measured by monoclonal radioimmunoassay or by the high-performance liquid chromatography assay should be maintained between 150 and 350 ng/mL.

CSA may cause significant toxicity; renal function should be monitored frequently. Hypertension, gingival hyperplasia, hypertrichosis, paresthesias, tremors, headaches, and electrolyte abnormalities are common side effects. Creatinine elevation calls for dose reduction or discontinuation. Seizures may also complicate therapy, especially if the patient is hypomagnesemic or if serum cholesterol levels are <3.1 mmol/L (<120 mg/dL). Opportunistic infections, most notably *Pneumocystis carinii* pneumonia, may occur with combination immunosuppressive treatment; prophylaxis should be given. Major adverse events occurred in 15% of patients in one large study, including nephrotoxicity not responding to dose adjustment, serious infections, seizures, anaphylaxis, and death of two patients. This high incidence suggests that vigorous monitoring by experienced clinicians at tertiary care centers may be required. To compare IV cyclosporine versus infliximab, a large trial was conducted in Europe by the GETAID group. The results indicated identical 7-day response rates between cyclosporine 2 mg/kg (with doses adjusted for levels of 150–250 ng/mL) and infliximab 5 mg/kg, with both groups achieving response rates of 85%. Serious infections occurred in 5 of 55 cyclosporine patients and 4 of 56 infliximab patients. Response rates were similar in the two groups at day 98 among patients treated with oral cyclosporine versus infliximab at the usual induction dose and maintenance dose regimen (40% and 46%, respectively). In light of data showing equal efficacy of CSA and infliximab in severe UC, more physicians are relying on infliximab rather than CSA in these patients.

TACROLIMUS

Tacrolimus is a macrolide antibiotic with immunomodulatory properties similar to CSA. It is 100 times as potent as CSA and is not dependent on bile or mucosal integrity for absorption. These pharmacologic properties enable tacrolimus to have good oral absorption despite proximal small bowel Crohn's involvement. It has shown efficacy in children with refractory IBD and in adults with extensive involvement of the small bowel. It is also effective in adults with glucocorticoid-dependent or refractory UC and CD as well as refractory fistulizing CD.

BIOLOGIC THERAPIES

Biologic therapy was traditionally reserved for moderately to severely ill patients with CD who had failed other therapies. However, it is now commonly given as an initial therapy for patients with moderate to severe CD in order to prevent future disease complications. Patients who respond to biologic therapies enjoy an improvement in clinical symptoms; a better quality of life; less disability, fatigue, and depression; and fewer surgeries and hospitalizations.

Anti-TNF Therapies The first biologic therapy approved for CD was *infliximab*, a chimeric IgG1 antibody against TNF-α, which is now also approved for treatment of moderately to severely active UC. Of active CD patients refractory to glucocorticoids, 6-MP, or 5-ASA, 65% will respond to IV infliximab (5 mg/kg); one-third will enter complete remission. The ACCENT I (A Crohn's Disease Clinical Trial Evaluating Infliximab in a New Long-Term Treatment Regimen) study showed that of the patients who experience an initial response, 40% will maintain remission for at least 1 year with repeated infusions of infliximab every 8 weeks.

Infliximab is also effective in CD patients with refractory perianal and enterocutaneous fistulas, with the ACCENT II trial showing a 68% response rate (50% reduction in fistula drainage) and a 50% complete remission rate. Reinfusion, typically every 8 weeks, is necessary to continue therapeutic benefits in many patients.

The SONIC (Study of Biologic and Immunomodulator-Naive Patients with Crohn's Disease) trial compared infliximab plus azathioprine, infliximab alone, and azathioprine alone in immunomodulator- and biologic-naive patients with moderate to severe CD. At 1 year, the infliximab plus azathioprine group had a glucocorticoid-free remission rate of 46% compared with 35% for infliximab alone and 24% for azathioprine alone. There was also complete mucosal healing at week 26 with the combined approach relative to either infliximab or azathioprine alone (44% vs 30% vs 17%). The adverse events were equal between groups.

Two large trials of infliximab in moderate to severe UC also showed efficacy with a response rate of 37–49%, with about one-fifth of patients maintaining remission after 54 weeks. Dosing for UC and CD are identical, with induction dosing at 0, 2, and 6 weeks and every 8 weeks thereafter. There is a similar study to SONIC in patients with moderate to severe UC. After 16 weeks of therapy, UC patients taking azathioprine plus infliximab had a glucocorticoid-free remission rate of 40% compared to 24% (article now published) and 22% of those on azathioprine and infliximab alone, respectively. This is even further evidence for "top-down" or more aggressive therapy for both moderate to severe CD and UC.

Adalimumab is a recombinant human monoclonal IgG1 antibody containing only human peptide sequences and is injected subcutaneously. Adalimumab binds TNF and neutralizes its function by blocking the interaction between TNF and its cell-surface receptor. Therefore, it seems to have a similar mechanism of action to infliximab but with less immunogenicity. Adalimumab has been approved for treatment of moderate to severe CD. CHARM (Crohn's Trial of the Fully Human Adalimumab for Remission Maintenance) is an adalimumab maintenance study in patients who responded to adalimumab induction therapy. About 50% of the patients in this trial were previously treated with infliximab. Remission rates ranged from 42–48% of infliximab-naïve patients at 1 year compared with remission rates of 31–34% in patients who had previously received infliximab. Another trial showed a remission rate of 21% at 4 weeks in patients who had initially responded to and then failed infliximab. In clinical practice, the remission rate in patients taking adalimumab increases with a dose increase to 40 mg weekly instead of every other week. Adalimumab is now also approved for the treatment of moderately to severely active UC.

Certolizumab pegol is a pegylated form of an anti-TNF Fab portion of an antibody administered SC once monthly. SC certolizumab pegol was effective for induction of clinical response in patients with active inflammatory CD. In the PRECISE II (Pegylated Antibody Fragment Evaluation in Crohn's Disease) trial of maintenance therapy with certolizumab in patients who responded to certolizumab induction, the results were similar to the CHARM trial. At week 26, the subgroup of patients who were infliximab naïve had a response of 69% as compared to 44% in patients who had previously received infliximab.

Golimumab is another fully human IgG1 antibody against TNF-α and is currently approved for the treatment of moderately to severely active UC. All of the patients in the golimumab trial were infliximab-naive. Like adalimumab and certolizumab, golimumab is injected SC.

Side Effects of Anti-TNF Therapies • ***DEVELOPMENT OF ANTIBODIES*** The development of antibodies to infliximab (ATIs) is associated with an increased risk of infusion reactions and a decreased response to treatment. Current practice does not include giving on-demand or episodic infusions in contrast to periodic (every 8 week) infusions because patients are most likely to develop ATIs. ATIs are generally present when the quality of response or the response duration to infliximab infusion decreases. Decreasing the dosing intervals or increasing the dosage to 10 mg/kg may restore the efficacy. There are commercial assays for both infliximab and adalimumab antibodies and trough levels to determine optimal dosing. If a patient has high ATIs and a low trough level of infliximab, it is best to switch to another anti-TNF therapy. Most acute infusion reactions and serum sickness can be managed with glucocorticoids and antihistamines. Some reactions can be serious and would necessitate a change in therapy, especially if a patient has ATIs.

NON-HODGKIN'S LYMPHOMA (NHL) The baseline risk of NHL in CD patients is 2:10,000, which is slightly higher than in the general population.