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Is There a Role for Thiopurines in IBD?

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Abstract: Immunosuppressive therapy (IM) is inexpensive and nearly one-third of patients with inflammatory bowel disease (IBD) experience a benefit from treatment. IM may be ideal for IBD patients at low risk for a disabling disease course or colectomy and/or those patients with inadequate access to biologic therapy. A majority of IBD patients benefit from early biologic therapy with improved short and likely long-term outcomes. Improved methods are needed to identify patients at the greatest risk for a severe disease course and that are likely to respond to the various forms of small molecule and biologic treatments. Health systems need to identify innovative methods to contain costs of biologic therapy.

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MAIN

Over the last 50 years, the efficacy of thiopurines to maintain medically induced remission in Crohn's disease (CD) and ulcerative colitis (UC) as well as to prevent postoperative recurrence in CD has been well established [1–4]. Outcome data that document drug effectiveness over longer periods of time in clinical trials are often limited to only 12–24 months. Therefore, other forms of data are often necessary to understand efficacy over the longer term. Medication persistence refers to the act of conforming to a recommendation of continuing treatment for the prescribed length of time [5]. Since it is unlikely that a patient adheres to an ineffective therapeutic regimen, particularly when other effective therapy is present, persistence can be used as a representative marker for long-term efficacy and tolerability.

In this month's issue of the *American Journal of Gastroenterology*, Targownik and colleagues present the results of a large population-based retrospective cohort study, evaluating the effectiveness of immunosuppressive monotherapy (IM) in patients with inflammatory bowel diseases (IBD) from Manitoba Health [6]. They demonstrate that ~30% of patients treated with IM will remain on therapy at 5 years; predictors of persistence with IM included older age at start of therapy (≥40 years) and no steroid use or hospitalizations in the year prior to initiation of treatment. Of all patients discontinuing thiopurines, nearly 30% discontinued therapy in the first 4 months following initiation or were started on combination therapy with anti-TNF. Most of the other discontinuations occurred over a period of 3 years after starting therapy. The authors conclude that IM is a reasonable, cost-effective strategy for patients with IBD, particularly those without risk factors for a disabling disease course or at increased risk of colectomy.

There are a number of weaknesses with the study which are openly addressed by the authors. The authors were not able to assess patient's symptoms, quality of life, or rates of mucosal healing. However, they were able to evaluate a number of important end points including hospitalizations, surgery, ongoing steroid use, and progression to anti-TNF use. One cannot argue that the latter end points are important. However, it is possible that patients treated with IM had ongoing symptoms due to inadequate treatment that negatively impacted their quality of life and could have had the potential of ongoing structural damage. Due to the limitations of the study described above as well as safety concerns with use of thiopurines, it is fair to ask the question, "Is there still value in prescribing thiopurine monotherapy?" The purpose of this editorial to provide opposing views and ultimately come to a consensus on prescribing immunosuppressive monotherapy. HH will provide the "Pro" argument and RKC will provide the "Con" argument, below.

PRO: THIOPURINE (AZATHIOPRINE, MERCAPTOPURINE) MONOTHERAPY IS AN EFFECTIVE THERAPY IN A SUBGROUP OF PATIENTS WITH IBD

The first question is about prevention of structural damage: Are thiopurines outdated and inferior? Recent studies in the field of rheumatology suggest that the timing of therapy is the most important factor to prevent clinically significant structural damage and not the initial intensity of therapy [7]. Given these findings in rheumatology, early azathioprine therapy in IBD in the setting of a step-up approach may be still justified. The Early Immunosuppressants in Crohn's Disease (RAPID) trial compared early azathioprine treatment to classical step-up therapy in patients with risk factors for the development of disabling disease, and the Azathioprine for Treatment or Early Crohn's disease in adults (AZTEC) trial compared azathioprine with a placebo

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at inducing sustained steroid-free remission in early CD [8, 9]. Both studies showed no effect of early azathioprine therapy in CD disease compared to placebo, which seems to argue against the early use of thiopurines. However, the interpretation of the results is not as straightforward as it seems. There are some caveats, including discrepancies in disease severity between groups and outcome definitions [10]. Interestingly in the RAPID trial, early azathioprine was associated with a significant reduction in new perianal fistula development and a post hoc analysis of the AZTEC study showed significantly lower rate of moderate to severe CD relapse with early azathioprine therapy (12% azathioprine vs. 30% placebo). More recent reports from large cohorts have shown that long-term azathioprine monotherapy prevents structural damage in patients with CD and colectomy in patients with UC [11, 12]. Given the results from the Manitoba cohort, there is clearly a group of IBD patients, who benefit from thiopurine monotherapy over the long term without hospitalization or resective surgery [6]. A post hoc analysis of the Study of Biologic and Immunomodulator Naive Patients in Crohn's Disease (SONIC) trial revealed that patients with an increase in mean corpuscular volume (MCV) of more than seven femtoliters were significantly more likely to be in steroid-free clinical remission at week 26 compared to patients with a lesser increase of MCV (64% of patients with Δ MCV >7 as compared with 3% of patients with a Δ MCV <7) [13]. An increase of MCV has been associated with 6-thioguanine nucleotides concentrations (6-TGN), which were not measured in SONIC. Thus, if the 6-TGN levels are optimized, this drug class appears to have the ability to modify the disease course. Additionally, thiopurines are significantly less expensive and from the patient's perspective, a more feasible therapy (since oral) in comparison with biologics [14].

It is widely perceived that thiopurines are inferior to anti-TNF therapy at inducing mucosal healing, which is a surrogate marker for the risk for later hospitalizations or resective surgery [15]. An older study by D'Haens et al. reported mucosal healing rates of 50–70% in patients in clinical remission on azathioprine for more than 24 months [16]. In the SONIC trial, the mucosal healing rate in patients in clinical remission was not significantly different between the azathioprine and anti-TNF monotherapy arms (36% vs. 43%) [17].

The use of thiopurines in a so defined "rapid step-up approach" is reasonable. Prescribers monitor drug effectiveness (achieving of clinical remission) with repeated confirmations that the patient tolerates the drug at the optimal dose, which may be additionally confirmed with drug levels [18]. If the patient has not improved within 12 weeks, a step-up to a biologic is indicated. Thus, in the absence of data showing that a delay of a therapy with biologics for 2–4 months (in the setting of initial failure of thiopurine monotherapy to maintain steroid-induced remission) results in irreversible structural damage or higher risk of colectomy, the concept of a rapid step-up approach remains valid.

The second question concerns how to put the results of persistence of thiopurine monotherapy in the Manitoba cohort reported by Targownik et al. in the context of persistence of monotherapy with an anti-TNF biologic. It is well documented that 20–30% of patients starting an anti-TNF are primary non-responders, meaning that the therapy needs to be modified in the first 2–4 months [19]. Similarly about 30–40% of patients stop thiopurine therapy in the first 4 months of treatment due to intolerance or ineffectiveness, a number, which was also recorded in the Manitoba population [6]. The annual risk of loss of response to anti-TNF has been estimated to be 13% per patient-year for infliximab and 20% per patient-year for adalimumab [20, 21]. Thus, a persistence rate of 30% for azathioprine over 5 years appears reasonable especially since the persistence of anti-TNF therapy at the original dosing in the same population was recently reported to be around 40% after 5 years [22]. However, it will be important to compare the same definitions of persistence in the same time frames between thiopurine and anti-TNF monotherapy in the same population. Similarly, regarding the requirement of steroids after start of thiopurine monotherapy, we have no information about the need for steroid prescriptions after start of anti-TNF therapy in the Manitoba cohort. In UC, controlled trials have shown that only 12–26% of steroid-dependent patients can completely stop steroids after 1 year of therapy with infliximab or adalimumab therapy [23, 24].

The study by Targownik et al. did not report side effects of immunosuppressive therapy. However, we currently perceive thiopurines to be inferior in regard to safety aspects compared to anti-TNF monotherapy. There is no doubt that thiopurines have significant side effects including the risk of lymphoma and non-melanoma skin cancer [25]. However, the absolute risk of lymphoma in the setting of thiopurine monotherapy appears to be small. Interestingly, the relative risk of lymphoma for thiopurine and anti-TNF therapy is actually quite similar (adjusted hazard ratio 2.41 vs. 2.60 for thiopurine vs. anti-TNF monotherapy, respectively) [26]. In contrast to thiopurine monotherapy, anti-TNF monotherapy is associated with an increased risk of serious mycobacterial and bacterial infections [27]. Thus, neither thiopurine or anti-TNF therapy is 100% safe and the risk benefit aspect should be discussed with each patient in the setting of shared decision-making [28].

CON: AZATHIOPRINE MONOTHERAPY SHOULD NOT BE USED IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE

Despite the positive interpretation of the findings by the authors, the results do not necessarily support a role of IM in patients with IBD. First, 25% and 40% of patients with CD and UC, respectively, required a prescription for steroids within 1 year after initiating IM, with 20% meeting criteria for steroid dependence. Second, although 20–25% of patients persist on immunosuppressive monotherapy at 5 years, only 10–20% persist on therapy after 10 years. Furthermore, if you look at age at initiation of the therapy, $<10\%$ of patients <40 years of age persist with treatment at 10 years. How can we recommend a therapy to our patients for which 90% of them will be off therapy in 10 years? A counter argument is that those who do not respond or lose response to treatment can simply escalate to biologic therapy. However, we know from subgroup analyses of pivotal anti-TNF trials that delays in starting therapy are associated with lower-response rates [29, 30]. Thus, we may be sacrificing anti-TNF success by starting IM and delaying initiation of anti-TNF treatment.

Another argument against IM are the results of several recent randomized controlled trials of early thiopurine use. An open-label trial from France did not show an improvement in trimesters free of steroids and in the proportion of patients free of intestinal surgery and anti-TNF use in those given early azathioprine compared to conventional management [9]. Similarly, a randomized controlled trial in newly diagnosed patients with CD demonstrated no benefit of azathioprine compared to placebo in steroid-free remission or relapse rates. Furthermore, 21% of patients discontinued azathioprine due to adverse events [8]. In patients with newly diagnosed CD naive to treatment, infliximab monotherapy and combination therapy with infliximab plus azathioprine resulted in significantly higher rates of steroid-free remission and mucosal healing rates at 6 months compared to azathioprine monotherapy [31]. These differences were even more striking in patients with confirmed inflammation at baseline and a disease duration of <18 months [32]. Similar results were noted in patients with UC, although rates of steroid-free remission were not significantly different between azathioprine and infliximab monotherapy groups. However, mucosal healing rates were higher in both the infliximab monotherapy and combination therapy groups compared to azathioprine monontherapy [33]. Consistent with these results, the persistence of infliximab or adalimumab for 5 years is around 40 and 35% in the Manitoba population, respectively, compared to 25% for thiopurines (including the patients with early discontinuation) [6, 22]. Use of anti-TNF optimization techniques such as proactive drug monitoring is associated with a fourfold increase in persistence rates compared to IM [34].

CONCLUSION: COMING TO CONSENSUS

As a clinician, how should you interpret these results and counsel your patient? In the era of shared decision-making, it is critical that the provider highlight the comparative effectiveness of immunosuppressive compared to anti-TNF monotherapy and combination therapy. This conversation should include a frank conversation of the fairly high rate of early adverse events associated with treatment with thiopurines as well as the comparative effectiveness of the respective therapies [35, 36]. However, this drug class is still recommended for maintenance of steroid-free remission in CD and UC in the most recent guidelines of the American College of Gastroenterology, American Gastroenterological Association (AGA), and the European Crohn's and Colitis Organisation [37–40]. It is not clear if providers can extrapolate the results of the comparative studies discussed above with use of other approved biologics, although it seems clear that getting patients started on vedolizumab and ustekinumab is better tolerated but also significantly more costly than thiopurines. Use of IM can be emphasized in patients at low risk for a disabling disease course and colectomy, consistent with the AGA Care Pathways for CD and UC, respectively [40, 41]. The authors make valid arguments regarding the cost of immunosuppressive compared to anti-TNF monotherapy. This is clearly important; however, when evaluating a patient about to escalate therapy to an immune suppressant, biologic treatment, or both, it is imperative that the provider put the best interests of the patients before those of the community at large. Processes are being initiated to decrease the costs of biologics, including but not limited to the introduction of biosimilars into the market and the adoption of home infusions for patients treated with infliximab and vedolizumab.

In summary, IM is relatively inexpensive and nearly one-third of patients benefit. The role of IM may be ideal for patients at low risk for a disabling disease course or colectomy, which may be the patients with the disease characteristics identified in the Manitoba cohort, and/or those with inadequate access to biologic therapy. A majority of patients benefit from early biologic therapy with improved short and likely long-term outcomes [15, 32]. Improved methods are needed to identify patients at the greatest risk for a severe disease course and that are likely to respond to the various forms of small molecule (thiopurines, methotrexate, and JAK-kinase inhibitors) and biologic treatments. Health systems need to identify innovative methods to contain costs of biologic therapy.

CONFLICT OF INTEREST

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