Azathioprine and/or 6-MP therapy increases the risk to about 4:10,000. The highest risk for thiopurine-associated NHL is in patients over 65 years old, with a moderate risk in those between the ages of 50 and 65. Anti-TNF therapy increases the risk to approximately 6:10,000.

HEPATOSPLENIC T CELL LYMPHOMA (HSTCL) HSTCL is a nearly universally fatal lymphoma in patients with or without CD. In patients with CD, events reported to the Food and Drug Administration Adverse Event Reporting System (FDA AERS) and search of PubMed and Embase published case reports demonstrate a total of 37 unique cases. Eighty-six percent of the patients were male, with a median age of 26 years. Patients had CD for a mean of 10 years before the diagnosis of HSTCL. Thirty-six cases had used either 6-MP or azathioprine, and 28 cases had used infliximab. Of these 28 cases, 27 had also used 6-MP or azathioprine. The other case had a history of both infliximab and adalimumab exposure.

SKIN LESIONS New-onset psoriasiform skin lesions develop in nearly 5% of IBD patients treated with anti-TNF therapy. Most often, these can be treated topically, and rarely, anti-TNF therapy must be decreased, switched, or stopped. The risk of melanoma is increased almost twofold with anti-TNF and not thiopurine use. The risk of nonmelanoma skin cancer is increased with thiopurines and biologics, especially with 1 year of follow-up or greater. Patients on these medications should have a skin check at least once a year.

INFECTIONS All of the anti-TNF drugs are associated with an increased risk of infections, particularly reactivation of latent tuberculosis and opportunistic fungal infections including disseminated histoplasmosis and coccidioidomycosis. It is recommended that patients have a purified protein derivative (PPD) or a QuantiFERON-TB gold test as well as a chest x-ray before initiation of anti-TNF therapy. Patients over 65 have a higher rate of infections and death on infliximab or adalimumab than those younger than 65 years of age.

OTHER Acute liver injury due to reactivation of hepatitis B virus and to autoimmune effects and cholestasis has been reported. Rarely, infliximab and the other anti-TNF drugs have been associated with optic neuritis, seizures, new onset or exacerbation of clinical symptoms, and radiographic evidence of central nervous system demyelinating disorders, including multiple sclerosis. They may exacerbate symptoms in patients with New York Heart Association functional class III/IV heart failure.

ANTI-INTEGRINS Integrins are expressed on the cell surface of leukocytes and serve as mediators of leukocyte adhesion to vascular endothelium. α4-Integrin along with its β1 or β7 subunit interact with endothelial ligands termed adhesion molecules. Interaction between α4β7 and mucosal addressin cellular adhesion molecule (MAdCAM-1) is important in lymphocyte trafficking to gut mucosa.

Natalizumab is a recombinant humanized IgG4 antibody against α4-integrin that has been shown to be effective in induction and maintenance of patients with CD. It has been approved since February 2008 for the treatment of patients with CD refractory or intolerant to anti-TNF therapy. The rates of response and remission at 3 months are about 60% and 40%, respectively, with a sustained remission rate of about 40% at 36 weeks.

One case of progressive multifocal leukoencephalopathy (PML) after eight infusions of natalizumab was observed among 1043 patients in the clinical trials for CD, and two patients developed PML in the multiple sclerosis (MS) trials after a median of 120 weeks. There were 410 postmarketing cases of PML, 408 in MS and 2 in CD. The most important risk factor for development of PML is exposure to the John Cunningham (JC) polyomavirus, seen in 50–55% of the adult population. The other two risk factors for development of PML are longer duration of treatment, especially beyond 2 years, and prior treatment with an immunosuppressant medication. Patients with all three risk factors have an estimated risk of 11:1000.

The FDA approved a commercial enzyme-linked immunosorbent assay (ELISA) kit to assay anti-JC viral antibodies (Stratify JCV Antibody ELISA; Focus Diagnostics, Cypress, CA) in early 2012. The test is 99% accurate in stratifying risk of PML. It is recommended that all patients be tested prior to initiating natalizumab therapy. JC virus serologies are then measured every 6 months because 1–2% of patients will seroconvert yearly. All patients taking natalizumab and their providers must be enrolled in the TOUCH (Tysabri Outreach Unified Commitment for Health) pharmacovigilance program. Natalizumab is administered IV, 300 mg every 4 weeks. Labeling requirements mandate that it not be used in combination with any immunosuppressant medications.

Vedolizumab, another leukocyte trafficking inhibitor, is indicated for patients who have had an inadequate response or lost response to, or were intolerant of a TNF blocker or immunomodulator; or had an inadequate response or were intolerant to, or demonstrated dependence on glucocorticoids. It is an option for patients who are JC antibody positive since it does not cross the blood-brain barrier. Vedolizumab is a monoclonal antibody directed against α4β7 integrin specifically and has the ability to convey gut-selective immunosuppression.

THERAPIES IN DEVELOPMENT

Ustekinumab, a fully human IgG1 monoclonal antibody, blocks the biologic activity of IL-12 and IL-23 through their common p40 subunit by inhibiting the interaction of these cytokines with their receptors on T cells, natural killer cells, and antigen presenting cells. It shows efficacy in moderate to severe CD in clinical trials.

Tofacitinib is an oral inhibitor of Janus kinases 1, 3, and, to a lesser extent, 2. It is expected to block signaling involving common gamma chain–containing cytokines including IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21. These cytokines are integral to lymphocyte activation, function, and proliferation. It is effective in moderate to severe UC in clinical trials.

NUTRITIONAL THERAPIES

Dietary antigens may stimulate the mucosal immune response. Patients with active CD respond to bowel rest, along with TPN. Bowel rest and TPN are as effective as glucocorticoids at inducing remission of active CD but are not effective as maintenance therapy. Enteral nutrition in the form of elemental or peptide-based preparations is also as effective as glucocorticoids or TPN, but these diets are not palatable. Enteral diets may provide the small intestine with nutrients vital to cell growth and do not have the complications of TPN. In contrast to CD, dietary intervention does not reduce inflammation in UC. Standard medical management of UC and CD is shown in **Fig. 351-12**.

SURGICAL THERAPY

Ulcerative Colitis Nearly one-half of patients with extensive chronic UC undergo surgery within the first 10 years of their illness. The indications for surgery are listed in **Table 351-8**. Morbidity is about 20% for elective, 30% for urgent, and 40% for emergency proctocolectomy. The risks are primarily hemorrhage, contamination and sepsis, and neural injury. The operation of choice is an ileoanal J pouch anastomosis (IPAA).

Because UC is a mucosal disease, the rectal mucosa can be dissected and removed down to the dentate line of the anus or about 2 cm proximal to this landmark. The ileum is fashioned into a pouch that serves as a neorectum. This ileal pouch is then sutured circumferentially to the anus in an end-to-end fashion. If performed carefully, this operation preserves the anal sphincter and maintains continence. The overall operative morbidity is 10%, with the major complication being bowel obstruction. Pouch failure necessitating conversion to permanent ileostomy occurs in 5–10% of patients. Some inflamed rectal mucosa is usually left behind, and thus endoscopic surveillance is necessary. Primary dysplasia of the ileal mucosa of the pouch has occurred rarely.

Patients with IPAA usually have about 6–10 bowel movements a day. On validated quality-of-life indices, they report better performance in sports and sexual activities than ileostomy patients. The most frequent complication of IPAA is pouchitis in about 30–50%