Immunosuppressive and Cytotoxic Therapy: Pharmacology, Toxicities, and Monitoring

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ABSTRACT

Treatment strategies for anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) are evolving. Cyclophosphamide (CYC) plus corticosteroids (CSs) is the mainstay of therapy for generalized, multisystemic AAV. Historically, the combination of CYC plus CS was used for a minimum of 12 months, but concern about late toxicities associated with CYC has led to novel treatment approaches. Currently, short-course (3 to 6 months) induction treatment with CYC plus CS, followed by maintenance therapy with less toxic agents (eg, methotrexate, azathioprine, mycophenolate mofetil) is recommended. Further, methotrexate combined with CS may be adequate for limited, non-life-threatening AAV. Recent studies suggest that rituximab may be useful for induction therapy or for CYC-refractory AAV. This article reviews the key agents used to treat AAV, with a focus on pharmacology, toxicities, and monitoring.

KEYWORDS: Vasculitis, anti-neutrophil cytoplasmic antibodies, immunosuppressive medications, azathioprine, cyclophosphamide, methotrexate, mycophenolate mofetil, tumor necrosis factor inhibitors, rituximab, intravenous immunoglobulin G

Cyclophosphamide (CYC) plus corticosteroids (CSs) is the mainstay of therapy for generalized, multisystemic anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV).[1] Historically, the combination of CYC plus CS was used for a minimum of 12 months,[2,3] but concern about late toxicities associated with CYC has led to novel treatment approaches. Recent regimens adopt an initial "induction phase" [to assure complete remission (CR)] followed by less intense "maintenance" therapy (to minimize long-term toxicities).[2,4–6] Currently, induction treatment with CYC plus CS has been considered optimal for severe AAV, but methotrexate (MTX) may be adequate for *limited, non-life threatening* AAV.[7,8] Following induction of CR, less toxic agents [eg, MTX,[6,8] azathioprine (AZA)[4,6] or mycophenolate mofetil (MMF)[1]] may be substituted as maintenance therapy. This maintenance regimen is continued for a course of 12 to 18 months.[2,5,6,9]

CSs are invaluable as adjunctive therapy for AAV and rapidly gain control of inflammatory manifestations of the disease. However, CSs have myriad side effects,[10] and recent treatment strategies for AAV advocate more rapid taper and/or low dosages of CSs.[1,11,12] The toxicities, dosage regimens, and contraindications to CS use are well known to most physicians and will not be further discussed here.

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More aggressive therapeutic options [eg, intravenous (IV) pulse methylprednisolone (1000 mg daily) or plasma exchange] may have an adjunctive role in severe AAV [eg, rapid progressive glomerulonephritis (RPGN) or diffuse alveolar hemorrhage (DAH)].[1,2,13,14] These adjunctive therapies are not addressed here.

This review focuses on the key immunosuppressive agents used to treat AAV, with an emphasis on pharmacology, dosing, toxicities, and monitoring. The discussion is limited to those agents that are considered "standard" therapy for either induction (eg, CYC, MTX) or maintenance of remissions (eg, AZA, MTX, MMF) but includes the newer biologics [eg, rituximab,[11,12] tumor necrosis factor-α (TNF-α) inhibitors,[15,16] intravenous immunoglobulin G (IV IgG)][17] that have been utilized increasingly over the past few years. Diverse other agents have been associated with anecdotal successes in small series of patients with AAV (usually failing or experiencing adverse effects with standard therapy). These therapeutic options include leflunomide,[18,19] calcineurin inhibitors (eg, cyclosporine, tacrolimus),[20] rapamycin,[21] antithymocyte globulin (ATG),[22] etoposide,[23] 15-deoxyspergualin,[24] alemtuzumab (Campath-1H, a monoclonal antibody directed against CD52),[25] and monoclonal antibodies against T cells.[26] A discussion of these nontraditional agents is beyond the scope of this paper.

CYCLOPHOSPHAMIDE

CYC (combined with CSs) has been the treatment of choice for severe or generalized vasculitis for more than 3 decades.[2,4,27] CYC has regulatory approval to treat diverse hematologic and nonhematologic malignancies and is used to treat a variety of autoimmune and inflammatory disorders.[28,29]

Mechanism of Action

CYC, a prodrug derived from mechlorethamine, exerts protean and diverse effects on cellular and humoral immunity.[29,30] Effects include a dose-dependent reduction of B and T lymphocyte numbers and function, more pronounced reduction of CD4 and CD8 (+) subsets, suppression of T cell activation and B cell immunoglobulin production, bone marrow suppression (all cell lines), and neutropenia.[28–30] CYC is more toxic to the bone marrow than other immunosuppressive agents such as AZA, MTX, MMF, or leflunomide.[28,30]

Dosage, Route of Administration, Pharmacology

CYC can be administered orally (dose 1 to 2 mg/kg/day)[3,31] or intravenously as a pulse (initial dose 0.50 to 0.75 g/m^2) once monthly.[27,30,31] Because severe nausea and vomiting may complicate IV pulse CYC, we recommend concomitant use of a 5-HT3 antagonist antiemetic (eg, ondansetron) plus CSs, diphenhydramine, and/or lorazepam.[29,32] To avoid bladder toxicity, patients should drink at least 3 L of fluids during the 24 hours prior to treatment, and normal saline is given during the IV infusion to assure adequate hydration. Urine output should be maintained >100 mL/hr for 24 hours, and complete bladder emptying must be assured.[29] We recommend administering sodium 2-mercaptoethane sulfonate (MESNA) every 12 hours for 24 hours to minimize bladder toxicity.[29] MESNA binds acrolein and other toxic CYC metabolites in the urinary bladder.[28] The monthly dose of IV CYC needs to be adjusted to maintain the total leukocyte count nadir above 2000/mm^3. In contrast, daily oral CYC dosing is titrated to maintain a total leukocyte count nadir above 3000/mm^3. We limit the maximum IV CYC dose to 1 g/m.[2,29] The frequency of IV pulse CYC may be reduced to every 3 months after a sustained remission has been achieved.[30] Both routes of administration (oral and IV) are equally efficacious in inducing remissions in AAV,[1,31] but relapses were more common with IV pulse CYC in some studies.[33–35] Oral CYC may be effective as rescue therapy for patients failing IV pulse CYC,[27] but additional agents (particularly biologics) may be required. Dose adjustments apply to both the oral and the IV routes, with lower doses given in the presence of renal failure, obesity, or inadequate bone marrow reserve.[29]

Toxicity

CYC has myriad potential toxicities[28–30] (discussed in detail in the following sections). Intermittent high-dose IV pulse CYC may reduce toxicities compared with daily oral CYC (particularly hemorrhagic cystitis and bladder cancer) secondary to a lower cumulative dose.[8,27,31,36]

Bone Marrow Suppression

CYC suppresses all cell lines within the bone marrow and is more toxic than other immunosuppressive agents (eg, AZA, MTX, MMF).[28,30] Maximum depression of circulating granulocytes and lymphocytes occurs within 7 to 14 days of a single dose of CYC,[30] though platelets are typically spared.[37] Chronic use (>1 year) may cause progressive lymphopenia, pancytopenia, and increased sensitivity to the drug.[30] Refractory pancytopenias may presage myelodysplastic syndrome or hematological malignancy.[3,38,39]

Gastrointestinal Toxicity

Nausea and/or vomiting occur in >25% of patients receiving IV pulse CYC, but in <10% of patients receiving oral CYC.[30] Antiemetics (eg, ondansetron)

plus dexamethasone may alleviate these symptoms.[32,40] CYC-induced hepatotoxicity is rare (<1%).[41,42] Elevations in transaminases resolve rapidly upon withdrawal of CYC.[41,42]

Pulmonary

Interstitial pneumonitis and progressive pulmonary fibrosis rarely complicate CYC therapy.[30,43] Cardinal histological features of pulmonary injury due to CYC (or other alkylating agents) include proliferating type 2 pneumocytes, cellular atypia, and varying degrees of interstitial inflammatory cells and fibrosis.[30,43] Given the rarity of pulmonary complications, screening with chest radiographs or pulmonary function tests (PFTs) is not necessary.[28]

Infections

Chronic CYC therapy increases the risk of infections, including bacterial, viral (particularly herpes zoster),[44] and opportunistic infections.[30,45] Leukopenia, increasing age, deteriorating renal function, or concomitant use of CSs (especially dosages equivalent to >20 mg/day of prednisone) increases the infectious risk.[30,45,46] The cumulative dose of CYC has also been correlated with an increased infection risk.[47] Pneumonia due to *Pneumocystis jiroveci* (PCP) complicates CYC therapy in 2 to 10% of patients[35,45] in the absence of prophylaxis. For both oral and IV CYC, we recommend trimethoprim/sulfamethoxazole (T/S) 80/480 (one single strength tablet) thrice weekly for prophylaxis against PCP and nocardiosis.[30] Routine vaccinations should also be given and dose adjustments made for age and renal insufficiency to reduce episodes of CYC-induced leukopenia.[48]

Hemorrhagic Cystitis and Carcinomas of the Bladder

Hemorrhagic cystitis complicates CYC use in 5 to 34% of patients and increases the risk of bladder fibrosis and carcinoma.[3,30,39,49–51] Acrolein, a metabolic of CYC, is considered to be the responsible toxin.[50] Clinical manifestations include microscopic or gross hematuria; rarely, massive, fatal hemorrhage has been reported.[49,50] Hemorrhagic cystitis is an absolute indication to stop CYC. CYC should *not* be reintroduced in *any* formulation even after symptoms resolve.

Transitional cell carcinoma develops in 2 to 15% of patients receiving long-term CYC.[49,50,52,53] The risk of bladder carcinoma is dose dependent and increases with duration of therapy.[49,53] Cumulative doses exceeding 50 g are associated with 6- to 14-fold increased risk[49,51–53]; cigarette smoking heightens the risk.[49,52] The risk of developing bladder cancer persists for years, even after cessation of CYC.[49–53] A long-term study of 146 patients with Wegener granulomatosis (WG) receiving chronic CYC identified seven cases of transitional cell carcinoma of the bladder.[49] Bladder cancer developed in six of 51 patients whose cumulative dose of CYC exceeded 100 g. By Kaplan-Meier analysis, the estimated incidence of bladder cancer following first exposure to CYC was 2% at 5 years, 5% at 10 years, and 16% at 15 years.[49] In a cohort of 416 patients with autoimmune disorders who received CYC for >3 months, five developed bladder cancers.[54] A long-term follow-up of 119 patients with rheumatoid arthritis (RA) identified nine bladder cancers.[52] In seven of nine patients with bladder cancer, the total cumulative dose of CYC exceeded 80 g.[52] These various studies underscore the importance of limiting the total cumulative dose of CYC. Bladder complications are less frequent with pulse IV CYC.[8]

Newer therapeutic regimens aimed at reducing the total dose of CYC by using alternative immunosuppressants appear to have a significant benefit with regard to risk of bladder complications. In a single-center, retrospective study using a strategy that avoided or limited CYC with either initial treatment with MTX or rapid transition to MTX after 3 to 6 months of CYC, no cases of hemorrhagic cystitis or bladder cancer were reported in 253 patients with a median follow-up period of 4.5 years.[8] Patients in this series were treated with daily oral CYC of 2 mg/kg, and MTX was continued for at least a 2-year period.[8]

Induction of Other Malignant Neoplasms

CYC has been associated with an increased risk of carcinomas of the skin,[50,55] female genital tract (predominantly cervical atypia),[56] and malignant lymphoproliferative disorders.[3,30,38,39,51] The risk of neoplasia associated with CYC is dose dependent. Malignancies may develop 5 to 15 years after initiation of therapy.[49,50,52,55] A prior history of malignancy or tobacco use increases the risk.[50,52] Leukemias, lymphoma, and myelodysplastic syndromes are the most dreaded complications and may be refractory to therapy.[3,30,38,39] In a sentinel study of patients with non-Hodgkin lymphoma treated with alkylating agents, the risk of developing leukemias was 1.5% per year up to 9 years.[38] Subsequent studies in autoimmune and inflammatory disorders affirmed an increased risk of hematologic malignancies with chronic CYC therapy.[50,55] In a retrospective long-term study of patients with WG treated with CYC, the incidence of malignancy was increased for squamous cell carcinoma of the skin [odds ratio (OR) = 7.3], leukemias (OR = 5.7), and malignant lymphomas (OR = 4.2).[57] In another retrospective series of WG patients, the risk of malignancies was not increased for patients treated with cumulative CYC doses of ≤36 g, but

there was an elevated risk of nonmelanoma skin cancers and a markedly elevated risk of acute myelogenous leukemia (AML) (59-fold increase in standardized incidence ratio) in those receiving a cumulative dose of $\geq$36 g.[39] By contrast, in a Swedish registry of scleroderma patients, the risk of malignancy was no higher in 246 patients treated with CYC compared with those treated with other medications.[58] The risk of malignancy is influenced by underlying disease and concomitant medications,[28] with a higher risk of solid tumors seen in one study of WG patients treated with the combination of CYC and etanercept.[59]

Gonadal Toxicity and Teratogenicity

Ovarian failure results from direct toxicity to the granulosa cell.[30] Ovarian failure is dose and age dependent and occurs with both oral and IV CYC.[3,30,60] In breast cancer patients, mean cumulative dosages of CYC resulting in ovarian failure in women in their twenties, thirties, or forties were 20, 9, and 5 g, respectively.[60] Oral contraceptives[61] or gonadotropin hormone-releasing analogues (eg, depot-leuprolide acetate)[62] may confer protection against ovarian fibrosis, and oocyte or embryo cryopreservation can also be considered. CYC is a potent teratogen; even a single dose during pregnancy can result in severe deformities.[63] Reliable contraceptive techniques should be employed during and 6 months after treatment with CYC. Azoospermia occurs in men[64] with the risk of irreversible infertility, and sperm banking should be considered. Testosterone supplementation during CYC may preserve testicular function in men.[29,65]

Miscellaneous Adverse Effects

Rarely, hyponatremia has been noted with IV pulse CYC if excessive water is administered intravenously.[30] Diffuse myocardial damage complicating CYC use has been described,[28,66] but is rare.

MONITORING

CYC exhibits bone-marrow suppressive effects.[28] With either oral or IV pulse CYC, complete blood counts (CBCs) and platelet counts should be obtained within 1 to 2 weeks of initiation of therapy. With oral CYC, CBCs should be obtained every 2 weeks for the first 6 weeks. Once a stable dose has been achieved, CBC at 4- to 6-week intervals is usually adequate. The oral dose should be reduced if total leukocyte count falls below 3000 mm^3. With IV CYC, CBCs are obtained on days 0, 7, and 14. The dose is adjusted to maintain total leukocyte count nadir >2000 mm^3. In cases of severe granulocytopenia, granulocyte colony-stimulating factor (G-CSF) may accelerate recovery. Refractory pancytopenias may warrant bone marrow biopsy with karyotyping to rule out myelodysplastic syndrome or malignancy.[39]

Because of potential bladder toxicity, urinalysis should be performed at least every 3 months during CYC therapy. Nonglomerular hematuria (microscopic or macroscopic) is a marker of CYC-induced bladder injury and warrants cystoscopy to exclude bladder carcinoma.[49] Patients with a history of hemorrhagic cystitis (even without cellular atypia) are at increased risk for bladder cancer; thus, in this context, we recommend urinalysis every 3 to 6 months and urine cytologies every 6 to 12 months even after CYC has been discontinued. Consideration should also be made for routine cystoscopy monitoring every 1 to 2 years in these patients.[67] For patients with no history of CYC-induced hemorrhagic cystitis, serial urinalyses are adequate for bladder cancer surveillance.

Age-appropriate cancer screening is also recommended, including annual Pap smears, and periodic assessment of liver function tests (LFTs) should be performed to rule out hepatotoxicity.[29]

CHLORAMBUCIL

Chlorambucil, an alkylating agent related to CYC,[30] was used to treat WG in early studies, with anecdotal successes,[68,69] but is oncogenic and has myriad toxicities.[29,30] Currently, chlorambucil has no role to treat vasculitis.

METHOTREXATE

MTX has regulatory approval to treat RA, psoriasis, and several malignancies[28,70] and has been used to treat diverse autoimmune and inflammatory disorders, including AAV.[30,70] MTX can be used as (1) *induction* therapy for patients with mild to moderate (non-life-threatening) AAV,[7,71,72] (2) *maintenance* therapy for patients who have achieved CRs after initial treatment with CYC,[5–8,72–74] and (3) *induction or salvage therapy* for patients experiencing adverse effects from CYC.[8,75]

Mechanism of Action

MTX (N-10-methyl-aminopterin) impairs folate synthesis via competitive inhibition of dihydrofolate reductase, resulting in impaired thymidylate and DNA synthesis.[70,76] MTX has antiinflammatory and immunomodulatory effects without substantial effects on cell numbers.[70,76] MTX inhibits neutrophil recruitment and responses to inflammatory mediators, neutrophil adherence to endothelial cells, neutrophil and monocyte chemotaxis, production or activation of numerous inflammatory cytokines (including TNF-α and interleukin-1), and B cell differentiation.[29,70,76]

Dosage, Route of Administration, Pharmacology

MTX can be administered orally or intramuscularly (dose range of 15 to 25 mg once weekly).[7,8,75,77] Both routes are comparable in efficacy, but parenteral administration is recommended for patients with gastrointestinal (GI) toxicity with oral MTX or under conditions of reduced oral bioavailability[70,76] We initiate therapy with an oral dose of 7.5 mg, with dose increases by 2.5 mg weekly up to 15 mg once weekly. Higher doses may be needed for disease poorly controlled at lower doses. The kidneys are the major route of MTX elimination, and toxicity is increased in the presence of renal insufficiency.[30] Conditions that may increase toxicity include hypoalbuminemia; concomitant drugs that affect absorption, clearance, or protein binding of MTX; and folate deficiency.[30] Acute renal failure, serum creatinine >2.0 mg%, or chronic liver disease are contraindications to MTX use.[8,72] The concomitant use of MTX and T/S 160 mg/800 mg twice daily may cause severe pancytopenia.[75] However, we believe low-dose T/S (80/400) thrice weekly can safely be used for prophylaxis against PCP, although this is controversial.

Toxicity

MTX has myriad potential toxicities, but it lacks bladder toxicity and is not oncogenic.[29,30,78] Adverse effects are dose dependent; drug discontinuation is necessary in 3% to >15% of patients due to side effects.[30,78] Life-threatening side effects are rare (<2%).[30,78] British investigators evaluated 673 patients treated with MTX for diverse rheumatologic disorders; side effects led to discontinuation of therapy in 36.3%.[78] Reasons for discontinuing therapy were GI symptoms (10.8%), abnormal LFTs (5.5%), peripheral blood cytopenias (5.5%), pulmonary symptoms (3%), and cutaneous abnormalities (2.1%). Concomitant administration of folic acid 1 mg/day attenuates toxicity, especially nausea and cytopenias, without reducing efficacy.[37,79,80]

Bone Marrow

Megaloblastic anemia, leukopenia, or thrombocytopenia complicates MTX use in 1 to 5% of patients, but severe bone marrow suppression is rare.[30,70,81] Hematologic complications are more common in patients with renal dysfunction, advanced age, decreased serum albumin, preexisting anemia or macrocytosis, dehydration, or concomitant administration of nonsteroidal antiinflammatory drugs (NSAIDs).[30,70,81] The use of T/S may potentiate bone marrow toxicity,[82] but this effect is usually minor.[70] Increases in mean corpuscular volume (MCV) or decreases in hemoglobin, leukocyte, or platelet counts should prompt temporary cessation of MTX.[30] We advocate supplemental folic acid 1 mg/day to reduce toxicity.

Gastrointestinal

GI symptoms (eg, nausea, anorexia, vomiting, diarrhea) are the most common adverse effects associated with MTX, noted in 10 to 40% of patients.[30,70,78] Rarely, severe mucositis involving the GI tract can cause bleeding or pain. Minor GI adverse effects are often resolved by reducing the oral dose or converting to the intramuscular route with withdrawal of therapy occurring in only ~10% of patients.[29,30,70,78] Parenteral administration bypasses the liver, with consequent diminution in hepatic synthesis of 7-hydroxy MTX, the main metabolite of MTX.[30]

Hepatic Toxicity

The most serious complication of MTX is hepatotoxicity and the development of hepatic steatosis and/or fibrosis.[70,78,83] Early studies of daily MTX therapy for psoriasis showed a high rate of progression to cirrhosis (3 to 10%).[70,84] Subsequent studies in RA and other inflammatory disorders cited a low risk of severe hepatotoxicity with once-weekly MTX in the absence of risk factors.[30,70,85–87] Factors associated with an increased risk of hepatotoxicity include preexisting liver disease, diabetes mellitus, excessive alcohol use, obesity, advanced age, concomitant use of NSAIDs, and renal insufficiency.[30,87] Several studies in RA patients receiving MTX found that severe liver disease or cirrhosis was rare (<0.5%).[28,30,83,87] In the setting of AAV, MTX use was associated with liver dysfunction in 5 to 14% of cases.[71,88] The American College of Rheumatology no longer recommends *routine* surveillance liver biopsies even in RA patients taking MTX for prolonged periods (>5 years).[87] However, routine monitoring of transaminases should be performed every 4 to 8 weeks throughout therapy. Liver biopsy should be considered for patients with sustained elevations of transaminases (>2 to 3 times normal) or with suspected liver disease.[30]

Pulmonary

Pulmonary toxicity occurs in 2 to 7% of patients on chronic MTX therapy.[29,30,89,90] Clinical features include dyspnea, cough, and pulmonary infiltrates; in some patients, fever and constitutional symptoms may mimic pneumonia.[30,89] Bronchoalveolar lavage (BAL) may reveal lymphocytosis and increased CD8:CD4 ratio.[91] Histological features of MTX pneumonitis are diverse and include nonspecific interstitial inflammatory cell infiltrates, granulomata, giant cells, bronchiolitis, and fibrosis.[30,89] The risk of MTX is not affected by gender, smoking, or duration of therapy.[30,89,90] One study in RA

patients found older age, diabetes, rheumatoid pleuropulmonary involvement, previous use of disease-modifying antirheumatic drugs (DMARDs), and hypoalbuminemia to be risk factors for the development of MTX-induced lung injury.[92] Most cases develop within the first year of MTX therapy, but pneumonitis can develop >3 years after chronic MTX therapy.[30,89,90] Routine high-resolution computed tomographic (CT) scans or PFTs do not predict which patients may develop pulmonary toxicity.[93] High-dose CSs may accelerate resolution and are recommended in severe or fulminant cases.[30,90] Rechallenge with MTX is dangerous with a high rate of recurrence and is thus ill advised.[30,94] The reported fatality associated with MTX-associated lung injury is ~17%.[94] Airway hyperresponsiveness has also been described with MTX[95] and may mimic asthma.

Infections

As with all immunosuppressive agents, MTX increases the risk of bacterial, viral, and opportunistic infections.[29,30,96,97] The risk is low among patients receiving monotherapy with MTX but is increased when concomitant CSs or other immunosuppressive agents are utilized.[30,96] In a review of 25 opportunistic infections complicating chronic MTX therapy, PCP was implicated in 10 (40%).[96]

Induction of Neoplasia

MTX may cause chromosomal breaks[98] but has no direct oncogenic effect.[30,98,99] Anecdotal reports of malignant lymphoproliferative disorders in patients with RA and dermatomyositis reflect Epstein-Barr virus (EBV) replication due to defective immune surveillance.[100–102] In a cohort of >16,000 RA patients receiving disease-modifying drugs, 39 developed hematologic malignancies (12 of whom had received MTX).[98] Malignancies in MTX-treated patients included nine lymphomas and three acute leukemias or myelodysplastic syndromes. Analysis of the oncogenic risk is complicated because the 12 MTX-treated patients developing malignancy had received a mean of 3.3 disease-modifying drugs. No correlations were observed between the dose or duration of MTX and development of malignancy.[98] Thus existing data do not clearly support a relationship between MTX use and hematologic malignancies. Interestingly, spontaneous regression of lymphomas (more commonly EBV-positive) has been reported after withdrawal of MTX therapy in both RA and transplant patients.[29]

Gonadal Toxicity and Teratogenesis

MTX is teratogenic and may induce abortion.[30,103] In animals, embryonic exposure to MTX may stunt fetal growth and cause birth defects (principally anomalies of the central nervous system or palate). Data in humans are limited, but exposure to MTX in the first trimester has been associated with multiple fetal anomalies.[30,103] MTX should not be used in women of childbearing age unless adequate birth control measures are utilized.[104,105] Conception should not be attempted if either partner has been exposed to the drug within 6 months. MTX is excreted in breast milk in small quantities[30]; breast-feeding during maternal use of MTX is not recommended. Oligospermia (typically reversible) and impotence in men[106] and amenorrhea in women[30] have rarely been described following MTX use.

Miscellaneous Adverse Effects

Other adverse effects of MTX include stomatitis (manifesting as painful oral ulcers), in 2 to 8%; cutaneous reactions (eg, vasculitis, rash, urticaria), in 2 to 6%; and alopecia in 1 to 5%.[30,70,81] Although MTX does not cross the blood–brain barrier, headache, dizziness, cognitive impairment, and dysphoria may complicate its use.[28,30,70] High-dose MTX may cause encephalomalacia.[30] Renal insufficiency can result from precipitation of MTX in the kidney, particularly in patients with preexisting renal insufficiency.[30,70]

MONITORING

Because of potential bone marrow and hepatic toxicity, we obtain CBCs, platelet counts, and LFTs within 4 weeks of initiation of therapy, and every 4 weeks for the first 3 months. Once a stable dose has been achieved, CBC and LFTs every 6 to 8 weeks is usually adequate.

AZATHIOPRINE

AZA has been used to prevent allograft rejection in organ transplant recipients and has a role as a steroid-sparing agent in diverse autoimmune and inflammatory disorders.[28–30] AZA is less effective than CYC and should *not* be used as *primary* therapy for AAV[2,107,108] but may be used as *maintenance* therapy in patients who remit with CYC and CSs.[4,6] In a prospective, open-label, multicenter trial, AZA was as effective as MTX *as maintenance therapy* for AAV.[6] The decision about whether to use MTX or AZA for remission maintenance must be made on an individual patient basis. Though it is not standard practice, anecdotal case reports cited remissions with IV pulse AZA for active refractory WG.[109] Given the availability of other therapeutic options, we do not recommend this approach.

Mechanism of Action

AZA, a purine analogue, inhibits DNA synthesis of proliferating cells and has minor inhibitory effects on

RNA and protein synthesis.[28,30] The drug is inactive as administered but is metabolized intracellularly to the purine antagonists 6-mercaptopurine (6-MP) and 6-thioinosinic acid.[30] AZA suppresses both humoral and cellular immunity.[30] It also induces lymphopenia, reduces T and B cell numbers, suppresses antibody synthesis, and depletes natural killer (NK) cells.[30] AZA is less potent than CYC and exerts its immunosuppressive effects more slowly, often over weeks or months.

Dosage, Route of Administration, Pharmacology

AZA is administered orally (dose 1 to 3 mg/kg/day).[30] An IV formulation has been developed and rarely used in pulse dosing (1200 to 1800 mg IV monthly), but data are limited, and we do not recommend parenteral administration. AZA is cleared by renal excretion and metabolic degradation.[30] Mercaptopurine (6-MP) is metabolized by the enzyme thiopurine methyltransferase (TPMT) to thiopurine analogues. Deficiency of this enzyme, secondary to a homozygous mutation for TPMT, occurs in one in 300 individuals[28] and may lead to increased toxicity.[110] Some investigators advise measuring TPMT activity before initiating AZA,[110] but we do not believe this practice is cost-effective. We initiate AZA at low dose (50 mg) and monitor clinically (symptoms, blood tests) for toxicity. Barring adverse affects, the dose can be increased every 2 weeks by 50 mg (maximum dose of 200 mg daily). Allopurinol inhibits the metabolism of 6-MP to 6-thiouric acid, thereby increasing the toxicity of AZA.[28] In patients receiving AZA, the doses of AZA and allopurinol should be reduced to one third the standard dose.[30]

Toxicity

AZA has myriad potential toxicities (principally bone marrow suppression,[111] heightened susceptibility to infections, and GI toxicities), but it lacks bladder toxicity and has low oncogenic potential.[29,30]

Bone Marrow Suppression

AZA has dose-dependent inhibitory effects on bone marrow; all cell lines are affected.[111,112] Severe toxicity is rare provided dose adjustments are made in response to peripheral blood counts. In 739 patients with inflammatory bowel disease (IBD) treated with AZA for a mean of 12.5 months, leukopenia developed in 28 (3.7%) and thrombocytopenia in 2.0%.[112] In a cohort of 393 patients with RA, AZA was associated with four episodes of leukopenia per 100 patient-years.[113] Chronic administration may result in anemia and thrombocytopenia.[30] Megaloblastosis may herald bone marrow toxicity.[30] In some cases, the onset of pancytopenia is abrupt; pure red cell aplasia has been described.[30] Bone marrow toxicity reverses with reducing the dose or discontinuing therapy. The risk of toxicity is increased in patients deficient in the enzyme TPMT, and severe myelosuppression can be seen in this setting.[114] The concurrent use of allopurinol and AZA also greatly enhances the hematologic toxicity.[37]

Gastrointestinal Toxicity

Nausea is common but rarely severe enough to warrant discontinuation of therapy.[30,112] Pancreatitis complicates the use of AZA or 6-MP in up to 3.3% of patients.[112] This usually occurs within the first month of therapy and promptly resolves following cessation of AZA.[112] Severe hepatotoxicity is rare (0.3%) but is more common in patients who are TPMT deficient.[112,115–117] Hepatitis and cholestatic jaundice usually reverse with drug cessation,[112] but venoocclusive disease is usually irreversible.[115,116] We obtain LFTs at 2 and 4 weeks fro initiation of AZA, and thereafter at 4- to 8-week intervals.

Pulmonary Toxicity

AZA is not considered a pulmonary toxin, but a single case of AZA-induced pulmonary hemorrhage was reported in a child following renal transplantation.[118]

Infections

As with all immunosuppressive agents, AZA increases the risk of bacterial, viral, and opportunistic infections.[29,30,112]

Induction of Neoplasia

The oncogenic potential associated with AZA is controversial. AZA has been associated with an increased risk of cutaneous[119] and cervical carcinomas[56,120] and lymphoproliferative disorders.[54,121–123] The risk of malignancy varies considerably according to the underlying disease. The risk of cutaneous squamous cell carcinoma was increased in RA and other immune disorders receiving AZA. Further, the course of cutaneous squamous cell carcinomas may be more aggressive in patients receiving AZA.[119] The incidence of hematological malignancies is increased up to 60-fold among organ transplant recipients receiving AZA combined with other immunosuppressive agents.[121] The risk of neoplasia is much lower among patients with autoimmune disease receiving AZA.[124] The risk of non-Hodgkin lymphoma was increased in patients receiving AZA for RA[54] or chronic liver disease.[123] In contrast, only one lymphoma was observed in more than 1100 patients with IBD treated with AZA or 6-MP in three series.[54,112,125] In

a cohort of 207 patients with multiple sclerosis treated for a mean of 4.2 years with AZA, five malignancies were identified compared with seven in a control group.[126] In a study of AZA in AAV, treatment for more than 12 months was associated with an all cancer standardized mortality rate of 3.0, though the majority of cases were skin carcinomas.[127] These data suggest that the oncogenic risk of AZA is overall low and depends upon the underlying disease(s).[29,30]

Gonadal Toxicity and Teratogenesis

AZA is teratogenic in animals[128] and is listed as a pregnancy category D drug, though its effects on fetal development in humans have not been clearly elucidated. However, AZA is safer than alkylating agents or MTX. The rate of fetal anomalies among women receiving AZA during pregnancy approximates 3%.[63,129] Maternal use of AZA has been associated with an increased risk of spontaneous abortions, prematurity, congenital malformations, and low birth weight as well as neonatal leukopenia or pancytopenia.[29,130] Most reports of adverse effects have occurred in woman taking concomitant drugs or with comorbidities.[63,129] We do not believe termination of pregnancy is warranted when women become pregnant while taking AZA. AZA does not cause permanent gonadal toxicity or sterility.[30] AZA is excreted in breast milk[129]; breast feeding while receiving AZA is not advised.

Miscellaneous Adverse Effects

An idiosyncratic hypersensitivity syndrome with fevers, rash, and arthralgias occurs in 2% of patients receiving AZA. These reverse with cessation of exposure and may recur with reexposure.[30] Other adverse effects of AZA include alopecia, stomatitis, and muscle weakness.[28]

MONITORING

Because of potential bone marrow and hepatic toxicity, we obtain CBCs, platelet counts, and LFTs within 2 weeks of initiation of therapy, and every 2 weeks for the first 6 weeks. Once a stable dose has been achieved, CBC and LFTs at 4- to 8-week intervals is usually adequate. We do not monitor therapy according to TMTP.

MYCOPHENOLATE MOFETIL

MMF has regulatory approval for prophylaxis of organ allograft rejection in cardiac, liver, and renal transplant recipients and has been used to treat diverse autoimmune and inflammatory disorders.[28,29] Mycophenolate has been used to induce or maintain remissions in AAV (principally WG),[131–134] but data are limited. Studies comparing MMF with other agents for AAV are lacking. However, MMF is at least as effective as AZA for the treatment of systemic lupus erythematousus,[135,136] and for prevention of rejection in transplant recipients.[137–140] In AAV (principally WG), small trials and observational studies cited successful remission induction and remission maintenance with MMF.[131–134,141] Only a single randomized, controlled trial compared the efficacy of MMF with AZA for AAV remission maintenance. In this trial, MMF was less effective than AZA for maintaining disease remission, and both treatments had similar adverse event rates.[142] Higher MMF dosing may improve its efficacy, but the doses used in this study were similar to or greater than doses previously reported for remission maintenance in AAV.[131–133] Based on this study, MMF should *not* be considered first-line therapy for remission maintenance in AAV, although it may still be considered for refractory cases.

Mechanism of Action

Following administration, MMF is rapidly converted to the active metabolite mycophenolic acid (MPA). MPA is a reversible, noncompetitive inhibitor of ionoside monophosphate dehydrogenase, a critical enzyme in de novo purine synthesis.[143] Lymphocytic proliferation relies almost exclusively on de novo purine synthesis, whereas most other cell types can utilize the salvage pathway as well. MMF inhibits T- and B-lymphocyte proliferation, induces apoptosis of activated T-lymphocytes, and suppresses primary antibody responses and expression of vascular adhesion molecules.[29,143]

Dosage, Route of Administration, Pharmacology

MMF is administered orally, typically with a daily dose of 1500 to 3000 mg in two divided doses.[29] African Americans metabolize MMF more rapidly than Caucasians and may require larger doses. Renal insufficiency may increase toxicity, and lower doses should be used in renal failure.[29] Mycophenolate sodium (Myfortic, Novartis Pharmaceuticals Corp., Hanover, NJ), a delayed release enteric formulation of MMF,[28] may be substituted for MMF in patients that exhibit poor tolerance of MMF (principally GI toxicities).

Toxicity

The most common reported toxicities of MMF include infections and gastrointestinal toxicity, but it may be better tolerated than alternative therapies. In a randomized, controlled trial of MMF versus AZA versus IV bolus CYC after induction of remission of lupus nephritis, the MMF group had a lower rate of hospitalizations, amenorrhea, infections, nausea, and vomiting.[144]

Bone Marrow Suppression

Because other cell types (nonlymphocytic) can use salvage pathways for purine synthesis,[28] MMF has less suppressive effects on bone marrow cell lines than CYC or AZA.[29] However, neutropenia can complicate its use and may require dose reduction.[28,145]

Gastrointestinal

GI adverse effects including nausea, vomiting, diarrhea, and abdominal pain are common in MMF-treated patients but may get better with time and usually do not require cessation of the drug.[29] For some patients, GI symptoms improve with more frequent dosing intervals maintaining the same total daily dose. Enteric-coated mycophenolate sodium (EC-MPS) was developed with the aim of improving the GI tolerability of mycophenolic acid. The few trials comparing EC-MPS with MPS have not shown a significant impact in the incidence of GI adverse events.[146,147] However, in a prospective, open-label trial, conversion from MMF to EC-MPS significantly reduced GI-related symptoms.[148]

Pulmonary

Dyspnea and cough are reported in the MMF prescribing information, but at similar rates to AZA and are probably related to respiratory infections.[29]

Infections

Consistent with other immunosuppressive agents, MMF is associated with heightened susceptibility to infections.[29,144] Although it is somewhat counterintuitive, MMF is reported to have some protective antimicrobial activity against intracellular pathogens, including PCP.[149,150] Regardless, for patients treated with MMF in conjunction with CSs, we recommend prophylaxis against PCP.

Induction of Neoplasia

MMF prescribing information includes a specific warning about lymphoma and other neoplasms as a result of immunosuppression, but the oncogenic potential of MMF is generally considered to be less than with CYC. However, the long-term risk of hematologic malignancy is unknown.

Gonadal Toxicity and Teratogenesis

Data regarding effects of MMF during pregnancy are scant. Teratogenicity has been cited in animals, but data in humans are limited.[29] MMF is pregnancy category C.[29] Contraception should be used in any patient taking MMF.

MONITORING

Serum MMF levels are unpredictable and highly variable,[151] and monitoring drug levels is cumbersome.[151–153] Given the uncertain benefit, we do not recommend monitoring drug levels. However, because of potential for bone-marrow toxicity, we obtain a CBC within 2 weeks of initiation of therapy, and every 2 weeks for the first 6 weeks. Once a stable dose has been achieved, repeating the CBC every 4 to 8 weeks is usually adequate.

TUMOR NECROSIS FACTOR INHIBITORS

Inhibitors of TNF-α have been used to treat active RA, psoriasis,[154] IBD,[155–157] ankylosing spondylitis (AS),[158] and diverse autoimmune and inflammatory disorders.[159–162] TNF-α antagonists most commonly used include etanercept (Enbrel, Immunex Corp., Thousand Oaks, CA), infliximab (Remicade, Centocor Ortho Biotech, Inc., Horsham, PA), and adalimumab (Humira, Abbott Laboratories, Rockville, MD)[157,160,162]; two newer agents, golimumab and certolimumab, are now available[161] but will not be further discussed here. The monoclonal antibodies infliximab and adalimumab are approved as therapy for active RA, juvenile RA, psoriatic arthritis, plaque psoriasis, AS, and IBD.[161,162] Etanercept is not effective to treat IBD but appears to be as effective as the preceding monoclonal antibodies to treat RA, psoriasis, and AS.[161,162] Data regarding the use of TNF-α inhibitors for vasculitis are limited (discussed elsewhere in this issue by Lynch and Tazelaar). TNF-α inhibitors have been used to treat giant cell vasculitis,[163,164] Behçet disease,[165,166] Churg-Strauss syndrome,[167] WG,[159] and AAV,[15,16,168–170] with anecdotal successes (particularly with infliximab). The Wegener Granulomatosis Etanercept Trial (WGET) randomized 180 patients with WG to etanercept or placebo in addition to standard therapy with CYC or MTX.[170] Patients were followed for a minimum of 12 months. Etanercept was no better than placebo. Based on this study, etanercept has no role as therapy for WG. Conversely, infliximab may be effective as induction therapy or treatment of refractory AAV. Five clinical trials[16,171–174] and anecdotal case reports[175–177] suggest a possible role for infliximab in refractory WG (discussed in greater detail in this issue by Lynch and Tazelaar). We are unaware of data assessing adalimumab as therapy for AAV. Placebo-controlled trials are necessary to ascertain the role of infliximab or other TNF-α inhibitors for AAV.

Mechanism of Action

Etanercept, a dimeric fusion protein composed of two p75 TNF-α receptors coupled to the Fc portion of a monoclonal human IgG_1, binds TNF-α in a one-to-one

fashion.[169] Infliximab, a chimeric mouse/human monoclonal antibody, binds to either membrane-bound or soluble TNF-α.[16] Blockage of TNF-α leads to inhibition of proinflammatory cytokines with potent antiinflammatory and antifibrotic effects.[160]

Dosage, Route of Administration, Pharmacology

Etanercept is administered subcutaneously (dose 25 to 50 mg twice weekly for 3 months, then once weekly). The dose of infliximab for RA and IBD has typically been 5 mg/kg body weight, administered via IV infusion at day 0, 2 weeks, 6 weeks, and thereafter every 8 weeks.[160–162] However, dose (range 3 to 10 mg/kg), frequency of dosing, and duration of therapy have varied in published series of autoimmune disorders and AAV.[160,162,173] Adalimumab is administered subcutaneously (dose 40 mg every 2 weeks) for most indications.[160] The optimal regimen for AAV (dose, frequency of administration, duration of therapy) has not been elucidated.

Toxicity

Major toxicities of TNF-α inhibitors include opportunistic infections,[178,179] heightened risk of malignancy,[179,180] induction of autoimmune antibodies and lupus-like syndromes,[181] and infusion or injection site reaction.[159] In contrast to immunosuppressive cytotoxic agents, bone marrow toxicity is rare.

Bone Marrow Suppression

Leukopenia, anemia, and thrombocytopenia rarely complicate the use of TNF-α inhibitors. The mechanism is not clear.[159]

Gastrointestinal Toxicity

GI adverse effects are uncommon. However, elevated transaminases, and rarely severe autoimmune hepatitis have been cited with TNF-α inhibitors.

Pulmonary Toxicity

The effect of TNF-α inhibitors on causing or modifying the course of lung disease is not clear.[182] TNF-α inhibitors have been used to treat diverse interstitial lung diseases (ILDs), such as sarcoidosis,[183–188] idiopathic pulmonary fibrosis,[189] and connective tissue disease–associated ILD,[181,190,191] but efficacy has not been convincing. Further, several case reports and small series cited either rapid progression of RA-associated ILD or new development of ILD following initiation of anti-TNF-α therapy.[181,192–196] However, this could reflect exacerbation of the underlying disease rather than a direct toxic effect of TNF-α inhibitors. A recent prospective study identified 367 patients with preexisting RA-ILD (299 were treated with TNF-α agents; 68, with DMARDs).[182] Mortality was no higher in patients receiving TNF-α inhibitors compared with DMARDs.

Infections

Serious opportunistic infections (ie, bacterial,[197] tuberculosis[178,198] or nontuberculous mycobacterial,[158] viral (particularly herpes zoster)[199] and cytomegalovirus (CMV),[156,166] hepatitis B reactivation,[200] PCP,[201] aspergillosis,[202,203] coccidioidomycosis,[158] cryptococcosis,[204] histoplasmosis,[205] listeriosis,[206] nocardiosis,[158] and other opportunistic infections have been associated with therapy with TNF-α antagonists.[178,179,207,208] In virtually all these reports, CSs or immunosuppressive agents were used concomitantly, confounding interpretation of the impact of TNF-α inhibitors. Data collected from the U.S. Food and Drug Administration (FDA) from January 1998 to September 2002 cited 716 granulomatous infections associated with the use of either etanercept or infliximab.[158] Data extracted from >346,000 U.S. patients treated over a 4.75-year period identified 374 reported cases of tuberculosis, 42 of histoplasmosis, and 223 with other granulomatous infections.[158] Overall, the rate of infections were 239 per 100,000 infliximab-treated patients compared with 74 per 100,000 etanercept-treated patients (<0.001). Tuberculosis was the most commonly reported granulomatous infection, cited in 144 per 100,000 infliximab-treated patients and in 35 per 100,000 etanercept-treated (<0.001).[158] Other granulomatous infections were also more common among patients receiving infliximab. Importantly, 208 infections occurred *without* concomitant use of immunosuppressive medications; of these, 189 were associated with infliximab and 19 with etanercept treatment. The median time to onset of infection was 40 days for infliximab and 236 days for etancercept (<0.001). In summary, infliximab was associated with a more than threefold risk of infections compared with etanercept, and infections occurred shortly after initiation of therapy. The time-frame suggests that most infections in infliximab-treated patients represented reactivation of latent infection. Data regarding adalimumab were not available in that report. Both infliximab and adalimumab carry a "black box" warning about the risk of tuberculosis and other opportunistic infections. Testing for latent tuberculosis [ie, tuberculin skin test (PPD) or TB-quantiferon-GOLD] should be performed in all patients before initiation of anti-TNF-α therapy. Patients with latent tuberculosis should be treated before initiation of anti-TNF-α therapy. A prospective study in the United Kingdom examined serious infection rates between 2002 and 2005 in a large

cohort of RA patients receiving TNF-α antagonists ($n = 7664$) or conventional DMARD ($n = 1354$).[178] There were 525 infections in the anti-TNF-α cohort, compared with 56 in the DMARD cohort. The overall incidence of infection, adjusted for baseline risk, was similar in both cohorts. However, the frequency of serious skin and soft tissue infections was increased in anti-TNF-α treated patients, with an adjusted incidence rate ratio (IRR) of 4.28. Further, all 19 bacterial intracellular infections [ie, *M. tuberculosis* ($n = 10$), *Listeria monocytogenes* ($n = 3$), other ($n = 6$)] occurred in the anti-TNF-α cohort. There was no difference between the three TNF-α antagonists (infliximab, adalimumab, or etanercept). German investigators prospectively studied 5040 RA patients receiving TNF-α inhibitors or DMARDs.[199] Eight-six herpes zoster infections were documented in 82 patients. The crude incidence per 1000 patient years was 11.1 for the monoclonal antibodies (infliximab or adalimumab), 8.9 for etanercept, and 5.6 for conventional DMARDs.

Induction of Neoplasia

Malignancies (solid and hematological) may complicate use of TNF-α antagonists, but the actual risk depends upon underlying disease(s), concurrent immunosuppressive or cytotoxic drug therapy, and preexisting history of malignancy, among other factors.[154,179,180,209] Some studies cited no increased risk of malignancies among patients receiving anti-TNF-α therapies, whereas others cited a more than threefold higher risk; this topic is elegantly reviewed elsewhere.[210,211] Several reports cited lymphomas (typically non-Hodgkin) in patients receiving chronic TNF-α antagonists (particularly those receiving concomitant immunosuppressive therapy), but the overall risk is low.[209,212–214] A study of >19,000 RA patients (55% were treated with TNF-α antagonists) cited no higher risk of lymphoma among patients receiving anti-TNF-α antagonists compared with controls (no anti-TNF-α therapy) (OR = 1.0).[209] Even among patients receiving *both* MTX and TNF-α antagonists, the OR for lymphoma development was 1.1 compared with controls (not significant). The overall incidence of lymphoma in the entire cohort was 1.059 per 1000 patient-years. British investigators prospectively evaluated >14,000 RA patients receiving anti-TNF-α therapy ($n = 10{,}735$) and no other biologic agent; the comparison group received DMARDs ($n = 3{,}352$).[180] Within this group, 293 RA patients had a prior history of malignancy who were subsequently treated with either anti-TNF-α therapy ($n = 177$) or DMARDs ($n = 117$).[180] Among these 293 patients, 20 new cancers developed. The rates of new ("incident") malignancy were 25.3 events/1000 person-years in the anti-TNF-α cohort and 38.3/1000 person-years in the DMARD cohort, generating an age- and sex-adjusted incidence rate ratio of 0.58 for the anti-TNF-α cohort compared with the DMARD cohort. Among patients with prior melanomas, three of 17 (18%) in the anti-TNF-α cohort developed an incident malignancy compared with 0 of 10 in the DMARD cohort. Data regarding malignancy risk in WG or AAV are limited. In the WGET study, 180 patients with WG were randomized to etanercept or placebo (both combined with conventional therapy).[59] Solid organ cancers developed in six of 89 patients in the etanercept group but in none of 91 control patients ($p < 0.01$). All patients developing malignancy receiving CYC concomitantly.[59] Given the small sample size, conclusions are limited.

Gonadal Toxicity and Teratogenesis

The effect of TNF-α inhibitors on gonadal function, reproductive capacity, or pregnancy is not known. Women should not breast feed their infants while receiving anti-TNF-α therapy.

Cardiovascular

TNF-α antagonists may have deleterious effects on serum lipids (increases in cholesterol and HDL)[215,216] but some small studies in RA patients found no difference in progression of carotid vascular disease[217] or coronary atherosclerosis.[217] British investigators prospectively assessed the rates of myocardial infarction (MI) in 8670 RA patients treated with anti-TNF-α agents and 2170 RA patients treated with traditional DMARDs.[218] Sixty-three MIs occurred in the anti-TNF-α cohort during 13,233 person-years of follow-up compared with 17 MIs in the DMARD cohort during 2893 person-years of follow-up. After adjustment for baseline risk factors, there was no reduction in the MI risk in the anti-TNF-α cohort compared with the DMARD cohort. However, analysis of patients who responded to anti-TNF-α treatment within 6 months cited a lower incidence of MI rates (3.5 events/1000 person-years compared with 9.4 events/1000 person-years in the DMARD cohort). Two studies of etanercept in RA patients were terminated early when interim analysis showed a lack of efficacy.[219] More importantly, high-dose infliximab was deleterious in patients with moderate to severe heart failure.[220] Thus severe heart failure is a contraindication to anti-TNF-α therapy.[216]

Miscellaneous Adverse Effects

Rarely, TNF-α inhibitors may cause demyelination (central and peripheral) syndromes[221] and other neurological manifestations [eg, optic neuritis,[222] multiple sclerosis (MS),[223,224] seizures,[159,225] and progressive multifocal leukoencephalopathy (PML)].[221,226] In a case series of 19 patients developing new onset demyelination during

anti-TNF-α therapy for arthritis, 17 patients were receiving etanercept and two were receiving infliximab.[221] Neurological manifestations may improve following prompt discontinuation of therapy.[221]

TNF-α inhibitors may be associated with acute infusion reactions (eg, with IV infliximab) or injection site reactions (typically pain, itching, erythema, or swelling) with subcutaneous etanercept or adalimumab.[159] Serious infusion reactions have been reported with infliximab (eg, hypotension, anaphylaxis) but are rare (< 1%).[227] Severe reactions mandate cessation of anti-TNF-α therapy. Mild to moderate infusion reactions may abate with slower infusion times, reducing the dose, or premedication with antihistamines, acetaminophen, and CSs.[227] Because infliximab is a chimeric antibody, autoantibodies develop in 15 to 50% of patients during the course of therapy; the concomitant use of MTX reduces the frequency of developing autoantibodies.[227] The rate of developing antibodies to other TNF-α inhibitors is lower (3 to 15%). Autoimmune disorders, with positive antinuclear antibodies (ANAs) and anti-double-stranded DNA antibody (dsDNA) may complicate therapy with TNF-α antagonists[159,160] and may lead to systemic lupus erythematosus (SLE),[181] lupus-like syndromes,[228] and leukocytoclastic vasculitis.[229] These manifestations may improve or resolve following discontinuation of therapy.[181,229]

RITUXIMAB

CYC and CSs have been the mainstays of induction therapy for AAV. Unfortunately, this treatment is associated with high mortality and serious adverse events. Recent studies indicate that rituximab (RTX), an anti-CD20 monoclonal antibody, has similar safety and efficacy to CYC in the setting of AAV, at least in the short term. In an open-label, parallel-design, randomized trial, patients with newly diagnosed, severe AAV received *either* RTX with two doses of IV CYC and CS ($n = 33$) *or* CYC and CS *without* RTX ($n = 11$). Rates of sustained remission and severe adverse events were similar at 12 months in both groups.[12] Similar and complementary findings were described by Stone et al from a multicenter, double-blind, double-dummy, non-inferiority trial that randomly assigned patients with severe, newly diagnosed, or relapsing AAV to CS plus *either* RTX ($n = 99$) *or* CYC ($n = 98$). Similar proportions of patients achieved CS-free remission at 6 months, and adverse event rates did not differ between these groups. However, the RTX-based regimen more effectively induced remission in patients with relapsing disease; 34 of 51 such patients treated with RTX achieved CS-free remission, compared with 21 of 50 those treated with CYC.[11] Moreover, favorable responses have been noted with RTX as salvage therapy for patients failing conventional AAV therapy.[230–243]

RTX is a monoclonal antibody that targets CD20, a specific B cell surface antigen and was the first monoclonal antibody approved for the treatment of non-Hodgkin lymphoma.[244] The FDA approved RTX for the treatment of refractory low-grade lymphoma in 1997.[245] It has since been used for the treatment of several CD20-positive B cell malignancies.[246,247] The selectivity of this drug for B cells led to further investigations involving autoimmune B cell driven diseases, including multiple rheumatologic diseases (particularly RA); RTX is approved for the treatment of RA.[248] However, there are multiple off-label uses, including chronic lymphocytic leukemia (CLL), SLE, MS, autoimmune hemolytic anemia, posttransplant lymphoproliferative disorder, graft-versus-host-disease, allograft rejection, pemphigus vulgaris, chronic immune mediated thrombocytopenia, and Evans syndrome.[249,250]

Mechanism of Action

RTX is a chimeric murine/human monoclonal immunoglobulin G1 antibody that targets the B cell differentiation marker CD20.[251] This B cell differentiation marker CD20 is a cell-surface marker specifically found on pre-B and mature B lymphocytes, but it is not found on the surface of most other cell types and is not free in the circulation.[251,252] Thus the predominant binding site for RTX is CD20 on B cells. The binding of RTX to cell surface CD20 results in destruction of the B cell by multiple mechanisms, including the induction of B cell apoptosis, complement-dependent cytotoxicity, and antibody-dependent cytotoxicity via opsonization with B cell destruction by mononuclear phagocytes and NK cells.[251,252]

Administration

RTX is administered intravenously at a typical dose of 375 mg/m^2 once weekly for 4 weeks (most diseases) or at 1000 mg on days 1 and 15 for RA patients. Typically patients are premedicated with an antihistamine with or without methylprednisolone and acetaminophen. With oncology uses, a uricostatic agent (eg, allopurinol) and aggressive hydration are recommended for patients at risk of tumor lysis syndrome.

In patients with CLL, prophylaxis for PCP and herpetic viruses is recommended during treatment (and for up to 6 to 12 months following treatment). In one study of AAV, patients treated with RTX also received CS and two pulses of IV CYC at initiation of therapy, but no additional maintenance therapy was given.[12] Whether RTX should be used with CS *alone* or CS *combined with* IV CYC has not been clarified.[253] The role for RTX long-term maintenance therapy in AAV has not been studied. Additional studies are required to assess indications for RTX, appropriate dosing and

frequency of administration, role for concomitant therapy, and long-term side effects.

The half-life of RTX ranges between 1.6 and 20 days, which is related to the dose and number of doses administered.[254] RTX remains detectable in the serum for up to 6 months after a single infusion. B cell depletion usually occurs by 2 weeks, and B cell recovery typically begins at 6 months and continues until 12 months.[255,256] Some patients may continue to have subtle abnormalities in B lymphocyte populations for several years following administration. Typically, patients postinfusion will require periodic laboratory follow-up with CBC, comprehensive metabolic panel, immunoglobulin levels, and lymphocyte counts/subpopulations. These results will vary depending on the patient, dose, indication, and duration of therapy. Importantly, if patients are found to have new neurologic or skin changes this needs to be evaluated because RTX has been associated with PML and severe mucocutaneous reactions.

Side Effects

FDA boxed warnings on the package insert include (1) transfusion reaction resulting in anaphylaxis characterized by fever, hypotension, bronchospasm, urticaria, and angioedema (80% of cases are seen with the first infusion); (2) PML, a serious central nervous system infection, due to the JC virus, that usually occurs within 12 months of the first infusion and requires magnetic resonance imaging and spinal tap for diagnosis[257]; (3) severe mucocutaneous reactions resembling Stevens-Johnson reactions or toxic epidermal necrolysis; (4) if used for a malignancy the patient can develop tumor lysis syndrome typified by hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia all of which can lead to acute renal failure; (5) opportunistic infections, including PCP and viral infections [eg, parvovirus B19, herpes zoster varicella (HZV), CMV, or herpes simplex virus (HSV)][258,259]; (6) hepatitis secondary to reactivation of hepatitis B resulting in fulminant hepatitis and hepatic failure.

Infusion-Related Reactions

Infusion-related reactions (defined as any adverse event reported during or within 24 hours of infusion) were higher with RTX versus placebo (29% vs 23%, respectively) during or following the first infusion.[260,261] Most of these reaction (eg, nasopharyngitis, pyrexia, hypertension, and dizziness) were of mild/moderate intensity and abated with further infusions. The signs and symptoms of acute infusion reactions (eg, pruritus, urticaria, rash, angioedema, fever, chills, rigors, sneezing, throat irritation/tightness, cough, bronchospasm, with or without hypotension or hypertension) were experienced by a greater proportion of RTX-treated patients (23%) than placebo-treated patients (18%) during the first infusion.[260,261] However, the likelihood of patients experiencing a reaction diminished with subsequent infusions. Only two RTX-treated patients experienced acute infusion reactions that were considered serious adverse events (anaphylaxis and hypertension, respectively). Premedication with IV methylprednisolone (100 mg 30 minutes before each infusion) significantly reduced both the incidence and severity of acute infusion reactions.[260,261]

Infections

There is some evidence suggesting that RTX, in addition to its effect on B cells, influences T cell immunity and predisposes to opportunistic infections.[262] Furthermore, the possible increased incidence of certain viral infections with the use of RTX supports the notion RTX may cause immunosuppression through several other mechanisms such as delayed-onset cytopenia, particularly neutropenia and hypogammaglobulinemia, especially when administered for long periods (eg, maintenance therapy).[263–265]

There are reports of an increased incidence of infections with RTX treatment in patients with lymphomas and RA.[266–268] Pooled data from 356 patients who received RTX monotherapy showed that the incidence rate of infectious events was 30%; 19% of patients had bacterial infections, 10% viral infections, 1% fungal infections, and 6% infections of unknown etiology. Severe infections, including sepsis, occurred in only 1% of patients during the treatment period, and in 2% during the follow-up period.[269] Another review involving 389 patients from 25 studies found the incidence of serious infections varied from 2.8 to 45% (mean 12.5%).[249] However, specific clinical trials will be required to determine the association of RTX with infections. In fact, many investigators suggest that infections in patients treated with RTX are likely a multifactorial process that is dependent on the patient's age, comorbidities, underlying disease, concurrent immunosuppression/chemotherapy, making the causal relationship between RTX and development of infection difficult to analyze.

With regard to bacterial infections there may be a small increase in serious bacterial infections in RA patients receiving RTX 1000 mg with or without a TNF-a blocking agent.[267,270] Overall, sinopulmonary infections are the most common bacterial infections that have been associated with the use of RTX, but further studies are needed.

In lymphoma clinical trials where a history of TB was not an exclusion criterion, no evidence of an increased incidence of TB was noted.[266] However, infection with other mycobacteria has rarely been associated

with RTX; thus physicians should remain cognizant of mycobacterial infections in patients receiving RTX.[271]

The most frequent viral infection complicating RTX therapy for lymphoma was hepatitis B virus (HBV) infection. HBV reactivation accounted for 39% of the reported cases, resulting in a high mortality of 52% due to hepatic failure; however, the increased risk is not clear with available data.[265,266,272–275] There are increasing reports of HBV reactivation following RTX therapy, either when used alone or in combination with chemotherapy.[276] In a recent study of lymphoma patients with prior resolved hepatitis B, among HB surface antigen (HBsAg)-negative/anti-HB core (HBc)-positive patients treated with RTX-CHOP, 25% developed HBV reactivation.[277] Some investigators suggest that the use of RTX in HBsAg-positive patients can be continued provided they receive a prophylactic antiviral for a prolonged duration (up to 6 months) after cessation of chemotherapy. Overall, HBV reactivation may occur in the setting of RTX use, and close monitoring of HBV DNA and LFTs during RTX therapy for at least 6 months after the completion of administration is required, with an alternative approach of prophylactic antiviral therapy to prevent liver complications.

RTX was reported to increase hepatitis C virus (HCV) viral load and alanine aminotransferase (ALT) levels in patients with HCV-related cryoglobulinemia and lymphoma.[278,279] Therefore, combined use of RTX with chemotherapy may lead to an additional risk for worsening of HCV infection. The influence of RTX on HCV replication is not well understood. Overall, the association of RTX with HCV infection remains complex (RTX may exacerbate HCV infection, but in other cases it has been used for the treatment of HCV-related autoimmune phenomena (eg, cryoglobulinemia).[265,266,278,279] Monitoring HCV viral load during RTX therapy may be important.

Infections with herpesviruses such as CMV, HZV, and HSV have been described in association with RTX use.[265,266] The most common herpesvirus associated with RTX is CMV.[26,265] However, more data are needed to establish the association of RTX with the development of herpes viral infections.

A recent study identified 57 patients with PML who had been treated with RTX.[257] Fifty-two patients had lymphoproliferative disorders; five had immune-mediated disorder (eg, SLE). All 57 patients had been treated with other aggressive immunosuppressives.[257] There are also reported cases of RTX-associated PML in RA. Case fatality rates were between 90 and 100% among those diagnosed with PML within 3 months of their last dose of RTX.[257] This may reflect the nature of the underlying disease and/or the inducible immune defect due to RTX. Determining the exact risk that RTX poses for the development of PML is difficult. For instance, the risk of PML with CLL may exceed 3% even in the absence of RTX.[280] Interestingly, some investigators proposed that RTX after high-dose therapy and hematopoietic stem cell transplant delays the onset of PML.[280] Furthermore, PML has also been reported with SLE and RA in the absence of RTX with an incidence rate between (0.4 to 4)/100,000 hospital discharges, indicating that there is an increased risk of PML with these disorders.[257,281–283] PML occurs a median of 5.5 months after the last RTX dose, but the causal relationship between PML and RTX remains unclear.[257,281–283]

PCP pneumonia is a common and life-threatening complication of immunosuppressive therapy in AAV, in particular with CYC treatment.[284] PCP has been strongly linked to low T cell counts, especially in patients infected with the human immunodeficiency virus. Therefore, B cell depletion induced by RTX treatment is not commonly considered a PCP risk factor. However, there have been at least 35 patients reported to develop PCP following RTX, with ~75% of the patients having lymphoma and receiving other chemotherapies. The remaining were on or had recent other aggressive immunosuppression for immune-mediated diseases (eg, hemolytic anemia, refractory pemphigus, and AAV). Importantly, these cases seemed to be associated with suboptimal chemoprophylaxis with cotrimoxazole.[285–288] Although there are only a few reports of patients with PCP following RTX treatment, in the absence of evidence to the contrary, patients treated with RTX should be considered at an increased risk for PCP. In patients with AAV, we give PCP chemoprophylaxis.

Pulmonary Toxicity

RTX infusion pulmonary toxicity is rare. It has been described as an alveolar-interstitial pneumonitis/pneumonia, pulmonary fibrosis, and cryptogenic organizing pneumonia. Some cases were lethal.[289–294] RTX-associated lung injury more commonly occurs in elderly patients with B cell malignancies. Future studies will be required to determine the exact incidence of this possible pulmonary complication of RTX use.

Hematologic Toxicities

Generally, RTX-associated hematologic toxicities are transient and self-limited. Although an episode of delayed-onset neutropenia associated with RTX therapy has been reported,[295] acute thrombocytopenia is extremely rare.[296]

Induction of Neoplasia

Among patients with exposure to RTX during the AAV trial,[11] malignant conditions developed in six of 124 (5%), as compared with one of 73 patients *without*

exposure to RTX; these differences were not statistically significant. With the exception of two cases of prostate cancer, all patients in whom malignant conditions developed had histories of exposure to at least two medications known to increase the risk of cancer (ie, CYC, AZA, or MTX). The specific types of solid malignant tumors among patients who received RTX were papillary thyroid cancer, uterine cancer, prostate cancer, colon cancer, bladder cancer, and lung cancer. More studies are required to determine whether there is any association between RTX therapy and the development of malignancies.

Gonadal Toxicity and Teratogenesis

Very few cases of rituximab administration during pregnancy have been described. There are cases of rituximab administration during the first to third trimester of pregnancy in women with immune diseases. Some report short-term to no significant effects on B cell counts or the immune status of the newborn.[297–299] The impact of RTX on gonadal toxicity or teratogenesis needs further investigation.

Monitoring Parameters

Screening for HBV and HCV in high-risk patients should be performed prior to initiation of RTX therapy. Carriers and patients with evidence of recovery from prior hepatitis infection should be monitored for clinical and laboratory signs of HBV and HCV infection during therapy and for up to a year following completion of treatment. CBC with differential and platelets should be obtained prior to treatment, at weekly to monthly intervals, and more frequently in patients with cytopenias. Some physicians advocate the monitoring of peripheral CD20 cells and immunoglobulins.

HIGH-DOSE INTRAVENOUS IMMUNOGLOBULIN

IV immunoglobulin (IVIg) contains pooled immunoglobulins extracted from the plasma of blood donors and was originally used to treat immunodeficiencies. However, high-dose IVIg (up to 2 g/kg), alone or combined with immunosuppressive agents, has been shown to be efficacious in diverse autoimmune and inflammatory disorders,[300] including Kawasaki disease and AAV refractory to or intolerant of conventional therapy.[2,17,301,302] Trials comparing IVIg with other salvage therapies have not been done, and the place for IVIg in the treatment algorithm for AAV remains unclear. One randomized, controlled trial in patients with persistent WG or MPA compared a single course of IVIg (0.4 g/kg/day for 5 days) versus placebo combined with other immunosuppressant therapy.[302] In this study, the IVIg group was more likely to achieve partial or complete remission at 3 months (82% vs 35%), but the benefit did not extend beyond 3 months. In another study, patients with relapsed WG or MPA were treated with IVIg (0.5 g/kg/day for 4 days) monthly for 6 months plus CSs added to stable doses of other immunosuppressant therapies.[17] Twenty-one out of 22 patients achieved remission between month 1 and month 5. However, seven patients had relapsed by month 9, and six additional patients relapsed between 9 and 24 months. Given the favorable safety and tolerability profile as compared with repeated cycles of CYC, high-dose IVIg can be considered in the therapeutic approach to AAV. However, future trials are required to determine optimal duration of IVIg and its use in place of, or in addition to, CS and other immunosuppressant therapies.

Mechanism of Action

IVIg exerts myriad immunomodulatory effects.[300] The exact mechanisms for IVIg's effects in AAV are unclear, but proposed mechanisms include neutralization of pathogenic circulating autoantibodies (including ANCAs), blockade of Fc receptors on phagocytic cells; downregulation of T- and B-cell function, preventing binding of activated complement components C3b and C4b, and modulating cytokine production.[300,303]

Dosage, Route of Administration, Pharmacology

The published experience in AAV has used high-dose IVIg (2 g/kg/day divided over 4 or 5 days).[17,301,302] Remission has been reported with a single high-dose IVIg course as well monthly high-dose IVIg courses for 6 months, but relapses appear to be common beyond 3 months from the last IVIg treatment.[17,302] These findings suggest that IVIg may hold the disease in check, but maintenance therapy after discontinuation of IVIg, or possibly continued use of IVIg, may be necessary.

Toxicity

IVIg is usually well tolerated, and side effects are generally mild and transient.[300] Adverse effects may be immediate or delayed.[304]

Immediate Adverse Effects

Immediate undesirable effects include headache, chills, nausea, fatigue, myalgia, arthralgia, back pain, and change in blood pressure that occur within the first 30 minutes of infusion and may be relieved by slowing the infusion rate.[304] Premedication with analgesics, NSAIDs, antihistamines, or IV CSs may prevent these

symptoms.[304] Anaphylactoid reactions following IVIg administration are rare.[304]

Delayed Adverse Effects

Severe late adverse effects are uncommon and mainly due to acute renal failure and thromboembolic events.

Renal Toxicity

Nephrotoxicity may occur 1 to 10 days after initiation of IVIg treatment, especially in patients with preexisting renal disease, diabetes mellitus, and concomitant use of nephrotoxic drugs.[304] The pathology is usually completely reversible and consistent with osmotic injury, thought to be related to sucrose contained in some IVIg products.[304] For patients at increased risk of renal failure, sucrose-free IVIg products should be used.

Hematologic Toxicity

Serious thromboembolic events following IVIg are most likely due to increased plasma viscosity following IVIg infusion.[304] The risk appears to be related to the rate of infusion. Lower daily doses and slower infusion rates (eg, 400 mg/kg/day over 8 to 12 hours for 5 days) may abrogate this effect. Neutropenia can also occur following IVIg infusion, but it is usually transient and not associated with increased infection risk.[304]

Pulmonary Toxicity

Respiratory complications are usually attributable to volume overload or vasomotor/allergic reaction.[304]

MONITORING

No monitoring is necessary or useful.

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