TREATMENT OF INFLAMMATORY MYOPATHIES

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There are four major categories of idiopathic inflammatory myopathy: dermatomyositis (DM), polymyositis (PM), immune-mediated necrotizing myopathy (IMNM), and inclusion body myositis (IBM), which are clinically, histologically, and pathogenically distinct.[1–3] There are many published retrospective studies and small case reports regarding the use of various immunosuppressive and immunomodulating therapies in different types of inflammatory myopathy. Unfortunately, most of these older studies are difficult to interpret because they group adult and childhood DM together with PM, IBM, and IMNM. Many of these reports were retrospective and unblinded and lacked placebo controls. Further, in several reports, patients with subjective improvement or lower serum CK levels were defined as positive responses rather than the more important objective improvement in muscle strength and function. There have been only a few published prospective, double-blinded, placebo-controlled trials in the treatment of PM and DM and none in IMNM.[4-8] Despite the paucity of prospective, double-blinded, placebo-controlled trials, it is clear to experienced clinicians that various modes of immunotherapy are helpful in DM, PM, and IMNM. In contrast, IBM is generally refractory to immunosuppressive therapy.

CORTICOSTEROIDS

Corticosteroids are the treatment of choice for DM, PM, and IMNM.[1-3,8-10] In patients with severe weakness or co-morbiditis (e.g., bad ILD, myocarditis), I often initiate treatment with a short course of intravenous Solumedrol (1 g daily for 3 days) prior to starting oral agents. Noticeable clinical improvement typically begins within 3–6 months of starting prednisone in most patients with DM or PM. IMNM is more refractory, often requires more than just prednisone alone, and usually takes longer to see a beneficial effect. When no response is noted after an adequate trial of high-dose prednisone, other alternative diagnoses (e.g., IBM or an inflammatory muscular dystrophy) and repeat muscle biopsy should be considered.

In patients with DM, PM, autoimmune necrotizing myopathy, and other idiopathic inflammatory myositides other than IBM (i.e., sarcoidosis), I generally initiate treatment with single-dose prednisone (0.75 to 1.5 mg/kg up to 100 mg) every morning (the most common dose used in adults is 60 mg daily). Some studies suggest that alternate day or intermittent pulses of intravenous corticosteroids may be equally efficacious and associated with fewer side effects than daily steroids.[8,10] I typically follow patients initially at every 2–4 weeks at the onset. I maintain them on high-dose prednisone until strength normalizes or until improvement in strength has reached a plateau (usually 4–6 months). Subsequently, I taper prednisone by 5 mg every 2–4 weeks. Once the dose is reduced to 20 mg every day or every other day, I decrease prednisone by 2.5 mg every 2-4 weeks. I try to get patients to prednisone10 mg daily or less.

Although most patients improve the response may not be complete and many will require at least a small dose of prednisone or a second-line agent to have a sustained remission. I monitor the serum CK levels; however, adjustments of prednisone and other immunotherapies are primarily based on the objective clinical examination and not the CK levels or the patients' subjective response.

Relapse of the myositis needs to be distinguished from steroid myopathy. This quandary may occur in patients who initially improved but then start developing progressive muscle weakness following long-term corticosteroid treatment because it can cause type 2 muscle fiber atrophy. Features that would suggest a "steroid myopathy" as opposed to relapse of myositis would be a normal serum CK, other clinical features of steroid excess such as ecchymoses and "moon facies", and absence of muscle membrane irritability on EMG. In contrast, patients who become weaker during prednisone taper, have increasing serum CK levels, and abnormal spontaneous activity on EMG are more likely experiencing a flare of the myositis.

CONCURRENT MANAGEMENT

I obtain a chest X-ray and, in at risk individuals, a PPD skin test with controls prior to initiating immunosuppressive medications. Patients with prior history of tuberculosis or a positive PPD may need to be treated prophylactically with isoniazid. If patients have ILD and are to be placed on prednisone plus another immunosuppressive agent, I also start Bactrim or atovaquonefor pneumocystis prophylaxis.

I measure bone density with dual-energy X-ray absorptiometry at baseline and yearly while patients are receiving corticosteroids. A bone density score of less than 2.5 standard deviations below normal is considered positive for osteoporosis. Calcium supplementation (1 g/d) and vitamin D (400–800 IU/d) are started for prophylaxis against steroid-induced osteoporosis. Postmenopausal women are also started on a bisphosphonate for prevention and treatment of osteoporosis. I prescribe alendronate 35 mg/week (or another bisphosphonate) as prophylaxis against steroid-induced osteoporosis or 70 mg/week in those with osteoporosis. Because the long-term side effects of bisphosphonates are not known, particularly in men and young premenopausal women, we prophylactically treat (alendronate 35 mg/week) these individuals only if the dual-energy X-ray absorptiometry scan demonstrates a density between 1 and 2.5 standard deviations below normal at baseline or if significant bone loss occurs on follow-up scans. If bone densities are in the osteoporosis range, these are treated with alendronate 70 mg/week. Alendronate can cause severe esophagitis, and absorption is impaired if taken with meals. Therefore, patients must be instructed to remain upright and not to eat for at least 30 minutes following the dose of alendronate in the morning.

Antihistamine-H_2 blockers are not routinely started unless the patient develops gastrointestinal discomfort or has a history of peptic ulcer disease. I instruct patients to start a low-sodium, low-carbohydrate, high-protein diet to prevent excessive weight gain. Physical therapy and an aerobic exercise program are helpful in fending off side effects of prednisone (e.g., weight gain) and preventing contractures and calcinosis that may result from immobility. Blood pressure is measured at each visit as accelerated hypertension and renal failure may occur, particularly in patients with scleroderma or MCTD. In addition, periodic eye examinations for cataracts and glaucoma should be performed. I periodically check fasting blood glucose and serum potassium levels while they are on high doses of prednisone.

SECOND-LINE THERAPIES

These agents are used primarily in patients poorly responsive to prednisone or who relapse during prednisone taper as well as for their potential steroid-sparing effect (**Table**).[1-3] There is equipoise regarding when to start second-line agents (e.g., methotrexate, azathioprine, mycophenolate, immunoglobulin, rituximab). The clinician must review with the patient the increased risks of immunosuppression versus possible benefits (e.g., faster improvement, steroid-sparing effect and/or avoidance of the morbidities associated with long-term steroid use). I usually start a second line agent along with corticosteroids in patients with severe weakness or other organ system involvement (e.g., myocarditis, interstitial lung disease), those with increased risk of steroid complications (e.g., diabetics, patients with osteoporosis, or post-menopausal women), and patients who we know from experience have difficult to treat myositis (e.g., IMNM).

A second-line agent should also be strongly considered in patients who fail to significantly improve after 2-4 months of treatment or if there is an exacerbation during treatment with prednisone. In patients who relapse during the taper, I double the dose of prednisone (no more than 100 mg/d). Once a patient has regained their strength, I resume the prednisone taper at a slower rate.

INTRAVENOUS IMMUNOGLOBULIN

Small, uncontrolled studies have reported beneficial response of IVIG in DM and PM.[9,11,12] A prospective, double-blind, placebo-controlled study of IVIG in 15 patients with DM demonstrated significant clinical improvement with IVIG.[7] I usually use IVIG in patients with DM, PM, and IMNM who are refractory to prednisone and at least one second-line immunosuppressive agent, though I have started up along these in patients with very severe myositis. I initiate IVIG (2 g/kg) slowly over 2–5 days and repeat infusions at monthly intervals for at least 3 months. Subsequently, I try to decrease or spread out or decrease the dosage: 2 g/kg every 2 months or 1 g/kg per month. Treatment schedule needs to be individualized. I generally give IVIG in combination with prednisone. There is no strong medical evidence in the literature regarding its efficacy as an initial monotherapy. Patients should also have renal function checked beforehand, especially those with diabetes mellitus, because of a risk of IVIG-induced renal failure. Flu-like symptoms—headaches, myalgias, fever, chills, nausea, and vomiting—are common and occur in as many as half the patients. Rash, aseptic meningitis, and stroke can also occur.

METHOTREXATE

There are no prospective, blinded, controlled studies of methotrexate in DM or PM. However, retrospective studies report that as many as 71–88% of patients with DM and PM, including those refractory to prednisone, improve at least partially with the addition of methotrexate.[1,13-15] Methotrexate is administered only 1 day a week. I usually begin methotrexate orally at 5.0 mg/week. The dose is gradually increased by 2.5 mg each week up to 20 mg/week given in three divided doses 12 hours apart. The dose should be reduced and used cautiously in patients with renal insufficiency. If there is no improvement after 1 month of 20 mg/week of oral methotrexate, I switch to weekly parenteral (usually subcutaneous) methotrexate and increase the dose by 5 mg every week -I rarely go higher than 35 mg/week. The major side effects of methotrexate are alopecia, stomatitis, ILD, teratogenicity, oncogenicity, risk of infection, and pulmonary fibrosis, along with bone marrow, renal, and liver toxicity. Doses over 50 mg/week require leukovorin rescue, although I do not use such high doses. However, all patients are concomitantly treated with folate.

Because methotrexate can cause pulmonary fibrosis, I usually try to avoid in those who already have the associated ILD and in patients with Jo-1 antibodies. I obtain baseline and periodic pulmonary function tests including forced vital capacity and diffusion capacity and repeat these periodically on patients treated with methotrexate. I monitor CBC and liver function tests (LFTs)—AST, ALT, bilirubin, and gamma-glutamyl transpeptidase (GGT) every 2 weeks until the patient is on a stable dose of methotrexate, then every 1–3 months. It is important to check the GGT, as it is the most reliable indicator of hepatic dysfunction, because the AST and ALT can be elevated from muscle involvement.

AZATHIOPRINE

Retrospective studies suggest that azathioprine is an effective therapy in DM and PM.[1] A prospective, double-blind study comparing azathioprine (2 mg/kg) in combination with prednisone to placebo plus prednisone found no significant difference in objective improvement at 3 months.[4] However, in the open-label follow-up period, patients on the combination of azathioprine and prednisone did better than those on prednisone alone and required lower doses of prednisone.[16]

Prior to beginning azathioprine, patients can be screened for thiopurine methyltransferase (TPMT) deficiency. Patients who are heterozygous for a mutation in TPMT may be able to tolerate azathioprine at lower dosages but those who are homozygous for TPMT mutations should not receive drug as they cannot metabolize it and may have severe bone marrow toxicity. In those patients without TPMT mutations, we initiate azathioprine at a dose of 50 mg/d in adults and increase the dose by 50 mg every 2 weeks up to 2–3 mg/kg/d. Approximately 12% of patients develop a systemic reaction characterized by fever, abdominal pain, nausea, vomiting, and anorexia that requires discontinuation of the drug.[17] This systemic reaction generally occurs within the first few weeks of therapy and resolves within a few days of discontinuing the medication. Recurrence of the systemic reaction usually follows restarting azathioprine. Other major side effects of azathioprine are bone marrow suppression, hepatic toxicity, pancreatitis, teratogenicity, oncogenicity, and increased risk of infection. Allopurinol should be avoided, because combination with azathioprine increases the risk of bone marrow and liver toxicity. A major drawback of azathioprine is that it may take 6–18 months to be effective.

CBCs and LFTs need to be followed closely. If the white blood count (WBC) falls below 4000/mm^3, we decrease the dose. Azathioprine is held if the WBC declines to 2500/mm^3 or the absolute neutrophil count falls to 1000/mm^3. Leukopenia can develop as early as 1 week or as late as 2 years after initiating azathioprine. The leukopenia usually reverses within 1 month, and it is possible to then rechallenge the patient with azathioprine without recurrence of the severe leukopenia.[17] In addition, we discontinue azathioprine if the LFTs increase more than twice the baseline values. Liver toxicity generally develops within the first several months of treatment and can take several months to resolve. Patients can occasionally be successfully rechallenged with azathioprine after LFTs return to baseline without recurrence of hepatic dysfunction.[17]

MYCOPHENOLATE MOFETIL

Mycophenylate mofetil inhibits the proliferation of T and B lymphocytes by blocking purine synthesis in only lymphocytes. Mycophenylate has been tried in patients with myositis with reported benefit.[1,18-21] The starting dose is 1.0 g twice daily and can be increased to 3 g daily in divided doses if necessary. Mycophenylate is renally excreted; therefore, the dose should be decreased (no more than 1 g/d total dose) in patients with renal

insufficiency. A benefit of mycophenylate compared to other immunosuppressive agents is the lack of renal or liver toxicity. Mycophenolate appears to be beneficial in some patients; however, we have seen a number of severe infections as a complication.[18] The most frequent side effect is diarrhea. Less common side effects include abdominal discomfort, nausea, peripheral edema, fever, and leukopenia.

RITUXIMAB

Rituximab is a monoclonal antibody directed against CD20+ B-cells, which it depletes for 6 months or more. A number of small series have suggested that rituximab may be effective in DM, PM, and necrotizing myopathies.[22-25] A large prospective, double-blind, NIH trial found no benefit but there were significant flaws in the study design.[5] A subset of patients do likely respond,[26] and it has been my experience that Rituximab can be beneficial in patients with refractory DM, PM, and IMNM. I use it in patients who are refractory to prednisone and at least one of the other second-line agents discussed above. The typical dosage is 750 mg/meter-squared (up to 1 gm) IV and then repeat the infusion in two weeks. Alternatively, patents can be treated with a 4 week course (375 mg/m^2 weekly x 4 weeks). A course of rituximab as above is usually repeated every 6 to 18 months depending on how well they are doing. There is a very small risk of progressive multifocal leukoencephalopathy, which is discussed with patients before prescribing.

CYCLOPHOSPHAMIDE

Some reports note improvement in individual patients with oral and intravenous cyclophosphamide.[1,27-29] However, other reports have found increased morbidity with intravenous cyclophosphamide without significant benefit. Cyclophosphamide has been advocated for use in myositis associated with ILD or vasculitis, but clinical studies are lacking. Given the controversy regarding the efficacy and the toxicity profile of cyclophosphamide, I reserve it for patients who are refractory to prednisone, methotrexate, azathioprine, mycophenolate, IVIG, and rituximab. When used, I usually pulse patients with cyclophosphamide at 0.5–1 g intravenously/m^2/month for 6–12 months. Cyclophosphamide can be given orally at a dose of 1.0–2.0 mg/kg/d, but there may be a greater risk of hemorrhagic cystitis. The major side effects are gastrointestinal upset, bone marrow toxicity, alopecia, hemorrhagic cystitis, teratogenicity, sterilization, and increased risk of infection and secondary malignancy. Prehydration with intravenous fluids prior to intravenous treatment and maintaining a high fluid intake (oral or intravenous therapy) and treatment with Mesna are important precautions to help avoid hemorrhagic cystitis. Urinalysis and CBCs are monitored closely (every 1–2 weeks at the onset of therapy and then at least monthly). The dose of cyclophosphamide should be decreased if the WBC decreases below 4000/mm^3. Cyclophosphamide is held if the WBC declines below 3000/mm^3, the absolute neutrophil count falls below 1000/mm^3, or there is evidence of hematuria. It can be restarted at a lower dose once the leukopenia has resolved, but we do restart the medication in patient with hematuria.

CHLORAMBUCIL

Chlorambucil is uncommonly used because of the significant side effects, which include bone marrow suppression, increased risk of cancer, infection, hepatotoxicity, Stevens–Johnson syndrome, and gastrointestinal disturbance. However, there are a few reports about chlorambucil being used to treat PM and DM.[1,30] CBCs and LFTs need to be monitored closely in patients treated with chlorambucil.

CYCLOSPORINE AND TACROLIMUS

Cyclosporine (2.5–10 mg/kg/d) may be effective in some patients with DM and PM, including childhood DM.[1,31-33] Improvement in strength may be seen within 2–6 weeks, and it may also serve as a steroid-sparing agent. However, the side effect profile has limited its use in most patients with myositis. Tacrolimus has also been reported to help patients with refractory myositis.[34] Side effects of cyclosporine and tacrolimus are renal toxicity, hypertension, electrolyte imbalance, gastrointestinal upset, hypertrichosis, gingival hyperplasia, oncogenicity, tremor, and risk of infection.

I start cyclosporine at a dose of 3.0–4.0 mg/kg/d in two divided doses and gradually increase to 6.0 mg/kg/d as necessary. The cyclosporine dose should initially be titrated to maintain trough serum cyclosporine levels of 50–200 ng/mL. Blood pressure, electrolytes and renal function, and trough cyclosporine levels need to be monitored closely.

Tacrolimus is started at a dose of 0.1 mg/kg and increased up to 0.2 mg/kg (in two divided doses daily). Dosing is titrated to maintain a trough level of 5–15 mg/mL. Blood pressure, electrolytes, and renal function need to be monitored closely and doses adjusted should renal insufficiency develop. With both of these agents, patients should be given a list of drugs to avoid that may increase the risk of renal toxicity.

INFLIXIMAB AND ETANERCEPT
These agents block TNF-alpha and are effective treatments in rheumatoid arthritis and other autoimmune disorders. Results in patients with PM and DM have been mixed and I do not routinely use them.[16]

PLASMAPHERESIS AND LEUKOPHERESIS
Uncontrolled series have reported improvement in DM, PM, and IBM with plasmapheresis or leukopheresis.[35-37] However, a controlled trial of 36 patients with DM and PM comparing plasmapheresis with leukopheresis and with sham apheresis demonstrated no improvement with either plasmapheresis or leukopheresis over the sham apheresis.[38]

TOTAL BODY IRRADIATION
There are a few case reports of refractory cases of DM and PM improving following total body irradiation.[39-41] Others have not found total body irradiation to be effective in PM.[42]

THYMECTOMY
Thymectomy has been performed on a small number of patients with PM and DM with improvement.[43]

SUMMARY
DM, PM, NM, and IBM are distinct categories of idiopathic inflammatory myopathy. DM, PM, NM are responsive to immunosuppressive therapy, in contrast to IBM, which is generally refractory to therapy. Prospective, double-blind, placebo-controlled trials are necessary to determine prognostic features for treatment responsiveness and the best treatment options for the different disorders.

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TABLE. IMMUNOTHERAPY FOR INFLAMMATORY MYOPATHIES

THERAPY	ROUTE	DOSE	SIDE EFFECTS	MONITOR
Prednisone	oral	0.75 to 1.5 mg kg/day to start	Hypertension, fluid and weight gain, hyperglycemia, hypokalemia, cataracts, gastric irritation, osteoporosis, infection, aseptic femoral necrosis	Weight, blood pressure, serum glucose/potassium, cataract formation
Methylprednisone	intravenous	1 gm in 100 ml/normal saline over 1-2 hours, daily or every other day for 3-6 doses	Arrhythmia, flushing, dysgeusia, anxiety, insomnia, fluid and weight gain, hyperglycemia, hypokalemia, infection	Heart rate, blood pressure, serum glucose/potassium
Azathioprine	oral	2-3 mg/kg/day; single a.m. dose	Flu-like illness, hepatotoxicity, pancreatitis, leukopenia, macrocytosis, neoplasia, infection, teratogenicity	Blood count, liver enzymes
Methotrexate	oral	7.5-20 mg weekly, single or divided doses; one day a week dosing	Hepatotoxicity, pulmonary fibrosis, infection, neoplasia, infertility, leukopenia, alopecia, gastric irritation, stomatitis, teratogenicity	Liver enzymes, blood count;
	subcutaneously	20-50 mg weekly; one day a week dosing	Same as oral.	Same as p.o.
Cyclophosphamide	Oral	1.5-2 mg/kg/day; single a.m. dose	Bone marrow suppression, infertility, hemorrhagic cystitis, alopecia, infections, neoplasia, teratogenicity	Blood count, urinalysis
	intravenous	0.5 to 1.0 g/m^2 per month x 6-12 months		
Cyclosporine	oral	4-6 mg/kg/day, split into two daily doses	Nephrotoxicity, hypertension, infection, hepatotoxicity, hirsuitism, tremor, gum hyperplasia, teratogenicity,	Blood pressure, creatinine/BUN, liver enzymes, cyclosporine levels,
Tacrolimus	oral	0.1 – 0.2 mg/kg/day in two divided doses	Nephrotoxicity, hypertension, infection, hepatotoxicity, hirsuitism, tremor, gum hyperplasia, teratogenicity,	Blood pressure, creatinine/BUN, liver enzymes, tacrolimus levels,
Mycophenolate mofetil	oral	Adults (1 gm BID to 1.5 gm BID) Children (600 mg/m^2/dose BID (no more than 1 gm per day in patients with renal failure)	Bone marrow suppression, hypertension, tremor, diarrhea, nausea, vomiting, headache, sinusitis, confusion, amblyopia, cough, teratogenicity, infection, neoplasia	Blood count
Intravenous Immunoglobulin	intravenous	2 gm/kg over 2-5 days; then 1-gm/kg every 4-8 weeks as needed	Hypotension, arrhythmia, diaphoresis, flushing, nephrotoxicity, headache, aseptic meningitis, anaphylaxis, stroke	Heart rate, blood pressure, creatinine/BUN
Rituximab	intravenous	A course is typically 750 mg-meter squared (up to 1 gm) and repeated in 2 wks Courses are then repeated usually every 6-18 months	Infusion reactions (as per IVIG), infection, progressive multifocal leukoencephalopathy	Some check B-cell count prior to subsequent courses (but this may not be warranted)

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