The only way to manage neurodegeneration in MS is to prevent it with effective anti-inflammatory therapy: No

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Rebuttal

If the statement were to be altered to read ‘the only way we currently have to manage neurodegeneration in multiple sclerosis (MS) is to try to prevent it with effective anti-inflammatory therapy’, then, I suspect, most would agree with its sentiment. We do only have drugs whose primary actions are anti-inflammatory to treat MS at present. These drugs are getting better and are making inroads into tackling neurodegeneration. But will anti-inflammatory therapy in isolation prevent neurodegeneration in all cases of MS? Or, to put it another way, is neurodegeneration in MS caused exclusively by inflammation? The evidence that has accumulated over the years would suggest the answer to these questions is no.

MS is an inflammatory condition of the central nervous system, of that there is little doubt. The presence of lesions containing inflammatory infiltrates in the brain and spinal cord are classical pathological hallmarks of the disease. Acute relapses reflect acute inflammatory injury within the central nervous system. Some degree of neurodegeneration (the major substrate for disease progression) is likely to be caused by inflammatory attack directed either specifically to neural antigens or as a bystander effect on axons and neuronal cell bodies. In MS brain tissue neuronal and axonal injury appear to be most marked in acute lesions. But this is unlikely to be the whole story, and evidence suggests that non-inflammatory mechanisms crucially play a part in neurodegeneration occurring after the establishment of disease progression.

Importantly, epidemiological studies in MS have demonstrated two significant observations concerning the relationship of relapses (acute inflammation) to disease progression (neurodegeneration). Firstly, once disease progression has ‘set in’ (equivalent to Expanded Disability Status Scale (EDSS) 3 or 4) further inflammatory relapses appear to have little influence on the rate of subsequent progression; and, secondly, the history of inflammatory episodes prior to the onset of disease progression has little relevance to the rate of later progression once it has begun (an amnesic process). Other factors, seemingly independent of inflammation, also influence the rate of disease progression, for instance age at disease onset. So, natural history studies suggest that later neurodegenerative disease progression appears to be mostly independent of inflammation-driven relapses.

Turning to treatment trials, a huge amount has been gleaned concerning the impact of reducing relapses on disease progression. Many of the published trials of disease-modifying therapies (DMTs) in progressive MS had hypothesised that reducing inflammatory activity/relapses would reduce disease progression. In the main, these trials have refuted this hypothesis and very few advocate the use of DMTs for non-relapsing established progressive MS. Perhaps the most impressive immunosuppressive agent that has been tested in MS is alemtuzumab (CAMPATH-1H), which targets the CDS2 antigen on lymphocytes and monocytes, causing a profound depletion of these cell types. This monoclonal antibody therapy dramatically cuts relapse frequency by more than 85%, yet, in those with established disease progression, increasing disability (measured by EDSS scores or brain atrophy measures) continues inexorably. More recent studies on the use of alemtuzumab in early relapsing disease have been more promising and have offered the tantalising prospect that early and aggressive therapy may keep progression at bay. Further trials and longer follow-up data are eagerly awaited.

And there is the crux of the matter. Anti-inflammatory therapies have a major role to play in the management of MS, and (some of them) probably do slow-down or reduce the degree of neurodegeneration in early relapsing and remitting disease, but will they prevent neurodegeneration in all cases of MS? The obvious group in whom anti-inflammatory treatments may not help in any major way are...
those with primary–progressive MS. Fifteen per cent or so of all MS patients present in a progressive fashion, and no anti-inflammatory therapy has been shown to significantly reduce disease progression in this group as a whole. It remains a possibility that inflammation may drive disease processes in primary progressive disease but by the time the disease has presented other mechanisms have been implicated in further deterioration. Granted, sub-group analysis of rituximab therapy in a primary–progressive MS trial suggested some benefit in younger patients with gadolinium-enhancing lesions, but overall it is hard to imagine that anti-inflammatory treatments in isolation are going to be the answer in these patients. A similar argument applies to those with established secondary progressive disease.

Another consideration is whether anti-inflammatory therapies might actually hinder repair. In experimental paradigms inflammation appears to enhance some aspects of nervous system repair (notably remyelination, and myelin itself may have neuroprotective properties) through the release of neurotrophic factors and other reparative cytokines. Anti-tumour necrosis factor (TNF) therapies agents worsened disease activity in MS, which highlights the delicate balance of cytokines in the disease. Indeed, experience with natalizumab and alemtuzumab has revealed that blocking one part of the immune system may lead to problems in other parts (progressive multifocal leukoencephalopathy (PML) and autoimmunity). We do not know enough yet about the inflammatory component of neurodegeneration at the moment to predict the precise effect of specific anti-inflammatory therapies on neurodegeneration.

If not anti-inflammatory drugs, then what treatments will manage neurodegeneration? Recent and on-going studies have looked at ion channel blockers (e.g. lamotrigine), cannabinoïds, stem cell therapies, statins and anti-glutamate drugs, among others. Experimental evidence and trial data are accumulating concerning these agents. The list will expand and, importantly, the realisation that strategies for tackling neurodegeneration in other neurological disorders might be cross-translated will help in this search. We need to learn more about what causes late non-inflammatory neurodegeneration in MS, and a number of mechanisms have been implicated including loss of trophic support from glia/myelin; mitochondrial dysfunction and axonal energy failure; and neuronal ion channel changes. Perhaps in the future, combinations of anti-inflammatory therapies during a critical time window and specific neuroprotective agents will be used in concert.

In summary, the evidence suggests that anti-inflammatory therapies are not indicated and are unlikely to help significantly in the management of established neurodegeneration. Whether such treatments will prevent neurodegeneration in all patients with MS whose disease has not entered the progressive phase is not yet clear. Given the complexity of disease processes in MS, the rather heterogeneous patient population and the chronic nature of the disease, it seems highly unlikely that, over the course of many years, neurodegeneration will be prevented completely in all patients by anti-inflammatory therapies alone.

Conflict of interest
Alastair Wilkins has received speaker’s fees from Bayer-Schering.

References