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doi:10.3748/wjg.14.5519

World J Gastroenterol 2008 September 28; 14(36): 5519-5522
World Journal of Gastroenterology ISSN 1007-9327

TOPIC HIGHLIGHT

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Are we giving azathioprine too much time?

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Received: August 18, 2008 Revised: August 25, 2008
Accepted: September 1, 2008
Published online: September 28, 2008

Abstract

Azathioprine is currently the key drug in the maintenance treatment of inflammatory bowel diseases. However, there are still some practical issues to be resolved: one is how long we must maintain the drug. Given that inflammatory bowel diseases are to date chronic, non-curable conditions, treatment should be indefinite and only the loss of efficacy or the appearance of serious side effects may cause withdrawal. As regards to efficacy and their maintenance over time, evidence supports the continuous usefulness of the drug in the long term: in fact its withdrawal very substantially increases the risk of relapse. About side effects, azathioprine is a relatively well tolerated drug and even indefinite use seems safe. The main theoretical risks of prolonged use would be the myelotoxicity, hepatotoxicity, and the development of cancer. In fact, serious bone marrow suppression or serious liver damage are uncommon, and can be minimized with proper use of the drug. Recent metanalysis suggests that the risk of lymphoma is real, but the individual risk is rather low, and decision analysis suggests a favorable benefit/risk ratio in the long term. Therefore, in patients with inflammatory bowel diseases in whom azathioprine is effective and well tolerated, the drug should not be stopped. This recommendation concerns the use of azathioprine as a single maintenance drug, and is not necessarily applicable to patients receiving concomitant biological therapy.

Key words: Azathioprine; Inflammatory bowel diseases; Maintenance treatment

Gomollón F, García López S. Are we giving azathioprine too much time? *World J Gastroenterol* 2008; 14(36): 5519-5522 Available from: URL: http://www.wjgnet.com/1007-9327/14/5519.asp DOI: http://dx.doi.org/10.3748/wjg.14.5519

INTRODUCTION

Azathioprine (AZA) is an effective drug in the treatment of inflammatory bowel disease (IBD), particularly in the maintenance of remission of patients with a complex clinical course, and there is little doubt that once indicated should be maintained for an extended period of time. However, when it takes some time without symptoms or signs of disease activity, both clinicians and patients often arise: should I withdraw the drug? After this question lies another: if I should withdraw it, when it's time? Given the chronic nature of these diseases, only two reasons could actually lead to the withdrawal: a loss of efficacy over time or appearance of adverse events that exceed the benefits of the drug. Our goal is to review the available evidence for answering the main question posed by the title of the article. Note that although we refer in the article usually only to AZA, all the above aspects are also valid for its active metabolite, mercaptopurine.

DOES AZATHIOPRINE MAINTAIN ITS EFFECTIVENESS IN THE LONG-TERM?

The long-term effectiveness of AZA in the maintenance of Crohn's disease (CD) is demonstrated in several clinical trials (5 randomized control trials[1-5]), a meta-analysis[6] and a Cochrane review[7]. In this last review, the rate of remission with and without AZA was 67% and 52% respectively, with an odds ratio of 2.16 (95% CI 1.35-3.47) and an NNT of 7 to prevent a relapse. These figures greatly improve if you use the adequate dose of the drug (using 2.5 mg/kg odds ratio increases to 4.13). This same study reflects its value in saving steroids with an NNT of approximately 3[7]. In addition, observational studies corroborate these findings. Thus, in one of the most important of these studies (many patients included and longer follow up), which include CD and ulcerative colitis patients, the life table analyses show that maintenance with AZA is clearly useful for up to 5 years

in both entities[8]. In another multicenter european study, aimed to evaluate the long-term effectiveness of the immunomodulators in IBD, results are quite similar[9]. It included 818 CD and 358 CU IBD patients treated with thiopurinic immunomodulators. The prolonged treatment with these drugs was associated with a lower relapse rate and steroid use. In the case of ulcerative colitis (UC), the data are somewhat more limited but also demonstrate long-term effectiveness of AZA as a maintenance therapy. Several randomized studies have been published although the number of included patients is usually low. A recent Cochrane meta-analysis examines 6 randomized controlled studies (286 patients) of at least 12 mo of duration, which compare AZA (or mercaptopurine) against placebo or mesalazine for UC[10]. The meta-analysis concludes that AZA is more effective than placebo (4 trials) while it is not possible to analyse properly the comparison with the salicylates, due to the significant heterogeneity of studies included (2 trials). The effect of saving steroids, although not evaluated in this meta-analysis, is evident in other 3 controlled trials. In the first of them, a recent study not included in the previous meta-analysis and may be the best trial of AZA in UC to date, effectiveness of AZA in active steroid dependent UC is demonstrated[11]. In this study 72 patients with steroid dependent active UC, are randomized to receive mesalamine or AZA plus prednisolone. At 6 mo, clinical and endoscopic remission free of steroids was achieved in 53% of patients on AZA compared to 21% on mesalamina (OR 4.78, 95% CI 1.57-14.5). In the second trial, 30 patients with steroid dependent UC were treated with AZA or placebo for 6 mo[12]. While in the placebo group was not possible to reduce the doses of steroids, in the AZA group did it. In the third study, with very similar design, the results were similar but even more marked: in the placebo group steroid dose was decreased to 13 mg/day and up to 2.3 mg/day in the AZA group[13]. The observational data provided similar results in support of AZA for UC maintenance. The best evidence of these studies comes from the 30-years cohort from Oxford[8]. In this study the proportion of patients on strict remission at 5 years were 62%, and the median time to relapse 1.5 years. Another important data is that derived form a recent Spanish study[14]. In this prospective study, AZA therapy results in a clear steroid sparing effect and reduction in the number of hospitalizations and surgery in 394 IBD patients (CD and UC, with similar effectiveness). In addition we must emphasize that both in CD and UC, we have over 40 years of clinical experience which confirms the results of the studies previously mentioned.

Once established the effectiveness of AZA in the long-term maintenance, we will analyze what happens if the drug is withdrawn. Virtually all papers reveal a marked increase in the rate of relapse following the discontinuation of AZA. In the case of Crohn's disease, three randomized controlled trials specifically analyze the impact of withdrawing AZA, in CD patients in remission with this drug over a period of time more or less prolonged[4,15,16]. The three trials clearly show the damage that causes the withdrawal of AZA. First study included 51 patients with CD in remission for more than 6 months on AZA, which are randomized to continue on or discontinue AZA[4]. One year of follow up, the cumulative risk of relapse was 5% against 41% in groups with and without AZA ($P < 0.01$). In the second study, open one-year trial, CD patients treated with AZA in remission for 2 or more years, were randomized to continue or not with the drug[15]. At one year, 11/13 patients on AZA and 7/15 without AZA maintained remission ($P = 0043$), being the differences more pronounced when higher doses of AZA were used. In the third trial results are similar, but even when the patients maintained remission on AZA for longer period of time. In this study, 83 CD patients in remission on AZA at least 3.5 years ($\geq$ 42 mo), were randomized to continue or not the drug. One year and a half later, relapse rate was 8% in patients continuing AZA and 21% in patients that stopped the drug[16]. Observational studies commented previously, show similar data, although some with longer surveillance. This is the case study of Fraser, in which the proportion of patients (both CD and UC) still in remission after 12, 24, 36, 48 and 60 mo was 0.63, 0.44, 0.34, 0.28 and 0.25 respectively[8]. Duration of remission on prior AZA did not affect the relapse rate after stopping the drug. However, some authors initially suggested the withdrawal of AZA if the patient maintains remission for a prolonged period (about 4 years). This idea comes essentially from a study published in 1996[17], which showed that while the effectiveness of AZA is maintained over time, extended therapy more than 4 years could have no additional clinical benefit. Although this study had a surprising impact, it is retrospective and has important limitations (does not take into account factors such as smoking or causes of withdrawal of the drug, number of patients followed over 5 years was very small). Only appear somewhat similar results in another study, also commented previously[9]. These data contrast sharply with those offered by controlled studies and other observational studies, which show clearly beneficial to continue indefinitely AZA in the CD (see previously). In the case of ulcerative colitis, available data may be considered weaker again, although there are one controlled trial and some observational studies. The controlled study showed that withdrawal of AZA was associated with a higher relapse rate than when the drug was maintained[18]. It was a randomized trial although did not use a double blind design. Seventy nine UC patients on AZA for more than 6 mo were randomized to continue or not with the drug. The one year relapse rate was 36% and 59% in group with and without AZA respectively. Observational data clearly suggest that AZA treatment is useful, maintain this efficacy over time and that discontinuation of AZA is followed by higher rate of relapse, even in patients being in prolonged remission with the drug[19,20,8,9].

In short, solid evidence sustains that AZA (or mercaptopurine) is effective long-term maintenance

treatment of IBD and that their withdrawal is followed by a clear increase of relapse rate. No "safe" period of time being in remission on AZA (or mercaptopurine) has been established after which these drugs could be stopped with no risk of relapse.

WHICH IS THE SAFETY OF USING AZATHIOPRINE INDEFINITELY?

The safety profile of AZA is well known and we have very extensive follow up and long term data with this drug. Side effects are relatively common and can lead the withdrawal of treatment between 10% and 20% (for example in the Cochrane review for CD, adverse effects that conditioned the withdrawal of AZA were at 9.3%)[7]. However, most adverse events are seen at the beginning of treatment and once after the first few weeks, tolerance to the drug is generally very good. The main risks of indefinite use of AZA are myelotoxicity, hepatotoxicity and perhaps development of neoplasms. Myelotoxicity has an incidence of 3 cases per patient and year, is serious in only a small proportion (less than 10%), and can be prevented partly with proper analytical monitoring[21]. Serious hepatotoxicity is also rare, and usually less relevant from a clinical point of view[22]. Regarding to a theoretical increase of cancer, lymphomas especially, it is an issue still unresolved after years of use of the drug, but has made questioned long-term use of AZA. The results of individual studies are inconclusive. A recent meta-analysis assesses the results of the 6 cohort studies designed to analyze cancer as a side effect of treatment[23]. In this study, the pooled relative risk in IBD patients treated with AZA versus general population was 4.18 (95% confidence interval 2.07-7.51; 11 cases observed, 2.63 expected). As the studies are all observational, the increased risk of lymphoma could be a result of the medications, the severity of the underlying disease, or a combination of the two previous factors. The only real way to evaluate this risk at this moment is through a decision analysis, which suggests that the benefits clearly outweigh the risk[24]. This decision analysis was planned to evaluate the impact of AZA therapy on survival and quality-adjusted life expectancy, taking into account both benefits of therapy and potential risk of lymphoma. In the base-case analysis, CD treatment of patients with a steroid-induced remission with AZA resulted in an increase in average life expectancy of 0.04 years and 0.05 quality-adjusted years. The incremental gain in life expectancy decreased with increasing patient age and increasing risk of lymphoma. These results show that AZA in CD patients results in increased quality-adjusted life expectancy. This benefit was greatest in young patients who have the lowest baseline risk of lymphoma and who have the greatest life expectancy in the absence of a CD-related death. However, even in the worst scenario, the absolute individual risk is very low. Finally, in the extensive data available from registries as TREAT[25] and other recent safety studies[26,27], AZA is not associated with increased mortality as an independent factor, and there is no increase in mortality.

In short, the safety profile of AZA is well known, both by the wide experience in clinical use as by the great amount of available published data, and we can say that it is a relatively safe drug when used long term. Of course, these data are valid for AZA (or mercaptopurine) given alone. The association with other drugs, particularly biologics, could result in different risks, and long-term follow-up data are relatively few yet.

CONCLUSION AND RECOMMENDATIONS

When AZA alone (not associated with biological agent), adequately indicated, is maintaining remission in a patient with inflammatory bowel disease, we should not withdraw it, even after several years of treatment maintaining remission, except if significant adverse effects appear (grade recommendation: A; level of evidence: I). The withdrawal of AZA is one of the frequent mistakes in the treatment of IBD, as shown by various studies (see previously). As the professor Sacha'r said "no safe number of years has been determined after which these medications can be withdrawn without risk of relapse…", and "azathioprine works when you take it (and you take it enough amount of it), so do not stop AZA (and give it soon)"[28].

As regards to the use of AZA associated with biological agents, the questions are more and it is not possible to establish strong recommendations. The rationale to add AZA to biologics is to minimize antibody formation and thereby to enhance agent efficacy (or at least to prolong it) and reduce infusion reactions. Any case, we do not know yet the real impact of associating AZA to biologics in these items, and even less is known about the potential increase in adverse events, especially long term. The advantages of long term treatment maintaining the two drugs, in terms of efficacy and safety, must be demonstrated, especially when biologics are used as regularly scheduled infusions.

Only time (once again time…) will answer some of the questions raised about the use of AZA in inflammatory bowel disease. Until then, it is necessary to recognize current key role of AZA in this scenario to use it properly in our clinical practice, providing a significant benefit to our patients[29,30].

REFERENCES

1 **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**: 674-678
2 **Summers RW**, Switz DM, Sessions JT Jr, Becktel JM, Best WR, Kern F Jr, Singleton JW. National Cooperative Crohn's Disease Study: results of drug treatment. *Gastroenterology* 1979; **77**: 847-869
3 **Willoughby JM**, Beckett J, Kumar PJ, Dawson AM. Controlled trial of azathioprine in Crohn's disease. *Lancet* 1971; **2**: 944-947
4 **O'Donoghue DP**, Dawson AM, Powell-Tuck J, Bown RL, Lennard-Jones JE. Double-blind withdrawal trial of azathioprine as maintenance treatment for Crohn's disease. *Lancet* 1978; **2**: 955-957
5 **Rosenberg JL**, Levin B, Wall AJ, Kirsner JB. A controlled trial of azathioprine in Crohn's disease. *Am J Dig Dis* 1975;

20: 721-726
6 **Pearson DC**, May GR, Fick GH, Sutherland LR. Azathioprine and 6-mercaptopurine in Crohn disease. A meta-analysis. *Ann Intern Med* 1995; **123**: 132-142
7 **Pearson DC**, May GR, Fick G, Sutherland LR. Azathioprine for maintaining remission of Crohn's disease. *Cochrane Database Syst Rev* 2000; CD000067
8 **Fraser AG**, Orchard TR, Jewell DP. The efficacy of azathioprine for the treatment of inflammatory bowel disease: a 30 year review. *Gut* 2002; **50**: 485-489
9 **Holtmann MH**, Krummenauer F, Claas C, Kremeyer K, Lorenz D, Rainer O, Vogel I, Bocker U, Bohm S, Buning C, Duchmann R, Gerken G, Herfarth H, Lugering N, Kruis W, Reinshagen M, Schmidt J, Stallmach A, Stein J, Sturm A, Galle PR, Hommes DW, D'Haens G, Rutgeerts P, Neurath MF. Long-term effectiveness of azathioprine in IBD beyond 4 years: a European multicenter study in 1176 patients. *Dig Dis Sci* 2006; **51**: 1516-1524
10 **Timmer A**, McDonald JW, Macdonald JK. Azathioprine and 6-mercaptopurine for maintenance of remission in ulcerative colitis. *Cochrane Database Syst Rev* 2007; CD000478
11 **Ardizzone S**, Maconi G, Russo A, Imbesi V, Colombo E, Bianchi Porro G. Randomised controlled trial of azathioprine and 5-aminosalicylic acid for treatment of steroid dependent ulcerative colitis. *Gut* 2006; **55**: 47-53
12 **Rosenberg JL**, Wall AJ, Levin B, Binder HJ, Kirsner JB. A controlled trial of azathioprine in the management of chronic ulcerative colitis. *Gastroenterology* 1975; **69**: 96-99
13 **Kirk AP**, Lennard-Jones JE. Controlled trial of azathioprine in chronic ulcerative colitis. *Br Med J* (Clin Res Ed) 1982; **284**: 1291-1292
14 **Gisbert JP**, Nino P, Cara C, Rodrigo L. Comparative effectiveness of azathioprine in Crohn's disease and ulcerative colitis: prospective, long-term, follow-up study of 394 patients. *Aliment Pharmacol Ther* 2008; **28**: 228-238
15 **Vilien M**, Dahlerup JF, Munck LK, Norregaard P, Gronbaek K, Fallingborg J. Randomized controlled azathioprine withdrawal after more than two years treatment in Crohn's disease: increased relapse rate the following year. *Aliment Pharmacol Ther* 2004; **19**: 1147-1152
16 **Lemann M**, Mary JY, Colombel JF, Duclos B, Soule JC, Lerebours E, Modigliani R, Bouhnik Y. A randomized, double-blind, controlled withdrawal trial in Crohn's disease patients in long-term remission on azathioprine. *Gastroenterology* 2005; **128**: 1812-1818
17 **Bouhnik Y**, Lemann M, Mary JY, Scemama G, Tai R, Matuchansky C, Modigliani R, Rambaud JC. Long-term follow-up of patients with Crohn's disease treated with azathioprine or 6-mercaptopurine. *Lancet* 1996; **347**: 215-219
18 **Hawthorne AB**, Logan RF, Hawkey CJ, Foster PN, Axon AT, Swarbrick ET, Scott BB, Lennard-Jones JE. Randomised controlled trial of azathioprine withdrawal in ulcerative colitis. *BMJ* 1992; **305**: 20-22
19 **Lobel EZ**, Korelitz BI, Xuereb MA, Panagopoulos G. A search for the optimal duration of treatment with 6-mercaptopurine for ulcerative colitis. *Am J Gastroenterol* 2004; **99**: 462-465
20 **George J**, Present DH, Pou R, Bodian C, Rubin PH. The long-term outcome of ulcerative colitis treated with 6-mercaptopurine. *Am J Gastroenterol* 1996; **91**: 1711-1714
21 **Gisbert JP**, Gomollon F. Thiopurine-induced myelotoxicity in patients with inflammatory bowel disease: a review. *Am J Gastroenterol* 2008; **103**: 1783-1800
22 **Gisbert JP**, Luna M, Gonzalez-Lama Y, Pousa ID, Velasco M, Moreno-Otero R, Mate J. Liver injury in inflammatory bowel disease: long-term follow-up study of 786 patients. *Inflamm Bowel Dis* 2007; **13**: 1106-1114
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
24 **Lewis JD**, Schwartz JS, Lichtenstein GR. Azathioprine for maintenance of remission in Crohn's disease: benefits outweigh the risk of lymphoma. *Gastroenterology* 2000; **118**: 1018-1024
25 **Lichtenstein GR**, Feagan BG, Cohen RD, Salzberg BA, Diamond RH, Chen DM, Pritchard ML, Sandborn WJ. Serious infections and mortality in association with therapies for Crohn's disease: TREAT registry. *Clin Gastroenterol Hepatol* 2006; **4**: 621-630
26 **Lewis JD**, Gelfand JM, Troxel AB, Forde KA, Newcomb C, Kim H, Margolis DJ, Strom BL. Immunosuppressant medications and mortality in inflammatory bowel disease. *Am J Gastroenterol* 2008; **103**: 1428-1435; quiz 1436
27 **Toruner M**, Loftus EV Jr, Harmsen WS, Zinsmeister AR, Orenstein R, Sandborn WJ, Colombel JF, Egan LJ. Risk factors for opportunistic infections in patients with inflammatory bowel disease. *Gastroenterology* 2008; **134**: 929-936
28 **Sachar DB**. Ten common errors in the management of inflammatory bowel disease. *Inflamm Bowel Dis* 2003; **9**: 205-209
29 **Gisbert JP**, Gomollon F, Mate J, Pajares JM. [Questions and answers on the role of azathioprine and 6-mercaptopurine in the treatment of inflammatory bowel disease] *Gastroenterol Hepatol* 2002; **25**: 401-415
30 **García-Paredes J**, Gomollón F, Santamaría DMC, Abreu L, Vera M, Fazio VW, Sandborn WJ. Steroid dependency and steroid resistance in inflammatory bowel disease. *Drugs Today* 2001; **37** (Suppl E): 17-18

S- Editor Xiao LL **E- Editor** Yin DH