

## Letter to the Editor

Dear Editor,

Studying the article by Pozzilli et al. on corticosteroid therapy [1] in MS, the reader invariably gets the impression that there is strong evidence to support the beneficial effect of this widely used treatment. Also, the authors claim that a “hit hard and early” therapy with high-dose i.v.-corticosteroids is to be preferred according to the recent evidence. Adverse effects, the authors imply, can be ignored due to the transient nature of their occurrence.

As the paper’s aim is a review of the “beneficial actions of corticosteroids in MS,” the authors may have intentionally avoided furnishing evidence casting a more balanced light on the treatment with corticosteroids in MS. This may be due to the need for “clear” treatment decisions that a patronising physician makes and a compliant patient happily accepts.

This is, of course, not congruent with recent views on the patient–physician relationship as, for example, stated by the GMC [2]. The way the evidence is presented by Pozzilli et al. does not enable physicians to put patients in the position to make an informed treatment decision. This inevitably requires a more critical and wider review of the current best evidence.

Incidentally, we have argued, at the same time, that the evidence on corticosteroid therapy in cases of acute relapses in MS is not at all clear and should not be crossed of [3]. Moreover, this is especially true for other therapeutic fields, e.g., the “chronic administration” of corticosteroids in secondary progressive MS.

Considering all this, we feel that the review by Pozzilli et al. ought not remain unchallenged.

Firstly, it is surprising that the article lacks a methods section and consequently, the reader is not given any information about a search strategy to identify the best evidence. This, of course, gives the impression that the aim of the review was in fact to state evidence for a result that had been established in advance.

Also, there is a special focus on the possible pharmacological effects of corticosteroids. It is indisputable that research in this area is extremely valuable. Nevertheless, results gained from *in vitro* and especially animal research can only be used to generate concepts for clinical research and can only lead to expert-opinion based evidence (class V) for a treatment concept in the absence of evidence from good clinical trials. This implies that these results do not

particularly help the patient and/or the physician to make a treatment decision.

If the laboratory evidence is as strong as reported, one wonders why the clinical patient-related effects of this concept remain so minimal. In fact, the postulated effects have not been sufficiently investigated in clinical trials.

Another important point not considered by the authors is that surrogate parameters, i.e., the level of MBP in the cerebrospinal fluid, cannot be used to claim a benefit for corticosteroid therapy as up until the present no biological parameter has been consistently proven to be a clinically relevant disease activity marker.

Once more the study by Beck et al. [4] is presented as evidence for the beneficial effect on the time it takes from conversion to definite MS. Not only did this study include patients with optical neuritis which was not even once reproduced but also its methodological problems have already been comprehensibly shown by Goodin [5] et al.

Concerning the effects of short-term therapies, it is not clear why there is no consideration of the Cochrane review by Fillipini et al. on this issue [6]. Included in this review is the study by Sellebjerg et al. on oral corticosteroids [7] which shows a similar effect of high-dose oral steroids compared to i.v.-application. Also, another study by Sellebjerg et al. on positive treatment effects of oral steroids in optic neuritis [8] has been omitted by the authors. Instead, Pozzilli et al. claim that studies on optic neuritis have shown that there is no beneficial effect of oral treatments.

The guidelines issued by the American Academy of Neurology [9] are cited twice. Pozzilli et al. give the impression that these, in conjunction with the meta-analysis by Miller et al. [10], do support the high-dose i.v.-therapy with methylprednisolone which is not the case. On the contrary, the guidelines state that ‘there is no compelling evidence to indicate that these clinical benefits are influenced by the route of glucocorticoid administration, the particular glucocorticoid prescribed, or the dosage of glucocorticoid’ [9].

In this critique, we have focussed on the therapy of the acute relapse, although it should be mentioned that in our view the authors’ conclusions on chronic use, use with interferon beta and effects on neutralising antibodies are also not supported by strong evidence.

Also, we consider the way adverse effects are tackled by the authors as not appropriate. Although potential side effects of the high-dose therapy are mentioned, this issue is

not discussed in any detail and possible implications for the patients are not mentioned at all. This is especially so in reference to the frequency of side effects. It is not made clear that side effects of this therapy are very common and as our own experiences show are fundamental for the patients and of course have to be weighted against the limited effects of the therapy. In contrast, in the conclusion, only the effects on bone density are considered which do not seem to be relevant in the therapy of acute relapses, the most common form of corticoid treatment in MS.

In conclusion, the article by Pozzilli et al. tackles an issue of extreme relevance for patients with MS and their carers. Regrettably, the authors fail to point out that there is an urgent need for more well-designed clinical trials. The way the authors embark upon this important matter does not help the clinician (and the patient accordingly) to make a decision about the therapy with corticosteroids in MS.

## References

- [1] Pozzilli C, Marinelli F, Romano S, Bagnato F. Corticosteroids treatment. *J Neurol Sci* 2004;223:47–51.
- [2] General Medical Council. Seeking patients' consent: The ethical considerations. [Article online] <http://www.gmc-uk.org/standard/default.htm>. Assessed on December 15, 2004.
- [3] Kopke S, Heesen C, Kasper J, Muhlhauser I. Steroid treatment for relapses in multiple sclerosis—the evidence urges shared decision-making. *Acta Neurol Scand* 2004;110:1–5.
- [4] Beck RW. The optic neuritis treatment trial: three-year follow-up results. *Arch Ophthalmol* 1995;113:136–7.
- [5] Goodin DS. Perils and pitfalls in the interpretation of clinical trials: A reflection on the recent experience in multiple sclerosis. *Neuroepidemiology* 1999;18:53–63.
- [6] Filippini G, Brusaferrri F, Sibley WA, Citterio A, Ciucci G, Midgard R, et al. Corticosteroids or ACTH for acute exacerbations in multiple sclerosis. *Cochrane Database Syst Rev* 2000 CD001331.
- [7] Sellebjerg F, Frederiksen JL, Nielsen PM, Olesen J. Double-blind, randomized, placebo-controlled study of oral, high-dose methylprednisolone in attacks of MS. *Neurology* 1998;51:529–34.
- [8] Sellebjerg F, Nielsen HS, Frederiksen JL, Olesen J. A randomized, controlled trial of oral high-dose methylprednisolone in acute optic neuritis. *Neurology* 1999;52:1479–84.
- [9] Goodin DS, Frohman EM, Garmany Jr GP, Halper J, Likosky WH, Lublin FD, et al. Disease modifying therapies in multiple sclerosis: Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the MS Council for Clinical Practice Guidelines. *Neurology* 2002;58:169–78.
- [10] Miller DM, Weinstock-Guttman B, Bethoux F, Lee JC, Beck G, Block V, et al. A meta-analysis of methylprednisolone in recovery from multiple sclerosis exacerbations. *Mult Scler* 2000;6:267–73.

Sascha Köpke

*Unit of Health Sciences and Education,  
University of Hamburg, Martin-Luther-King-Platz 6,  
D-20146 Hamburg, Germany*

*E-mail address: sascha.koepke@uni-hamburg.de.*

*Corresponding author. Tel.: +49 40428387224;*

*fax: +49 40428383732.*

Christoph Heesen

*Department of Neurology, University Hospital Eppendorf,  
Hamburg, Germany*

23 November 2004