



Neurological diseases: Which treatments are appropriate for psoriasis patients with neurological diseases?

Narrative review of the existing literature was conducted.

Results/Answer:

Standard systemic therapy

Ciclosporin

Neurotoxicity is a well-established complication of CsA although it receives surprisingly little attention in literature. A comprehensive review¹ referencing data from (primarily) the transplant population, estimated that 10 and 28 % of patients receiving calcineurin-inhibitors experience neurotoxic side effects ranging from mild paraesthesia and peripheral neuropathy through to centrally mediated complications such as altered cognition, visual disturbances and seizures. Of these tremor and paraesthesia are the commonest, and in the early trials in psoriasis, affected 40 and 25 % of participants receiving 5mg/kg respectively². Calcineurin is major component of neural tissue, and plays a key role in the regulation of nerve cell function, and neurotransmission^{3,4}; toxicity is dose-dependent and largely reversible. Ciclosporin does not readily cross the blood-brain barrier, however, conditions that disrupt the integrity of this, such as neurodegenerative disease, systemic infections, or hypertension, may perhaps also make patients more prone to the neurotoxic effects of CsA³. Additional factors such as CsA-related hypomagnesaemia⁵ may also contribute. No studies were identified specifically reporting on outcomes in people with pre-existing neurological disease treated with CsA for psoriasis. Existing guidelines and the SmPC do not stipulate neurological disease to be a contra-indication to treatment.

Fumarates

Dimethyl fumarate (DMF) has more recently been licensed and developed for use in psoriasis and is also a licensed treatment for MS (reviewed in⁶) at doses of 240 mg BID. Fumarates may be a preferred option for the treatment of psoriasis in people with established MS. There have been a total of nine reports of confirmed progressive multifocal leukoencephalopathy (PML) in patients with psoriasis treated with fumarates; six with Fumaderm[®], two with Psorinovo[®] (a slow release DMF formulation) and one with compounded fumaric acid esters⁷⁻¹⁵. In all cases, a degree of lymphopenia and/or other contributory factors for PML are thought to have been of direct etiological relevance.



Methotrexate

CNS toxicity is a well-recognized AE of high dose MTX, especially with intra-thecal administration. Low dose oral and s/c MTX have rarely been reported to cause a reversible leukoencephalopathy (see ^{16,17} for recent reports and reviews). The SmPC cites drowsiness, ataxia, blurred vision, transient subtle cognitive dysfunction, mood alteration, and unusual cranial sensations as occasionally reported with low-dose MTX. No studies were identified specifically reporting on outcomes in people with pre-existing neurological disease treated with MTX for psoriasis. Existing guidelines and the SmPC do not stipulate neurological disease to be a contra-indication to treatment.

Biological therapy

TNF antagonists

In vitro, murine and human data suggest that TNF has an important role in the pathogenesis of inflammatory demyelinating disease (reviewed in ¹⁸). However, an early report of increased lesion activity in two MS patients receiving infliximab ¹⁹ as well as the withdrawal of Lenercept (a soluble p55 receptor developed for the treatment of MS) due to increasing severity and duration of symptoms in clinical trial subjects led to heightened awareness of potential risk of TNF antagonist therapy in the context of MS. More recently ²⁰, the single nucleotide polymorphism (SNP) rs1800693 in the TNFRSF1A gene associated with MS but not psoriasis (or other autoimmune conditions) has been shown to direct expression of a novel, soluble form of TNFR1 that can block TNF, hence lending further biological plausibility to a causal relationship between TNF-antagonism and demyelination.

All five TNF antagonists have been associated with aggravation of MS and/or new onset central demyelination, which have been reviewed by Mahil *et al* and Bosch *et al* ^{21,22}. Case reports in more recently licensed anti-TNF agents golimumab ^{23,24} and certolizumab ²⁵ have been described. Of 84 cases of central demyelination reported in patients with psoriasis, the majority occurred within the first year of therapy; 33% (25/76) achieved complete recovery after cessation of anti-TNF +/- adjunctive therapy, 72% (55/76) did not achieve complete clinical recovery after cessation of TNF antagonist therapy. There were fourteen cases of worsening neurological disease despite cessation of anti-TNF therapy and several reports of new, clinically silent lesions detected on follow-up imaging ^{21,24-35}.

A case control study in rheumatoid arthritis using Canadian administrative claims and an electronic medical records database showed a trend towards an increased rate of demyelination in 891 patients with no risk factors (for demyelination). The authors suggested that TNF antagonist therapy may increase the risk of truly incident demyelinating events by ~30 %, although this result failed to meet statistical significance (adjusted rate ratio 1.31 [95% CI 0.68 to 2.50]) ³⁶. To date, trial and



pharmacovigilance registry data have not shown any increased risk, although this may relate to a low overall incidence, as well as exclusion of people at particular risk.

With respect to peripheral disease, all forms of demyelinating neuropathies, including Guillain-Barré syndrome, Miller-Fisher syndrome, multifocal motor neuropathy with conduction blocks, Lewis-Sumner syndrome, and chronic polyradiculoneuritis have been reported in association with TNF antagonist therapy, although the number of case reports in the literature are fewer when compared to central demyelination^{22,37,38}. One report of five patients providing longer term data (up 3-4 years) indicated that once triggered, chronic demyelinating neuropathy may persist or recur irrespective of whether the TNF antagonist is discontinued³⁸. Isolated cases of axonal neuropathy and vasculitis neuropathy are also reported²². US, UK and German psoriasis guidelines all advise avoidance of or caution with TNF antagonists in people with demyelination and caution in those at risk. Prescribers and patients should also be made aware of symptoms of demyelination when prescribing TNF-antagonists to ensure early identification and drug discontinuation.

IL12/23 pathway inhibitors

The IL (interleukin) 12 p40 family of cytokines (IL-12 and IL-23) has been strongly implicated in the pathogenesis of both MS and experimental autoimmune encephalomyelitis (EAE), an animal model that mimics many clinical and histological characteristics of MS. This prompted a phase II study evaluating the role of ustekinumab in patients with relapsing and remitting MS. Patients were randomly assigned 1:1:1:1 to placebo or 27 mg, 90 mg, or 180 mg ustekinumab every four weeks or 90 mg ustekinumab every eight weeks up to week 23. A total of 200 patients received at least one dose of ustekinumab and whilst there was no evidence of benefit, there was no evidence of worsening neurological disease or increase in AEs when compared to placebo. To date, there has been one case report of primary progressive MS in a patient taking ustekinumab for refractory Crohn's disease³⁹ with the first neurological symptoms occurring around one year into therapy. She had received TNF antagonist therapy (infliximab, adalimumab, and certolizumab) prior to ustekinumab. With respect to peripheral demyelinating disease, a single case of Guillain Barré has been reported in a 23-year-old male with refractory Crohn's disease one year after commencing treatment with ustekinumab, having previously been treated with adalimumab⁴⁰. A further isolated case of peripheral neuropathy of unspecified etiology after three doses of ustekinumab was reported in an observational, retrospective 5-year follow-up study of ustekinumab in psoriasis⁴¹. Furthermore, the first case of reversible posterior leukoencephalopathy syndrome (RPLS) in a 65-year-old woman who received ustekinumab for over 2.5 years for psoriasis has been reported. She presented with mild hypertension, confusion, headache,



nausea, vomiting, multiple seizures. Computed tomographic scans and magnetic resonance images of her head revealed characteristic findings of RPLS. Complete clinical recovery and reversal of the radiologic findings occurred, which is also considered typical of RPLS ⁴². No data on the newer p19 inhibitors were identified.


IL-17 inhibitors

The IL 17A/F pathway is implicated in both psoriasis and multiple sclerosis, with elevated levels of IL-17A and IL-17F levels detected in both diseases ⁴³. Phase II randomised controlled data has shown encouraging results with secukinumab associated with a reduction in both the number of active and new MRI brain lesions in patients relapsing-remitting MS which were reduced by 49% and 67% respectively ⁴⁴; but this is yet to be replicated in further studies. There are five cases in the literature of patients receiving Secukinumab for immune-mediated inflammatory diseases with concomitant MS. 80% (4/5) of patients with MS remained stable with no progression of disease and achieved remission of psoriasis/psoriatic arthritis/ankylosing spondylitis. 20% (1/5) had a relapse of MS and required treatment with rituximab ⁴⁵⁻⁴⁸. There are no reported de novo cases of central demyelination with secukinumab, however longer-term safety data is required. No published data on other IL17 agents (ixekizumab, bimekizumab and brodalumab) were identified.

Summary and synthesis of recommendations

With the exception of TNF antagonists, any of the standard or biologic treatments can be used in people with co-existing neurological disease. Although neurotoxicity is reported with CsA, and (rarely) with MTX, there is no evidence that those with pre-existing neurological disease are more at risk. The causal association between TNF antagonists and demyelination remains yet to be proven, although accumulating anecdotal reports, biological plausibility and expert consensus indicate that this class of drugs should be avoided in patients with a clear history of central demyelination. Given evidence for a genetic basis to MS ⁴⁹, and that asymptomatic first-degree relatives may have morphological evidence of subclinical disease and/or CSF oligoclonal bands (reviewed in ⁵⁰), it would seem prudent to use TNF antagonists with caution in this group too. Dimethyl fumarate is licensed for use in MS, and so may be a preferred first line option, however, surveillance monitoring of peripheral leukocyte counts is strongly recommended in order to minimise the risk of PML. Ustekinumab p19 and anti - IL 17 represent alternative treatment options.



<p>We suggest using fumarates in psoriasis patients with multiple sclerosis.</p>	<p>↑</p>	
<p>We recommend against using TNF antagonist therapy in psoriasis patients with a diagnosis of multiple sclerosis or other demyelinating disease.</p>	<p>↓↓</p>	<p>STRONG CONSENSUS¹</p> <p style="text-align: center;"></p>
<p>In psoriasis patients with a first-degree relative with multiple sclerosis or other demyelinating disease, we suggest against the use of TNF antagonist therapy if other suitable treatment options are available.</p>	<p>↓</p>	<p>EXPERT CONSENSUS</p>

¹ due to personal-financial conflict of interest 3 abstentions

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