Complete Summary

GUIDELINE TITLE

American Gastroenterological Association Institute medical position statement on corticosteroids, immunomodulators, and infliximab in inflammatory bowel disease.

BIBLIOGRAPHIC SOURCE(S)

Lichtenstein GR, Abreu MT, Cohen R, Tremaine W. American Gastroenterological Association Institute medical position statement on corticosteroids, immunomodulators, and infliximab in inflammatory bowel disease. Gastroenterology 2006 Mar;130(3):935-9. PubMed

GUIDELINE STATUS

This is the current release of the guideline.

According to the guideline developer, the Clinical Practice Committee meets three times a year to review all American Gastroenterological Association Institute (AGAI) guidelines. This review includes new literature searches of electronic databases followed by expert committee review of new evidence that has emerged since the original publication date.

COMPLETE SUMMARY CONTENT

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SCOPE

DISEASE/CONDITION(S)

Inflammatory bowel disease, including Crohn's disease and ulcerative colitis

GUIDELINE CATEGORY

Management
Treatment

CLINICAL SPECIALTY

Colon and Rectal Surgery
Family Practice
Gastroenterology
Internal Medicine

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To assist physicians in the appropriate use of medications to treat patients with inflammatory bowel disease (IBD)

TARGET POPULATION

Adult patients with inflammatory bowel disease, including Crohn's disease (CD), and ulcerative colitis (UC)

INTERVENTIONS AND PRACTICES CONSIDERED

1. Corticosteroids (budnesonide [Entocort™], prednisone, mesalamine, topical hydrocortisone)
2. Azathioprine (AZA)
3. 6-Mercaptopurine (6-MP)
4. Methotrexate
5. Cyclosporine
6. Infliximab

Note: Use of Mycophenolate Mofetil was considered but not recommended.

MAJOR OUTCOMES CONSIDERED

- Remission rate
- Symptom relief
- Adverse effects of treatment

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

An exhaustive review of the literature was performed using electronic databases (MEDLINE, PubMed, and Ovid; key words included "inflammatory bowel disease," "ulcerative colitis," and "Crohn's disease"). Standard textbooks with chapters on inflammatory bowel disease were evaluated, and the reference lists were also compiled for all articles to obtain references before a preliminary document was drafted.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Quality of Evidence on Which a Recommendation is Based

Grade A: Homogeneous evidence from multiple well-designed, randomized (therapeutic) or cohort (descriptive) controlled trials, each involving a number of participants to be of sufficient statistical power.

Grade B: Evidence from at least 1 large well-designed, clinical trial with or without randomization from cohort or case-control analytic studies or well-designed meta-analysis.

Grade C: Evidence based on clinical experience, descriptive studies, or reports of expert committees.

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

The paper was approved by the American Gastroenterological Association (AGA) Clinical Practice and Economics Committee on November 22, 2005, and by the AGA Governing Board on January 12, 2006.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

The strength of the evidence supporting each guideline statement is graded (Grade A-C). Definitions for the strength of evidence are provided at the end of the "Major Recommendations" field.

Recommendations for Corticosteroid Use

Mild to Moderate Inflammatory Bowel Disease (IBD)

- Ileal-release preparations of budesonide (Entocort™) are indicated for the treatment of patients with ileal and right-sided colonic Crohn's disease (CD). Ileal-release preparations of budesonide are not effective in patients with ulcerative colitis (UC) (Grade A).
- The use of conventional corticosteroids such as prednisone is generally reserved for patients with moderate to severe disease who failed to respond to first-line therapies for IBD such as mesalamine (UC) or budesonide (CD) (Grade B).
- Topical therapy with either hydrocortisone (Grade A) or budesonide (Grade B) is effective for distal colonic inflammation.

Moderate to Severe IBD

- Corticosteroids such as prednisone are effective in both patients with CD and patients with UC (Grade A).
- Corticosteroids are not effective for the treatment of patients with perianal fistulas (Grade C).

Severe and Fulminant IBD

- Hospitalization for parenteral corticosteroids is indicated for patients failing to respond to oral corticosteroids or for patients with severe disease with UC (Grade A) or CD (Grade B).

Maintenance Therapy

- Conventional corticosteroids are not efficacious in maintenance treatment of patients with CD (Grade A) or patients with UC (Grade B).
- Budesonide therapy is effective in the maintenance of short-term (3 months) but not long-term (1 year) remission compared with placebo in patients with mild to moderate ileocecal CD (Grade A).

Dosing and Tapering for IBD

- Dosages in the range of 40-60 mg/day or 1 mg/kg/day of prednisone or equivalent are effective for induction of remission (Grade A).
- Induction of response averages 7 to 14 days. A gradual taper by 5 mg/week of prednisone (or equivalent corticosteroid) to a dose of 20 mg and then 2.5 to 5 mg/week below 20 mg is recommended (Grade B).
- Budesonide may be tapered gradually from the initial induction dose of 9 mg to doses of 6 mg and subsequently 3 mg. Budesonide does suppress the adrenocortical axis; clinicians should evaluate for adrenal insufficiency as warranted by clinical symptoms (Grade C).
- An inability to taper corticosteroids is an indication for antimetabolite and/or infliximab therapy (see the American Gastroenterological Association technical review on corticosteroids, immunomodulators, and infliximab in inflammatory bowel disease [refer to the "Availability of Companion Documents" field in this summary]) (Grade A).
- For patients failing to respond to 7 to 14 days of high-dose oral prednisone or equivalent corticosteroid therapy, parenteral corticosteroids are indicated (Grade C).
- Dosages for parenteral corticosteroids typically are in the range of methylprednisolone 40 to 60 mg/day or hydrocortisone 200 to 300 mg/day (Grade A).

Monitoring for Complications

- Periodic bone mineral density assessment is recommended for patients on long-term corticosteroid therapy (>3 months) (Grade A).
- Annual ophthalmologic examinations are recommended for patients on long-term corticosteroid therapy (Grade C).
- Patients with corticosteroid use within the past year are at greater risk for adrenal insufficiency, especially following surgery, and may need stress-dose corticosteroids postoperatively (Grade C).
- Patients who are using corticosteroids should be monitored for glucose intolerance and other metabolic abnormalities (Grade B).
- Patients being treated with corticosteroids are at increased risk for infectious complications (Grade B).

Recommendations for Azathioprine/6-Mercaptopurine (AZA/6-MP) Use

- When initiating therapy with either 6-MP or AZA, measurement of complete blood count with differential is advocated at least every other week as long as doses of medications are being adjusted. Thereafter, the measurement of complete blood count with differential should be performed as clinically appropriate at least once every 3 months. Periodic measurement of liver-associated chemistries is also advocated (Grade C).
- Current U.S. Food and Drug Administration (FDA) recommendations suggest that individuals should have thiopurine methyltransferase (TPMT) genotype or phenotype assessed before initiation of therapy with AZA or 6-MP in an effort to detect individuals who have low enzyme activity (or who are homozygous deficient in TPMT) in an effort to avert AZA or 6-MP therapy and thus avoid potential adverse events. Individuals who have intermediate or normal TPMT activity (wild type or heterozygotes) need measurement of frequent complete blood counts (as above) in addition to TPMT assessment because these individuals may still develop myelosuppression subsequent to use of AZA or 6-MP (Grade B).
- Long-term treatment with corticosteroids is undesirable. Patients with chronic active corticosteroid-dependent disease (either CD or UC) should be treated with AZA 2.0 to 3.0 mg/kg/day or 6-MP 1.0 to 1.5 mg/kg/day in an effort to lower or preferably eliminate corticosteroid use. Infliximab is another option in this situation, as is combination infliximab/antimetabolite therapy (Grade A).
- Individual patients with either CD or UC who experience a severe flare of disease requiring corticosteroid treatment or require re-treatment during the year with another course of corticosteroids should be considered for initiation of therapy with AZA 2.0 to 3.0 mg/kg/day or 6-MP 1.0 to 1.5 mg/kg/day in an effort to avoid future corticosteroid use (Grade C). Infliximab is another option in this situation, as is combination infliximab/antimetabolite therapy.
- 6-MP (and likely AZA) is modestly effective for decreasing postoperative recurrence in CD both endoscopically and clinically. Use of this agent should be considered for patients at high risk for postoperative recurrences or in whom postoperative recurrence would have deleterious effects (Grade B).
- Some studies have shown AZA 2.0 to 3.0 mg/kg/day or 6-MP 1.0 to 1.5 mg/kg/day to have some efficacy in treating and healing perianal and enteric fistulae (Grade C).
- Thiopurine metabolite monitoring in the treatment of patients with 6-MP or AZA is useful when attempting to determine medical noncompliance and may be helpful for optimizing dose and monitoring for toxicity (Grade C).
- AZA 2.0 to 3.0 mg/kg/day or 6-MP 1.0 to 1.5 mg/kg/day is effective for maintenance of remission in patients with CD regardless of disease distribution (Grade A).
- AZA 2.0 to 3.0 mg/kg/day or 6-MP 1.0 to 1.5 mg/kg/day is effective for reducing corticosteroid dose in patients with UC regardless of disease distribution (Grade A). These drugs may also be effective in maintaining remission in patients with UC, but data are conflicting and this has not been confirmed by large well-controlled studies.
- Patients with gastrointestinal intolerance (except for fever, pancreatitis, or hypersensitivity reactions) to AZA may be cautiously tried on 6-MP before being considered for other therapy or surgery (Grade C). Similarly, patients with gastrointestinal intolerance (except for fever, pancreatitis, or hypersensitivity reactions) to 6-MP may be cautiously tried on AZA before being considered for other therapy or surgery (Grade C).

Recommendations for Methotrexate Use

- Parenteral methotrexate is indicated for induction of remission in patients with active CD (Grade B).
- Parenteral methotrexate is indicated for maintenance of remission in patients with inactive CD (Grade B).
- The currently available evidence supports the use of methotrexate for induction of remission with corticosteroid withdrawal in patients with active CD who are corticosteroid dependent (Grade B).
- Methotrexate maintenance therapy (15 to 25 mg intramuscularly weekly) is effective for patients whose active CD has responded to intramuscular methotrexate (Grade A).
- Methotrexate 25 mg intramuscularly weekly for up to 16 weeks followed by 15 mg intramuscularly weekly is effective in patients with chronic active CD (Grade A).
- Methotrexate is absolutely contraindicated in pregnancy (Grade B)
- The currently available evidence is insufficient to support the use of methotrexate for the induction or maintenance of remission in patients with active UC (Grade B).
- Routine monitoring of laboratory parameters, including complete blood counts and liver-associated laboratory chemistries, is recommended in patients who are treated with methotrexate (Grade C).
- Patients with persistently abnormal liver-associated chemistries should either discontinue therapy with methotrexate or undergo liver biopsy (Grade C).

Recommendations for Cyclosporine Use

- Intravenous cyclosporine is effective as a means of avoiding surgery in patients with severe corticosteroid-refractory UC (Grade A).
- Intravenous cyclosporine at 2 to 4 mg/kg/day or colectomy should be considered if a patient with severe UC has failed to respond to medical therapy with 7 to 10 days of high-dose oral or parenteral corticosteroids (Grade B).
- Concomitant administration of intravenous corticosteroids is recommended, but not required, to induce a clinical response in patients with severe UC receiving intravenous cyclosporine (Grade B).
- A response or remission induced with intravenous cyclosporine in patients with IBD typically requires continuation of therapy with oral cyclosporine for a few months, along with a tapering dose of corticosteroids, initiation of AZA or 6-MP therapy, and prophylaxis against *Pneumocystis carinii* (Grade B). The purine analogue should be continued as maintenance therapy (Grade B).
- Oral cyclosporine is efficacious in patients with corticosteroid-refractory UC (Grade C) but requires AZA or 6-MP for maintenance of remission (Grade C).
- Neither intravenous (Grade C) nor oral (Grade A) low-dose cyclosporine has proven efficacy in patients with luminal CD. High-dose oral cyclosporine (7.6 mg/kg) has short-term efficacy (Grade B).
- Intravenous cyclosporine is effective for the treatment of patients with fistulizing CD (Grade B). AZA or 6-MP should then be used for maintenance of fistula closure (Grade C).

Recommendations for Infliximab Use

The recommended initial dose of infliximab for all IBD indications is 5 mg/kg body weight, administered by intravenous infusion over 2 hours in an induction regimen of 3 doses at weeks 0, 2, and 6. This should be followed by maintenance therapy every 8 weeks in patients who respond. For patients with CD who respond and then lose their response, consideration may be given to treatment with 10 mg/kg. The treatment should be administered under the supervision and control of a specialized health care deliverer, with emergency equipment for severe infusion reactions available. A follow-up observation period of approximately 1 hour is advocated. Current indications for infliximab include the following:

1. Treatment of moderately to severely active CD or UC in patients who have not responded despite complete and adequate therapy with a corticosteroid or an immunosuppressive agent (AZA, 6-MP, or methotrexate). These patients are individuals who are resistant to medical therapy (complete and adequate therapy with a corticosteroid or an immunosuppressive agent) or who cannot receive such therapies due to intolerance to medications (corticosteroids or medical contraindications [therapy intolerant]).
    - For induction therapy, the administration of infliximab at time 0 and 2 and 6 weeks is recommended; in the case of nonresponse to 3 infusions, further treatment with infliximab is not recommended.
    - Withdrawal or tapering of concomitant corticosteroid therapy: if a patient is on infliximab and achieves remission, an attempt to withdraw or taper any concomitant corticosteroid therapy is sensible.
    - Patients who respond to induction therapy should receive maintenance therapy with infusions every 8 weeks.
2. Treatment of CD with fistulas in patients who have not responded despite complete and adequate therapy with conventional treatments (including antibiotics, surgical drainage with examination under anesthesia, and/or immunosuppressive therapy): the use of infliximab should be avoided in patients with known hypersensitivity to infliximab, active infections, demyelinating disorders, severe congestive heart failure, and current or recent malignancy. Appropriate screening for latent and active tuberculosis should be performed on all patients before administration of infliximab.

Definitions:

Quality of Evidence on Which a Recommendation is Based

Grade A: Homogenous evidence form multiple well-designed randomized (therapeutic) or cohort (descriptive) controlled trials, each involving a number of participants to be of sufficient statistical power

Grade B: Evidence from at least 1 large well-designed clinical trial with or without randomization, form cohort or case-control analytical studies, or well-designed meta-analysis

Grade C: Evidence based on clinical experience, descriptive studies, or reports of expert committees

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for most recommendations (see "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate treatment and management of adult patients with inflammatory bowel disease (IBD), Crohn's disease (CD), and ulcerative colitis (UC)

POTENTIAL HARMS

Side effects of medications used to treat inflammatory bowel disease (IBD), Crohn's disease (CD), and ulcerative colitis (UC)

CONTRAINDICATIONS

CONTRAINDICATIONS

- Infliximab is contraindicated in patients with active tuberculosis and other serious infections, such as sepsis, undrained abscess, and opportunistic infections, such as herpes zoster, cytomegalovirus, or *Pneumoncystis carinii*. In patients with moderate to severe congestive heart failure (New York Heart Association Class III or Class IV), infliximab should not be administered because an increased mortality when compared with controls has been reported in this patient population. Individuals with known hypersensitivity to infliximab or other murine proteins should avoid exposure to infliximab. It is generally not advocated that infliximab should be given to patients with known or suspected demyelinating disorders, optic neuritis, or recent malignant tumors and lymphomas.
- Methotrexate is contraindicated in pregnancy and during breastfeeding.

QUALIFYING STATEMENTS

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The Medical Position Statements (MPS) developed under the aegis of the American Gastroenterological Association (AGA) and its Clinical Practice and Economics Committee (CPEC) were approved by the AGA Governing Board. The data used to formulate these recommendations are derived from the data available at the time of their creation and may be supplemented and updated as new information is assimilated. These recommendations are intended for adult patients, with the intent of suggesting preferred approaches to specific medical issues or problems. They are based upon the interpretation and assimilation of scientifically valid research, derived from a comprehensive review of published literature. Ideally,

the intent is to provide evidence based upon prospective, randomized placebo-controlled trials; however, when this is not possible, the use of experts' consensus may occur. The recommendations are intended to apply to health care providers of all specialties. It is important to stress that these recommendations should not be construed as a standard of care. The AGA stresses that the final decision regarding the care of the patient should be made by the physician with a focus on all aspects of the patient's current medical situation.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Lichtenstein GR, Abreu MT, Cohen R, Tremaine W. American Gastroenterological Association Institute medical position statement on corticosteroids, immunomodulators, and infliximab in inflammatory bowel disease. Gastroenterology 2006 Mar;130(3):935-9. PubMed

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2006 Mar

GUIDELINE DEVELOPER(S)

American Gastroenterological Association Institute - Medical Specialty Society

SOURCE(S) OF FUNDING

American Gastroenterological Association Institute

GUIDELINE COMMITTEE

American Gastroenterological Association Institute Clinical Practice Committee

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

- Dr. Lichtenstein is a consultant for Abbott Corporation, Astra-Zeneca, Inc., Axcan Corporation, Berlex, entocor, Inc., Elan, Genetics Institute, Human Genome Sciences, Inkine, Inc., Intesco Corporation, ISIS Corporation, Millenium Pharmaceuticals, Otsuka Corporation, Proctor and Gamble, Prometheus Laboratories, Inc., Protein Design Labs, Protomed Scientific, Salix Pharmaceuticals, Schering-Plough Corporation, Serono, Shire Pharmaceuticals, Smith Kline Beecham Corporation, Solvay Pharmaceuticals, Synta Pharmaceuticals, UCB, and Wyeth.
- Dr. Tremaine is a consultant for Procter and Gamble, NPS Pharma, and Solvay Pharma.
- Dr. Abreu is a consultant for Procter and Gamble, Abbott, UCB, Prometheus, and Salix.
- Dr. Cohen is a consultant for Salix, Centocor, Abbott, Elan, Isis, Kenwood, McNeil, Pfizer, Protein Design Labs, Astra-Zeneca, Axcan-Scandipharm, Procter and Gamble, Salix, Solvay, and Shire.
- The American Gastroenterological Association received financial support form AstraZeneca LP to retain a contractor to assist in performing the background literature search for this work.

GUIDELINE STATUS

This is the current release of the guideline.

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GUIDELINE AVAILABILITY

Electronic copies: Available from the American Gastroenterological Association Institute (AGAI) *Gastroenterology* journal Web site.

Print copies: Available from the American Gastroenterological Association Institute, 4930 Del Ray Avenue, Bethesda, MD 20814.

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- American Gastroenterological Association technical review on corticosteroids, immunomodulators, and infliximab in inflammatory bowel disease. Gastroenterology 2006 Mar;130(3);940-987.

Electronic copies: Available from the American Gastroenterological Association Institute (AGAI) *Gastroenterology* journal Web site.

Print copies: Available from American Gastroenterological Association Institute, 4930 Del Ray Avenue, Bethesda, MD 20814.

PATIENT RESOURCES

None available

NGC STATUS

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