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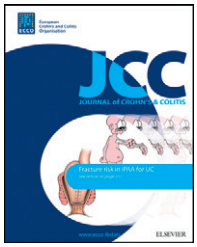

VIEWPOINT

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

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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.

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.[1,2] 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,[1] 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

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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.[3] 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 to reduce the indications for surgery.[4] It should be noted that the conclusions in the Panes study "that the lack of success for Azathioprine when given early was not more successful than placebo to achieve sustained remission" but was "more effective in preventing moderate to severe relapse."[2] We don't believe either that the results of the Markowitz Trial in the pediatric population led to the conclusion that 6MP should always be started so early but rather that it was beneficial to start it whenever indicated.[5]
3. Consideration of high risk CD based on (a) age younger than 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,[6] 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.[4] 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,[7] and current verification that lymphomas are indeed increased but remain rare.[8] Allergic reactions can often be handled by desensitization if warranted or by switching from 6MP to AZA and vice versa.[9] Pancreatitis was originally reported in 3% but currently we think it is less.[10] 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[11] 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 conduction 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[12] while at the same time the study at Lenox Hill and Mount Sinai hospitals showed the statistically highly significant success of 6-Mercaptopurine.[4] This issue was highlighted in an editorial published by us in Gastroenterology in 1981.[13]
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,[4] 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,[5] 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[14] and decrease the incidence of perirectal surgery[15] as agreed in the study by Cosnes et al.[1] 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

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