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

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This document presents the official recommendations of the American Gastroenterological Association Institute (AGA) on the use of thiopurines, methotrexate, and anti–tumor necrosis factor (TNF)-α biologic drugs for the induction and maintenance of remission in inflammatory Crohn's disease (CD). In clinical practice, CD 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 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 that publication for in-depth consideration of topics covered by this guideline.

To develop this document, the members of the guideline panel 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 members of the guideline panel 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 a 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 to be considered. 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 Thiopurine Monotherapy to Induce Remission in Patients With Moderately Severe CD (Weak Recommendation, Moderate-Quality Evidence)

Because of the delay in the onset of action of thiopurines (6-mercaptopurine or azathioprine), concomitant therapy with systemic corticosteroids or an anti–TNF-α drug is required to provide rapid symptom

Abbreviations used in this paper: AGA, American Gastroenterological Association Institute; CD, Crohn's disease; GRADE, Grading of Recommendations Assessment, Development and Evaluation; PICO; population, intervention; comparator, and outcome; TNF, tumor necrosis factor.

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relief among patients with moderately severe CD. The addition of thiopurines to corticosteroids makes the induction of remission no more likely than with corticosteroid therapy alone. However, thiopurines can maintain a corticosteroid-induced remission (see recommendation 7). Therefore, starting a thiopurine at the same time as corticosteroids in a patient with moderately severe CD is a reasonable treatment strategy. The comparative effectiveness of this treatment strategy compared with others, such as induction and maintenance of remission with an anti–TNF-α drug alone or in combination with a thiopurine, is not known.

2. We Suggest Against Using Methotrexate to Induce Remission in Patients With Moderately Severe CD (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 CD treated with corticosteroids. However, the 2 randomized controlled trials differed markedly with respect to the dose and route of administration. Although studies have failed to show or prove that methotrexate is effective in inducing remission, based on clinical experience it is likely that methotrexate in sufficient doses can induce remission. As with thiopurines, methotrexate can maintain a corticosteroid-induced remission (see recommendation 8). Therefore, starting methotrexate at the same time as corticosteroids in a patient with moderately severe CD is a reasonable treatment strategy.

3. We Recommend Using Anti–TNF-α Drugs to Induce Remission in Patients With Moderately Severe CD (Strong Recommendation, Moderate-Quality Evidence)

The anti–TNF-α drugs infliximab or adalimumab are more likely than placebo to induce remission in patients with moderately severe CD refractory to other therapies, including mesalamine, antibiotics, corticosteroids, and immunomodulators. The ability to induce remission in patients who have not responded to treatment with corticosteroids or immune modulators is an important feature of these drugs. However, certolizumab pegol has not been found to be more effective than placebo in inducing remission in patients with moderately severe CD and, unlike infliximab or adalimumab, is not approved by the US Food and Drug Administration for this indication. The rate of serious infections is not increased among patients receiving anti–TNF-α drug induction. We conclude that the benefits of anti–TNF-α drug inductive therapy in patients with moderately severe CD outweigh the harms. These drugs are expensive, but the cost of uncontrolled CD may be greater.

4. We Recommend Using Anti–TNF-α Monotherapy Over Thiopurine Monotherapy to Induce Remission in Patients Who Have Moderately Severe CD (Strong Recommendation, Moderate-Quality Evidence)

There is a single randomized controlled trial (SONIC; Study of Biologic and Immunomodulator Naive Patients in Crohn's Disease) 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 CD and were naïve to both agents. Infliximab was superior to azathioprine in this population. These data are consistent with those previously mentioned showing that the anti–TNF-α drugs, but not the thiopurines, are superior to placebo in inducing remission in patients with moderately severe CD who fail to respond to standard therapies. Over the course of 1 year of treatment in SONIC, there were no more serious infections with infliximab as compared with azathioprine therapy. Although there have been no studies directly comparing the thiopurines with adalimumab in patients with moderately severe CD, we believe that the conclusions drawn from SONIC can be extrapolated to adalimumab 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 CD (Strong Recommendation, High-Quality Evidence)

Two trials, SONIC and one from the GETAID investigators, have shown the superiority of combination infliximab and azathioprine therapy to azathioprine monotherapy for the induction of remission in patients with moderately severe CD. As with recommendation 4, although there have been no studies directly comparing adalimumab plus thiopurines with thiopurines alone in patients with moderately severe CD, we believe that the conclusions drawn from SONIC can be extrapolated to adalimumab as well. Combination therapy was not associated with any increase in serious infections over 12 months.

6. We Suggest Using Anti–TNF-α Drugs in Combination With Thiopurines Over Anti–TNF-α Drug Monotherapy to Induce Remission in Patients Who Have Moderately Severe CD (Weak Recommendation, Moderate-Quality Evidence)

The results of SONIC showed that the combination of infliximab and azathioprine was superior to infliximab alone in inducing remission in patients with moderately severe CD 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 previously failed to respond to use of thiopurines. For