Treatment of Crohn disease in adults: Dosing and monitoring of tumor necrosis factor-alpha inhibitors

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INTRODUCTION

Tumor necrosis factor (TNF)-alpha inhibitors, including infliximab, adalimumab, and certolizumab pegol, are biologic agents used for treating patients with moderately to severely active Crohn disease.

Dosing, monitoring, and adverse effects of anti-TNF agents for the treatment of Crohn disease in adults will be reviewed here. The decision whether to use infliximab, adalimumab, or certolizumab pegol in patients requiring anti-TNF-alpha therapy is influenced by the indication, patient preference, patient medical history, and availability in individual countries. Overviews of the medical management of Crohn disease and use of thiopurines are discussed separately:

- (See "Overview of the medical management of mild (low risk) Crohn disease in adults".)
- (See "Medical management of moderate to severe Crohn disease in adults".)
- (See "Overview of azathioprine and mercaptopurine use in inflammatory bowel disease".)
- (See "Management of Crohn disease after surgical resection".)

TUMOR NECROSIS FACTOR INHIBITORS

Infliximab, adalimumab, and certolizumab pegol are monoclonal antibodies directed against tumor necrosis factor (TNF)-alpha. The basis for their use in Crohn disease is that tumor

necrosis factor (TNF)-alpha has several biologic activities that may be directly related to the pathogenesis of inflammatory bowel disease and to the dysregulation of the immune system that occurs in patients with IBD. (See "Overview of biologic agents in the rheumatic diseases", section on 'Anticytokine approaches'.)

- Infliximab – Infliximab is a chimeric monoclonal antibody comprised of 75 percent human and 25 percent murine sequences, which has a high specificity for and affinity to tumor necrosis factor (TNF)-alpha. Infliximab neutralizes the biologic activity of TNF-alpha by inhibiting binding to its receptors. In contrast to some other TNF inhibitors (eg, etanercept), infliximab can also induce apoptosis of activated lymphocytes in the gut mucosa [1-3].

- Adalimumab – Adalimumab is a recombinant fully human monoclonal antibody that binds to TNF-alpha, thereby interfering with binding to TNF-alpha receptor sites and subsequent cytokine-driven inflammatory processes. The humanized construction of adalimumab is presumed to lower the risk of forming anti-drug antibodies compared with infliximab. (See "Tumor necrosis factor-alpha inhibitors: Induction of antibodies, autoantibodies, and autoimmune diseases", section on 'Adalimumab-induced human anti-human antibodies'.)

- Certolizumab pegol – Certolizumab pegol is a humanized monoclonal antibody Fab fragment linked to polyethylene glycol that increases its plasma half-life and reduces the requirement for frequent dosing, possibly reducing immunogenicity as well. In vitro studies suggest that certolizumab pegol also has a higher binding affinity for TNF as compared with adalimumab or infliximab [4].

  Certolizumab pegol does not have an Fc region; as a result, it does not activate the complement pathway, result in cell- or antibody-mediated cytotoxicity, or induce apoptosis [4]. However, the clinical significance of these differences is unclear.

PRETREATMENT SCREENING

Prior to starting an anti-TNF agent, we obtain the following screening tests in all patients:

- Hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), and hepatitis B core antibody (HBcAb).

  Patients with serologic evidence of hepatitis B virus (HBV) infection (HBsAg-positive or anti-HBc-positive) are at risk for HBV reactivation if they receive immunosuppressive therapy.

Prevention, diagnosis, and treatment of HBV reactivation are discussed separately. (See "Hepatitis B virus reactivation associated with immunosuppressive therapy".)

- Interferon-gamma release assay such as QuantiFERON-TB Gold In-Tube assay (preferred) or tuberculin skin test.

  If the screening test for latent tuberculosis is positive, a chest radiograph is obtained and the patient is referred to an infectious disease specialist for further evaluation.

  - (See "Tuberculosis infection (latent tuberculosis) in adults: Approach to diagnosis (screening)".)
  - (See "Risk of mycobacterial infection associated with biologic agents and JAK inhibitors", section on 'Screening'.)
  - (See "Use of interferon-gamma release assays for diagnosis of tuberculosis infection (tuberculosis screening) in adults".)

CONTRAINDICATIONS

The contraindications to the use of anti-TNF therapies include the following (see "Treatment of axial spondyloarthritis (ankylosing spondylitis and nonradiographic axial spondyloarthritis) in adults", section on 'Use of TNF inhibitors'):

- Active, uncontrolled infection
- Latent (untreated) tuberculosis
- Demyelinating disease (eg, multiple sclerosis, optic neuritis)
- Heart failure (New York Heart Association class III/IV) (table 1)
- Active lymphoma

The safety of anti-TNF therapies and risk of recurrent malignancy in patients with a history of malignancy is less well established than in patients without such a history; the available data are discussed in detail separately. (See "Tumor necrosis factor-alpha inhibitors: Risk of malignancy".)

DOSING AND ADMINISTRATION

Overview — This section describes the induction and maintenance dosing for infliximab, adalimumab, and certolizumab pegol. In addition, options for dose escalation are included for patients with loss of response while on maintenance therapy. The approach to the patient who

is not responding to induction anti-TNF therapy, including the use of adjuvant glucocorticoids or immunomodulators, is discussed separately. (See "Medical management of moderate to severe Crohn disease in adults", section on 'Induction therapy'.)

Decisions regarding dose adjustments for patients on maintenance therapy who lose response can be guided by therapeutic drug monitoring (table 2). (See 'Monitoring' below and "Overview of dosing and monitoring of biologic agents and small molecules for treating ulcerative colitis in adults", section on 'Monitoring'.)

Infliximab — The induction dose of infliximab for treatment of patients with moderately to severely active Crohn disease, including fistulizing disease, is 5 mg/kg intravenously at zero-, two-, and six- weeks [5,6].

Patients who achieve an adequate response (based on clinical, endoscopic, and laboratory findings) to initial therapy will require repeat infusions of 5 mg/kg, usually every eight weeks, to maintain remission.

Patients who have a disease flare while on maintenance dosing can be managed by escalating the dose [7]. Additionally, individuals who achieve an incomplete response can be managed in a similar fashion. Dose escalation can be accomplished by either decreasing the dosing interval (eg, from eight weeks to six weeks) or by increasing the dose (eg, from 5 mg/kg to 10 mg/kg). The maximal dose of infliximab is 10 mg/kg every four weeks.

Adalimumab — Induction therapy with adalimumab is given subcutaneously with the following regimen:

- Week zero, initial dose – 160 mg once
- Week two – 80 mg once
- Week four and thereafter – 40 mg every other week (maintenance dose)

We suggest the same induction regimen for patients who are being switched to adalimumab from another anti-tumor necrosis factor (TNF) agent. Adalimumab is available in a single-use prefilled pen (Humira Pen) or in a single-use prefilled glass syringe.

For patients who have a disease flare while on maintenance dosing, the dosing interval can be shortened to every week [8]. A meta-analysis of 39 studies showed that the mean percentage of loss of response to adalimumab among primary responders was 18 percent and the annual risk was 20 percent per patient-year; the mean percentage of patients who required dose escalation (ie, shortening the dosing interval) among primary responders to adalimumab was 37 percent and the annual risk was 25 percent per patient-year [9].

In this pooled analysis of outcomes following dose escalation, response was achieved in 71 percent of patients, and remission was achieved in 40 percent of patients [9]. A large number of factors predicted loss of response or need for dose escalation in patients treated with adalimumab (male gender, high body mass index, current/former smoking, family history of inflammatory bowel disease, isolated colonic disease, extraintestinal manifestations, 80/40 mg induction therapy, longer disease duration, greater baseline Crohn Disease Activity Index, concomitant glucocorticoid use, absence of deep remission at week 12, low serum trough concentrations of adalimumab, previous infliximab non-response, and prior treatment with an anti-TNF-alpha agent) [9,10].

In addition to loss of response, some patients do not respond initially to anti-TNF induction therapy (primary nonresponse), and rates of primary nonresponse have ranged from 10 to 40 percent in clinical trials and observational studies [11]. In addition, studies have suggested that primary nonresponse has often been related to inadequate drug concentrations [12]. Thus, it seems most appropriate to escalate the dose of anti-TNF therapy during induction for patients who are not responding and utilize therapeutic drug monitoring. (See 'Therapeutic drug monitoring' below.)

Certolizumab pegol — The recommended dose of certolizumab pegol for induction of remission in Crohn disease is 400 mg subcutaneously at weeks zero, two, and four, and then every four weeks for maintenance therapy [13]. For patients who have loss of response while on maintenance dosing and who are candidates for dose escalation, options include shortening the interval between doses (eg, every two to three weeks) or giving a single re-induction dose (ie, 400 mg) between scheduled four-week doses [14,15].

MONITORING

In addition to clinical observation, monitoring the response to anti-TNF agents may include therapeutic drug monitoring (checking drug trough levels, anti-drug antibodies) and levels of biomarkers (C-reactive protein [CRP], fecal calprotectin). Time intervals for follow-up colonoscopy are discussed separately. (See "Medical management of moderate to severe Crohn disease in adults".)

Therapeutic drug monitoring — Therapeutic drug monitoring involves measuring serum drug trough concentrations and antidrug antibodies to optimize the use of anti-TNF agents for patients with inflammatory bowel disease (IBD). For patients with clinical features of inflammation (eg, symptoms, laboratory studies, endoscopic appearance), therapeutic drug monitoring can help the clinician decide whether a dose increase is needed or if switching to a

different drug is preferred. Approximately 40 percent of patients who initially achieve remission will develop secondary loss of response during the first year of therapy [5,16]. Potential causes of secondary loss of response include (table 2) [17]:

- Low drug levels (due to either immune or non-immune mediated clearance mechanisms)
- Mechanistic failure (eg, non-TNF-mediated cytokine pathways may be playing a greater role in pathogenesis of IBD)

Available drug assays report both drug concentration and anti-drug antibodies. The suggested target drug trough concentrations are generally based on cross-sectional studies of patients on maintenance therapy [17]:

- Infliximab: ≥5 microg/mL for luminal disease. Some but not all studies have reported that higher infliximab trough levels were associated with healing of perianal fistula related to Crohn disease [18-22], and a trough level of ≥10 microg/mL has been suggested for patients with fistulizing disease [19].
- Adalimumab: ≥7.5 microg/mL.
- Certolizumab pegol: ≥20 microg/mL.

Patients with active disease despite maintenance therapy — A guideline from the American Gastroenterological Association (AGA) suggests that adult patients with active inflammatory bowel disease who are being treated with an anti-TNF agent receive reactive therapeutic drug monitoring using drug trough levels and anti-drug antibodies [17]. The drug trough level should be drawn no more than 24 hours prior to the next scheduled dose of the drug. Measurement of drug levels and anti-drug antibodies with dose adjustments to reach a target drug trough concentration can result in fewer flares during the course of treatment and is more cost-effective compared with empiric dose escalation in patients with a loss of response (table 2) [23-25]. Because antibodies to anti-TNF agents can reduce drug blood levels, a subset of patients will lose their response and have recurrence of symptoms between treatment intervals.

Patients with sustained anti-drug antibodies — For patients with sustained, high levels of anti-drug antibodies, it is appropriate to discontinue the index agent and switch to another drug. If the patient has inadequate (ie, subtherapeutic) drug trough concentrations, switching to an alternative anti-TNF agent is suggested. If the patient has adequate (ie, therapeutic) drug trough concentrations, switching to another mechanism of treatment (eg, anti-integrin antibody [vedolizumab], anti-IL-12/23 antibody [ustekinumab], anti-IL-23 antibody [risankizumab]) is preferred [17,23].

While transient anti-drug antibodies can disappear spontaneously or can be overcome by dose optimization (particularly when drug concentrations are low), sustained, high anti-drug antibody levels may lead to permanent loss of response and necessitate discontinuation of the index drug. In contrast to target drug trough concentrations, the reporting of anti-drug antibodies has varied among commercial assays and has not been standardized [17]. (See 'Therapeutic drug monitoring' above.)

For patients with anti-drug antibodies who switch to a different biologic agent within the same class, the addition of an immunomodulator may be helpful. The use of immunomodulators (ie, azathioprine, 6-mercaptopurine or methotrexate) decreases the rate of formation of antibodies to anti-TNF agents and results in higher response and remission rates [26-28]. In a meta-analysis of 24 studies including over 4600 patients with inflammatory bowel disease, patients who were treated with combination therapy (ie, anti-TNF agent and immunomodulator) were less likely to develop antibodies against tumor necrosis factor antagonists (anti-TNFs) compared with patients treated with anti-TNF monotherapy (RR 0.49, 95% CI 0.41-0.59) [28] (see "Overview of azathioprine and mercaptopurine use in inflammatory bowel disease").

Preliminary data suggested that patients who develop antibodies against one anti-TNF agent were more likely to develop antibodies against another anti-TNF agent, thus highlighting this concept [29].

One retrospective study analyzed 788 serum samples from 57 infliximab-treated patients with IBD in whom anti-infliximab antibodies had been detected at least once during follow-up [30]. In this study, patients with transient anti-infliximab antibodies had significantly lower median anti-infliximab antibodies levels than those with persistent antibodies (6 and 18 units/mL respectively). In patients with transient anti-infliximab antibodies, antibodies disappeared spontaneously or after infliximab dose optimization in 42 and 58 percent, respectively. A higher proportion of patients with persistent anti-infliximab antibodies discontinued treatment as compared with those with transient antibodies (74 versus 26 percent).

Patients in remission — While therapeutic drug monitoring is useful in the setting of active IBD (ie, reactive drug monitoring), we do not routinely use therapeutic drug monitoring for patients in clinical remission (ie, proactive drug monitoring) because data from randomized trials suggested that proactive monitoring did not improve outcomes. We reserve proactive monitoring for patients who are at higher risk of complications from a disease flare. In a meta-analysis of nine trials including 1405 patients with IBD who were in remission, there were no significant differences in rates of sustained remission, anti-drug antibodies, or serious adverse events between patients who had proactive drug monitoring compared with conventional management [31]. (See 'Therapeutic drug monitoring' above.)

Biomarkers of inflammation — In addition to therapeutic drug monitoring, obtaining biomarkers of inflammation including CRP and fecal calprotectin can help guide therapy to achieve endoscopic and clinical remission in patients with Crohn disease [32,33]. Although the AGA has published guidelines on therapeutic drug monitoring, biomarker monitoring is used at the discretion of the clinician.

Biomarkers of inflammation are typically obtained before initiating therapy, and as an example, CRP levels have been used to predict response to treatment [34,35]. In addition, elevated biomarkers can be followed after initiating biologic therapy to see if the biomarkers improve with treatment.

In a trial of 244 patients with Crohn disease, patients who were monitored by clinical symptoms and with biomarkers (ie, CRP and fecal calprotectin) and in whom biologic and/or immunomodulator therapy was started and escalated based on those results, were more likely to have mucosal healing at 48 weeks compared with patients who were monitored by clinical symptoms alone (46 versus 30 percent, adjusted risk difference 16 percent [95% CI 3.9-28.3]) [32].

- CRP – A high baseline CRP level that normalizes with treatment has been associated with a higher chance of having a response to infliximab [26,36]. In a study of 718 patients with Crohn disease who were receiving infliximab, patients with elevated CRP levels before treatment were more likely to respond to infliximab compared with patients with normal levels (91 versus 83 percent) [36]. Early normalization of the CRP level was associated with a sustained, long-term response and CRP levels remained significantly higher in patients who lost their response to infliximab than in patients who had a sustained response.

- Fecal calprotectin – Fecal calprotectin can be used to monitor response to anti-TNF therapy in patients with IBD, but because of limited sensitivity and specificity it should be used in conjunction with other laboratory tests and symptoms to arrive at clinical decisions [37]. Fecal calprotectin levels correlate with endoscopic disease activity and may differentiate between active and inactive IBD [38-41]. Calprotectin is a zinc and calcium binding protein that is derived mostly from neutrophils and monocytes, and fecal calprotectin levels are increased in patients with mucosal inflammation. (See "Approach to the adult with chronic diarrhea in resource-abundant settings", section on 'General laboratory tests'.)

ADVERSE EVENTS

The tumor necrosis factor (TNF)-alpha inhibitors have multiple potential adverse events that are listed below and discussed in more detail separately [42-45] (see "Tumor necrosis factor-alpha inhibitors: An overview of adverse effects"):

- Infection (see "Risk of mycobacterial infection associated with biologic agents and JAK inhibitors" and "Tumor necrosis factor-alpha inhibitors: Bacterial, viral, and fungal infections").
- Malignancy (see "Tumor necrosis factor-alpha inhibitors: Risk of malignancy").
- Induction of autoimmunity (see "Tumor necrosis factor-alpha inhibitors: Induction of antibodies, autoantibodies, and autoimmune diseases").
- Demyelinating disease.
- Heart failure.
- Injection site reactions.
- Neutropenia.
- Infusion reactions (table 3 and algorithm 1).
- Cutaneous reactions, including psoriaform lesions (suggest referring the patients with skin lesions to dermatology for further evaluation).

Severe adverse reactions may result in discontinuation of anti-TNF therapy. In other cases, the reaction may be manageable, and stopping anti-TNF therapy may not be necessary.

Risks with combination therapy — The risk of lymphoma in patients on infliximab (or other anti-TNF agents) in combination with an immunomodulator (azathioprine or 6-mercaptopurine), along with an increased incidence of infections in patients on more than one immunosuppressive agent, has led to the use of anti-TNF monotherapy in some patients with IBD.

The magnitude of the risk of developing lymphoma is low when viewed in absolute terms (ie, less than one case per 1000 person years) [46]. In a large cohort study including over 189,000 patients with inflammatory bowel disease, the risk of lymphoma was increased in patients exposed to combination therapy (adjusted hazard ratio [aHR] 6.11, 95% CI 3.46-10.8), anti-TNF monotherapy (aHR 2.41, 95% CI 1.6-3.64), or thiopurine monotherapy (aHR 2.6, 95% CI 1.96-3.44) compared with patients who were not exposed to any of these drug regimens during a median follow-up of 6.7 years [46].

Long-term thiopurine use (more than two years) appears to be a common denominator in cases of hepatosplenic T-cell lymphomas, and this issue is addressed separately [47]. (See "Medical management of moderate to severe Crohn disease in adults", section on 'Hepatosplenic T-cell lymphoma'.)

PREGNANCY

The use of anti-TNF agents during pregnancy and lactation is discussed elsewhere. (See "Fertility, pregnancy, and nursing in inflammatory bowel disease", section on 'Anti-tumor necrosis factor agents'.)

BIOSIMILARS FOR BIOLOGIC AGENTS

Copies of biologic agents, including several of the tumor necrosis factor inhibitors, have been marketed and are under development. A "biosimilar" is a copy which is similar but not identical to the original ("reference" or "legacy") product and is no longer under patent protection. Infliximab-dyyb is an example of a biosimilar. Biosimilars for biologic agents are discussed separately. (See "Overview of biologic agents in the rheumatic diseases", section on 'Biosimilars for biologic agents'.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Crohn disease in adults".)

The American Gastroenterological Association (AGA) guidelines on the use of anti-TNF agents for Crohn disease and on therapeutic drug monitoring can be accessed through the AGA website [17,48,49]. In addition, the American College of Gastroenterology (ACG) has issued practice guidelines that can be accessed through the ACG website [50].

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given

condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Crohn disease in adults (The Basics)")
- Beyond the Basics topics (see "Patient education: Crohn disease (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- **Anti-tumor necrosis factor (TNF) therapy** – Tumor necrosis factor (TNF)-alpha inhibitors, including infliximab, adalimumab, and certolizumab pegol, are biologic agents used for treating patients with moderately to severely active Crohn disease. The decision whether to use infliximab, adalimumab, or certolizumab pegol in patients requiring anti-TNF therapy is influenced by the indication, patient preference, and availability in individual countries. (See 'Introduction' above and "Medical management of moderate to severe Crohn disease in adults".)

  Infliximab, adalimumab, and certolizumab pegol are all monoclonal antibodies directed against TNF-alpha. (See 'Tumor necrosis factor inhibitors' above.)

- **Contraindications to use of anti-TNF agents** – Contraindications to the use of anti-TNF therapies include the following (see 'Contraindications' above):

  - Active infection
  - Latent (untreated) tuberculosis
  - Demyelinating disease (eg, multiple sclerosis, optic neuritis)
  - Heart failure (NYHA class III/IV) (table 1)
  - Active lymphoma

  The safety of anti-TNF therapies and risk of recurrent malignancy in patients with a history of malignancy is discussed in detail separately. (See "Tumor necrosis factor-alpha inhibitors: Risk of malignancy".)

- **Therapeutic drug monitoring** – Therapeutic drug monitoring involves measuring serum drug trough concentrations and anti-drug antibodies to optimize the use of anti-TNF agents for patients with inflammatory bowel disease. Some patients who initially achieve remission will develop secondary loss of response during the first year of therapy. Reactive drug monitoring in this setting can help the clinician decide whether dose escalation is needed or if switching to a different drug is preferred.

  For patients in clinical remission, we reserve therapeutic drug monitoring for patients at higher risk of complications from a disease flare, rather than performing it routinely in all patients. (See 'Therapeutic drug monitoring' above.)

- **Adverse events** – Potential adverse events associated with TNF-alpha inhibitors include (see 'Adverse events' above):

  - Infection
  - Malignancy
  - Induction of autoimmunity
  - Demyelinating disease
  - Heart failure
  - Injection site reactions
  - Infusion reactions
  - Neutropenia
  - Cutaneous reactions, including psoriaform lesions

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REFERENCES

1. Lügering A, Schmidt M, Lügering N, et al. Infliximab induces apoptosis in monocytes from patients with chronic active Crohn's disease by using a caspase-dependent pathway. Gastroenterology 2001; 121:1145.

2. ten Hove T, van Montfrans C, Peppelenbosch MP, van Deventer SJ. Infliximab treatment induces apoptosis of lamina propria T lymphocytes in Crohn's disease. Gut 2002; 50:206.
3. Van den Brande JM, Braat H, van den Brink GR, et al. Infliximab but not etanercept induces apoptosis in lamina propria T-lymphocytes from patients with Crohn's disease. Gastroenterology 2003; 124:1774.
4. Nesbitt A, Fossati G, Bergin M, et al. Mechanism of action of certolizumab pegol (CDP870): in vitro comparison with other anti-tumor necrosis factor alpha agents. Inflamm Bowel Dis 2007; 13:1323.
5. Hanauer SB, Feagan BG, Lichtenstein GR, et al. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. Lancet 2002; 359:1541.
6. Present DH, Rutgeerts P, Targan S, et al. Infliximab for the treatment of fistulas in patients with Crohn's disease. N Engl J Med 1999; 340:1398.
7. Roda G, Jharap B, Neeraj N, Colombel JF. Loss of Response to Anti-TNFs: Definition, Epidemiology, and Management. Clin Transl Gastroenterol 2016; 7:e135.
8. D'Haens GR, Panaccione R, Higgins PD, et al. The London Position Statement of the World Congress of Gastroenterology on Biological Therapy for IBD with the European Crohn's and Colitis Organization: when to start, when to stop, which drug to choose, and how to predict response? Am J Gastroenterol 2011; 106:199.
9. Billioud V, Sandborn WJ, Peyrin-Biroulet L. Loss of response and need for adalimumab dose intensification in Crohn's disease: a systematic review. Am J Gastroenterol 2011; 106:674.
10. Bultman E, de Haar C, van Liere-Baron A, et al. Predictors of dose escalation of adalimumab in a prospective cohort of Crohn's disease patients. Aliment Pharmacol Ther 2012; 35:335.
11. Ben-Horin S, Kopylov U, Chowers Y. Optimizing anti-TNF treatments in inflammatory bowel disease. Autoimmun Rev 2014; 13:24.
12. Kennedy NA, Heap GA, Green HD, et al. Predictors of anti-TNF treatment failure in anti-TNF-naive patients with active luminal Crohn's disease: a prospective, multicentre, cohort study. Lancet Gastroenterol Hepatol 2019; 4:341.
13. Schreiber S, Rutgeerts P, Fedorak RN, et al. A randomized, placebo-controlled trial of certolizumab pegol (CDP870) for treatment of Crohn's disease. Gastroenterology 2005; 129:807.
14. Stein AC, Rubin DT, Hanauer SB, Cohen RD. Incidence and predictors of clinical response, re-induction dose, and maintenance dose escalation with certolizumab pegol in Crohn's disease. Inflamm Bowel Dis 2014; 20:1722.

15. Ehrenberg R, Griffith J, Theigs C, McDonald B. Dose Escalation Assessment Among Targeted Immunomodulators in the Management of Inflammatory Bowel Disease. J Manag Care Spec Pharm 2020; 26:758.
16. Colombel JF, Sandborn WJ, Rutgeerts P, et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. Gastroenterology 2007; 132:52.
17. Feuerstein JD, Nguyen GC, Kupfer SS, et al. American Gastroenterological Association Institute Guideline on Therapeutic Drug Monitoring in Inflammatory Bowel Disease. Gastroenterology 2017; 153:827.
18. Davidov Y, Ungar B, Bar-Yoseph H, et al. Association of Induction Infliximab Levels With Clinical Response in Perianal Crohn's Disease. J Crohns Colitis 2017; 11:549.
19. Yarur AJ, Kanagala V, Stein DJ, et al. Higher infliximab trough levels are associated with perianal fistula healing in patients with Crohn's disease. Aliment Pharmacol Ther 2017; 45:933.
20. Strik AS, Löwenberg M, Buskens CJ, et al. Higher anti-TNF serum levels are associated with perianal fistula closure in Crohn's disease patients. Scand J Gastroenterol 2019; 54:453.
21. El-Matary W, Walters TD, Huynh HQ, et al. Higher Postinduction Infliximab Serum Trough Levels Are Associated With Healing of Fistulizing Perianal Crohn's Disease in Children. Inflamm Bowel Dis 2019; 25:150.
22. Plevris N, Jenkinson PW, Arnott ID, et al. Higher anti-tumor necrosis factor levels are associated with perianal fistula healing and fistula closure in Crohn's disease. Eur J Gastroenterol Hepatol 2020; 32:32.
23. Ordás I, Feagan BG, Sandborn WJ. Therapeutic drug monitoring of tumor necrosis factor antagonists in inflammatory bowel disease. Clin Gastroenterol Hepatol 2012; 10:1079.
24. Steenholdt C, Brynskov J, Thomsen OØ, et al. Individualised therapy is more cost-effective than dose intensification in patients with Crohn's disease who lose response to anti-TNF treatment: a randomised, controlled trial. Gut 2014; 63:919.
25. Vande Casteele N, Ferrante M, Van Assche G, et al. Trough concentrations of infliximab guide dosing for patients with inflammatory bowel disease. Gastroenterology 2015; 148:1320.
26. Colombel JF, Sandborn WJ, Reinisch W, et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. N Engl J Med 2010; 362:1383.
27. Baert F, Noman M, Vermeire S, et al. Influence of immunogenicity on the long-term efficacy of infliximab in Crohn's disease. N Engl J Med 2003; 348:601.

28. Qiu Y, Mao R, Chen BL, et al. Effects of Combination Therapy With Immunomodulators on Trough Levels and Antibodies Against Tumor Necrosis Factor Antagonists in Patients With Inflammatory Bowel Disease: A Meta-analysis. Clin Gastroenterol Hepatol 2017; 15:1359.
29. https://ddw.scientificposters.com/epsAbstractDDW.cfm?id=3 (Accessed on October 19, 2020).
30. Vande Casteele N, Gils A, Singh S, et al. Antibody response to infliximab and its impact on pharmacokinetics can be transient. Am J Gastroenterol 2013; 108:962.
31. Nguyen NH, Solitano V, Vuyyuru SK, et al. Proactive Therapeutic Drug Monitoring Versus Conventional Management for Inflammatory Bowel Diseases: A Systematic Review and Meta-Analysis. Gastroenterology 2022; 163:937.
32. Colombel JF, Panaccione R, Bossuyt P, et al. Effect of tight control management on Crohn's disease (CALM): a multicentre, randomised, controlled phase 3 trial. Lancet 2017; 390:2779.
33. Peyrin-Biroulet L, Sandborn W, Sands BE, et al. Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE): Determining Therapeutic Goals for Treat-to-Target. Am J Gastroenterol 2015; 110:1324.
34. Cioffi M, Rosa AD, Serao R, et al. Laboratory markers in ulcerative colitis: Current insights and future advances. World J Gastrointest Pathophysiol 2015; 6:13.
35. Vermeire S, Van Assche G, Rutgeerts P. Laboratory markers in IBD: useful, magic, or unnecessary toys? Gut 2006; 55:426.
36. Jürgens M, Mahachie John JM, Cleynen I, et al. Levels of C-reactive protein are associated with response to infliximab therapy in patients with Crohn's disease. Clin Gastroenterol Hepatol 2011; 9:421.
37. Sipponen T, Savilahti E, Kärkkäinen P, et al. Fecal calprotectin, lactoferrin, and endoscopic disease activity in monitoring anti-TNF-alpha therapy for Crohn's disease. Inflamm Bowel Dis 2008; 14:1392.
38. Schoepfer AM, Beglinger C, Straumann A, et al. Fecal calprotectin correlates more closely with the Simple Endoscopic Score for Crohn's disease (SES-CD) than CRP, blood leukocytes, and the CDAI. Am J Gastroenterol 2010; 105:162.
39. Langhorst J, Elsenbruch S, Koelzer J, et al. Noninvasive markers in the assessment of intestinal inflammation in inflammatory bowel diseases: performance of fecal lactoferrin, calprotectin, and PMN-elastase, CRP, and clinical indices. Am J Gastroenterol 2008; 103:162.
40. Lobatón T, López-García A, Rodríguez-Moranta F, et al. A new rapid test for fecal calprotectin predicts endoscopic remission and postoperative recurrence in Crohn's disease. J Crohns Colitis 2013; 7:e641.

41. D'Haens G, Ferrante M, Vermeire S, et al. Fecal calprotectin is a surrogate marker for endoscopic lesions in inflammatory bowel disease. Inflamm Bowel Dis 2012; 18:2218.
42. Colombel JF, Loftus EV Jr, Tremaine WJ, et al. The safety profile of infliximab in patients with Crohn's disease: the Mayo clinic experience in 500 patients. Gastroenterology 2004; 126:19.
43. Ljung T, Karlén P, Schmidt D, et al. Infliximab in inflammatory bowel disease: clinical outcome in a population based cohort from Stockholm County. Gut 2004; 53:849.
44. Cohen RD, Tsang JF, Hanauer SB. Infliximab in Crohn's disease: first anniversary clinical experience. Am J Gastroenterol 2000; 95:3469.
45. Farrell RJ, Shah SA, Lodhavia PJ, et al. Clinical experience with infliximab therapy in 100 patients with Crohn's disease. Am J Gastroenterol 2000; 95:3490.
46. Lemaitre M, Kirchgesner J, Rudnichi A, et al. Association Between Use of Thiopurines or Tumor Necrosis Factor Antagonists Alone or in Combination and Risk of Lymphoma in Patients With Inflammatory Bowel Disease. JAMA 2017; 318:1679.
47. Kotlyar DS, Blonski W, Diamond RH, et al. Hepatosplenic T-cell lymphoma in inflammatory bowel disease: a possible thiopurine-induced chromosomal abnormality. Am J Gastroenterol 2010; 105:2299.
48. Feuerstein JD, Ho EY, Shmidt E, et al. AGA Clinical Practice Guidelines on the Medical Management of Moderate to Severe Luminal and Perianal Fistulizing Crohn's Disease. Gastroenterology 2021; 160:2496.
49. Terdiman JP, Gruss CB, Heidelbaugh JJ, et al. 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. Gastroenterology 2013; 145:1459.
50. Lichtenstein GR, Loftus EV, Isaacs KL, et al. ACG Clinical Guideline: Management of Crohn's Disease in Adults. Am J Gastroenterol 2018; 113:481.

Topic 4078 Version 46.0

GRAPHICS

NYHA and other classifications of cardiovascular disability

Class	NYHA functional classification[1]	Canadian Cardiovascular Society functional classification[2]	Specific activity scale[3]
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	Ordinary physical activity, such as walking and climbing stairs, does not cause angina. Angina with strenuous or rapid prolonged exertion at work or recreation.	Patients can perform to completion any activity requiring ≥7 metabolic equivalents (ie, can carry 24 lb up 8 steps; do outdoor work [shovel snow, spade soil]; do recreational activities [skiing, basketball, squash, handball, jog/walk 5 mph]).
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Slight limitation of ordinary activity. Walking or climbing stairs rapidly, walking uphill, walking or stair-climbing after meals, in cold, in wind, or when under emotional stress, or only during the few hours after awakening. Walking more than 2 blocks on the level and climbing more than 1 flight of ordinary stairs at a normal pace and in normal conditions.	Patients can perform to completion any activity requiring ≥5 metabolic equivalents (eg, have sexual intercourse without stopping, garden, rake, weed, roller skate, dance foxtrot, walk at 4 mph on level ground) but cannot and do not perform to completion activities requiring ≥7 metabolic equivalents.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less-than-ordinary	Marked limitation of ordinary physical activity. Walking 1 to 2 blocks on the level and climbing 1 flight in normal conditions.	Patients can perform to completion any activity requiring ≥2 metabolic equivalents (eg, shower without stopping, strip and

	physical activity causes fatigue, palpitation, dyspnea, or anginal pain.		make bed, clean windows, walk 2.5 mph, bowl, play golf, dress without stopping) but cannot and do not perform to completion any activities requiring >5 metabolic equivalents.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Inability to carry on any physical activity without discomfort. Anginal syndrome may be present at rest.	Patients cannot or do not perform to completion activities requiring >2 metabolic equivalents. Cannot carry out activities listed above (specific activity scale III).

NYHA: New York Heart Association.

References:

1. *The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels, 9th ed, Little, Brown & Co, Boston 1994. p.253.*
2. *Campeau L. Grading of angina pectoris. Circulation 1976; 54:522.*
3. *Goldman L, Hashimoto B, Cook EF, Loscalzo A. Comparative reproducibility and validity of systems for assessing cardiovascular functional class: Advantages of a new specific activity scale. Circulation 1981; 64:1227.*

Graphic 52683 Version 19.0

Interventions based on therapeutic drug monitoring in patients with inflammatory bowel disease and loss of response to anti-TNF agents

Anti-drug antibody (ADAb)	Drug trough concentration*	
	Inadequate (subtherapeutic)	**Adequate (therapeutic)**
Undetectable	Non immune-mediated pharmacokinetic failure: ▪ Escalate dose of index drug¶	Mechanistic failure: ▪ Switch to drug out of classΔ
Detectable	Immune-mediated pharmacokinetic failure: ▪ If low level ADAb: escalate dose of index drug¶ ▪ If high level ADAb: switch to drug in class◇	Mechanistic failure: ▪ Switch to drug out of class

Refer to UpToDate for additional discussion on therapeutic drug monitoring.

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* Target drug trough concentration: infliximab ≥5 mcg/mL; adalimumab ≥7.5 mcg/mL; certolizumab pegol ≥20 mcg/mL.

¶ Dose can be escalated by either shortening dosing interval or increasing drug dose.

Δ An alternative is to escalate anti-TNF dose, especially for patients in clinical remission but with endoscopic disease activity.

◇ In addition to switching to a drug in class, some patients may also benefit from adding an immunomodulator.

Original table modified for this publication. From: Vande Casteele N, Herfarth H, Katz J, et al. American Gastroenterological Association Institute Technical Review on the Role of Therapeutic Drug Monitoring in the Management of Inflammatory Bowel Diseases. Gastroenterology 2017; 153:835. Table used with the permission of Elsevier Inc. All rights reserved.

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Administration of infliximab: Guidelines for drug administration and the recognition and initial approach to infusion reactions

Description
Intravenous (IV) administration of infliximab, a tumor necrosis factor-alpha antagonist biologic therapy. Infliximab, a chimeric antibody, is administered in the form of periodic infusions (zero, two, and six weeks and, depending on the subsequent course of the disease, every six to eight weeks thereafter).
Contraindications to treatment
Known hypersensitivity to the drug or murine proteins
Active systemic or localized infections
History of infection related to a prosthesis that remains in place
Infection with human immunodeficiency virus
Active infection with hepatitis B virus
Congestive heart failure classified on the New York Heart Association scale as functional class III/IV
History of demyelinating disease
History of cancer (except when there has been no recurrence in the preceding five years and in the case of patients with basal cell carcinoma)
Patients with a history of systemic lupus erythematosus
Live vaccines should not be administered during treatment: yellow fever, German measles, measles, polio, or bacillus Calmette-Guérin (BCG)
Patient care during IV administration of infliximab
Objectives
To prepare patients physically and psychologically so that they undergo treatment in the best possible conditions
To ensure the patient's safety throughout the infusion process
To prevent treatment-related problems and ensure prompt detection of any such problems
Preparation of the patient before the procedure
Ascertain what the patient knows about the treatment they are about to receive
Patients may eat breakfast or lunch and take their usual medication unless they have a history of moderate to severe infusion reactions (risk of vomiting)
Make the patient comfortable in a seat or bed, depending on the preference and physical state of each individual

Check whether the patient's chart includes an order for laboratory testing before the procedure, and whether premedication has been prescribed
Personnel: nursing staff
Procedure
Personnel: nursing staff
Materials: ▪ Esmarch bandage ▪ Cotton ▪ Antiseptic ▪ 20 G catheter ▪ Catheter securement dressings ▪ Pump ▪ Filter (pore size ≤1.2 microns) ▪ Infusion pump ▪ 10 mL syringe ▪ 21 G needle ▪ 10 mL of double-distilled water for each vial of infliximab ▪ Infliximab (store in refrigerator at between 2 and 8°C) ▪ 250 mL of 0.9% saline solution
Implement laboratory testing order, if any, prior to infusion. Administer prescribed premedication, if any. This can only be diphenhydramine or hydrocortisone.
Check arterial blood pressure, heart rate, respiratory rate, and temperature at the start and after completion of infusion and whenever required by the patient's physical condition
Preparation of the drug
Aseptic technique
Reconstitute each 100 mg vial of infliximab with 10 mm of double-distilled water
Aim the double-distilled water against the side of the vial to prevent foaming
Ensure that the contents of the vial have dissolved completely, but avoid prolonged and energetic movements
Allow the solution to stand for five minutes
The solution should be colorless to slightly yellowish and may contain translucent particles (protein) ▪ The solution should not be administered if it is inappropriately colored or contains visible opaque particles
From the bottle of saline solution, withdraw a volume of saline equal to the volume of infliximab solution to be used in order to obtain a final volume of 250 mL and a concentration of between 0.4 and 4 mg/ml

The solution must be infused within three hours of reconstitution

Never dissolve infliximab in dextrose solution

Cannulate the venous line

Administer the drug using a volumetric infusion pump
- The first, second, third, and fourth infusions should be administered over two hours (125 mL/hour)
- Starting with the fifth infusion, the dose can be infused in one hour (250 mL/hour)

Assess response to treatment; if the patient does not present any anomalous symptoms, he or she can be discharged and return to normal daily activity

Patients must be instructed to telephone their clinician or the nursing staff if they experience any reaction symptoms after the infusion

Observations

Infusion time can be modified by the clinician responsible for the patient

Description of problems related to the procedure and remedial action

Acute infusion reactions

Mild in the presence of	Moderate in the presence of	Severe in the presence of
▪ Headache ▪ Diaphoresis ▪ Throat irritation ▪ Lumbar pain ▪ Hyperemia ▪ Nausea ▪ Palpitations ▪ Itching ▪ Cutaneous eruption ▪ Flushing ▪ Vertigo ▪ Vomiting	The same symptoms as mild reactions and ▪ Dysphagia ▪ Hypotension or hypertension (± 20 mmHg with respect to baseline) ▪ Chest pain or tightness ▪ Edema of the face, hands, or lips ▪ Suffocating sensation ▪ Hyperemia (accompanied by a sensation of heat or fever) ▪ Hyperthermia (<39°C) ▪ Palpitations, tachycardia ▪ Urticaria	The same symptoms as moderate reactions and ▪ Severe hypotension or hypertension (± 40 mmHg with respect to baseline) ▪ Hyperthermia and chills (≥39°C) ▪ Swelling of the larynx or pharynx with stridor ▪ Dyspnea ▪ Severe bronchospasm ▪ Convulsive seizure ▪ Clinically significant chest pain

Action to be taken:
- Stop the infusion
- Monitor blood pressure, heart rate, respiratory rate, and temperature
- Notify the treating clinician

▪ If the reaction does not resolve, follow appropriate procedures for management of an acute reaction to infusion of infliximab ▪ If extravasation occurs, stop the infusion immediately, notify the treating clinician, attempt to aspirate the extravasated fluid with a 10 to 20 mL syringe, withdraw the IV line, mark the affected area, and follow the hospital's treatment protocol covering such events
Important points
To ensure early detection of infusion reactions, monitor the patient's response to treatment
Ensure that the intravenous line is open
Assessment indicators
The nursing record should include details of the results of vital signs monitoring before and after treatment
The nursing record should provide details of the assessment of tolerance to treatment, that is, the occurrence or absence of incidents
Records
The following information should be recorded: ▪ Vital signs ▪ The assessment and preparation of the patient prior to treatment ▪ Incidents (presence or absence) related to the procedure ▪ Assessment of the patient's condition after treatment

Original figure modified for this publication. Puig Sanz L, Sáez E, Lozano MJ, et al. [Reactions to infliximab infusions in dermatologic patients: consensus statement and treatment protocol. Working Group of the Grupo Español de Psoriasis de la Academia Española de Dermatología y Venereología.] Actas Dermosifiliogr 2009; 100:103. Table used with the permission of Elsevier Inc. All rights reserved.

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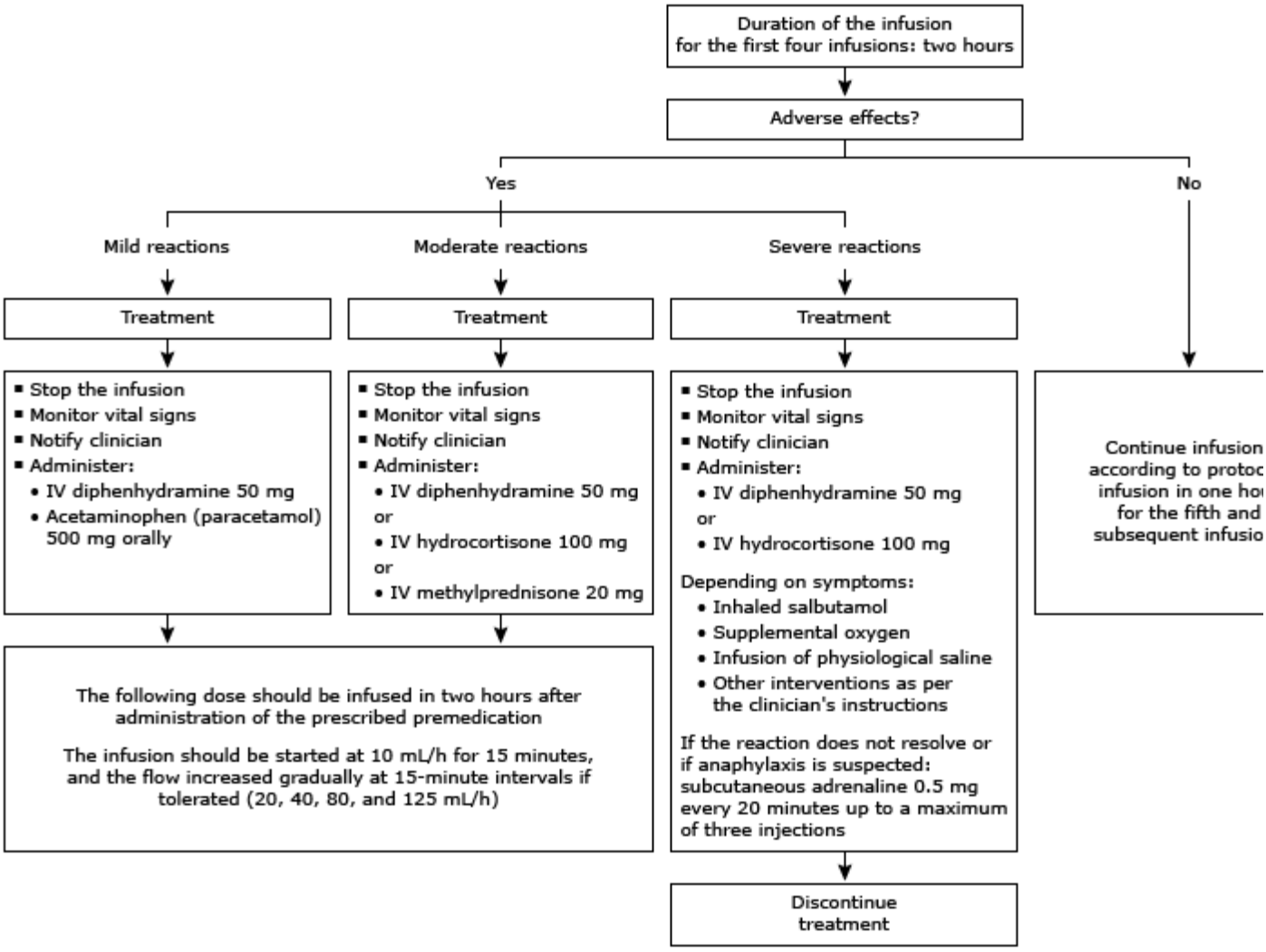
Procedure to be followed in the case of an acute reaction to infliximab infusion



IV: intravenous.

Original figure modified for this publication. Puig Sanz L, Sáez E, Lozano MJ, et al. [Reactions to infliximab infusions in dermatologic p consensus statement and treatment protocol. Working Group of the Grupo Español de Psoriasis de la Academia Española de Dermato Venereología.] Actas Dermosifiliogr 2009; 100:103. Illustration used with the permission of Elsevier Inc. All rights reserved.

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Contributor Disclosures

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