's disease: definitive surgery for fistulas and recurrent abscesses. *Am J Surg* 1980; **139**: 394-397 [PMID: 7362011 DOI: 10.1016/0002-9610(80)90301-3]
31 **Korelitz BI**, Present DH. Favorable effect of 6-mercaptopurine on fistulae of Crohn's disease. *Dig Dis Sci* 1985; **30**: 58-64 [PMID: 2856904 DOI: 10.1007/BF01318372]
32 **Baiocco PJ**, Korelitz BI. The influence of inflammatory bowel disease and its treatment on pregnancy and fetal outcome. *J Clin Gastroenterol* 1984; **6**: 211-216 [PMID: 6144706]
33 **Rajapakse RO**, Korelitz BI, Zlatanic J, Baiocco PJ, Gleim GW. Outcome of pregnancies when fathers are treated with 6-mercaptopurine for inflammatory bowel disease. *Am J Gastroenterol* 2000; **95**: 684-688 [PMID: 10710057 DOI: 10.1111/j.1572-0241.2000.01846.x]
34 **Zlatanic J**, Korelitz BI, Rajapakse R, Kim PS, Rubin SD, Baiocco PJ, Panagopoulos G. Complications of pregnancy and child development after cessation of treatment with 6-mercaptopurine for inflammatory bowel disease. *J Clin Gastroenterol* 2003; **36**: 303-309 [PMID: 12642735 DOI: 10.1097/00004836-200304000-00005]
35 **Francella A**, Dyan A, Bodian C, Rubin P, Chapman M, Present DH. The safety of 6-mercaptopurine for childbearing patients with inflammatory bowel disease: a retrospective cohort study. *Gastroenterology* 2003; **124**: 9-17 [PMID: 12512024 DOI: 10.1053/gast.2003.50014]
36 **Akbari M**, Shah S, Velayos FS, Mahadevan U, Cheifetz AS. Systematic review and meta-analysis on the effects of thiopurines on birth outcomes from female and male patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2013; **19**: 15-22 [PMID: 22434610]
37 **Lémann M**, Mary JY, Duclos B, Veyrac M, Dupas JL, Delchier JC, Laharie D, Moreau J, Cadiot G, Picon L, Bourreille A, Sobahni I, Colombel JF. Infliximab plus azathioprine for steroid-dependent Crohn's disease patients: a randomized placebo-controlled trial. *Gastroenterology* 2006; **130**: 1054-1061 [PMID: 16618399 DOI: 10.1053/j.gastro.2006.02.014]
38 **Colombel JF**, Sandborn WJ, Reinisch W, Mantzaris GJ, Kornbluth A, Rachmilewitz D, Lichtiger S, D'Haens G, Diamond RH, Broussard DL, Tang KL, van der Woude CJ, Rutgeerts P. Infliximab, azathioprine, or combination therapy for Crohn's disease. *N Engl J Med* 2010; **362**: 1383-1395 [PMID: 20393175 DOI: 10.1056/NEJMoa0904492]
39 **Di Sabatino A**, Liberato L, Marchetti M, Biancheri P, Corazza GR. Optimal use and cost-effectiveness of biologic therapies in inflammatory bowel disease. *Intern Emerg Med* 2011; **6** Suppl 1: 17-27 [PMID: 22009609 DOI: 10.1007/s11739-011-0673-9]

P- Reviewers Capasso R, Fitzpatrick LR, Kaymakoglu S
S- Editor Wen LL **L- Editor** A **E- Editor** Zhang DN