6-Mercaptopurine/Azathioprine remains an important contributor in managing Crohn's disease

Burton I. Korelitz, Daniel H. Present

Gastroenterology, Lenox Hill Hospital, New York, NY, United States
New York University School of Medicine, United States
ICAHN School of Medicine at Mount Sinai Hospital, New York, NY, United States

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Abstract
Two large studies concluded that AZA started early after diagnosis of Crohn's disease have no late maintenance value. This is contrary to previous studies on 6MP for Crohn's disease and could lead to negating the value of two of the few drugs that have been proven successful. We here outline the many reasons why 6MP remains a valuable drug in the treatment of Crohn's disease.

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How discouraging it is to read that our colleagues from France and Spain have concluded that an early role of Azathioprine for Crohn's disease (CD) does not prolong clinical remission and that it is no more effective than placebo in this setting.† Of course we fear that many gastroenterologists will now entirely eliminate immunosuppressives from what is already a limited number of successful therapeutic weapons against CD rather than only negating their use in early onset as these 2 multicenter studies suggest. As we carefully read these reports, we find many reasons why no generalities about immunosuppressives for CD should be drawn from their conclusions:

1. The concept of initiating the immunosuppressive drug early is not in common usage in the everyday management of CD anyway. First of all, consider the issue of date of onset of CD for the purposes of a protocol which calls for the introduction of AZA within 6 months,† and even more so 8 weeks,2 particularly when the major obstacle to taking this path when the CD activity might be minimal is "serious adverse reactions" to the drug. When, in fact, does CD begin and what should serve as the date of diagnosis? Should the discovery of large anal skin tags of questionable duration prior to the onset of diarrhea or abdominal pain be the date of onset or should it be the result of the diagnostic work up then revealing ileitis or colitis? Should the true onset be when...
a child or teenager who has been seen by a pediatrician or primary care physician because of diarrhea and responds successfully to non-specific drug therapy thereby postponing the real diagnosis of CD for months or even years or later when the diagnosis is confirmed?

2. Even when the diagnosis of CD is made, it has not been the standard of care to initiate immunosuppressive therapy without first trying more conservative therapies such as 5ASA products and a brief or limited trial of corticosteroids. The possibility of drug toxicity, which is emphasized throughout as a major contraindication, is exaggerated. The most common are allergic reactions to 6MP or Azathioprine which can often be eliminated without depriving the patient of full remission and ultimate avoidance of surgery. In the trials of 6MP for CD, launched more than 40 years ago, many patients had poor prognostic signs; in many cases the CD was advanced and the immunosuppressives had less opportunity to work because of some irreversible tissue destruction, but even most of those patients responded well and many never required surgical intervention thereafter and if required was usually done electively. Others improved sufficiently to await the era of biological therapy with success serving as a major indication.

3. Consideration of high risk CD based on (a) age younger to 40 years is far too broad a criterion since so many patients of all ages never require treatment beyond 5ASA products and indeed sometimes the diagnosis of CD is made as an incidental finding, and (b) active perianal lesions sometime persist and are not always eliminated by either immunosuppressives or biologicals but cause the patient a minimum of inconvenience, and (c) corticosteroids used within 3 months of diagnosis should hardly be a contraindication since one trial of steroids is often warranted after or coincident with diagnosis.

The mean time for the response to 6MP in the Present/ Korelitz Trial was 3 months, but many patients improved sooner and a few required up to a year to be able to eliminate steroids and maintain remission. 20% took longer than 3 months to have clinical remission.

4. The possible adverse reactions to immunosuppressives of course must be considered in using them in the treatment of CD but fortunately as the years have passed fewer and fewer have been observed. This is attributable to using caution in the presence of fever or leucopenia, recognizing transaminitis as a controllable entity by reducing or temporarily stopping the immunosuppressive, observing over the past 50 years that the risk of malignancy in general is no greater than for IBD patients not treated with immunosuppressives, and current verification that lymphomas are indeed increased but remain rare. Allergic reactions can often be handled by desensitization if warranted or by switching from 6MP to AZA and vice versa. Pancreatitis was originally reported in 3% but currently we think it is less. We agree that toxicity is the main consideration in avoiding immunosuppressives, and they should not be launched during the early weeks or months of CD anyway unless the symptoms or prognostic features truly warrant it.

5. The main reason for continuing to use the CDAI as an index of CD activity is the devotion and labor of its originators and the experience with wide usage, but as has been progressively expressed in the years since its introduction, its validity has rightfully been questioned and eventually must be replaced by tissue or serological indicators alone or in combination. In many instances the CDAI proves to be significantly elevated in patients with irritable bowel syndrome after careful workup excluding Crohn’s disease. The scores are calculated by a large variety of individuals which further diminish its accuracy.

6. A sensitive issue remains the conduct of multi-center trials. While the great advantage is obviously accumulation of large numbers of patients suitable for following a protocol, the disadvantage is that each center and multiple contributors to each center provide and assess data so that bias cannot be eliminated and the statistician ultimately depends on the information provided without having the personal contact with the patient. This led to the wrong conclusion being drawn in regard to the National Cooperative Crohn’s Disease Study that Azathioprine was ineffective while at the same time the study at Lenox Hill and Mount Sinai hospitals showed the statistically highly significant success of 6-Mercaptopurine. This issue was highlighted in an editorial published by us in Gastroenterology in 1981.

7. The differences between Azathioprine and 6-Mercaptopurine have never been resolved. While we know that AZA is metabolized to 6MP in roughly a 2:1 ratio, this has never been fine-tuned so that variation is not defined. In the trial of 6MP for CD we used a standardized dose of 1-½ mg/kg, and that has been adapted to all trials using 6MP ever since. Nevertheless, we found soon after the trial that the dose had to be adapted according to leucopenia on the one hand and lack of efficacy on the other. This later led to a rapid increase in dose in many cases, without waiting for the results of serological tests, so that the dose of 6MP was never again standardized at 1.5 mg/kg in our own studies. Furthermore, in the Markowitz study, the children with CD achieving remission was significantly better achieved in the 6-Mercaptopurine (rather than the Azathioprine) group than those receiving prednisone alone.

8. Indeed, treatment with 6MP has been shown to increase the rate of fistula closure and decrease the incidence of perirectal surgery as agreed in the study by Cosnes et al. When closing fistulas in any location is harder to treat than other manifestations of CD, the value of immunosuppressives in accomplishing this goal is unquestionable in the support of this form of therapy.

9. The need for change in management from immunosuppressives to other drugs, the requirements for corticosteroids and the need for surgical intervention often lies...
in the eyes of the beholder. These circumstances also include the adverse events with thiopurines and how to handle them. The choice for surgical intervention in perirectal disease and the choice for surgical intervention with bowel resection, the increase in dose of the immunosuppressive, and the large number of centers involved in the Cosnes study (24) and in the Panes study (31), all raise this consideration, and the strength of the data becomes further diluted by the number of participants contributing to the data from each center.

10. On the issue of cost, in this day and age to exclude treatment with immunosuppressives would serve to increase the expense by at least 10 times.

11. Another issue infrequently mentioned in discussing the efficacy of immunosuppressives is variation in the quality of the drug. Our knowledge of the manufacturing process is limited, but in all production we know that quality varies. We have been taught through various routes that the brand name is more effective than the generic product. Furthermore, the drug Imuran was never fully supported for its use in the treatment of Crohn’s disease and ulcerative colitis since it was already approved by the FDA in the United States for treatment of rheumatoid arthritis and therefore available by prescription. Subsequently the generic Azathioprine became available and was used interchangeably with the original product. In our early studies of 6MP for Crohn’s disease and ulcerative colitis only the brand name was utilized. Since the generic 6MP was less expensive, both patients and insurance companies have campaigned to substitute the generic for the brand name. Many patients thereafter notified us that since the switch to the generic, after a few weeks to a few months their symptoms are recurring, and upon return to the brand name they again went into remission. Currently, the brand name has been eliminated from the market so that only the generic 6MP is available. We do not know the efficacy of the azathioprine used for these studies from France and Spain.2

12. In the Editorial accompanying the 2 studies from France and Spain entitled: “Is there still a role for Thiopurines in Crohn’s disease?”, Rogler and Sandborn16 seem to accept the conclusions of Cosnes et al. and Panes et al., by stating that “Top-down therapy with azathioprine therapy is not more effective than placebo or conventional therapy in adults with newly diagnosed Crohn’s disease”. They further state that the two remaining indications for primary therapy with thiopurines are (1) maintenance of steroid-induced remission (presumably in Crohn’s disease) starting within a few months or even weeks, and steroid sparing in patients not newly diagnosed, and (2) prevention of post-operative recurrence. In the latter, the medication for this statistically significant result was even compromised by limiting the dose of 6MP to a steady 50 mg/day to accommodate a standardized protocol without the option of increasing the dose at the first sign of endoscopic recurrence, which if available I believe the outcome would have been still better.17 At the same time the authors acknowledge that azathioprine combined with infliximab work better together than either alone17 as in the study by Colombel, Sandborn, et al.19 Furthermore, there is now evidence that 6MP resulting in reduction of inflammation also reduces the risk of colon cancer in ulcerative colitis and Crohn’s disease of the colon.19,20 The rare lymphoma complicating 6MP/AZA therapy has no worse prognosis than that occurring independently in IBD or in the general population; in due time we feel it will be shown that the lymphoma occurring after 6MP/AZA will also be eliminated.

13. The recent publication by Camus, et al.21 from the same group in France which includes Cosnes concludes that patients with CD responded to AZA with less years of active disease and are less likely to require surgery than patients not receiving immunosuppressives.

Conclusions

For all of the reasons we expressed above, we maintain that there are still many roles for the use of 6MP and Azathioprine in the treatment of Crohn’s disease and probably ulcerative colitis as well, and their “failure of the use of Azathioprine in early onset Crohn’s disease to maintain a later remission” as presented by Cosnes, et al. and Panes, et al. should not serve to diminish these roles in treatment. “Those who fail to learn from history are doomed to repeat it.”

Conflicts of interest

The authors declare no financial or competing interests.

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