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

JONATHAN P. TERDIMAN, CLAUDIA B. GRUSS, JOEL J. HEIDELBAUGH, SHAHNAZ SULTAN, YNGVE T. FALCK–YTTER, and the AGA Institute Clinical Practice and Quality Management Committee

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 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, 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
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
this common clinical scenario, there are no high-quality data that show the superiority of combination therapy. In addition, the superiority of combination therapy when using the other anti-TNF-α drugs remains uncertain, as does the comparative effectiveness of this treatment strategy with emerging strategies, such as the combination of an anti-TNF-α drug and oral methotrexate. Finally, some patients prefer anti-TNF-α drug monotherapy rather than combination therapy because they place a higher value on avoiding any potential increase in risk of a serious complication, even if this risk is very low, and a comparatively lower value on the increased chance of attaining and remaining in remission associated with combination therapy.

### Recommendations for Maintenance of Remission

7. We Recommend Using Thiopurines Over No Immunomodulator Therapy to Maintain a Corticosteroid-Induced Remission in Patients With CD (Strong Recommendation, Moderate-Quality Evidence)

A common clinical scenario in patients with moderately severe CD involves corticosteroid-induced remission. Among these patients, discontinuation of corticosteroids is associated with very high rates of relapse. In this setting, thiopurines are significantly more likely to maintain clinical remission than placebo. Although high-quality data are lacking, it does appear that long-term use of thiopurines is associated with a 1.5- to 5-fold increased risk of lymphoma and with a possibly slightly higher risk of serious infection, although the absolute rates of these adverse events are low, and the benefits of maintaining remission outweigh the risks associated with thiopurines.

Although thiopurines do not increase the likelihood that a patient with moderately severe disease will enter remission, it is appropriate to start therapy with thiopurines at the same time as starting induction therapy with corticosteroids if the intention is to ultimately maintain remission with thiopurines.

8. We Suggest Using Methotrexate Over No Immunomodulator Therapy to Maintain Corticosteroid-Induced Remission in Patients With CD (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 CD. The optimal dose and route of administration remain 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 only very rare reports that associate use of methotrexate with an increased risk of lymphoma. However, there are no published data regarding the risk of infection in patients with CD 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. The anti-TNF-α drugs are superior to placebo in maintaining remission among patients with moderately severe CD who had remission induced by these drugs. In contrast to the individual drug data on induction of remission, the effect estimates for all 3 of the Food and Drug Administration-approved anti-TNF-α drugs (infliximab, adalimumab, and certolizumab) are very similar and substantial. Although direct data are lacking, we also believe that the anti-TNF-α drugs will maintain a corticosteroid-induced remission. Maintenance use of the anti-TNF-α drugs is not associated with an overall increased rate of serious infection, and there is not an increased risk of lymphoma. However, opportunistic 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 the risk of lymphoma 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.

9. We Recommend Using Anti-TNF-α Drugs Over No Anti-TNF-α Drugs to Maintain Corticosteroid- or Anti-TNF-α–Induced Remission in Patients With CD (Strong Recommendation, High-Quality Evidence)

The data on the benefits of combination therapy versus use of an anti-TNF-α drug alone are conflicting. In SONIC, the benefits of combination therapy versus infliximab monotherapy were still present after 1 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 they do not suggest that combination therapy increases the risk of serious infection. However, combination therapy is associated with an 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 CD. 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 pertaining to the rate of serious adverse events associated with use of these 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 a more objective, albeit intermediate clinical end point, such as endoscopic healing; or how to respond to early or late treatment failures or drug intolerance. We urgently need more comparative effectiveness studies of competing treatment strategies for moderately severe CD such as corticosteroid induction combined with thiopurine maintenance versus induction and maintenance with an anti-TNF-α drug with no exposure to corticosteroids. Furthermore, these guidelines do not address special patient populations, such as patients with fistulizing CD, patients with surgically induced remission, or children. Nevertheless, these guidelines are the first to address medical therapy in CD using a widely adopted methodology that explicitly assesses the balance of benefits and risks of an intervention and the patient’s values and preferences in addition to the quality of evidence as determined by a systematic review of the relevant data.

References


Correspondence

Address correspondence to: Jonathan Terdiman, MD, University of California, San Francisco Medical Center, 1701 Divisadero Street Suite 110, San Francisco, California 94115. fax: (415) 502-2249.

Acknowledgments

Members of the Clinical Practice and Quality Management Committee included Spencer D. Dorn, Division of Gastroenterology and Hepatology, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina; Sharon L. Dudley-Brown, Johns Hopkins University, Baltimore, Maryland; Joseph K. Lim, Yale Liver Center, Yale University School of Medicine, New Haven, Connecticut; Lena B. Palmer, Department of Gastroenterology and Nutrition, Loyola University Chicago Stritch School of Medicine, Maywood, Illinois; Yvonne Romero, Division of Gastroenterology, Mayo Clinic, Rochester, Minnesota; Joel H. Rubenstein, Veterans Affairs Center for Clinical Management Research, Ann Arbor, Michigan, and Division of Gastroenterology, University of Michigan Medical School, Ann Arbor, Michigan; David S. Weinberg, Department of Medicine, Fox Chase Cancer Center, Philadelphia, Pennsylvania; and Yu-Xiao Yang, Division of Gastroenterology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania.

Conflicts of interest

The authors disclose the following: Dr Dudley-Brown has served as a consultant for Shire and as an advisory board member for Salix, Centocor, and UCB. The remaining authors disclose no conflicts.
A

Moderately severe Crohn’s despite standard therapies\(^1\)

- Use anti-TNF monotherapy\(^2\)
  - Over no therapy (Rec #3)
  - Over thiopurine monotherapy (Rec #4)

- Use anti-TNF + thiopurine\(^2\)
  - Over thiopurine monotherapy (Rec #5)
  - Over anti-TNF monotherapy (Rec #6)\(^3\)

\(^1\)Standard therapies include mesalamine, antibiotics, steroids, immunomodulators.

\(^2\)Induction with a steroid + immunomodulator (thiopurine or MTX) is an option in steroid-responsive patients.

\(^3\)Combination therapy with IFX and AZA is more likely to induce remission than IFX therapy alone. However, significant uncertainty exists regarding the relative value patients place on the greater likelihood of attaining remission with combination therapy, versus the value they place on avoiding the potentially higher risks of serious complications incurred by use of combination therapy.

B

Remission

Steroid induced

- Immunomodulator (thiopurine or MTX) over no immunomodulator (Rec #7 + #8)

Anti-TNF induced

- Anti-TNF +/- thiopurine\(^4\) over no anti-TNF (Rec #9)

Anti-TNF + thiopurine induced

- Anti-TNF +/- thiopurine\(^4\) over no anti-TNF (Rec #9)

- Anti-TNF +/- thiopurine\(^4\) over no anti-TNF (Rec #9)

\(^4\)Combination therapy or anti-TNF monotherapy are appropriate for the maintenance of remission, and we make no recommendation between the two treatment approaches (Rec #10).

1. Use of methotrexate in Crohn’s
   a. Is clearly superior to placebo in maintaining remission
   b. Parenteral dosing seems to be better than oral
   c. Can be used as monotherapy to induce remission
   d. Long-term risk of infection is unknown
   e. Lymphoma risk is either not increased or minimally increased
   f. Cannot be used in patients contemplating pregnancy or not using contraception

True or False

2. Thiopurines, when added to infliximab, is superior to infliximab alone in inducing a remission particularly in patients naïve to both drugs

3. Certolizumab pegol has not been found to be more effective than placebo in inducing a remission in patients with moderately severe Crohn’s disease.

4. Anti-TNF’s are able to induce remission in Crohn’s disease refractory to other therapies, but carry an increased risk of serious infections

5. Thiopurines, when added to corticosteroids, increase the chances that a remission will be achieved compared to corticosteroids alone

6. Thiopurines, as a single agent, may be used to induce remission in patients with mild to moderate Crohn’s disease

7. There is no high quality data supporting the long-term use of thiopurines + anti-TNF therapy to maintain remission.