American Gastroenterological Association Institute Guideline on the Use of Thiopurines, Methotrexate and Anti-TNF-α Biologic Agents for the Induction and Maintenance of Remission in Inflammatory Crohn’s Disease

Jonathan P. Terdiman,¹ Claudia Gruss,² Joel J. Heidelbaugh,³ Shahnaz Sultan,⁴ Yngve T. Falck-Ytter,⁵ and the AGA Institute Clinical Practice and Quality Management Committee.

¹Division of Gastroenterology, University of California, San Francisco School of Medicine, San Francisco, California; ²ProHealth Physicians, Farmington, Connecticut; ³Departments of Family Medicine and Urology, University of Michigan Medical School, Ann Arbor, Michigan; ⁴Department of Medicine, University of Florida College of Medicine, Gainesville, Florida; ⁵Division of Gastroenterology, Case Medical Center, Case Western Reserve University, Cleveland, Ohio

Conflict of interest disclosure: All members were required to complete disclosure statement. These statements are maintained at the American Gastroenterological Association Institute (AGA) headquarters in Bethesda, Maryland and pertinent disclosure are published with the report. Dr. Gruss: Officer of Connecticut State Medical Society, CEPAC, PCPI

This document presents the official recommendations of the American Gastroenterological Association Institute (AGA) on the use of thiopurines, methotrexate and anti-TNF-α biologic agents for the induction and maintenance of remission in inflammatory Crohn’s disease. In clinical practice, Crohn’s disease of moderate severity is defined as disease requiring systemic corticosteroids for symptom control.

This clinical practice guideline was developed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology,¹ and it was drafted by an AGA Institute Guideline Panel, reviewed by the Clinical Practice and Quality Management Committee, and approved by the AGA Institute Governing Board. The guideline is published in conjunction with a technical review on the same subject,² and interested readers are encouraged to refer to this publication for in-depth considerations of topics covered by this guideline.
To develop this document, the guideline panel members met with the authors of the technical review in Chicago on March 16, 2013. Also attending the meeting were the current and incoming chairs of the AGA Clinical Practice and Quality Management Committee, senior members of the AGA staff and a consumer representative. The authors of the technical review presented to the group the results of the systematic review of the evidence for each clinical question to be addressed in the guideline, organized in the PICO format (population, intervention, comparator and outcome). For each PICO, the group came to an agreement regarding the overall quality of the evidence, the balance between desirable and undesirable effects, patient values and preferences regarding the desirable and undesirable effects, and whether or not the intervention in question represents a prudent use of resources. Based on these parameters, the guideline panel members then reached consensus regarding a recommendation for or against each intervention, and rated the strength of the recommendation as either strong or weak. Strong recommendations were made when: 1) the overall quality of the evidence was moderate or high regarding the efficacy and safety of the intervention; 2) there was little or no uncertainty regarding the balance of desirable and undesirable effects of the intervention; 3) there was little or no uncertainty regarding patient’s values and preferences regarding the intervention and its effects; and 4) there was little or no uncertainty as to whether or not the intervention was too costly given the expected benefits.

The implication of a strong recommendation is that most patients should receive the recommended course of action, and that adherence to this recommendation could be used as a quality of care indicator. The implication of a weak recommendation is that the course of action is suggested, but that additional factors, such as the patient’s values and preferences will need consideration. The majority of fully informed patients would still want to follow this course of
action, but many would not. The final decision regarding the course of action would be the product of shared decision-making between the health care provider and patient.

Recommendations for induction of remission

1. We suggest against using thiopurines to induce remission in patients with moderately severe Crohn’s disease (weak recommendation, moderate quality evidence).

Because of the delay in the onset of action of thiopurines (6-mercaptopurine or azathioprine), concomitant steroids are required to provide rapid symptom relief among patients with moderately severe Crohn’s disease. The addition of thiopurines to steroids makes the induction of remission no more likely than with steroid therapy alone.

2. We suggest against using methotrexate to induce remission in patients with moderately severe Crohn’s disease (weak recommendation, low quality evidence).

As with the thiopurines, the data show that methotrexate is no better than placebo in inducing remission in moderately severe Crohn’s disease treated with steroids. However, the two randomized controlled trials differed markedly with respect to the dose and route of administration. It remains possible, but in our judgment unproved, that parenteral methotrexate in sufficient doses can induce remission.

3. We recommend using anti-TNF-α drugs to induce remission in patients with moderately severe Crohn’s disease who have not responded to standard therapies (strong recommendation, moderate quality evidence).

As a group, the three anti-TNF-α drugs that are FDA-approved for the treatment of Crohn’s disease (infliximab, adalimumab and certolizumab pegol) are more likely than placebo to induce remission in patients with moderately severe Crohn’s disease refractory to standard therapies. Standard therapies include mesalamine, antibiotics, steroids and
immunomodulators. An analysis of the data for each of the three agents separately indicates that certolizumab may be less effective in inducing remission than the other two agents. Head-to-head comparisons of these agents are thus clearly needed. The rate of serious infections is not increased among patients receiving anti-TNF induction. We conclude that the benefits of anti-TNF inductive therapy in patients with moderately severe Crohn’s disease outweigh the harms. These drugs are expensive, but the cost of uncontrolled Crohn’s disease may be greater.

4. We recommend using anti-TNF-α monotherapy over thiopurine monotherapy to induce remission in patients who have moderately severe Crohn’s disease (strong recommendation, moderate quality evidence).

There is a single randomized controlled trial (SONIC) that performed a head-to-head comparison of an anti-TNF-α drug, infliximab, with a thiopurine drug, azathioprine, for the induction of remission in patients who had moderately severe Crohn’s disease and were naïve to both agents. Infliximab was superior to azathioprine in this population. These data are consistent with those previously mentioned that demonstrate that the anti-TNF-α drugs as a group are superior to placebo in inducing remission in patients with moderately severe Crohn’s disease failing to respond to standard therapies, including prior use of thiopurines. Over the course of one year of treatment in the Sonic trial, there were no more serious infections with infliximab as compared to azathioprine therapy. Although there have been no studies directly comparing the thiopurines to adalimumab or certolizumab in patients with moderately severe Crohn’s disease, we believe that the conclusions drawn from the Sonic trial can be extrapolated to these two anti-TNF agents as well.

5. We recommend using anti-TNF-α drugs in combination with thiopurines over thiopurine monotherapy to induce remission in patients who have moderately severe Crohn’s disease (strong recommendation, high quality evidence).
Two trials, SONIC and GETAID, have demonstrated the superiority of combination infliximab and azathioprine therapy to azathioprine monotherapy for the induction of remission in patients with moderately severe Crohn’s disease. Combination therapy was not associated with any increase in serious infections.

6. We recommend using infliximab in combination with thiopurines over infliximab monotherapy to induce remission in patients who have moderately severe Crohn’s disease and are naïve to both (strong recommendation, moderate quality evidence).

The SONIC trial found that the combination of infliximab and azathioprine was superior to infliximab alone in inducing remission in patients with moderately severe Crohn’s disease who had not previously received either therapy. In addition, combination therapy was not associated with any increased risk of serious infection during the trial. However, the benefits of combination therapy versus infliximab alone remain uncertain in patients who have moderately severe disease who have previously failed to respond to prior use of thiopurines. For this common clinical scenario, there are no high quality data that demonstrate the superiority of combination therapy. In addition, the superiority of combination therapy when using the other anti-TNF-α drugs, adalimumab or certolizumab, remains uncertain.

Recommendations for maintenance of remission

7. We recommend using thiopurines over no immunomodulator therapy to maintain a steroid-induced remission in patients with Crohn’s disease (strong recommendation, moderate quality evidence).

A common clinical scenario in patients with moderately severe Crohn’s disease involves steroid-induced remission. Among these patients discontinuation of steroids is associated with very high rates of relapse. In this setting, thiopurines are significantly more likely to maintain clinical remission than placebo. Though high quality data are lacking, it does appear that long-
term use of thiopurines is associated with a higher risk of serious infection and lymphoma, though the absolute rates of these adverse events are low, and the benefits of maintaining remission outweigh the risks associated with thiopurines. However, patients who are at an elevated risk for these serious adverse events, such as older patients, and those who place a much higher value on the avoidance of these adverse events, and a lower value on a large reduction in disease relapse, may opt to decline thiopurine maintenance therapy.

Although thiopurines do not increase the likelihood that a patient with moderately severe disease will enter remission, due to their slow onset of action, it is advisable to start therapy with thiopurines at the same time as starting induction therapy with steroids, if the intention is to ultimately maintain remission with thiopurines.

8. We suggest using methotrexate over no immunomodulator therapy to maintain a steroid or methotrexate-induced remission in patients with Crohn’s disease (weak recommendation, low quality evidence).

Pooled data indicate that methotrexate is likely, but not definitely, superior to placebo in maintaining remission in patients with moderately severe Crohn’s disease. The optimal dose and route of administration remains uncertain, but the available data suggest that parenteral methotrexate may be superior to oral methotrexate for this purpose. Methotrexate is considered safe for long-term use, and there are no reports that associate methotrexate use with a risk for lymphoma. However, there are no published data regarding the risk of infection in Crohn’s patients on maintenance methotrexate therapy. Patients who want to conceive cannot use methotrexate, and this is a major barrier to long-term use in young adults. The poor quality of evidence regarding efficacy, and the near complete lack of safety data, lead to substantial uncertainty regarding the balance of benefits versus harms with this therapy.
9. We recommend using anti-TNF-α drugs over no anti-TNF-α drugs to maintain an anti-TNF-α drug-induced remission in patients with Crohn’s disease (strong recommendation, high quality evidence).

The anti-TNF-α drugs are superior to placebo in maintaining remission among patients with moderately severe Crohn’s disease who had remission induced by these drugs. In contrast to the individual drug data on induction of remission, the effect estimates for all three of the FDA approved anti-TNF-α drugs (infliximab, adalimumab and certolizumab) are very similar and substantial. Maintenance use of the anti-TNF-α drugs is not associated with an increase rate of serious infection, nor is there an increased risk for lymphoma. However, serious infections, such as tuberculosis or fungal infections, can occur as a direct consequence of use of these drugs. Failure to observe an increased rate of these infections in the trials may be secondary to the relatively short follow-up period. Also, it is important to note that the data regarding lymphoma risk are of very low quality, and the risk of lymphoma with the ongoing use of these drugs alone or in combination with thiopurines remains uncertain. Long-term use of these drugs is expensive, but there is a reduction in direct and indirect costs associated with avoidance of disease relapse. Overall, we conclude that the benefits of treating patients with these drugs to maintain remission outweigh the harms or burdens these therapies may cause for most patients.

10. We make no recommendation for or against the combination of an anti-TNF-α drug and a thiopurine versus an anti-TNF-α drug alone for the maintenance of the remission in patients with moderately severe Crohn’s disease in remission after medical therapy (no recommendation, low quality evidence).

The data on the benefits of combination therapy versus use of an anti-TNF-α drug alone are conflicting. In the SONIC trial the benefits of combination therapy versus infliximab
monotherapy were still present after a year of treatment. However, SONIC was not designed to study maintenance of remission, but rather was an induction trial with long-term follow-up. The only randomized trial examining this question was a small and open label trial that found that combination maintenance therapy with infliximab and azathioprine was not superior to infliximab alone. The data on the relative safety of long-term combination therapy versus use of an anti-TNF-α drug alone are of very low quality, but do not suggest that combination therapy increases the risk for serious infection, though it does suggest a possible increase in the rate of lymphoma.

Discussion

We used the GRADE methodology to create a guideline with a set of recommendations regarding the optimal use of immunomodulators and anti-TNF-α drugs for the induction and maintenance of remission in patients with moderately severe Crohn’s disease. The purpose of this guideline is to inform clinical decision-making, as well as to establish quality of care indicators by making transparent and actionable recommendations. Our ability to make strong recommendations across all of the relevant clinical questions, however, was limited by poor quality data, especially those data pertaining to the rate of serious adverse events associated with use of the medications. A lack of high quality data also did not permit recommendations to be made for a host of very pressing clinical questions, including when in the disease course to start these drugs, whether to follow symptoms or assess some more objective, albeit intermediate clinical endpoint, such as endoscopic healing, or how to respond to early or late treatment failures or drug intolerance. These guidelines, also, do not address special patient populations, such as patients with fistulizing Crohn’s, patients with surgically induced remission or children. Nevertheless, these guidelines are the first to address medical therapy in Crohn’s
disease using a widely adopted methodology that explicitly assesses the balance of benefits and risks of an intervention and patient’s values and preferences in addition to the quality of evidence as determined by a systematic review of the relevant data.

References
