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Myelopathy in Sjögren's Syndrome
Role of Nonsteroidal Immunosuppressants

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Abstract

The incidence, aetiology and optimal treatment of CNS Sjögren's syndrome, including myelopathy associated with Sjögren's syndrome, are unknown at the present time. CNS Sjögren's syndrome is thought to be the result of an autoimmune vasculitis, but other mechanisms may be important. Spinal cord involvement in CNS Sjögren's syndrome may present as acute transverse myelitis, progressive myelitis, Brown-Séquard syndrome, neurogenic bladder or lower motor neurone disease. Optic nerve pathology frequently accompanies spinal cord involvement. Acute transverse myelitis has a high mortality and appears to be the most frequent form of spinal cord involvement in CNS Sjögren's syndrome, occurring in about 1% of all patients with Sjögren's syndrome.

The patient's symptomatology and clinical course dictate current treatment of myelopathy. First-line treatment appears to be corticosteroid therapy. However, when the patient's condition fails to improve or deteriorates a nonsteroidal immunosuppressant agent should be considered. Agents used to treat myelopathy include cyclophosphamide, chlorambucil, azathioprine, ciclosporin (cyclosporin) and methotrexate in conjunction with corticosteroids. Most data exist as anecdotal reports. The agent of first choice, based on adverse effect profile and efficacy, appears to be cyclophosphamide given intravenously in pulse doses. Other nonsteroidal immunosuppressant agents should be considered, especially when lack of efficacy of, or intolerance to, cyclophosphamide exists in the patient's history. Glandular and other extraglandular symptoms may benefit concomitantly from the immunosuppressant treatment.

In addition, when acute relief of symptomatology is needed, the patient may benefit from a trial of plasmapheresis or intravenous immunoglobulin. Infliximab (anti-tumour necrosis factor-α antibodies) has not been used as a treatment modality for myelopathy, but has shown some usefulness in the treatment of extraglandular symptoms, as well as peripheral nervous system manifestations of Sjögren's syndrome. This agent might be considered when all other treatment modalities have failed given the presumed importance of tumour necrosis factor in the pathogenesis of Sjögren's syndrome.

Sjögren's syndrome is a chronic, progressive autoimmune-mediated inflammatory exocrinopathy involving both humoral and cellular immunity alterations. This disorder may be classified as primary or

secondary. In secondary Sjögren's syndrome the disease is associated with another connective tissue disorder, most commonly rheumatoid arthritis (RA), or less commonly, systemic lupus erythematosus (SLE) and other disorders. With primary Sjögren's syndrome there is an immunological attack on multiple exocrine glands in the body, including most commonly the salivary and lacrimal glands, leading to the sicca complex. The sicca complex consists of keratoconjunctivitis sicca (dry eye) and xerostomia (dry mouth) along with recurrent or chronic episodes of major salivary gland enlargement. Non-exocrine tissue may also be involved, including the lungs, kidney, vascular walls, muscle, joints, gastrointestinal tract and the nervous system (both peripheral and central).

1. Pathogenesis

The pathogenesis of Sjögren's syndrome is still unknown although inappropriate B-cell activation is thought to be one of the most prominent immunoregulatory aberrations in the disease. Inappropriate B-cell activation can follow various stages of evolution from polyclonal activation, evolving to polyclonal-oliglonal-monoclonal activation to the extreme situation of malignant monoclonal proliferation.[1] Malignant transformation of B cells to produce lymphoma occurs in about 5% of patients with Sjögren's syndrome. Because of polyclonal B-cell hyper-reactivity, patients with Sjögren's syndrome display hypergammaglobinaemia, circulating immune complexes and multiple autoantibodies directed against both organ-specific and non-organ-specific autoantigens. The most clinically important and best characterised are the autoantibodies anti-Ro(SSA) and anti-La(SSB), which are antibodies against cellular heterogeneous ribonucleoprotein complexes consisting of antigenic proteins.[1,2] The antibodies recognise autoantigens, which form part of ribonucleoprotein particles consisting of a 60kD SS-A/Ro RNA binding protein, hY1 RNAs and 48kD RNA binding protein, which facilitates maturation of RNA polymerase III transcripts such as precursors to tRNA and 5S-RNA.[3] These antibodies are found in approximately 50% of patients with Sjögren's syndrome, and are associated more with severe glandular and extraglandular manifestations.[4]

Inappropriate cellular immunity is also important in the pathogenesis of Sjögren's syndrome. It has been determined that mononuclear cells (primarily T cells) infiltrate salivary and lacrimal glands, with partial destruction of acinar and ductal structures. The T cells as well as the glandular cells release cytokines (especially interleukin [IL]-1, IL-6 and tumour necrosis factor [TNF]-α). These cytokines, along with autoantibodies and metalloproteinases, reduce the release of neurotransmitters and decrease the response of the residual glandular cells to available neurotransmitters, resulting in symptoms commonly seen in primary Sjögren's syndrome.[5]

Interaction between constitutional factors (hormones and major histocompatibility complex) and environmental factors (most likely viruses) is also thought to be important in the aetiology of Sjögren's syndrome.[4] In addition, chronobiology may be important since Sjögren's syndrome usually develops at age 40–50 years.[3] Females are affected by Sjögren's syndrome at a ratio of 9 **:** 1 compared with males, although Sjögren's syndrome does not improve with menopause and hormonal replacement has not been shown to cause an exacerbation of the disease.[6] Therefore, it is believed by some experts that multiple hormones, estrogens, reactive hypothalamic and hypophyseal peptide hormones, and dehydroepiandrosterone may play a role in the aetiology/symptoms of Sjögren's syndrome.[3] Primary Sjögren's syndrome is associated with HLA-DR3 and linked genes B8, DQ 2 and the C4 null gene in about 50% of patients.[7] Although data have been conflicting from various studies, potential viral triggers postulated to play a role in the aetiology of primary Sjögren's syndrome include herpes viruses, particularly Epstein-Barr virus, cytomegalovirus and human herpes virus-6. [4] In addition, there has been speculation about the role that retroviruses may play in the aetiology of Sjögren's syndrome.[1,5]

2. CNS Involvement in Sjögren's Syndrome

The prevalence of CNS involvement in primary Sjögren's syndrome, including myelopathy, is unknown at the present time. Data gathered from studies suggest a prevalence range of 0–48%.[8] Myelopathy may occur in about 1% of patients with Sjögren's syndrome.[9] Factors that have made the actual determination of prevalence elusive include the use of different classification schemes to diagnose Sjögren's syndrome, lack of adherence to strict diagnostic criteria, and use of different inclusion and exclusion criteria. None of the past, current or proposed classification schemes have been universally accepted. Recently, the European-American Classification scheme has been proposed to overcome the problems with the currently used schemes, i.e. the San Diego Classification scheme and the European Classification scheme (see table I), the latter having been validated with a sensitivity of 97.5% and a specificity of 94.2%.[10]

CNS involvement in either primary or secondary Sjögren's syndrome can be quite variable (see table II). Symptoms can be diffuse or focal. Spinal cord involvement may present as acute transverse myelitis, progressive myelitis, Brown-Séquard syndrome, neurogenic bladder or lower motor neurone disease. Optic nerve involvement frequently accompanies spinal cord involvement.[13] The occurrence of myelopathy in primary CNS Sjögren's syndrome appears to be not that uncommon, with acute transverse myelitis being the most frequently occurring form of spinal cord involvement. Acute transverse myelitis symptoms can develop abruptly, with severe neck and interscapular pain followed by sensory and motor deficits below the thoracic level of the lesion. This form of myelopathy occurring in CNS Sjögren's syndrome has high mortality, probably caused by vasculitis. The subacute or chronic form of myelopathy usually develops with sensory symptoms, sphincter incontinence and difficulty walking, progressing to spastic paraplegia. It is often associated with optic neuropathy.[14]

CNS Sjögren's syndrome can mimic multiple sclerosis in presentation because of similar symptoms in both diseases and their relapsing-remitting course. Therefore caution should be employed in the diagnosis of these disorders, especially in female patients presenting at a late age of onset.[15] Even if patients are of younger chronological age, if myelopathy is present, they should be queried regarding sicca symptoms.

The pathogenesis of CNS Sjögren's syndrome is still unclear, but is thought to be caused by an inflammatory ischaemic vasculopathy with small vessel angiitis.[16,17] Biopsies of peripheral nerves in patients with peripheral nervous system symptoms have shown vasculitis or mononuclear cell infiltration. CNS biopsies taken from patients with CNS Sjögren's syndrome have shown unambiguous vasculitis in some cases, but more often perivascular mononuclear infiltration extending into surrounding brain parenchyma. Thus, vasculopathy may be a better description of pathogenesis. Nevertheless, there is no consensus of opinion regarding pathogenesis.[18]

It has been suggested that anti-Ro(SSA) antibodies could play a role in the immunopathogenesis of primary CNS Sjögren's syndrome.[19-21] Antineuronal antibodies may also be important in producing symptoms in CNS Sjögren's syndrome and in some patients they may produce paraneoplastic-type lesions.[22,23]

3. Treatment of Myelopathy

3.1 Role of Nonsteroidal Immunosuppressants

The optimal treatment for CNS Sjögren's syndrome, including myelopathy, is not known at the present time. When neurological symptoms are severe or are rapidly getting worse, most experts recommend treatment with an immunosuppressant agent after corticosteroid therapy has failed, with corticosteroid therapy being continued along with the immunosuppressant agent.[8,13,18] However, concern has been raised regarding the use of immunosuppressants, especially cyclophosphamide, azathioprine and chlorambucil, to treat a disease where lymphoma occurs at a higher incidence than in the

Table I. Comparison of European, European-American and San Diego classification schemes in Sjögren's syndrome (SS)

Category	European[10]	European-American[11]	San Diego[12]
Ocular symptoms	Positive response to one of three questions pertaining to dry eyes	Same as European	Symptoms of ocular dryness
Ocular signs	Positive Schirmer test (<5mm in 5 min) or positive rose bengal staining	Same as European but Schirmer test is performed without anaesthesia	Positive Schirmer test (<8mm in 5 min) and positive rose bengal staining of cornea
Oral symptoms	Positive response to one of three questions pertaining to dry mouth	Same as European	Symptoms of oral dryness
Histopathological findings	Focus score ≥1 in minor salivary gland biopsy findings	Same as European with criteria that biopsy must be evaluated by an expert histopathologist with a focus score ≥1 defined as number of lymphocytic foci (which are adjacent to normal-appearing mucous acini and contain >50 lymphocytes) per 4 mm^2 of glandular tissue	Abnormal biopsy findings of minor salivary gland (focus score >2 on average of four lobules)
Salivary gland involvement	Objective evidence of salivary gland involvement at least one of the following: salivary scintigraphy or parotid sialography or unstimulated salivary flow ≤1.5 mL/15 min	Same as European with salivary scintigraphy showing delayed uptake, reduced concentration and/or delayed excretion of tracer. Parotid sialography showing presence of diffuse sialectasias (punctate, cavitary or destructive pattern), without evidence of obstruction in the major ducts	Decreased parotid flow rate (e.g. Lashley cups)
Serological test results or autoantibodies	Presence of autoantibodies in serum to Ro(SSA) or La(SSB) or both	Same as European	Serological evidence of systemic autoimmunity RF >1 : 320 or ANA >1 : 320 or positive Ro(SSA) or La(SSB) antibodies
Classification	'Primary' SS: presence of any four of the previous six categories	Same as European for 'Primary' SS, but must be either histopathologically or serologically positive as one of the four categories, and three of the four objective criteria must be present (ocular signs, histopathology, salivary gland involvement and autoantibodies). Classification tree procedure is a valid alternative method, although use is more appropriate in clinical-epidemiological survey	Ocular signs and ocular symptoms must be present; oral symptoms, histopathological findings and salivary gland involvement must all be present. 'Definite': objective evidence of dry eyes/mouth, autoantibodies and characteristic minor salivary gland biopsy results. 'Primary' SS: characteristic signs and symptoms (above) without associated autoimmune disease
	'Secondary' SS: potentially associated connective tissue or autoimmune disease with the first two categories (ocular symptoms and ocular signs), plus any two of the next three categories (oral symptoms, histopathological findings and salivary gland involvement)	'Secondary' SS: one or two (ocular or oral symptoms) and any two (ocular signs, histopathology, salivary gland involvement)	'Secondary' SS: same as primary SS plus RF, SLE, polymyositis, scleroderma or biliary cirrhosis

Continued next page

Table I. Contd

Category	European[10]	European-American[11]	San Diego[12]
Exclusion criteria	Sialadenosis, AIDS, pre-existing lymphoma, sarcoidosis, graft-versus-host disease, use of antidepressant, antihypertensive, neuroleptic and parasympatholytic drugs	Past head and neck radiation treatment, hepatitis C infection, AIDS, pre-existing lymphoma, sarcoidosis, graft-versus-host disease, use of anticholinergic drugs (since a time shorter than 4-fold the half-life of the drug)	Keratitis sicca, salivary gland enlargement, hepatitis C or B infection, HIV infection, pre-existing lymphoma, primary fibromyalgia, other known causes of autonomic neuropathy

ANA = antinuclear antibody; **La(SSB)** = single-stranded anti-La antibody; **RF** = rheumatoid factor; **Ro(SSA)** = single stranded anti-Ro antibody; **SLE** = systemic lupus erythematosus.

rest of the population.[1,8,17] This is an important point but reports of these agents causing malignancies (lymphoma, leukaemia) generally occur in patients treated with high doses, and placed on continuous and/or long-term therapy. Alternative dosage regimens, such as pulse doses, may be safer.[13] In addition, lymphoma occurring in patients with Sjögren's syndrome has characteristics different from the lymphomas induced by immunosuppressive drugs and seems to be partly related to B-cell hyper-reactivity.[24]

Lastly, several investigators have identified predisposing factors for the occurrence of B cell non-Hodgkin's lymphoma in patients with Sjögren's syndrome, which might be taken into account when deciding whether or not to use one of these agents long term. Researchers have found that the primary predisposing factor is the presence of a mixed monoclonal cryoglobulinaemia, which is usually asymptomatic.[25] Other factors associated with cryoglobinaemia are a low C4 level or purpurea (primarily palpable).[26] Another study identified the early clinical appearance of leg ulcers, swollen salivary glands and lymphadenopathy predictive of the development of a distinct non-Hodgkin's lymphoma of mucosa-associated lymphoid tissue.[27]

There is a paucity of case reports and no trials of patients with primary Sjögren's syndrome-associated myelopathy undergoing treatment with immunosuppressants (see table III). Eight patients have been reported in the literature and all of them had improvement of neurological symptoms with the addition of the immunosuppressive agent (six patients received cyclophosphamide,[9,14,28,29] one patient chlorambucil[30] and two patients azathioprine[29,31]). All patients continued with corticosteroid treatment and four of them were also maintained on low-dose oral azathioprine (2 mg/kg/day[9] or 100 mg/day[31]).

3.2 Individual Agents

3.2.1 Cyclophosphamide

Cyclophosphamide is probably the most frequently used immunosuppressant in the treatment of patients with CNS Sjögren's syndrome. Dosage protocols were initially established to mimic those used in the US National Institutes of Health protocol to treat SLE nephritis.[32] Current treatment regimens consist of a monthly single intravenous bolus of drug for 6–12 months and then, if needed, every 3–6 months for the second year. Doses used are 0.75–1.0 g/m^2.[8] Long-term oral cyclophosphamide therapy has been used also in the treatment of CNS Sjögren's syndrome but is associated with the development of bladder cancer in patients with Sjögren's syndrome.[13] Short-term daily oral or intravenous therapy may be appropriate to induce a remission in those patients who are seriously ill with rapidly deteriorating neurological status.[13]

The most common severe adverse effects associated with cyclophosphamide are haemorrhagic cystitis and myelosuppression. Haemorrhagic cystitis can be prevented by adequate hydration and the use of mesna (mercaptoethanesulphonate sodium), a sulphydryl compound that binds to the toxic metabolite formed by cyclophosphamide, thus preventing it from binding to the bladder wall and causing damage. Myelosuppression may be dose limiting, with the white blood cell nadir occurring 7–10 days after treatment.

As an antineoplastic agent, cyclophosphamide is part of the class of alkylating agents, which work by interfering with DNA replication and transcription to RNA; it is chemically related to nitrogen mustard. However, the immunological activity responsible for the efficacy of cyclophosphamide in the treatment of CNS Sjögren's syndrome has not been determined. It is known that the drug selectively suppresses B-cell function and depletes B cells. It can also suppress lymphocyte functions that are mediated by T cells.[33]

3.2.2 Chlorambucil

Chlorambucil is another alkylating agent related to nitrogen mustard. The drug is available only in an oral formulation. Although there are anecdotal reports concerning the use of chlorambucil in CNS Sjögren's syndrome, there is only one case published in the literature documenting the use of the drug in the treatment of CNS Sjögren's syndrome[30] (see table III).

Chlorambucil causes myelosuppression, which is dose limiting, but does not cause haemorrhagic cystitis. The mechanism of action of chlorambucil in the treatment of CNS Sjögren's syndrome is most likely to be similar to that of cyclophosphamide.

Table II. Spectrum of CNS involvement in Sjögren's syndrome[8]

Focal symptoms
Motor and/or sensory deficit
Aphasia/dysarthria
Seizure disorders
Movement disorders/pyramidal tract signs
Brain stem syndrome
Cerebellar syndrome
Diffuse nonfocal symptoms
Acute or subacute encephalopathy
Aseptic meningoencephalitis (often recurrent)
Cognitive dysfunction/dementia
Psychiatric abnormalities
Spinal cord involvement
Transverse myelitis
Chronic progressive myelitis
Brown-Séquard syndrome
Neurogenic bladder
Lower motor neurone disease
Miscellaneous
Optic neuropathy
Mood disorders (depression, anxiety)
Multiple sclerosis-like disease

3.2.3 Azathioprine

Although there are anecdotal reports in the literature on the use of azathioprine in the treatment of CNS Sjögren's syndrome,[13] there appears to be only three published reports in the literature.[9,29,31] In two cases the patients improved with the use of the drug along with corticosteroid treatment[29,31] (see table III). In one of these cases the patient relapsed on cyclophosphamide therapy and was then tried on azathioprine.[29] In another case, neither azathioprine (150 mg/day for 2 months) nor cyclophosphamide (750 mg/m^2 for 3 months) used on separate occasions with a corticosteroid was useful in preventing neurological and cognitive decline in a 72-year-old woman who had cerebral amyloid angiopathy on brain biopsy and was positive for antineuronal antibodies.[22]

Azathioprine was studied in patients with uncomplicated primary Sjögren's syndrome in a double-blind, placebo-controlled trial and was found to be ineffective at a dosage of 1 mg/kg/day for 6 months. In addition, four of the 13 patients treated with the drug dropped out of the trial at 1 month because of adverse effects from the drug.[34]

The most serious adverse effects associated with the use of azathioprine are myelosuppression, which appears to be dose related, as well as gastrointestinal disturbance, stomatitis and hepatotoxicity.

As an antineoplastic agent, azathioprine, a purine analogue, is believed to work through its conversion to 6-mercaptopurine, which interferes with DNA and RNA synthesis resulting in inhibition of cell proliferation. It is not known how azathioprine may work in the treatment of CNS Sjögren's syndrome; however, the drug also inhibits T-cell proliferation with resulting down-regulation of interferon-γ.[34]

3.2.4 Ciclosporin

As with some of the other immunosuppressants, there are anecdotal reports on the use of ciclosporin (cyclosporin) in the treatment of CNS Sjögren's syndrome.[8] For example, one author has described how ciclosporin, along with a corticosteroid, was effective in the treatment of a patient with mono-

Table III. Reported cases of myelopathy treated with nonsteroidal immunosuppressants in patients with primary Sjögren's syndrome

Reference	Sex/age (y)	Clinical abnormalities	Level of myelopathy	Treatment/dosage	Outcome
Ménage et al.[28] (1993)	F/64	Brown-Séquard syndrome, ON	Cervical	IV methylprednisolone 500mg bolus × 1 + cyclophosphamide 900mg bolus × 1	Improved but lost to follow-up
Wright et al.[30] (1999)	M/41	ON, Trm	Thoracic	Prednisone + chlorambucil (8 mg/day; 0.1 mg/kg/day); changed to 4 mg/day; total 18mo	Improved with no relapse
Williams et al.[14] (2001)	F/63	ON, CPMy	Cervicothoracic	IV methylprednisolone (1g/d × 3 doses); prednisone + IV cyclophosphamide (0.75 g/m^2/mo for 6 mo)	Improved with no relapse
Hermisson et al.[31] (2002)	F/66	CPMy	Cervicothoracic	Prednisone + azathioprine (100 mg/day); still on drug after 18mo	Improved with no relapse
Hawley & Hendricks[29] (2002)	F/67	Trm	Thoracic	IV methylprednisolone (1g/d × 3 doses); Prednisone high dose taper then low dose prednisone + IV cyclophosphamide pulsed for maintenance	Improved but relapsed when cyclophosphamide stopped because of alopecia + cystitis
		CPMy[a]		Prednisone + azathioprine 150mg	Improved with azathioprine
Vincent et al.[9] (2003)	F/36	Trm, ON, urinary retention	Cervical, T4 level	Prednisolone (1 mg/kg) + monthly IV cyclophosphamide (pulsed 10 mg/kg) Oral prednisolone (7.5 mg/day) + azathioprine (2 mg/kg)	Complete resolution by 9 mo. Continued on low-dose prednisone + azathioprine
Vincent et al.[9] (2003)	F/55	Trm	Thoracic, T6 level	IV methylprednisolone (1 mg/kg) [with no improvement] then prednisolone (1 mg/kg) + monthly IV cyclophosphamide (10 mg/kg)	No change with IV corticosteroids. Complete recovery with cyclophosphamide
				Prednisolone (7.5 mg/day) + azathioprine (2 mg/kg)	
Vincent et al.[9] (2003)	F/NS	Trm	Thoracic, T9-12 level	IV methylprednisolone (1 mg/kg) [with no improvement] then prednisolone (1 mg/kg) + monthly IV cyclophosphamide (10 mg/kg) then prednisolone (7.5 mg/day) + azathioprine (2 mg/kg)	No change with IV corticosteroids. Complete recovery with oral corticosteroids + cyclophosphamide

a At time of azathioprine treatment.

CPMy = chronic progressive myelitis; **F** = female; **IV** = intravenous; **M** = male; **mo** = months; **NS** = not stated; **ON** = optic neuropathy; **Trm** = transverse myelitis.

lateral optic neuritis.[13] In the treatment of uncomplicated primary Sjögren's syndrome, ciclosporin has been used with improvement in xerostomia, but worsening of the immunopathology of the minor salivary glands. In addition, no improvement was seen in the function of the salivary or lacrimal glands.[35]

Ciclosporin is a potent modulator of the immune system that decreases production of cytokines involved in T-cell activation, as well as having direct effects on B cells, macrophages, bone and cartilage cells. In the treatment of CNS Sjögren's syndrome, ciclosporin may also work by inhibiting IL-2, which leads to suppression of T-cell proliferation.[36] The onset of effect of ciclosporin is 1–3 months and the drug is available only in an oral formulation.

Serious adverse effects seen at dosages used clinically (1–10 mg/kg/day), which may discourage its use, are hypertension, hyperglycaemia, nephrotoxicity, tremor, gastrointestinal intolerance, hirsutism and gingival hyperplasia.

3.2.5 Methotrexate

Only anecdotal reports exist in the literature involving the use of methotrexate in the treatment of CNS Sjögren's syndrome, with treatment outcomes not mentioned.[13]

Methotrexate has been used in an open-label trial in the treatment of patients with uncomplicated pri-

mary Sjögren's syndrome at a dosage of 0.2 mg/kg/week, with improvement in subjective oral and ocular symptoms, but no improvement in objective oral or ocular symptoms.[37]

The mechanism of action of methotrexate as an antineoplastic agent is a result of its ability to partially deplete reduced folates, as well as its ability to inhibit purine and thymidylate biosynthesis. However, its utility in the treatment of CNS Sjögren's syndrome may be because of its anti-inflammatory effect through inhibition of cytokine production, inhibition of purine biosynthesis, and its ability to stimulate the release of adenosine.[38] The drug may also inhibit lymphocyte multiplication.[39]

Serious adverse effects seen with the use of methotrexate include myelosuppression (primarily thrombocytopenia), gastrointestinal intolerance, stomatitis, hepatotoxicity and pulmonary toxicity.

3.3 Miscellaneous Immunomodulating Treatments

Other treatment modalities that might be useful to try in the treatment of patients with CNS Sjögren's syndrome-associated myelopathy are plasmapheresis, intravenous immunoglobulin (IVIG) and infliximab.

There is one case report involving the successful use of plasmapheresis in conjunction with corticosteroids in the treatment of acute transverse myelitis.[40] Although invasive and somewhat expensive, plasmapheresis may offer immediate treatment for the patient who is rapidly deteriorating and/or who is waiting for an immunosuppressant to work.

There are no case reports in the literature involving the use of IVIG in the treatment of CNS Sjögren's syndrome-associated myelopathy; however, a case of successful treatment of a patient with CNS vasculitis-associated Sjögren's syndrome has been reported.[41] The dosage the patient received was 400 mg/kg/day for 5 days along with a corticosteroid, with additional monthly doses of IVIG for 6 months and then every 2–5 months as indicated by the patient's neurological symptoms.[41] Like plasmapheresis, this form of therapy is expensive but response can be relatively rapid.

TNF antagonism might also be a worthwhile treatment modality in CNS Sjögren's syndrome-associated myelopathy given the importance of the cytokine, TNFα, in the pathology of the disease.[5,42] There has been one open-label trial using infliximab (chimeric human-mouse anti-TNFα antibodies) in the treatment of primary Sjögren's syndrome with extraglandular involvement. A dose of 3 mg/kg infused at weeks 0, 2 and 6 was given to 16 patients. All patients showed dramatic improvement in mouth dryness, asthenia and pain, without the development of significant adverse effects. In addition, improvement in symptoms was maintained for up to 8 weeks after the third infusion.[43]

There is also one case report of a patient with primary Sjögren's syndrome with neuronopathy who showed marked improvement in clinical and neurophysiological deficits associated with the neuronopathy. The dose used was 3 mg/kg given at weeks 0, 2, 6 and every 12 weeks thereafter.[44] However, there are no reports on the use of infliximab in CNS Sjögren's syndrome and, therefore, caution is advised.

4. Conclusions

The nonsteroidal immunosuppressant agent of choice appears to be cyclophosphamide (in conjunction with a corticosteroid) in the treatment of myelopathy associated with Sjögren's syndrome, based on clinical anecdotal experience and drug adverse effect profile. However, data are very limited with the use of these agents. Other immunosuppressants such as chlorambucil, azathioprine, ciclosporin and possibly methotrexate should be considered, particularly when cyclophosphamide has been shown to be ineffective or has not been tolerated by a patient. When a patient's symptoms are acutely worse, plasmapheresis or IVIG might be considered, especially until the immunosuppressant agent begins to work. Although there are no documented cases of infliximab being used in the treatment of myelopathy, it may be worthwhile to cautiously consider this agent, especially when all other therapies have failed, since infliximab has recently been shown to be useful in

the treatment of extraglandular symptoms[43] as well as neuronopathy in Sjögren's syndrome.[44]

Lastly, because of the absence of large, randomised studies of immunosuppressant agents in the treatment of Sjögren's syndrome, there remains a real need for such studies to be designed and conducted to help determine optimal treatment.

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