Intrathecal corticosteroids might slow Alzheimer's disease progression

Joseph Martin Alisky[1,2]

[1]Marshfield Clinic Research Foundation; [2]Marshfield Clinic-Thorp Center, Marshfield, Wisconsin, USA

Abstract: Anti-inflammatory drugs for treatment and prevention of Alzheimer's disease have to date proved disappointing, including a large study of low-dose prednisone, but higher dose steroids significantly reduced amyloid secretion in a small series of nondemented patients. In addition, there is a case report of a patient with amyloid angiopathy who had complete remission from two doses of dexamethasone, and very high dose steroids are already used for systemic amyloidosis. This paper presents the hypothesis that pulse-dosed intrathecal methylprednisolone or dexamethasone will produce detectable slowing of Alzheimer's progression, additive to that obtained with cholinesterase inhibitors and memantine. A protocol based on treatment regimens for multiple sclerosis and central nervous system lupus is outlined, to serve as a basis for formulating clinical trials. Ultimately intrathecal corticosteroids might become part of a multi-agent regimen for Alzheimer's disease and also have application for other neurodegenerative disorders.

Keywords: Alzheimer's disease, inflammation, corticosteroids

Background

Epidemiological evidence suggests that drugs which counteract inflammation might have efficacy for the prevention and treatment of Alzheimer's disease, but up to now clinical trials have failed to show any clear-cut benefits for nonsteroidal anti-inflammatory drugs (NSAIDs), hydroxychloroquine, anti-leprosy agents or prednisone (Endoh et al 1999; Aisen et al 2000; van Gool et al 2001; ADAPT et al 2007). In the case of prednisone, however, it may be that much higher doses might be effective where lower doses were not. In the largest clinical trial to date, patients were given prednisone starting at 20 mg per day for one month, followed by one year at 10 mg daily and then tapering off over another 4 months (Aisen et al 2000). By contrast, in a series of 16 nondemented patients aged 25 to 82 who were given prednisolone 30–60 mg per day for at least month for treatment of various conditions, there was significant reduction in cerebrospinal fluid amyloid beta peptides in 15 out of 16 patients, up to about a 50% decline for patients receiving 50 and 60 mg of prednisolone (Tokuda et al 2002). If amyloid is indeed a cause of Alzheimer's disease (Hardy 2006), the above data suggests high dose steroids could suppress Alzheimer's disease by reducing amyloid. Along the same lines, there is a report of a patient where two single doses of dexamethasone 4 mg completely suppressed amyloid angiopathy, reversed white matter changes on brain imaging, and restored cognitive function (Harkness et al 2004). In that patient, 8 mg of dexamethasone would correspond to 80 mg of prednisone, or four times the starting dose of prednisone used in the Alzheimer's disease clinical trial but given in a single dose.

If the above line of reasoning is on the right track, it is important to note that high dose corticosteroids are already used clinically for treatment of primary systemic amyloidosis, in amounts orders of magnitude greater than those used in the Alzheimer's

Correspondence: Joseph Martin Alisky
704 South Clark Street, Thorp, Wisconsin 54771 USA
Tel +1 715 669 5536
Fax +1 715 669 5084
Email alisky.joseph@marshfieldclinic.org/ josalmd@yahoo.com

disease trial. For example, in one recently published study of a regimen combining dexamethasone and interferon, patients were given several days of dexamethasone in an amount of 40 mg per day, which would be equivalent to 400 mg of prednisone daily (Dhodapkar et al 2004). Even if amyloid is only a marker, not a cause, for Alzheimer's disease (Lee 2006), high-dose corticosteroids could have beneficial effects by reducing inflammatory cytokines, which have been strongly linked to Alzheimer's disease pathogenesis (Town and Nikolic 2005; Cagnin et al 2006; Galimberti et al 2006; McGeer et al 2006; Rota et al 2006). Finally, there is a case report of a 64-year-old man with multiple myeloma who had a temporary remission of Alzheimer's disease while receiving chemotherapy with vincristine, carmustine, melphalan, cyclophosphamide, and prednisone (Keimowitz 1997).

Obviously megadose steroids or cytotoxic chemotherapy as a treatment for Alzheimer's disease would be hard to justify, but if one can knock down amyloid production, inflammation or both with corticosteroids alone, there should be at least some therapeutic effects. The key is delivering high enough doses of corticosteroids to have efficacy without devastating or killing patients with steroid-induced side effects in the process. Building on several case reports of patients with central nervous system lupus erythematosus and multiple sclerosis who responded to intrathecal prednisolone, dexamethasone, or triamcinalone after failing oral and intravenous steroids (Funauchi et al 2003; Hellwig et al 2004, 2006), this paper proposes that a similar therapeutic strategy could be pursued for patients with Alzheimer's disease. Studies in rhesus monkeys and pigs indicate that that intrathecal steroids maximize biodistribution within the brain and minimize it within the rest of the body (Marynick et al 1976; Koszdin et al 2000).

Presentation of the hypothesis

A short pulse of high dose intrathecal methylprednisolone, dexamethasone or triamcinalone will result in detectable slowing of Alzheimer's disease as assessed by neuropsychological testing, cerebrospinal fluid studies and functional brain imaging. It is further predicted that this route of administration will minimize the risk of steroid-induced side effects, which include diabetes, cataracts, glaucoma, poor wound healing, myopathy, increased susceptibility to infection, osteoporosis and altered fat distribution, based on the premise that the bioavailability of steroids would be almost exclusively within the central nervous system. Central nervous system side effects may be more difficult to control. Steroid-induced dementia that remits once steroids are stopped has been described in case reports (Varney 1997; Sacks and Shulman 2005), but memantine, a noncompetitive antagonist of N-methyl-D-aspartate glutamate receptors, should reduce or eliminate this risk. Memantine, which acts by protecting against excitoxic neuronal cell death, is already a mainstay of treatment for Alzheimer's disease, with disease modifying activity that is maximized when given alongside cholinesterase inhibitors (Tariot et al 2004). Corticosteroids down-regulate glutamate transporter protein in microglia (Jacobsson et al 2006), which in turn increases excitoxicity, so memantine which blocks glutamate excitotoxicty would seem to be ideal for preventing this problem. Cholinesterase inhibitors should provide further protection against steroid-induced dementia. These agents improve learning and memory by increasing synaptic levels of acetylcholine, and cholinesterase inhibitors produce symptomatic improvement not only for Alzheimer's disease but vascular, multiple sclerosis, Parkinsonian, and Lewy body dementias and delirium. They in essence boost cognitive reserve to cope with cognitive impairment no matter what the etiology, which would presumably include the minority of patients who have cognitive impairment specifically from steroids. Thus, by doing all pulse dose steroid regimens alongside both cholinesterase inhibitors and memantine, it is predicted that there will be no worsening of dementia but rather additive effects on top of the benefits of cholinesterase inhibitors and memantine have on their own.

Testing the hypothesis

A protocol is outlined here based on regimens described for central nervous system lupus and multiple sclerosis, to be used as a starting point for designing future clinical trials. Investigators should follow all recommended guidelines for research involving human subjects, such as institutional review board approval and informed consent. After obtaining a baseline positron emission tomography (PET) scan and neuropsychological tests, patients with early Alzheimer's disease already taking a cholinesterase inhibitor and memantine would be given six intrathecal injections of 10 mg of dexamethasone, 100 mg of prednisolone, or 40 mg triamcinalone. Intrathecal injections can be done in the office with a bedside spinal tap or under fluoroscopic guidance, if desired. Patients should be followed for at least one year in the initial study, repeating PET scans, cerebrospinal fluid studies, and neuropsychological testing at the end of the study. Subsequently the patients could be followed out over years and decades. PET scanning has emerged as an important modality for studying Alzheimer's disease and its response to treatment (Alexander et al 2002).

Alongside functional brain imaging, cerebrospinal fluid should be assayed for amyloid peptide and other Alzheimer's disease biomarkers, such as neural thread protein (Chong et al 1992; Mrak and Griffin 2005). It would be predicted that levels of these biomarkers should fall over time, if steroids indeed have efficacy for halting dementia progression. Studies should focus on patients with the earliest signs of cognitive impairment so that they can be followed for longer periods of time. Also, there may be a window of opportunity for use of steroids only earlier in the disease process. Many of the inflammatory cytokines peak with mild cognitive impairment and early Alzheimer's disease and are actually declining by the late stages (Galimberti et al 2006).

Concluding remarks

Validation of the proposed hypothesis could be an important step towards the ultimate aim of curing Alzheimer's disease. Pulse dosed intrathecal corticosteroids might become part of a future multi-agent regimen for halting Alzheimer's disease progression, along-side cholinesterase inhibitors, memantine, and other drugs currently under investigation. Given that activated microglia are thought to play a role in the pathogenesis of other neurodegnerative diseases such as Parkinson's disease, amyotrophic lateral sclerosis and HIV dementia (Wojtera et al 2005), success of intrathecal corticosteroids for Alzheimer's disease would encourage trials for these other disorders. For all these reasons, I am presenting this idea here for maximum exposure to the widest possible interested audience. *Andiamo avanti* (let us go forward).

Disclosure

The author reports no conflicts of interest in this work.

References

ADAPT Research Group, Lyketsos CG, Breitner JC, et al. 2007. Naproxen and celecoxib do not prevent AD in early results from a randomized controlled trial. *Neurology*, 68:1800–8.

Aisen PS, Davis KL, Berg JD, et al. 2000. A randomized controlled trial of prednisone in Alzheimer's disease. Alzheimer's Disease Cooperative Study. *Neurology*, 54:588–93.

Alexander GE, Chen K, Pietrini P, et al. 2002. Longitudinal PET evaluation of cerebral metabolic decline in dementia: a potential outcome measure in Alzheimer's disease treatment studies. *Am J Psychiatry*, 159:738–45.

Cagnin A, Kassiou M, Meikle SR, et al. 2006. In vivo evidence for microglial activation in neurodegenerative dementia. *Acta Neurol Scand Suppl*, 185:107–14.

Chong JK, Cantrell L, Husain M, et al. 1992. Automated microparticle enzyme immunoassay for neural thread protein in cerebrospinal fluid from Alzheimer's disease patients. *J Clin Lab Anal*, 6:379–83.

Dhodapkar MV, Hussein MA, Rasmussen E, et al. 2004. Clinical efficacy of high-dose dexamethasone with maintenance dexamethasone/alpha interferon in patients with primary systemic amyloidosis: results of United States. *Blood*, 104:3520–6.

Endoh M, Kunishita T, Tabira T. 1999. No effect of anti-leprosy drugs in the prevention of Alzheimer's disease and beta-amyloid neurotoxicity. *J Neurol Sci*, 165:28–30.

Funauchi M, Ohno M, Nozaki Y, et al. 2003. Intrathecal corticosteroids for systemic lupus erythematosus with central nervous system involvement. *J Rheumatol*, 30:207–8.

Galimberti D, Schoonenboom N, Scheltens P, et al. 2006. Intrathecal chemokine synthesis in mild cognitive impairment and Alzheimer disease. *Arch Neurol*, 63:538–43.

Hardy J. 2006. Has the amyloid cascade hypothesis for Alzheimer's disease been proved? *Curr Alzheimer Res*, 3:71–3.

Harkness KA, Coles A, Pohl U, et al. 2004. Rapidly reversible dementia in cerebral amyloid inflammatory vasculopathy. *Eur J Neurol*, 11:59–62.

Hellwig K, Stein FJ, Przuntek H, et al. 2004. Efficacy of repeated intrathecal triamcinolone acetonide application in progressive multiple sclerosis patients with spinal symptoms. *BMC Neurol*, 4:18.

Hellwig K, Schimrigk S, Lukas C, et al. 2006.Efficacy of mitoxantrone and intrathecal triamcinolone acetonide treatment in chronic progressive multiple sclerosis patients. *Clin Neuropharmacol*, 29:286–91.

Jacobsson J, Persson M, Hansson E, et al. 2006. Corticosterone inhibits expression of the microglial glutamate transporter GLT-1 in vitro. *Neuroscience*, 139:475–83.

Koszdin KL, Shen DD, Bernards CM. 2000. Spinal cord bioavailability of methylprednisolone after intravenous and intrathecal administration: the role of P-glycoprotein. *Anesthesiology*, 92:156–63.

Keimowitz RM. 1997. Dementia improvement with cytotoxic chemotherapy. A case of Alzheimer disease and multiple myeloma. *Arch Neurol*, 54:485–8.

Lee HG, Zhu X, Nunomura A, et al. 2006. Amyloid beta: the alternate hypothesis. *Curr Alzheimer Res*, 3:75–80.

Marynick SP, Havens WW 2nd, Ebert MH, et al. 1976. Studies on the transfer of steroid hormones across the blood-cerebrospinal fluid barrier in the Rhesus Monkey. *Endocrinology*, 99:400–5.

McGeer PL, Rogers J, McGeer EG. 2006. Inflammation, anti-inflammatory agents and Alzheimer disease: the last 12 years. *J Alzheimers Dis*, 9(3 Suppl):271–6.

Mrak RE, Griffin WS. 2005. Potential inflammatory biomarkers in Alzheimer's disease. *J Alzheimer Dis*, 8:369–75.

Rota E, Bellone G, Rocca P, et al. 2006. Increased intrathecal TGF-beta1, but not IL-12, IFN-gamma and IL-10 levels in Alzheimer's disease patients. *Neurol Sci*, 27:33–9.

Sacks O, Shulman M. 2005. Steroid dementia: an overlooked diagnosis? *Neurology*, 64:707–9.

Tariot PN, Farlow MR, Grossberg GT, et al. 2004. Memantine treatment in patients with moderate to severe Alzheimer disease already receiving donepezil: a randomized controlled trial. *JAMA*, 291:317–24.

Tokuda T, Oide T, Tamaoka A, et al. 2002. Prednisolone (30–60 mg/day) for diseases other than AD decreases amyloid beta-peptides in CSF. *Neurology*, 58:1415–8.

Town T, Nikolic V. 2005. The microglial "activation" continuum: from innate to adaptive responses. *J Neuroinflammation*, 2:24.

Van Gool WA, Weinstein HC, Scheltens P, et al. 2001. Effect of hydroxychloroquine on progression of dementia in early Alzheimer's disease: an 18-month randomised, double-blind, placebo-controlled study. *Lancet*, 358:455–60.

Varney NR. 1997. A case of reversible steroid dementia. *Arch Clin Neuropsychol*, 12:167–71.

Wojtera M, Sikorska B, Sobow T, et al. 2005. Microglial cells in neurodegenerative disorders. *Folia Neuropathol*, 43:311–21.