A. Introduction

Rescue treatments are herein defined as treatments designed to produce an immediate and clinically evident benefit in one of two situations after failure of standard therapy:

1. an acute attack of MS that leads to severe disability from which a patient has no or a poor response following intravenous high dose corticosteroids

2. patients with aggressive step-wise or continuously worsening disability accompanied by evidence for active inflammatory disease typically detected as an or multiple gadolinium-enhancing lesions on MRI images in a patient who has been managed with one or more of the “first line” disease-modifying therapies (interferon beta 1a or b; glatiramer acetate).

The mechanisms responsible for the disease and for the treatment benefits in these two different contexts may differ, be the same, or overlap. Patients with progressive forms of MS without clinical or radiological evidence of active inflammation and patients with pseudo-exacerbations for whom immunomodulating treatments are either not indicated or less likely to be effective are excluded from consideration.

Rescue treatments are considered successful when they result in reversal of a recently acquired neurological deficit or arrest of rapidly deteriorating MS. From that point of view, they are easier to study than long term treatments, for which no immediate effects are usually perceived by patients or their physicians. However, such patients constitute a small minority (“hyperacute” course, estimated in one study as 8% of MS cases1). The pathogenesis of their diseases may be diverse, their natural history is highly variable, and the ethics of their enrollment into placebo- and sham-controlled studies is complex. No template for conduct of clinical trials is readily available especially considering the multitude of different presentations, which in general are more heterogeneous than seen in progressive forms of MS. Unfortunately, the evaluation of rescue treatment remains an art, informed by limited numbers of open-label/uncontrolled studies, small controlled trials of a limited number of agents and subset analyses of clinical trials that have included patients who may not have one of the two clinical situations mentioned above.

B. General approach

Faced with a patient considered to be a candidate for a rescue treatment, the following diagnostic and therapeutic evaluations are appropriate:

1. Does the patient have demyelinating disease? Consider other mimics of MS, especially multifocal inflammatory diseases, gliomatosis cerebri, vasculitis, among others. Be sure to consider whether a functional (non-neurological) disorder may be present. Are objective findings consistent with organic neurological disease present?

2. If the patient has a demyelinating disease, does he/she have prototypic MS? Could the patient have neuromyelitis optica (severe optic nerve and spinal cord disease, but may also have brain lesions of a variety of types, including symptomatic lesions)? If neuromyelitis optica spectrum disorder, interferon and glatiramer acetate treatments are likely ineffective, and the patient should be on an immunosuppressive agent. Could the patient have acute disseminated encephalomyelitis (ADEM)? If acute disseminated encephalomyelitis, corticosteroids and supportive therapy is standard. One should be wary of making a diagnosis of acute disseminated encephalomyelitis, especially in an adult: aggressive MS rather than ADEM is more likely.

3. Is this a true exacerbation or is the deterioration step-wise/accompanied by gadolinium-enhancing lesions or new/evolving T2 lesions? If radiological evidence for active inflammatory disease is not present — consider pseudo-exacerbation, which is particularly likely to manifest in the context of progressive disease with substantial neurological deficit. Such patients are generally not managed with aggressive immunotherapy.

Department of Neurology, Mayo Clinic College of Medicine (200, First Street, SW Rochester, MN 55905)
(Received: 21 May 2009)
4. If it is demyelinating and associated with features consistent with prototypic MS, decide which of the two scenarios best applies to the patient’s recent course:
   a. An acute attack with a severe non-resolving neurological deficit on a background of previously stable disease or a first demyelinating episode: If so, plasma exchange has a 40% chance of being helpful. Plasma exchange is also of value in neuromyelitis optica and possibly in other acute demyelinating disease presentations.
   b. A stepwise succession of individually less severe attacks cumulatively leading to significant and relatively rapid accumulation of permanent disability or non-stepwise rapid progression of disability conforming to the “hyperacute” definition (EDSS 7 within 5 years, or likely-to-be hyperacute if no effective suppression of disease is possible). If so, successively more aggressive immunosuppression to suppress ongoing inflammatory activity so as to avert early, severe and permanent disability is warranted.

C. Treatment of Acute Attacks
   a. Plasma Exchange
      Plasma exchange has been assessed as a treatment for patients with MS since 1980 in a series of uncontrolled reports including both cases with acute attacks and patients with progressive MS with variable degrees of benefit. The most promising results were reported in the small number of patients with acute, catastrophic attacks\(^3\). A controlled clinical trial reported in 1989 failed to convincingly show benefit when plasma exchange was studied as an adjunct to adrenocorticotropic hormone (ACTH) and cyclophosphamide for acute attacks of MS\(^3\), although a modest short-term benefit was reported for relapsing-remitting MS only.
      Rodriguez et al. reported six patients with acute severe attacks of multiple sclerosis who experienced rapid and dramatic recovery following plasma exchange\(^4\). All patients in this case series were quadriplegic, hemiplegic, or paraplegic. Additionally, two patients were aphasic and two required artificial ventilation. In these corticosteroid-refractory patients, plasma exchange was administered as a monotherapy. All patients in this series responded to treatment and five had experienced excellent results. Improvement began within days of initiation of treatment. The therapeutic benefit was sustained on follow up.
      To resolve the discrepancies between the Mayo Clinic experience reported by Rodriguez and the equivocal benefit in the US randomized study, between 1995 and 1998, neurologists at Mayo Clinic conducted a randomized clinical trial of plasma exchange in the setting of acute, severe attacks of MS or other idiopathic inflammatory demyelinating dis-

   cases\(^5\). They enrolled 22 patients failed to respond to corticosteroid therapy (“rescue therapy”) over 4 years. Patients included in the trial had either clinically definite MS (n = 12) or other inflammatory demyelinating diseases (n = 10), most commonly acute transverse myelitis. Two patients were enrolled with a diagnosis of neuromyelitis optica. All patients had acute attacks of major proportion of at least three weeks duration and failed to improve a minimum of two weeks after having received methylprednisolone therapy at a minimum dose of 500 mg/day. All patients enrolled had quadriplegia, paraplegia, or hemiplegia as a “targeted neurological deficit”. In addition, one patient with a clinical diagnosis of acute disseminated encephalomyelitis was comatose, and two patients who had cerebral hemisphere lesions were aphasic. The spectrum of neurological deficits of patients enrolled in this controlled trial was typical of those of the patients previously reported in the series of Rodriguez et al.
      The study was conducted using a crossover design. However, only patients who failed to improve in the first treatment period crossed over. This approach was feasible because the improvement in responders was evident very early in the course of treatment and was unlikely to occur subsequent to crossover related to the first course of treatment. This approach guaranteed access to the active treatment to all patients who had not improved, which was the only ethical and feasible way that a sham-controlled trial could be conducted in this setting. Furthermore, we suspected that this approach might enhance the power of the study, as patients who failed sham treatment and subsequently were responders to active treatment would be particularly informative.
      The treatment administered was standard plasma exchange by continuous-flow centrifugation. On average, 1.1 plasma volumes (54 mls/kg) were exchanged every-other day for 7 treatments and replaced with a mixture of 5% albumin and saline. In the sham-treated patients, blood was separated in an identical fashion into the cell and plasma fractions but then recombined and returned to the patient unchanged. The endpoint was moderate-to-marked (functionally important) improvement in the targeted neurological deficit without any worsening in any other existing deficit and without any newly developing neurological deficit. This endpoint allowed the decision about success to be individualized to the patient’s specific attack-related neurological deficit.
      Five of the 11 patients undergoing active plasma exchange in the first treatment period improved versus 1 out of 11 who received sham therapy. None of the six treatment failures in the active treatment first group improved after crossover. However, three out of eight surviving treatment failures in
the sham treatment first group improved to a moderate-to-marked degree after crossover. There were two patients who died in the study, both of whom received only sham exchange. One died of progressive increased intracranial pressure and herniation; acute disseminated encephalomyelitis was confirmed at autopsy. The second patient died of a pulmonary embolus in the setting of heparin-associated thrombocytopenia syndrome.

Overall, 8 of 19 individuals (42.1%) receiving active treatment were treatment successes (moderate or greater, functional significant improvement) versus 1 of 17 (5.9%) who received sham treatment. \( p = 0.01 \).

Adverse effects related to treatment were few, the most common being significant anemia, which developed in most patients and in 4 of 22 patients was severe (hemoglobin < 8.0). The anemia was invariably asymptomatic and corrected within one month. Central intravenous catheters were necessary in 13 of 22 patients, but this was accomplished without sequelae. There were no other common serious adverse effects. A number of incidental side effects unrelated to the specific treatment also occurred.

A long-term benefit from the treatment was not anticipated, and was not the primary endpoint of the study. In fact, 4 of 8 patients who received active treatment and were treatment successes had recurrent attacks during the six-month follow-up period. Ten of 12 patients who were treatment failures failed to recover over 6 months of follow up, though 2 out of 12 did meet the criteria for moderate improvement at 6 months. These data suggest but do not prove that the patients that were selected for this clinical trial were unlikely to experience spontaneous improvement in the absence of treatment.

The mechanism of action was unclear from this study. However, the success of plasma exchange as a monotherapy could suggest that a humoral factor is responsible for sustaining disability in at least 40% of patients with acute catastrophic attacks. Considerable evidence has recently emerged that suggests a role for humoral autoimmunity in MS\(^1\) and more recently in NMO\(^2\). The nature of the target for humoral factor or factors remains elusive for MS, but it has recently become clear that aquaporin-4-directed IgG is likely pathogenic in NMO\(^2\), although only 60-70% of individuals can be demonstrated to be seropositive in cross-sectional studies; treatment does appear to reduce titers. Plasma exchange is selective in that it targets only humoral factors but nonselective in that it removes all components of plasma. A subsequent study revealed that only patients with demonstrable immunoglobulin and activated terminal complement on retrospectively analyzed CNS biopsy samples improved (10/10 with this pattern were responders compared to 9/9 who lacked these immunopathological findings\(^1\))\(^1\). Some patients may have not responded either because they did not have the specific humoral components or perhaps because they sustained such severe axonal injury that they were unable to benefit from treatment, which may complicate subsequent analysis of serum components for association with clinical benefit.

The American Society for Apheresis has rated plasma exchange as a category II indication (generally accepted in a supportive role) for acute demyelinating diseases unresponsive to corticosteroids\(^1\)

There have been several confirmatory studies of the benefits of plasma exchange in series of patients, albeit none have been controlled. Rensel et al have reported good results with the use of plasma exchange in treating acute attacks of neuromyelitis optica\(^1\) as have Watanabe et al\(^1\). Keegan et al have recently reviewed their complete experience at Mayo Clinic with the use of plasma exchange for acute attacks of demyelinating disease. They have confirmed that the response rate in their uncontrolled experience, using a similar definition of success as was used in the randomized trial described above, was virtually identical at approximately 44%. Included in that series were 10 patients with acute attacks of neuromyelitis optica, and the success rate was 60% in that subgroup, which was somewhat (though not significantly) better than that seen in other IIDDs perhaps in part due to the important role of humoral factors in this disorder\(^1\). Kurrecht et al have shown the benefit of plasma exchange in acute, severe optic neuritis\(^1\). Meca-Lallana et al (Spain) and Bennetto et al (U.K.) have confirmed the benefit in patients with severe MS attacks with a variety of deficits\(^1\)\(^2\).

b. Intravenous immunoglobulin

Current evidence for the use of IVIg in acute relapses is sparse. Proponents of the use if IVIG for acute attacks largely argue of its possible effectiveness by analogy of the comparable effectiveness of IVIg and TPE (see next section) in other neurological autoimmune diseases such as Guillain Barre syndrome and chronic inflammatory demyelinating polyneuropathy. Soukop and Tschabitscher studied the use of IVIg (50 mg/kg) to 22 patients with an acute relapse and found clinical improvement in 15 patients (68%) within 24 hours; however, the benefit persisted for only 2 weeks\(^1\). Sahlas et al. reported dramatic clinical improvement in 2 patients with acute disseminated encephalomyelitis (ADEM)\(^1\). Using serial gadolinium enhanced MRI, Nos et al. studied the blood brain barrier in patients with acute relapse receiving IVIg. This study compared IVIg treatment with a combination of IVIg and prednisone, and found a dramatic decrease in enhancement in serial scans in the latter group only\(^1\).
D. Treatment of Step-wise Worsening or Rapidly Worsening Demyelinating Disease

The most commonly applied approach in patients with aggressive step-wise worsening or rapidly worsening MS associated with MRI evidence of accumulation of new T2 lesions and/or gadolinium enhancing lesions is aggressive immunosuppression. Rapid improvement over the course of one to two weeks in an existing major neurological deficit such as paraplegia has not been adequately proven to occur following any immunosuppressive treatment (in contrast to plasma exchange), although occasional reports of this occurring exist. However, the primary goal in these patients with ongoing inflammatory disease activity is the arrest of continuous worsening of disability. A major challenge is to define the point that rapidly worsening MS can be reliably identified and determined to be inexorable. The commonest treatments applied include cyclophosphamide and mitoxantrone, and more recently, natalizumab has been shown to be effective in patients with aggressive MS, even when first line treatments have failed. Similarly, alemtuzumab has been reported to be effective in such patients. Stem cell (bone marrow) auto-transplantation after immuneablation is an additional aggressive option that won’t be considered here nor will combination treatment of first line treatments for MS for which evidence of efficacy is unavailable.

i. Mitoxantrone

MTX is an antineoplastic agent that has been used for prostate cancer and nonlymphocytic leukemia in adults. MTX produces DNA protein cross-links and strand breaks, interfering with DNA repair and RNA synthesis, thereby interfering with cellular proliferation. This agent has been approved for worsening RRMS, secondary progressive MS, and progressive relapsing MS based on phase III clinical trials.

In 1997, Edan et al. reported the results of the French and British multicenter, randomized, unblinded controlled trial of MTX in 42 patients with active CDMS treated with MP and MTX\(^\text{21}\). Patients who entered the trial had either RRMS or SPMS and were required to have either two relapses with sequelae within the 12 months preceding entry to the study or progression of two points on the EDSS scale during the same time period, respectively. Three monthly gadolinium-enhanced MRI scans were performed in a baseline period of two months, and only patients developing at least one active MRI lesion during the baseline period were included. Patients were randomized to receive either monthly MTX (20 mg IV) and methylprednisolone or methylprednisolone alone over six months. MRI data showed an 80% reduction in gadolinium enhancing lesions in the MTX group. Fewer relapses were observed in the MTX group (7 vs. 31 relapses). Additionally, the MTX group experienced improvement in impairment (EDSS score) in 12 and deterioration in 1 patient compared to the methylprednisolone group that experienced improvement in 3 and deterioration in 6. The improvement of sustained existing disability suggested that some patients in this trial had a reversible component to their progression—hybrids between “relapse” and “progression”.

Considering its toxicity, mitoxantrone should be considered for patients with rapidly worsening MS refractory to treatment with steroids and who have substantial clinical deterioration that is refractory to other less toxic immunotherapies. Nausea, alopecia, bone marrow dysfunction, gonadal dysfunction including amenorrhea, and cardiotoxicity are adverse effects. 12 mg/m\(^2\) administered at 3 monthly intervals until a maximum cumulative dose of 140 mg/m\(^2\) is reached is a standard dose regimen. Recent studies suggest that treatment-related leukemia (usually acute promyelocytic leukemia) occurs in approximately 1% of treated patients.

ii. Cyclophosphamide

Cyclophosphamide (CTX) is an alkylating agent with immunosuppressive properties and is commonly used in treatment of immune-mediated disease. Uncontrolled data suggests that CTX may be an effective alternative to mitoxantrone for rapidly worsening MS. However, it is likely less effective or possible ineffective in gradually worsening progressive MS without evidence for active inflammation on MRI.

In an open-label, unblinded, controlled study, Weinstock-Guttman et al. treated 17 consecutive patients with fulminant MS, refractory to corticosteroid treatment, with IV CTX 500 mg/m\(^2\) with IV MP 1.0 g for 5 consecutive days, followed by a 5-day tapering course of prednisone\(^{21}\). Maintenance immunotherapy was initiated about 8 weeks after CTX/MP induction, and consisted of methotrexate, MP, or interferon beta-1b at the discretion of the treating neurologist. Patients were followed for 24 months. 13 of 17 (76%) patients and 10 of 17 (59%) patients improved after 3 and 6 months, respectively. 13 of 17 (76%) patients remained stable or improved after 1 year and 9 of 13 (69%) at 2 years. All patients who worsened after 3 months continued to deteriorate during this follow up period despite maintenance immunotherapy. Of 10 patients who were nonambulatory at the time of induction therapy (EDSS ≥8.0), five (50%) became ambulatory. The authors suggested that CTX/MP may represent an effective therapeutic option for the rare MS patients with a fulminant progressive course.

Khan et al. studied CTX in fourteen consecutive CDMS with a clinical course marked by severe deterioration refrac-
tory to conventional immunomodulatory agents and IVMP in the year preceding treatment with CTX. Patients received 1,000 mg/m² in the first month and subsequent treatments over 6 months were titrated to yield nadir WBC two weeks post infusion of 2000/mm³. Patients all stabilized or improved at 6 months, and the benefit was sustained at 18 months after the onset of treatment with CTX²⁰.

In an unblinded, uncontrolled study, Patti et al. studied the effects of combined treatment with CTX and interferon-beta in selected patients with “rapidly transitional” MS who were previously treated with beta interferon²¹. Monthly treatment with CTX administered to obtain a lymphopenia of 600 to 900/mm³ produced a significant reduction in the relapse rate, disability, and reduction of T2 MRI burden of the lesion as compared with the beta interferon treatment period preceding the study. The treatment was safe and well-tolerated in the short term follow-up of this study. Smith et al reported results of a randomized study of treatment of patients with active disease on interferon beta therapy with added CTX 800 mg/m² plus 1 g of methylprednisolone monthly for 6 months versus added methylprednisolone only. In 59 patients, they found a significantly greater reduction in the frequency of gadolinium enhancing lesions from baseline in those who received the CTX-containing regimen over 24 months followup (rate ratio 0.30; range 0.12-0.75; p = 0.01)²².

Recently, Krishan et al reported the Johns Hopkins experience with high dose CTX (50 mg/kg/day × 4 days followed by administration of granulocyte colony-stimulating factor) in 9 patients with relapsing remitting MS who met the following criteria: 2 or more gadolinium-enhancing lesions on each of 2 MRI scans; at least 1 clinical exacerbation in the last 12 months OR a sustained increased of 1.0 EDSS points over one year. Enrolled patients either failed or refused other therapies; only one was treatment naïve. The mean EDSS decrease was 2.11 ± 1.97 (39.4% decrease). Gadolinium enhancing lesions declined from 6.5 ± 2.1/year to 1.2 ± 2.3 at followup at 23 months²³. The authors propose that this may be an alternative to immunosuppression and stem cell transplantation.

Potential side effects include nausea, vomiting, bone marrow suppression with leukopenia, transient alopecia, amenorrhea, oligospermia and infertility, bladder toxicity, and potential for bladder and hematological malignancies.

Despite its controversial role in progressive disease, CTX may be effective in selected patients experiencing rapid progression of disability refractory to conventional therapy, similar to the situations in which MTX is appropriately administered. These immunosuppressant drugs are most effective when administered in active inflammatory disease to arrest rapidly deteriorating neurological dysfunction.

With FDA-approval of MTX for rapidly worsening MS, many clinicians have use MTX rather than CTX, although cardiotoxicity is not an issue with CTX. There has been no comparative study of CTX and MTX.

iii. Natalizumab

Natalizumab is a humanized anti-α4 integrin reactive monoclonal antibody that interferes with trafficking of immune cells into the central nervous system. It has been recently reviewed²⁵ and is now approved for management of relapsing forms of multiple sclerosis, although its association with progressive multifocal leukoencephalopathy has interfered with its acceptance as a widely accepted first line agent for MS; otherwise the drug is well tolerated. Although comparative studies with other MS disease modifying therapies are to date unavailable, it appears to have greater efficacy than previously available disease modifying treatments and as such has been reasonably been considered for “rescue therapy”. Whether natalizumab is also highly effective in patients who have failed standard treatment or have aggressive forms of MS have now been addressed to a limited extent in a study of 234 patients with active MS who had ≥ 2 attacks or worsening by 2 EDSS points over the previous year, 175 of whom remained active in spite of first line disease modifying treatments. In a mean followup of 11.3 months (range 3-21.5), the majority of patients were attack free and the decline in the annual relapse rate was comparable to that observed in the pivotal studies of relapsing remitting MS²⁶.

iv. Alemtuzumab

Alemtuzumab (CAMPATH) is a monoclonal antibody reactive with CD52, a glycoprotein present on the surface of most lymphocyte lineage cells. It causes prolonged T cell depletion, especially of CD4 cells. Hirst et al reported in 2007 the clinical experience with this agent as a rescue treatment for aggressive relapsing multiple sclerosis in 39 patients from 3 different UK institutions (Bristol, Cardiff and Plymouth)²⁷. Patients selected for treatment in this unblinded and uncontrolled study had disease duration shorter than 6 years, high relapse rate, rapidly accumulating disability and early motor, cerebellar or cognitive dysfunction or combinations thereof. With alemtuzumab treatment the relapse rate fell from 2.48/year to 0.19/year. Mean EDSS change was −0.36 overall and −0.15 in those completing at least 1 year of followup. 83% were stable or improved following treatment. Side effects of this agent include infusion reactions, opportunistic infection and autoimmunity, especially thyroid and idiopathic thrombocytopenic purpura: 12 of 39 developed serological evidence of autoimmunity, and 5 developed clinical autoimmunity, 2 thyroid and 1 skin (pityriasis lichenoides chronicus). The authors concluded that alemtuzumab may be of use in patients with aggressive relapse-related disease.
References


