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PARANEOPLASTIC SYNDROMES (F GRAUS, SECTION EDITOR)

Treatment of Paraneoplastic Cerebellar Degeneration

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Opinion statement

Paraneoplastic cerebellar degeneration is an uncommon autoimmune disorder characterized clinically by progressive, ultimately incapacitating ataxia and pathologically by destruction of cerebellar Purkinje cells, with variable loss of other cell populations. The disorder is most commonly associated with gynecological and breast carcinomas, small cell carcinoma of the lung, and Hodgkin's disease and in most cases comes on prior to identification of the underlying neoplasm. The hallmark of paraneoplastic cerebellar degeneration is the presence of an immune response reactive with intracellular proteins of Purkinje or other neurons or, less commonly, against neuronal surface antigens. Evidence-based treatment strategies for paraneoplastic cerebellar degeneration do not exist; and approaches to therapy are thus speculative. Diagnosis and treatment of the underlying neoplasm is critical, and characterization of the antibody response involved may assist in tumor diagnosis. Most investigators have initiated treatment with corticosteroids, plasma exchange, or intravenous immunoglobulin G. Cyclophosphamide, tacrolimus, rituximab, or possibly mycophenolate mofetil may warrant consideration in patients who fail to stabilize or improve on less aggressive therapies. Plasma exchange has been of questionable benefit when used alone but should be considered at initiation of treatment to achieve rapid lowering of circulating paraneoplastic autoantibodies. Because the course of illness is one of relentless neuronal destruction, time is of the essence in initiating treatment. Likelihood of clinical improvement in patients with longstanding symptoms and extensive neuronal loss is poor.

Introduction

Paraneoplastic cerebellar degeneration is a remote (nonmetastatic) complication of cancer characterized clinically by progressive ataxia, often associated with vertigo, nausea, and nystagmus or opsoclonus [1–3]. The disorder is most frequently associated with adenocarcinomas of the ovaries, uterus, or adnexa, adenocarcinomas of the breast, and

small cell carcinoma of the lung (SCLC) [1, 4, 5] (Table 1). A smaller number of cases has been reported in association with Hodgkin's disease, and rare cases have been reported with other malignancies [1, 6]. Paraneoplastic cerebellar degeneration may have its onset up to 5 years prior to cancer detection. Disease progression typically leads to complete incapacitation, the patient often being unable to sit without assistance, speak clearly, or assist in any aspects of his or her care. In most instances, recovery of neurological function is limited.

Patients with paraneoplastic cerebellar degeneration frequently exhibit serum and cerebrospinal fluid (CSF) antibody responses directed against neurons or other neuroglial populations, often with oligoclonal bands and other evidence of antibody synthesis within the central nervous system (CNS) [7]. Many of the known paraneoplastic antineuronal autoantibodies also react with patient tumors, and it is thought that the antineuronal antibody response seen in affected patients is elicited by tumor proteins immunologically similar to neuronal antigens [7]. Blood and CSF of patients with paraneoplastic neurological syndromes may also contain activated T lymphocytes reactive with the antigens recognized by the paraneoplastic autoantibody response [8–11].

Paraneoplastic and related neurological disorders fall into 2 groups: those characterized by an antibody response against intracellular neuronal proteins (Group 1), and those characterized by an antibody response directed against antigens expressed on neuronal membranes (Group 2) [11, 12]. Most patients with paraneoplastic cerebellar degeneration belong to Group 1: associated antibodies include anti-Yo (Purkinje cell antibody 1 or PCA1), found in patients with ovarian and breast malignancies; anti-Hu (Antineuronal nuclear antibody 1 or ANNA1), found in patients with small cell and neuroendocrine malignancies; anti-Ri (Antineuronal nuclear antibody 2 or ANNA2), found in patients with breast and small cell cancers; and anti-Tr, found in patients with Hodgkin's disease (Table 1). A few cases have been reported, essentially all in patients with small cell lung neoplasms, with antibodies directed against anti-amphiphysin, anti-Zic4, and anti-Purkinje cell antibody 2 (PCA-2) (Table 1) [13].

Patients falling into Group 2 comprise only a minority of affected patients: these include patients with antibodies reactive with the metabotropic glutamate receptor subunit mGluR1, and antibodies to voltage gated calcium channels [14–16]. A small number of patients, most without identified cancer, develop ataxia in the setting of antibodies to glutamic acid decarboxylase (GAD) [17]. Unlike cases of limbic encephalitis associated with antibodies to cell membrane antigens [11, 12], patients with cerebellar degeneration associated with antibodies neuronal surface antigens often have underlying cancer and may be treatment-resistant.

Paraneoplastic cerebellar degeneration is an uncommon illness, and the rarity of the condition greatly complicates development of effective treatment [18]. Few individual institutions encounter enough patients to organize a prospective clinical trial, and multi-institutional collaborative studies employing standardized methods of diagnosis and treatment have not yet been reported. In most series, paraneoplastic cerebellar degeneration is included as a subset in treatment trials of a variety of paraneoplastic disorders. The majority of published reports have thus dealt with individual patients, and even the most extensive published articles—which are few in number—have been uncontrolled case series, often with internal variation in dose and duration of the treatments employed [18–22]. In many studies, treatment has been initiated weeks or months after the onset of symptoms, after irreversible cerebellar injury may already have occurred. In a study by Shams'ili et al only 63 % of patients were still ambulatory at the time of neurological diagnosis [23].

To date no studies above the level of Class IV have been reported for paraneoplastic cerebellar degeneration. Three major approaches have been used in attempting to stabilize or reverse neurological injury in affected patients: modulation of paraneoplastic autoimmune response by immunosuppression or intravenous immunoglobulin G; removal of antibody by plasma exchange; or induction of tumor remission through surgery or chemotherapy.

Treatment

Pharmacological treatment

Pharmacological treatment of paraneoplastic neurological syndromes may be divided into 2 categories: treatment directed at patient symptoms

Table 1. Major autoantibodies associated with paraneoplastic cerebellar degeneration: characteristics and response to treatment

Autoantibody	Antigenic targets within cerebellum	Association with neoplasia	Major associated neoplasms	Response to immunomodulatory therapy	Response to tumor treatment
Reactive with intracellular neuronal antigens					
Anti-Yo (APCA, PCA1)	34-kDa and 62-kDa Purkinje cell cytoplasmic proteins	Almost invariable	Gynecologic and breast neoplasms	Poor	Poor in most cases
Anti-Hu (ANNA-1)	35-kDa to 42-kDa proteins present in cytoplasm and nuclei of all neurons	Almost invariable	Small cell carcinoma (usually lung), neuroendocrine tumors, myxoid chondrosarcoma	Improvement in occasional cases	Improvement in occasional cases
Anti-Ri (ANNA-2)	55-kDa proteins present in cytoplasm and nuclei of all neurons	Almost invariable	Breast cancer, small cell lung carcinoma	Good in some patients	Good in some patients
Anti-Tr	Purkinje cell cytoplasm: delta/Notch-like epidermal growth factor-related receptor	Almost invariable	Hodgkin's disease	Usually poor; improvement in rare cases	Usually poor; improvement in rare cases
Anti-PCA2	280 kDa Purkinje cell cytoplasmic protein	Almost invariable	Small cell lung cancer	Usually poor	Usually poor
Anti-GAD[a]	Purkinje cells	Uncommon	Thymoma, renal cell carcinoma, other	Good	Unknown
Anti-Zic4	Cerebellar granule cells > Purkinje or molecular layer neurons	Probably invariable	Small cell carcinoma (lung)	Poor	Poor
Anti-mGluR1[a,b]	Purkinje cells,	2/3 reported cases	Hodgkin's disease	Stabilized in one case	Unknown
Reactive with neuronal cell surface antigens[a]					
Anti-voltage-gated calcium channel (VGCC)	Purkinje and granule cells	Approximately 1/3 of patients	Small cell carcinoma (lung or other sites)	Poor in most cases	Poor

[a]May occur in patients without neoplasms

[b]The metabotropic glutamate receptor mGluR1 is expressed intracellularly and is also expressed within dendritic spines and on neuronal cell membranes. The response of patients with this pattern of antibody response to treatment, however, more closely parallels that seen in patients with anti-Yo or anti-Hu antibodies. For this reason, anti-mGluR1 antibodies are included in Group 1

APCA anti-Purkinje cell antibody, *PCA1* Purkinje cell autoantibody 1, *GAD* glutamic acid decarboxylase, *GluR* glutamate receptor subunit, *mGluR* metabotropic glutamate receptor subunit. (*Adapted from* Greenlee [18])

and immunomodulatory therapy directed against the underlying autoimmune process.

Symptomatic treatment

Marked symptomatic improvement following treatment with clonazepam was described in a single patient with paraneoplastic cerebellar degeneration accompanying Hodgkin's disease [24]. Apart from this 1 case, pharmacological treatment capable of improving cerebellar symptoms in affected patients have not been described.

Immunotherapeutics

Reports of immunomodulatory or immunosuppressive therapy in paraneoplastic cerebellar degeneration are limited, and no controlled trial or even extensive series has been published. Published reports consist largely of retrospective individual cases, with only a few case series. In the majority of reported patients, immunomodulatory and/or immunosuppressive treatment is often combined with therapy directed at the underlying tumor, making it difficult to ascertain the role of either intervention. Most patients have been treated with corticosteroids, intravenous immunoglobulin G, and/or cyclophosphamide, singly, or in combination. Although clinical improvement has been reported following treatment in individual patients, most patients fail to improve [23, 25, 26]. Stark et al reported limited clinical improvement in 2 women with anti-Yo antibody response treated with cyclophosphamide [27]. Uchuya et al treated 22 patients with paraneoplastic syndromes, 4 of whom had paraneoplastic cerebellar degeneration associated with anti-Yo antibodies with between 1 and 11 courses of intravenous immunoglobulin G. [28]. Treatment was initiated 2–8 months following onset of symptoms. Functional status of these patients at initiation of treatment was not described. Improvement was not observed in any of the 4 patients [28]. Keime-Guibert et al treated 8 (7 with anti-Yo antibodies and 1 with anti-Hu) with 1–7 courses of combined intravenous immunoglobulin G (0.5 g/kg/day for 5 days) plus methylprednisolone (1 gram daily for 3 days) plus cyclophosphamide (600 mg/m2 given on day 4 of IV IgG), with additional treatments administered according to patient status [19]. Interval between onset of symptoms and treatment ranged between 2 weeks and 3 months in patients with anti-Yo antibody and was 10 months in the patient with anti-Hu antibody. Clinical stabilization was observed in 3 patients; 5 patients continued to progress [19]. Prognosis may be better in patients with anti-Ri antibody response and ataxia, where improvement has been reported in individual patients in response to treatment with corticosteroids, intravenous immunoglobulin G, or cyclophosphamide, along with treatment of the underlying tumor [29–32].

An important question is whether initiation of therapy early in the clinical course might improve prognosis. One of the patients treated with cyclophosphamide by Stark et al gained almost complete functional recovery following initiation of treatment 24 days after onset of symptoms [27]. Moll et al reported a patient with atypical antineuronal antibody

response in whom intravenous immunoglobulin G initiated 26 days after symptoms onset resulted in clinical improvement; in this patient plasma exchange initiated at day 10 had been unsuccessful [33]. Widdess-Walsh et al noted a good response to intravenous immunoglobulin G and prednisone in 3/4 patients with paraneoplastic cerebellar degeneration and anti-Yo antibodies syndromes in whom treatment was begun within 1 month of disease onset [29]. Vernino et al investigated 20 patients with central paraneoplastic syndromes associated with anti-Yo, anti-Hu, and anti-CV2 antibodies. Patients were excluded if bedridden or with symptoms of over 1 year in duration, weighting the study towards individuals earlier in the course of illness [22]. Eleven patients had paraneoplastic cerebellar degeneration, all associated with anti-Yo antibodies. Improvement by at least 1 point on the Rankin Score was seen in 2 of the 4 patients receiving plasma exchange plus cyclophosphamide and in 2/11 patients receiving plasma exchange plus antineoplastic chemotherapy; this degree of improvement was often of functional significance. However, only 1 patient demonstrated marked improvement. This patient, treated with plasma exchange and cyclophosphamide, began treatment 12 days after symptom onset [22].

Recently, partial clinical remission of paraneoplastic cerebellar degeneration has been reported following treatment with tacrolimus plus prednisone [34••]. In this uncontrolled trial minor improvement in neurological status was noted in 13 of 19 patients with paraneoplastic cerebellar degeneration and anti-Yo antibody following treatment with tacrolimus and prednisone [34••]. However, none of the patients regained functional neurological independence. Partial remission of symptoms has also been described in 3 patients following treatment with rituximab [35, 36, 37•]. Two of these patients were women positive for anti-Yo antibodies [35, 36]; the third patient was a child with paraneoplastic cerebellar degeneration occurring in the setting of Hodgkin's disease and anti-Tr antibodies [37•]. Clinical improvement has also been reported in one case of cerebellar degeneration associated with anti-mGluR1 antibodies following treatment with IVIgG plus ongoing mycophenolate mofetil [16].

Corticosteroids

Standard dosage Treatment regimens have varied among clinical studies, but in general 2 approaches have been used: administration of intravenous methylprednisolone, 1,000 mg daily for 3–5 days, and use of prednisone at a dose of 60–80 mg daily for a period of time depending on its effect on disease. Frequently, intravenous methylprednisolone is used initially, to be followed by oral prednisone with eventual taper. In some instances high-dose intravenous methylprednisolone has also been used in repeating courses.

Main drug interactions Corticosteroids may decrease efficacy of live nasal influenza or other vaccines and may reduce efficacy of aldesleukin, mifepristone, and growth hormone. Use of corticosteroids is not recommended with natalizumab, alefacept, nevirapine, or telbivudine.

Main side effects Corticosteroids may induce hypertension. They frequently also alter glucose metabolism and diabetic control and may also, in occasional patients, produce mania or psychosis. Long-term use of corticosteroids may predispose to

a variety of infections including oral candidiasis and can cause osteoporosis, aseptic necrosis of bone, diabetes, and cataracts. Pulse methylprednisolone is usually well-tolerated. In rare patients, however, infusion of methylprednisolone succinate has been followed by anaphylaxis.

Special points Short-term use of high-dose methylprednisolone appears to have little immediate effect on immune function, as opposed to longer term use of oral prednisone.

Immunoglobulin G

Intravenous infusion of preparations of immunoglobulin G have been used successfully for myasthenia gravis, Lambert-Eaton myasthenic syndrome, and stiff-person syndrome. Its use in paraneoplastic cerebellar degeneration, however, is speculative. The mechanisms by which intravenous immunoglobulin G affects host immunity are not understood. Possible mechanisms include reduction of T cell proliferation and induction of lymphopenia; suppression of pro-inflammatory cytokines; induction of lymphocyte monocyte apoptosis; suppression of B cell differentiation; and endogenous immunoglobulin synthesis; and modulation of anti-idiotypic networks involved in immune tolerance [18, 38, 39].

Standard dosage 0.4 g/kg intravenously for 5 days to a total dose of 2 gm/kg. Courses of intravenous IgG can be repeated if necessary, usually as a course of 1–2 gm/kg. Several IgG preparations are commercially available, and dosage regimens differ somewhat among them. In general, however, infusion should begin at a rate of 0.01–0.02 ml/kg body weight per minute for 30 minutes. If this is well-tolerated, then the rate may be gradually increased to a maximum of 0.08 ml/kg body weight per minute. If the patient reacts adversely to the infusion, then the rate should be reduced, or the infusion halted, until symptoms subside [18]. In patients with limited or compromised acid-base compensatory mechanisms and in patients in whom there is already an expanded fluid volume (eg, during pregnancy), consideration should be given to the effect of additional fluid or protein load. Because administration and side-effect profiles may differ among IgG preparations, the treating physician should be familiar with the properties and side-effects profile of the preparation being used in a given patient [18].

Contraindications Intravenous immunoglobulin G should not be administered to individuals who are known to have had an anaphylactic or severe systemic response to the agent. The agent should not be used in patients with selective IgG deficiencies who have known antibody against IgA (IgA antibody), since administration of may result in severe allergic reactions to IgA present in trace amounts.

Main drug interactions Intravenous immunoglobulin G has little interaction with other drugs. Because of its effects on the immune system, however, it is recommended that live viral vaccines should not be given until approximately 6 months after immunoglobulin G administration.

Main side effects Anaphylaxis may occur. In addition, a syndrome resembling anaphylaxis, including hypotension may occur, including in patients not known to be sensitive to the agent; this may be related to rate of infusion. Infusion reactions have also been reported. These may be characterized by symptoms of flushing, anxiety, abdominal cramps, myalgias, arthralgias, dizziness, fever, chills, headache, nausea, chest tightness, and fluctuations in blood

pressure, or heart rate. Some patients experience chronic malaise. Hypertension has been described during infusion. Intravenous immunoglobulin G has produced aseptic meningitis, with fever, headache, photophobia, nuchal rigidity [18]. Onset is usually within several hours to 2 days. CSF in these cases usually has a predominantly neutrophilic CSF pleocytosis with elevated protein and usually normal glucose. Recovery without sequelae usually occurs within several days after the infusions have been discontinued [40]. A study by Sekul et al suggests that patients with migraine may be at greater risk for this complication of the drug [40]. Work by Jayabose et al in children with immune thrombocytopenia suggests that pretreatment with corticosteroids may reduce the risk of meningitis [41]. Occasional patients may develop reversible renal insufficiency. Intravenous IgG increases blood viscosity, and thromboembolic events, including myocardial infarction, stroke, and intracranial venous sinus thrombosis, have been reported in up to 3 % of patients [42–44].

Special points The infusion should be given in a separate line not being used for fluids or other medications. Preparations of IgG from different manufacturers should not be combined [18]. Some preparations (eg, Gamimune) may not be compatible with saline. Patients should be closely monitored during infusion for changes in vital signs or other evidence of adverse response to therapy. Epinephrine should be available to treat anaphylactic response.

Cyclophosphamide

An alkylating agent which cross-links DNA. The drug is a powerful and toxic immunosuppressive agent, which has profound effects on T lymphocyte function but may not affect titers of specific antibody in blood or CSF.

Standard dosage 1.5–3 mg/kg per day by mouth.

Contraindications Cyclophosphamide is contraindicated during the pregnancy (Category D), during nursing, in patients with pre-existing bone marrow depression, leukopenia, thrombocytopenia, or renal or hepatic insufficiency. Cyclophosphamide is not to be used in patients receiving live virus vaccines.

Main drug interactions [18] Cyclophosphamide has significant additive effects when used with other immunomodulatory or immunosuppressive agents, drugs such as clozapine which are capable of causing myelosuppression, the folic acid antagonist pyrimethamine, and antiviral agents such as zidovudine [18]. Cyclophosphamide may also prolong succinylcholine-induced neuromuscular blockade. The drug may cause increased bleeding risk if used with warfarin. Inhibitors of the enzyme Cytochrome P_{450} 3A4 (CYP3A4) inhibitors increase levels of cyclophosphamide. These include ritonavir and several other protease inhibitors used to treat HIV, antibiotics such as clarithromycin, chloramphenicol, or erythromycin, azole antifungal agents such as ketoconazole or voriconazole, and, to a lesser extent, calcium channel blockers such as verapamil or diltiazem.

Main side effects These include anemia, leukopenia, and/or thrombocytopenia. Patients are at risk for hemorrhagic cystitis and for secondary malignancies, including carcinoma of the bladder, and are also susceptible to opportunistic infections. The agent may be associated with Stevens-Johnson syndrome. Nausea and vomiting are common and may be controlled with ondansetron. The drug may cause alopecia and/or stomatitis and, its use may result in amenorrhea or oligospermia. A syndrome of inappropriate antidiuretic hypersecretion

(SIADH) has been reported in individuals receiving doses of greater than 50 mg/kg or 1 g/m^2.

Special points Patients should be aggressively hydrated to avoid hemorrhagic cystitis. Amount of drug given should be reduced by 25 % in patients with a creatinine clearance of <10. In hemodialysis patients 50 % of the standard drug dose should be given after each dialysis.

Tacrolimus (FK506; prograf, astellas pharma)

A macrolide immunosuppressive agent derived from the fungus, *Streptomyces tsukubaensis*. The drug inhibits T cell activation and IL-2 transcription by preventing dephosphorylation of T cell calcineurin.

Standard dosage Dosage in transplantation range from 0.075 to mg/kg/day to 0.1–0.2 mg/kg/day. In 1 study of its use in paraneoplastic cerebellar degeneration the drug was given at 0.15–0.30 mg/kg per day, in 2 divided oral doses, administered with 60 mg of prednisone daily [34••]. Tacrolimus was administered for no longer than 4 weeks, and prednisone was tapered over weeks 1–4 [34••].

Contraindications Tacrolimus is contraindicated in patients with a hypersensitivity to the drug and in pregnancy or in nursing mothers. The injectable form of the agent is contraindicated in patients with a hypersensitivity to polyoxyl 60 hydrogenated castor oil.

Main drug interactions As is the case with cyclophosphamide, blood levels of tacrolimus may be increased by CYP3A4 inhibitors (see above) and may be decreased by CYP3A4 inducers such as rifampin. The drug should not be used concomitantly with cyclosporine or sirolimus.

Main side effects Tacrolimus has been associated with increased risk of infection, increased risk of malignancy, development of diabetes mellitus, hypertension, hyperkalemia, nephrotoxicity, and central neurotoxicity manifested as posterior reversible encephalopathy syndrome (PRES) [45–47]. Infections have included JC virus-induced progressive multifocal leukoencephalopathy (PML), BK virus-induced nephropathy, and cytomegalovirus infection. Malignancies have included lymphomas, post-transplant lymphoproliferative disorder, and cutaneous neoplasms. Risk of developing diabetes mellitus appears higher in Hispanic and African-American patients. Tacrolimus has also been associated with cardiac hypertrophy and with pure red cell aplasia.

Special points Trough concentrations of tacrolimus should be carefully monitored. Live virus vaccines should not be administered to patients receiving tacrolimus. Patients receiving tacrolimus should not drink grapefruit juice. Tacrolimus is typically given in combination with corticosteroids.

Rituximab

Rituximab (Roche Ltd, Basel, Switzerland) is a chimeric monoclonal agent which consists of human IgG1 constant regions and murine variable regions. The agent is specific for CD20, a transmembrane protein which is expressed on pre-B lymphocytes and B cells but not on plasma cells . CD20 is important in B-cell activation, proliferation, and differentiation [48]. Rituximab is currently approved for treatment of B cell (non-Hodgkin's) lymphoma and rheumatoid arthritis and has been found to be of value in treatment of multiple sclerosis [49]. The agent has reduced B cells in both blood and CSF, with B cell numbers remaining depressed for between 3 and 12 months [50, 51]. In studies of children with opsoclonus-myoclonus

treated with rituximab, Prazatelli et al found that CSF B cell populations (including CD27+ memory, CD38+ activated, and CD5+ subsets) remained significantly depressed in CSF for 12–18 months despite repopulation of these cells in blood [52]. Although CD20 is not expressed on plasma cells, Petereit et al have reported depletion of plasma as well as B cells from both serum and cerebrospinal fluid of a patient treated with rituximab [51]. However, despite its effect on B lymphocytes, rituximab may fail to reduce titers of specific antibody in serum or CSF [36, 51]. Only limited use of the agent has thus far been reported in paraneoplastic cerebellar degeneration. In an uncontrolled study of 9 patients with paraneoplastic neurological syndromes treated with rituximab, Shams'ili et al reported clinical improvement in 1 patient with paraneoplastic cerebellar degeneration associated with anti-Yo antibodies [36]. Yeo et al reported substantial improvement in cerebellar symptoms following treatment with rituximab in a pediatric patient with Hodgkin's disease after chemotherapy for the malignancy failed to produce neurological improvement [37•]. A closely related humanized monoclonal, ocrelizumab, has been shown of value in treatment of multiple sclerosis, but its use has not yet been reported in paraneoplastic neurological disease [53, 54]

Standard dosage

A standard dosage regimen for use of rituximab in paraneoplastic disorders has not yet been established. Treatment of neuromyelitis optica has employed regimens of 375 mg/M2 for up to 4 infusions given at 4 week intervals or, alternatively 1,000 mg infused twice with 2 weeks between infusions [55]. Use in paraneoplastic cerebellar degeneration has involved a regimen of 375 mg/M2 for up to 4 infusions given at 4 week intervals [36].

Contraindications

Rituximab is contraindicated in patients with allergy to mouse proteins and should be used with caution in elderly individuals, patients with a history of cardiac disease (angina or cardiac arrhythmias), cancer patients with high tumor burden, patients receiving cisplatin, or patients with known chronic infections including hepatitis B. There is increased risk of infusion reactions in patients with pulmonary conditions.

Main drug interactions

The use of live virus vaccines, including nasal influenza vaccines, is contraindicated, as is simultaneous treatment with natalizumab or TNF blocking agents. Concomitant use of antihypertensive agents during infusion may exacerbate hypotension.

Main side effects

The drug has been associated with fatal infusion reaction complex (hypoxia, pulmonary infiltrates, ARDS, MI, ventricular fibrillation, and/or cardiogenic shock), and PRES [56]. Post-exposure side effects in the weeks following infusion may include tumor lysis syndromes with renal failure, Stevens-Johnson syndrome, and severe mucocutaneous reactions [18]. Neutropenia has been reported as a late complication of therapy [57]. Bowel obstruction and perforation have been reported, as has renal toxicity, and sensory neuropathy. A variety of infectious complications may arise, in the months following infusion. These have included reactivation of hepatitis B, progressive multifocal leukoencephalopathy (JC virus), and infections with West Nile virus, hepatitis C, herpes simplex virus, cytomegalovirus, and parvovirus B19 [58–60]. It should be noted that many of the patients developing opportunistic infections have also been on other immunosuppressive agents.

Special points Patients should be premedicated with an antihistamine (usually Benadryl) and acetaminophen 30 minutes prior to dosing and should be closely monitored during the infusion. Patients may require treatment with methylprednisolone 100 mg IV or its equivalent 30 minutes prior to each infusion. Infusion reactions may require Benadryl, intravenous fluids, glucocorticoids, epinephrine, bronchodilators, or oxygen. Infusion reaction can usually be managed by slowing the rate by at least 50 %. Although unusual in paraneoplastic disorders, patients with high numbers of circulating malignant cells (≥25,000/mm^3) may be at increased risk for tumor lysis syndrome. Ocrelizumab, a humanized monoclonal with specificity similar to rituximab, has not yet been studied in paraneoplastic cerebellar degeneration but may an alternative agent in patients allergic to mouse proteins.

Mycophenolate mofetil

Mycophenolate mofetil (CellCept) is converted to mycophelolic acid (MPA) after ingestion. MPA targets inosine monophosphate dehydrogenase, a rate-limiting enzyme in *de novo* synthesis of guanosine nucleotides essential for DNA synthesis [45, 61]. The enzyme plays a particularly important role in T- and B-lymphocytes and is 5-fold more potent in inhibiting the isoform of inosine monophosphate dehydrogenase found in activated lymphocytes compared with the isoform found in most other cells [61]. The agent induces apoptosis of activated lymphocytes and may also reduce lymphocyte recruitment by suppressing expression of adhesion molecules and suppressing production of inducible nitric oxide synthetase (iNOS). MPA also suppresses primary (but not secondary) antibody responses [61]. Mycophenolate mofetil has received extensive use in myasthenia gravis [62, 63] and has been used, often in combination with prednisone, in treatment of limbic encephalitis associated with antibodies to neuronal surface antigens [64–67]. Its use has not been reported in proven paraneoplastic cerebellar degeneration, but it has been used to induce disease stabilization in 1 patient with mGluR1-associated cerebellitis in whom no tumor was found [16].

Standard dosage Mycophenolate mofetil is usually given as 1,000–1,500 mg twice daily.

Contraindications The drug is contraindicated in patients who are hypersensitive to the agent, during pregnancy, and in patients with Lesch-Nyhan syndrome or Kelly Seegmiller syndrome. The agent is used with caution in elderly patients or in patients with severe gastrointestinal or renal disease, or in patients who have depressed bone marrow function.

Main drug interactions The use of live virus vaccines is contraindicated, as is simultaneous treatment with natalizumab or TNF blocking agents. Increased free blood levels of MPA may occur in patients treated with agents which compete with MPA for albumen binding, such as phenytoin, xanthine bronchodilating agents, and salicylic acid Absorption of the mycophenolate mofetil may be inhibited by antacids containing aluminum or magnesium and by cholestyramine or protein pump inhibitors. Antibiotics, including macrolides, cephalosporins, penem antibiotics, penicillins, and sulfonamides may decrease MPA blood levels by inhibiting enterohepatic circulation of the drug. Blood levels of MPA may be increased in patients taking probenecid, acyclovir, gancyclovir, or valgancyclovir.

Main side effects The most common side effects include gastrointestinal symptoms of diarrhea, nausea, or vomiting; these symptoms may occasionally be severe. Some patients may develop elevated liver transaminases. The drug may produce leukopenia or, less frequently, anemia, or thrombocytopenia. Both the gastrointestinal and hematological side effects of mycophenolate mofetil may resolve with continued treatment. The drug has been associated with pure red cell aplasia; this has been reported to resolve upon discontinuation of the drug. A variety of opportunistic viral, bacterial, mycobacterial, and fungal infections has been reported in patients receiving the drug [45, 68–73]. Many of these patients have received prior or concomitant treatment with other immunosuppressive agents [45, 68–73].

Special points Complete blood count, liver function tests, and creatinine should be obtained prior to beginning the drug, then weekly for 1 month (or longer if dosage of the drug is increased after that time), then twice monthly for 2 months, and then monthly for the first year. Serum creatinine and liver function tests may be checked every 2–3 weeks initially and during dose escalation, and then every 2–3 months once stable dosage is reached [45].

Interventional procedures

Plasma exchange

Therapeutic plasma exchange involves a process of blood purification using an extracorporeal device designed to remove particles of large molecular weight from plasma [18, 74]. The process removes antibodies and immune complexes nonspecifically and also removes cytokines and other mediators of inflammation [74]. The procedure has been of value in treatment of autoimmune neurological disorders associated with antibodies directed against cell membrane components [11, 12]. However, it does not reliably remove IgG from cerebrospinal fluid [75, 76]. Although individual cases of clinical improvement have been reported following plasma exchange in patients with paraneoplastic disorders [5, 22, 77], most patients have failed to improve [18, 22, 24, 78–81].

Standard procedure Different investigators have used a wide range of protocols. A reasonable regimen would be a course of 5–6 exchanges of 1–1.25 plasma volumes carried out over 10–14 days [82]. Vernino et al in their study of plasma exchange and other modalities in patients with paraneoplastic disorders employed 1 plasma volume exchange every other day for a total of 5 exchanges [18, 22].

Contraindications Plasma exchange is contraindicated in patients with precarious hemodynamic status (eg, cardiogenic shock), unstable angina pectoris, or pericardial effusions) [18]. The procedure is also contraindicated in patients with uncontrolled sepsis or septic shock.

Complications In a prospective study, the most common adverse effects were fever (7.1 % of patients); hypocalcemic symptoms including paresthesias, and muscle cramps (8.2 %) due to infused citrate; mild hypotension (8.1 %); nausea (4.7 %), vomiting (4.1 %), and tachycardia (4.4 %) [18,

83]. Severe hypotension was noted in 2.2 % of patients. Urticaria and pruritus were more common in patients receiving fresh frozen plasma. Complication rates were higher in patients who were significantly anemic [83]. Risk of infection due to vascular access and reduction in immunoglobulins and complement is a significant concern. Hypocoagulable states may occur, usually during a period from 8–12 hours after exchange. Subsequently (usually between 24 and 72 hours) a rebound hypercoagulable state due to delayed recovery of antithrombin 3 levels may rarely occur and may require treatment with heparin.

Surgical and medical treatment of the underlying neoplasm

Therapy directed against the underlying tumor is of fundamental importance not only because of the need to deal with the cancer itself, but also because of its potential effect on progression of the paraneoplastic disorder [20–22]. Candler et al in a study in which patients with paraneoplastic neurological syndromes were followed over time, found that treatment of the underlying tumor, with or without immunosuppressive therapy, was the only measure which was associated with stable or improved neurological condition [21]. Likelihood of improvement or stabilization of paraneoplastic neurological syndromes may depend the duration of paraneoplastic symptoms prior to tumor remission and on the specific autoantibody involved. Clinical outcome appears to be poorest in patients with anti-Yo, anti-Hu, anti-Tr, and anti-mGluR1antibodies but significantly better in patients with anti-Ri antibody [23]. Partial remission in cerebellar symptoms was reported in 3/3 patients undergoing successful treatment of Hodgkin's disease [84].

Emerging therapies and future directions

- Therapies specifically designed for treatment of paraneoplastic cerebellar degeneration are not available. For the foreseeable future, treatment of these disorders will involve off-label use of agents designed for other disorders.
- Overall, therapies designed to depress T cell-mediated immunity, including tacrolimus, have had, at best, marginal success. Most treatments used have had, at best, variable effect on antibody titers.
- Early, uncontrolled studies with rituximab are relatively promising, but larger numbers of patients need to be studied in controlled fashion. Use of other monoclonal immunosuppressive drugs has not been reported. Agents such as bortezomib, which affects plasma cells directly, may warrant investigation [85, 86].
- Rapid diagnosis and institution of treatment are essential to prevent irreversible neurological injury, and the clinician may need to begin immunosuppressive therapy on strong clinical suspicion while awaiting results of studies to detect antineuronal antibodies.
- There remains a great need for multi-institutional controlled studies instituting treatment early in disease and employing standardized

methods for diagnosis, strictly regulated treatment protocols, and uniform criteria for follow-up.

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Disclosure

No potential conflicts of interest relevant to this article were reported.

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