CLINICAL THERAPEUTICS

John A. Jarcho, M.D., *Editor*

Tumor Necrosis Factor Inhibitors for Inflammatory Bowel Disease

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This Journal *feature begins with a case vignette that includes a therapeutic recommendation. A discussion of the clinical problem and the mechanism of benefit of this form of therapy follows. Major clinical studies, the clinical use of this therapy, and potential adverse effects are reviewed. Relevant formal guidelines, if they exist, are presented. The article ends with the authors' clinical recommendations.*

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A 35-year-old man presents with an exacerbation of Crohn's ileocolitis. He received a diagnosis of Crohn's disease 8 years ago and has been treated on three previous occasions with prednisone. Because of a recurrent need for glucocorticoids, treatment with azathioprine (150 mg per day) was started 1 year ago. He now reports abdominal pain in the right lower quadrant, which developed 1 week ago, with an increase in stool frequency to eight to nine stools per day. Laboratory tests show a hemoglobin concentration of 10.7 g per deciliter and a C-reactive protein level of 21 mg per liter. Magnetic resonance enterography shows inflammation localized to the distal ileum and colon. The patient is referred to a gastroenterologist. An ileocolonoscopy reveals patchy erythema and ulcerations near the hepatic flexure as well as similar lesions in the terminal ileum. Biopsy specimens obtained during colonoscopy show acute and chronic granulomatous inflammation, and the gastroenterologist recommends treatment with a tumor necrosis factor (TNF) inhibitor.

THE CLINICAL PROBLEM

Inflammatory bowel disease, an umbrella term for a range of diseases of which ulcerative colitis and Crohn's disease are the two prevailing entities, is a common chronic gastrointestinal disorder. Extrapolation from available data suggests that in the United States and Canada, more than 780,000 persons have ulcerative colitis and 630,000 have Crohn's disease, and the global incidence of both disorders is increasing.[1]

Inflammatory bowel disease has serious effects in terms of morbidity and quality of life.[2] In the era before biologic therapy was available, the rate of hospitalization owing to medical complications, the need for surgery, or both was 194 admissions per 1000 patient-years in a population-based cohort of patients with Crohn's disease.[3] In the first 10 years after a diagnosis of Crohn's disease, the cumulative rate of surgery is 40 to 55%.[3] In a recent large, population-based epidemiologic study of ulcerative colitis, the rate of colectomy 20 years after diagnosis was 14.8%.[4] Furthermore, extraintestinal manifestations (rheumatologic, dermatologic, ophthalmologic, hematologic [including thromboembolic], and hepatic complications) may at any time affect a third of all patients with inflammatory bowel disease.[5]

According to meta-analyses of studies in unselected population-based cohorts, the risk of colorectal cancer is modestly increased among patients with both ulcerative colitis and Crohn's disease,[6] and the latter disorder also carries a markedly increased relative risk of small-bowel cancer among those with ileal inflammation,[7] although the absolute risk is low. However, these data are primarily from studies conducted at a time when there were fewer treatment options than there are today.

More recent data suggest that the overall risk of colorectal cancer is no longer increased among patients with inflammatory bowel disease, although some subgroups of patients remain at increased risk.[8]

PATHOPHYSIOLOGY AND EFFECTS OF THERAPY

As an important part of the immune system, the intestine recognizes and reacts to environmental stimuli, including the microbes in the gut lumen. This interaction is highly regulated and prevents the induction of mucosal inflammation by the commensal bacteria of the normal microbiome, a phenomenon that has been called intestinal homeostasis.[9] The general hypothesis is that inflammatory bowel disease develops as a result of a persistent, inappropriate perturbation of this complex interaction, resulting in changes in the microbiome (dysbiosis) and in mucosal inflammation.[9] These changes, which are to a large degree genetically determined, may include disruption of the barrier function (mainly in ulcerative colitis), dysfunction of microbe sensing (mainly in Crohn's disease), and changes in the regulation of adaptive immune responses (in both disorders).[10]

The proinflammatory cytokine TNF-α has been identified as playing a pivotal role in the inflammatory cascade that causes chronic intestinal inflammation in inflammatory bowel disease.[11] Synthetic anti–TNF-α antibodies have been shown to mitigate this inflammatory process. Figure 1 illustrates how TNF inhibitors can neutralize TNF-α–mediated signaling.[12] In addition, TNF inhibitors have been shown to induce apoptosis of TNF-α–producing immune cells,[13] reducing the production of a variety of downstream proinflammatory cytokines from these and other cells.[14]

The first TNF inhibitor shown to be beneficial in the treatment of inflammatory bowel disease was infliximab, a chimeric antibody (25% murine sequence and 75% human sequence) that specifically binds TNF-α and that was initially evaluated in patients with Crohn's disease.[15,16] Attempts to reduce immunogenic responses induced by chimeric antibodies led to the creation of a fully humanized monoclonal antibody. This anti–TNF-α monoclonal antibody, adalimumab, was also shown to be efficacious in the treatment of Crohn's disease,[17,18] as was certolizumab pegol, a humanized anti-TNF antibody Fab′ fragment conjugated with a polyethylene glycol molecule.[19-21] The observed efficacy of TNF inhibitors in patients with Crohn's disease provided a rationale for trials in patients with ulcerative colitis. Recently, another human anti–TNF-α monoclonal antibody, golimumab, was shown to be efficacious in the treatment of ulcerative colitis.[22]

Etanercept, which is a nonantibody soluble recombinant TNF receptor–Fc fusion protein, is not effective in the treatment of inflammatory bowel disease.[23] The reason for this difference is not well established, but it may be that etanercept does not induce mucosal T-cell apoptosis in the way that antibody-based TNF inhibitors do.[24]

CLINICAL EVIDENCE

Several placebo-controlled trials have shown that infliximab,[16,25] adalimumab,[17,18,26] and certolizumab pegol[20] are efficacious in the treatment of moderate-to-severe Crohn's disease, both as first-line therapy and in patients with inadequate responses to standard treatment (discussed below).[27] Benefits of therapy include the achievement of disease remission and the maintenance of a treatment response.[21,25,28,29] In addition to reducing signs and symptoms of disease, TNF inhibitors allow tapering of glucocorticoids (glucocorticoid-free remission)[17,25] and promote mucosal healing.[30] The former is considered a clinically relevant benefit, and the latter suggests protection against disease progression.

Infliximab is also effective in the treatment of fistulizing Crohn's disease.[15,31] In addition, small studies have suggested that early treatment with infliximab or adalimumab (within 4 weeks after surgery) might prevent histologic and endoscopic recurrence after ileal resection.[32,33]

Randomized, controlled trials involving patients with ulcerative colitis have shown infliximab,[34] adalimumab,[35,36] and golimumab[22] to be effective in inducing and maintaining clinical remission (including glucocorticoid-free remission) in patients with moderate-to-severe disease activity in whom conventional therapy has failed. A post hoc analysis of two trials showed that infliximab reduced the rate of colectomy after 1 year from 17% in the placebo group to 10% in the infliximab group (number needed to treat to prevent one colectomy, 14).[37] TNF inhibitors may also be used as rescue therapy in hospitalized patients with severe ulcerative colitis.[38]

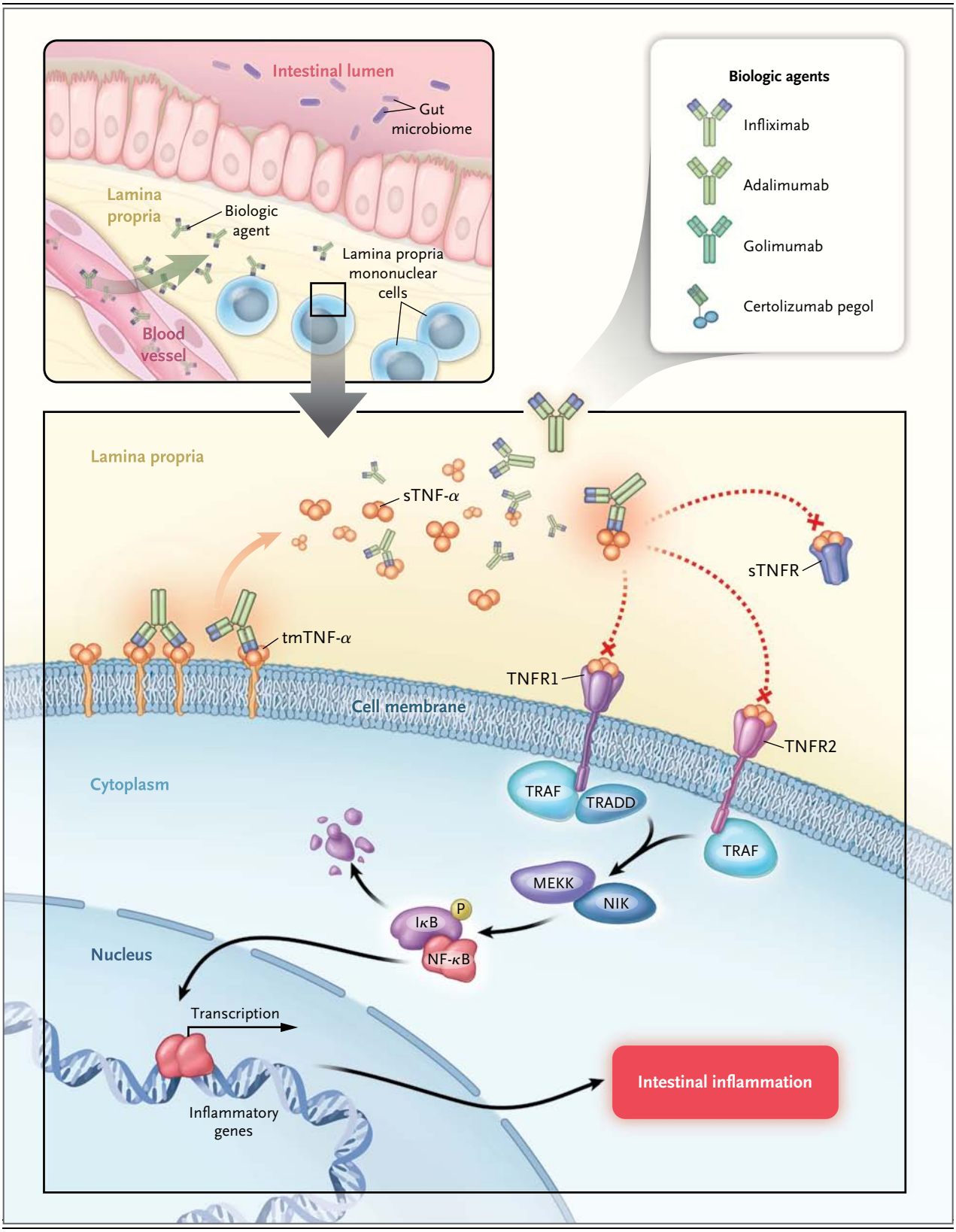

Figure 1 (facing page). Mechanism of Therapeutic Effect of Anti–Tumor Necrosis Factor α (TNF-α) Antibodies in Inflammatory Bowel Disease.

Anti–TNF-α antibodies bind to two types of homotrimeric TNF-α: the precursor transmembrane TNF-α (tmTNF-α) and the soluble TNF-α (sTNF-α), which is processed from tmTNF-α. Thus, these biologic agents block the interaction between TNF-α molecules and TNF-α receptor type 1 and type 2 (TNFR1 and TNFR2) as well as soluble TNF-α receptors (sTNFR), neutralizing TNF-α–mediated proinflammatory cell signaling and inhibiting the expression of inflammatory genes. Infliximab, the first TNF inhibitor on the market, is used as an example in this figure. IκB denotes inhibitor of κB, MEKK mitogen-activated protein kinase kinase, NF-κB nuclear factor κB, NIK NF-κB–inducing kinase, P phosphorylated protein, TRADD TNFR1-associated death domain protein, and TRAF TNFR-associated factor.

CLINICAL USE

Conventionally, a step-up strategy is used in the management of inflammatory bowel disease (Fig. 2). Treatment with 5-aminosalicylic acid is considered appropriate for mild cases of ulcerative colitis, both for induction of remission and for prevention of relapse. Although 5-aminosalicylic acid was previously also used for mild cases of Crohn's disease, recent meta-analyses do not indicate that this drug has any clinically relevant efficacy in patients with this condition.[39-41] For these patients, topical glucocorticoids (for distal colonic disease) and budesonide (for distal ileal involvement) are treatment options, and occasionally, antibiotics may be used in patients with Crohn's ileocolitis. Patients with moderate-to-severe inflammatory bowel disease (or those with mild disease in whom 5-aminosalicylic acid treatment fails) are treated with short courses (2 to 4 months) of glucocorticoids. Patients who have a relapse on tapering of glucocorticoids (indicating glucocorticoid-dependent disease) are offered immunomodulators such as thiopurines (e.g., azathioprine or mercaptopurine) or methotrexate (the latter only for patients with Crohn's disease).[42]

For patients who do not have a response to glucocorticoids (indicating glucocorticoid-refractory disease) or who have a relapse despite immunomodulator therapy, a TNF inhibitor is an appropriate treatment option. There have been no head-to-head comparisons of the various TNF inhibitors, and consequently, direct evidence of their relative efficacy and safety is lacking. However, the clinical trials suggest similar efficacy among the available drugs.[16-18,22,25,26,34-36,43]

Because TNF inhibitors interfere with the normal inflammatory response, they are contraindicated in patients with uncontrolled infections. Before initiating therapy, patients should be screened for hepatitis B and evaluated for tuberculosis exposure (with chest radiography and an interferon-γ release assay, if the patient is already immunosuppressed, because a tuberculin skin test may be inconclusive). There is no evidence that hepatitis C is reactivated by these drugs.[44,45] Patients requiring TNF-inhibitor treatment should have their vaccination status reviewed and updated. In particular, vaccinations against pneumococcal infection, influenza, and human papillomavirus infection (with the use of inactivated vaccines) are recommended for all patients receiving immunosuppressive therapy, including TNF inhibitors.[46] Live vaccines are contraindicated during biologic therapy and for at least the first 3 months after discontinuation of treatment (with the possible exception of the varicella–zoster vaccine[47]). In addition, TNF inhibitors are contraindicated in patients with severe congestive heart failure (New York Heart Association class III or IV) and those with hypersensitivity to the active ingredient or any excipients.[48] TNF inhibitors should be used cautiously in patients with a history of cancer or demyelinating disorders of the central nervous system, owing to the risk of recurrence.

Infliximab is administered intravenously at a dose of 5 mg per kilogram of body weight at weeks 0, 2, and 6 (induction therapy); thereafter, it is given every 8 weeks. Adalimumab is administered subcutaneously at a dose of 160 mg at week 0, followed by 80 mg at week 2 and then 40 mg every second week.[18] Certolizumab pegol is given subcutaneously, with an induction dose of 400 mg at weeks 0, 2, and 4 and then every 4 weeks thereafter.[20] Golimumab is administered subcutaneously at a dose of 200 mg at week 0, followed by 100 mg at week 2 and then 100 mg every 4 weeks.[22]

During treatment with TNF inhibitors, patients should be monitored for signs and symptoms of intercurrent infection (e.g., upper respiratory tract infection and skin ulcers). The following assessments should be performed before the initiation of treatment and at regular intervals (every 8 to 12 weeks) during treatment: urinalysis,

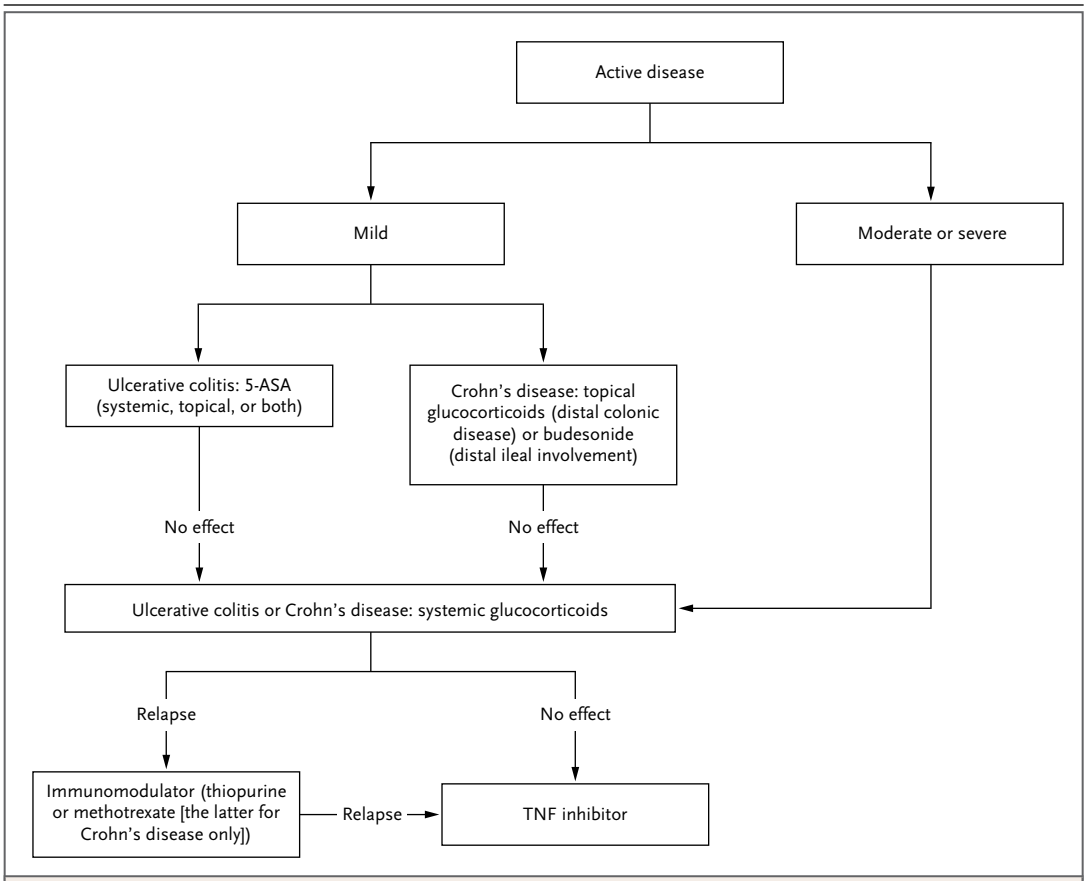

Figure 2. Algorithm for the Use of TNF Inhibitors in Patients with Inflammatory Bowel Disease.
This algorithm depicts the conventional step-up strategy used in the treatment of ulcerative colitis and Crohn's disease. 5-ASA denotes 5-aminosalicylic acid.

a complete blood count, and measurement of levels of acute-phase reactants (e.g., C-reactive protein), creatinine, and electrolytes. Measurement of liver enzyme levels should be performed every 2 weeks in the first 1 to 2 months of treatment and every 8 to 12 weeks thereafter.[49] In addition, patients should be monitored carefully for symptoms and signs suggestive of cancer or the worsening of a coexisting illness, such as congestive heart failure or diabetes.

A considerable number of patients with Crohn's disease (10 to 40%, depending on selection criteria) do not have a clinically relevant response to currently available TNF inhibitors (primary treatment failure),[15-18,20] and among patients with ulcerative colitis, this proportion may be as high as 50%.[34-36] In addition, only about one third to one half of patients with Crohn's disease have a complete remission,[16-18,20] and about two thirds of patients do not have a response that is sustained during 12 months of continuous treatment (secondary treatment failure).[17,21,31] Patients who do not have a response or who have a relapse during continued therapy should undergo clinical reassessment. Noninflammatory causes of symptoms (e.g., diarrhea induced by bile-salt malabsorption, which may occur after ileal resection, or abdominal pain induced by fibrotic strictures) should be treated appropriately. Adjustment of antiinflammatory treatment should be considered only if persistent inflammation can be documented. In this situation, options include increasing the dose,[25,50] switching to another TNF inhibitor,[26,51,52] or switching to an agent other than a TNF inhibitor. The most appropriate strategy will vary from patient to patient because the cause of treatment failure varies. For patients treated with infliximab or adalimumab, measurement of antidrug antibodies and drug levels may aid in evaluating the cause of treatment failure.[53]

In patients with persistent inflammation despite standard doses of infliximab, an increase in the dose (e.g., up to 10 mg per kilogram) or of the frequency of administration (e.g., every 4 weeks instead of every 8 weeks) may induce a response in up to 90% of patients.[54] However, the durability of the response is unknown.[55] Similarly, among patients who have disease flares with adalimumab at a dose of 40 mg every other week, a response may be regained in up to 70% of patients by escalating the dose to either 80 mg every other week or 40 mg per week.[50,56] For patients who have an initial response to certolizumab pegol at a dose of 400 mg every 4 weeks, followed by a relapse, the dose interval may be shortened to every 2 weeks.[52] Recommendations on dose escalation are currently unavailable for patients treated with golimumab for ulcerative colitis.

The annual projected cost of each of the biologic agents for a 70-kg patient with inflammatory bowel disease is approximately $19,000 in the first year and $15,000 in subsequent years, according to data on drug use in a U.S. managed-care population.[57] These figures exclude costs associated with administration and dose escalation.

ADVERSE EFFECTS

Acute infusion reactions occur in approximately 10% of patients treated with infliximab[58] and can include fever or chills (3%), cardiopulmonary reactions such as chest pain or dyspnea (1%), and pruritus or urticaria alone or combined with cardiopulmonary reactions (1%). Serious infusion reactions, including anaphylaxis, convulsions, erythematous rash, and hypotension, occur in less than 1% of patients.[59] Infusion reactions are not a concern with the subcutaneously administered TNF inhibitors. However, injection-site reactions and even anaphylactic reactions have been reported during the use of these agents.[60] In rare cases (<1 per 1000 patients), treatment induces serum sickness (especially after retreatment) and leukocytoclastic vasculitis.[61] Biologic agents should be stopped if jaundice or marked elevations in liver enzymes develop.[49]

Neurologic events (e.g., a new onset or an exacerbation of demyelinizing neuropathy, including optic neuritis and multiple sclerosis) are rare (<1 event per 1000 patients) during TNF-inhibitor treatment. The prognosis is usually good if the event is recognized immediately and the treatment is discontinued.[62]

In general, infections occur more often in patients with Crohn's disease than in the general population,[63] but biologic therapy is associated with a further risk of infections, including sepsis, sinusitis, pneumonia, histoplasmosis, listeriosis, and other opportunistic infections, and may reactivate latent tuberculosis,[45,64] hepatitis B infection,[45] and other viral infections.[45] Data on patients enrolled in the Crohn's Therapy, Resource, Evaluation, and Assessment Tool registry, established by the manufacturer of infliximab to prospectively study its long-term safety, showed an increased risk of serious infections with infliximab alone.[65] However, a meta-analysis did not identify any increased risk of serious infections (i.e., those requiring antimicrobial therapy or hospitalization) among patients with Crohn's disease who were receiving TNF inhibitors, as compared with patients not receiving these drugs.[27]

Combinations of glucocorticoids, immunomodulators, and TNF inhibitors may be associated with an increased risk of cancers (non-Hodgkin's lymphoma, lung cancer, skin cancer, and others).[63,66,67] No causal associations between biologic agents alone and cancer have been shown.[68] However, the major clinical trials were short, and the long-term risk of cancer may not yet have become apparent.

AREAS OF UNCERTAINTY

The value of concomitant treatment with immunosuppressive agents and TNF inhibitors has been debated intensively. Studies have shown that the efficacy of combination therapy with infliximab and azathioprine is superior to that of infliximab or azathioprine alone in the treatment of both Crohn's disease[69] and ulcerative colitis.[70] In addition, the development of antibodies to infliximab (which in some cases may be associated with loss of effect) is reduced by concomitant immunosuppression.[71]

The step-up approach to therapy described above has been the standard of care in inflammatory bowel disease. In this approach, combined immunomodulatory and TNF-inhibitor treatment is not introduced until both glucocorticoid therapy and immunomodulatory therapy have failed. Inspired by the treatment paradigm in rheumatoid arthritis, in which early combined treatment has been advocated to preserve joint function and prevent disability, some gastroenterologists have suggested that a more aggressive approach be adopted,

with combined treatment or single-agent TNF-inhibitor treatment introduced at an earlier stage.[72] Although such an approach appears to provide better control of symptoms,[73] there are no data to confirm that it is actually superior to conventional step-up therapy in terms of disease progression.

Another crucial question is when to stop biologic therapy. The STORI (Study of Infliximab Discontinuation in Crohn's Disease Patients in Stable Remission on Combined Therapy with Immunosuppressors) trial identified predictors of a relapse after the cessation of infliximab therapy.[74] These included male sex, the absence of surgical resection, leukocyte counts of more than 6.0×10^9 per liter, a hemoglobin level of up to 14.5 g per deciliter, a C-reactive protein level of at least 5.0 mg per liter, and a fecal calprotectin level of at least 300 μg per liter. Patients with a maximum of two of these risk factors had a 15% risk of relapse within 1 year. These risk factors may be useful in identifying patients who are candidates for the withdrawal of infliximab.[74]

Episodic treatment with TNF inhibitors increases the risk of the development of human antibodies to the biologic agent, which can result in loss of a response and an increased risk of adverse reactions.[75] A recent prospective study evaluated treatment responses after reintroduction of infliximab in patients who had a prior response. In this study, 37 of 40 patients went into remission on reintroduction, a finding that suggests that a flare after stopping therapy may not rule out future use of infliximab.[74]

GUIDELINES

A guideline issued by the American College of Gastroenterology in 2009[76] recommends the use of TNF-α monoclonal antibodies (infliximab, adalimumab, or certolizumab pegol) in patients with moderately to severely active Crohn's disease who have not had a response to adequate therapy with a glucocorticoid or an immunomodulator. TNF inhibitors may be used as alternatives to glucocorticoid therapy in selected patients with Crohn's disease in whom glucocorticoids are contraindicated or not desired. The corresponding guideline issued by the European Crohn's and Colitis Organization in 2010 has similar recommendations.[77] The European guideline distinguishes between glucocorticoid-refractory and glucocorticoid-dependent Crohn's disease but recommends TNF inhibitors for both types of disease.[77] Both guidelines recommend TNF inhibitors for maintenance of remission and prevention of relapse.[76,77] However, neither guideline provides firm recommendations for the duration of treatment.[76,77]

With regard to ulcerative colitis, the guideline issued by the American College of Gastroenterology recommends the use of infliximab in patients with mild-to-moderate disease that is glucocorticoid-refractory or glucocorticoid-dependent despite adequate doses of an immunomodulator or who have intolerable adverse events with these medications.[78] The guideline also recommends infliximab for patients with severe disease in whom standard treatment has failed. Finally, the guideline mentions infliximab as an option for patients with severe ulcerative colitis who require high-dose glucocorticoids and hospital admission but do not have a response to this treatment.[78] The European guideline provides similar recommendations.[79] Both guidelines recommend infliximab maintenance treatment in patients with ulcerative colitis who have a response to this treatment.[78,79] Adalimumab and golimumab are not mentioned in these guidelines because they were approved very recently for this indication, after the guidelines were published. Certolizumab has not been approved for the treatment of ulcerative colitis.

RECOMMENDATIONS

The patient described in the vignette is a candidate for TNF-inhibitor treatment because he has active inflammation (documented by magnetic resonance enterography, endoscopy, histologic findings, and an elevated C-reactive protein level) despite having received standard treatment for Crohn's disease. Any of the approved agents could be used. The extent of clinical experience with the various TNF inhibitors favors infliximab, whereas the other agents offer the greater convenience of subcutaneous administration. Before initiation of TNF-inhibitor treatment, the patient should be carefully screened for chronic infections, in particular hepatitis B and tuberculosis, and should be counseled regarding recommended vaccinations for patients receiving immunosuppressive therapy. Azathioprine treatment can be continued, but the benefit of combined treatment with azathioprine and a TNF inhibitor for more than 12 months is uncertain. Furthermore, there are no firm data to provide the basis for general recommendations regarding the duration

of TNF-inhibitor treatment. During TNF-inhibitor treatment, the patient's symptoms should be monitored on a regular basis, together with routine blood testing as described above.

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