

Benefit of repetitive intrathecal triamcinolone acetonide therapy in predominantly spinal multiple sclerosis: prediction by upper spinal cord atrophy

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Abstract: Intrathecal injection of triamcinolone acetonide (TCA) has been shown to provide substantial benefit in a subset of progressive multiple sclerosis (MS) patients with predominant spinal symptoms. We examined whether atrophy of the upper spinal cord (USC) as measured by MRI can serve as a predictive marker for response to repetitive intrathecal TCA application. Repetitive administration of 40 mg TCA was performed in 31 chronic progressive MS patients up to six times within 3 weeks. Expanded Disability Status Scale (EDSS) and maximum walking distance (WD) were assessed before and after the treatment cycle. Cervical 3D T1-weighted images were acquired on a 1.5T scanner at baseline. Mean cross-sectional area of the USC was determined using a semi-automated volumetry method. Results were compared with a group of 29 healthy controls to group patients into those with and without atrophy. Results show a negative correlation between the degree of USC atrophy and treatment benefit. A higher treatment benefit in patients with little USC atrophy but short initial maximum WD was observed. Absence of USC atrophy as measured on MRI is a predictive marker for intrathecal TCA therapy outcome in progressive MS. Patients with initial poor walking abilities, but only little or no atrophy, benefited most from TCA therapy.

Keywords: atrophy, MRI, multiple sclerosis, spinal cord, triamcinolone acetonide

Introduction

In multiple sclerosis (MS), the spinal cord is a common site of involvement, affecting the cervical region more frequently than the thoracic and lumbar regions [Evangelou *et al.* 2005; Kidd *et al.* 1993]. Damage in this region can dramatically affect the functional outcome of patients. Acute symptoms are often caused by active lesions which are frequently associated with cord swelling [Thielen and Miller 1996]. While newer imaging modalities have improved the detection of MS lesions in the spinal cord, conventional magnetic resonance imaging (MRI) still lacks histopathological specificity [Kidd *et al.* 1993]. Techniques such as the measurement of spinal cord atrophy have become of significant importance. A number of cross-sectional and longitudinal studies have shown that spinal cord atrophy correlates with clinical disability [Rashid *et al.*

2006; Bakshi *et al.* 2005; Liu *et al.* 1999]. Amount and severity of MS pathology in the cervical cord are greater in the progressive forms of the disease [Filippi *et al.* 2000]. It is assumed that axonal loss in MS is an important factor for the occurrence of atrophy and that atrophy in general represents the endpoint of tissue destruction [Lin and Blumhardt 2001; Matthews 1999; Silber and Sharief 1999; Rovaris *et al.* 1997; Silver *et al.* 1997]. Since spinal cord atrophy already develops in the early phases of MS, the quantification of spinal cord volume by MRI is a potential marker to quantitatively monitor the course of the disease and furthermore to monitor treatment efficacy.

For patients with progressive multiple sclerosis available immunomodulatory and conventional steroid treatment regimens provide only a limited

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symptomatic benefit. Intrathecal application of a small dosage of a slow release steroid compound can be superior to i.v. injection since it facilitates higher drug concentrations at the origin of inflammation and the agent is released at long term without the typical adverse effects of systemic low or high dose steroid administration [Rohrbach *et al.* 1988]. Repeated intrathecal application of the sustained release steroid triamcinolone acetonide (TCA) can significantly improve the disability status and especially the walking capacities in progressive MS patients with predominant spinal symptoms [Hellwig *et al.* 2006a; Hoffmann *et al.* 2006, 2003]. Furthermore, a follow-up study demonstrated that in a majority of patients treatment benefit of TCA therapy remained stable during further intermittent TCA injections over one year [Hellwig *et al.* 2006a]. Although these studies demonstrated the safety of appropriate intrathecal TCA application, serious side effects, for example, sterile meningitis or adhesive arachnoiditis, may occur. Given the invasive character of this therapeutic approach, and the lack of class I evidence studies, a clinical or radiological predictor of treatment response would be useful in both aspects. The aim of this prospective study was to determine whether atrophy of the upper spinal cord (USC) as measured by MRI can serve as a predictive marker for response to repetitive intrathecal TCA application.

Methods

Subjects

Thirty-one progressive MS-patients [22 with secondary progressive (SPMS), 9 with primary progressive (PPMS) disease course] with an Expanded Disability Status Scale (EDSS) score lower than 7.5 were enrolled in this study. Clinical characteristics are given in Table 1. All patients had to have experienced a distinct progression of MS symptoms, which corresponds to an EDSS change of at least one point in the last 2 years before study entry. Furthermore all patients had to be clinically stable for at least 4 weeks before inclusion and exhibit no enhancing USC lesions. EDSS before the start of the TCA therapy was in similar ranges in the SPMS and the PPMS group (range: 4.5–7.0). Subjects did not receive steroids for at least 4 weeks before study entry. Furthermore, in case of pretreatment patients had to be on a stable immunomodulatory or immunosuppressive drug treatment for at least 4 weeks before study entry. Patients with a history of seizure, subdural hematoma and/or severe post-lumbar puncture syndrome were not included in the study. All patients were treated with repetitive administration of 40 mg triamcinolone acetonide of three to six times within 3 weeks. EDSS and maximum walking distance (WD) without support by walking aids were assessed at the same day prior and after the end of the treatment

Table 1. Clinical data of MS patients and healthy controls.

	All patients (<i>n</i> = 31)	SPMS (<i>n</i> = 22)	PPMS (<i>n</i> = 9)	Healthy controls (<i>n</i> = 29)
Age/years	43.3 ± 9.7 [24–9]	42.7 ± 7.4 [27–3]	46.6 ± 13.0 [26–9]	42.7 ± 15.7 [23–3]
Female : male	21 : 10	13 : 9	8 : 1	16 : 13
Disease duration/years	9.5 ± 7.8 [1–42]	8.7 ± 8.8 [1–22]	11.7 ± 11.7 [1–42]	
Years since conversion from RRMS to SPMS		3.8 ± 2.0 [1–7]		
EDSS before therapy	5.5 ± 0.9 [4.5–7.0]	5.5 ± 0.9 [4.5–7.0]	5.4 ± 1.0 [4.5–7.0]	
Max. WD before therapy	194 m [10–800 m]	168 m [10–400 m]	257 m [40–800 m]	
Pretreatment: (number of patients)				
None	19	11	8	
Immunomodulatory	9	9	0	
Immunosuppressive	3	2	1	

Data are quoted as mean (±SD) [range], *n*, number of subjects. Max. WD, maximum walking distance; SPMS, secondary progressive MS; PPMS, primary progressive MS; RRMS, relapsing–remitting MS. Immunomodulatory pretreatment: interferon, glatiramer acetate, immunoglobulins. Immunosuppressive pretreatment: azathioprine, mitoxantrone.

cycle (mean: 19 ± 1 days) (Table 2). To compare imaging findings a cohort of 29 age and gender-matched healthy controls was additionally enrolled in this study. The study was approved by the local ethics committee. All MS patients gave their written informed consent to intrathecal treatment and MRI examination as well as the further use of anonymized data.

TCA administration

In all patients an atraumatic (Sprotte[®]) needle was used for intrathecal treatment in order to reduce the risk for onset of postlumbar puncture syndrome. All patients were treated with repetitive administration of 40 mg TCA three to six times within 3 weeks. The individual decision on the number of injections depended on the improvement of the clinical parameters in each patient, which in earlier studies became evident after the third application and more significant after the sixth injection. The details of the procedure are given in Hoffmann *et al.* [2006].

Neuroimaging and data analysis

MRI scans were obtained from all the patients and control subjects using a standardized MRI protocol on a 1.5T scanner (Magnetom SymphonyTM, Siemens, Erlangen, Germany) at study entry. For assessing spinal cord cross-sectional area a sagittal high-resolution 3D T1-weighted MRI data set (MPRAGE; magnetization prepared rapid gradient echo) covering the whole brain and upper cervical spinal cord was acquired by using a Turbo FLASH 3D sequence (TE [echo time]: 3.93 ms, TR [repetition time]: 1900 ms, TI [inversion time]: 1100 ms, flip angle: 15°, resolution: 1 mm × 1 mm, 128 sagittal slices, slice thickness: 1.5 mm). All subjects were positioned within the head coil using a standard

procedure according to outer anatomical markers. In addition we performed sagittal T1 post-GdDTPA images of the cervical cord to rule out active enhancing lesions, which can be associated with cord swelling. Patients with acute lesions were excluded from this study under the assumption that acute cord swelling may alter spinal cord volumetry.

Postprocessing of MR images

Images were postprocessed by an evaluator blinded to the subject's identity using a semi-automated volumetry method combining a marker-based segmentation and an automatic histogram analysis. Spinal cord volume was segmented and quantified within a section of 50 mm thickness starting at upper border of C2 rostrally (Figure 1). The mean cross-sectional area within this volume was then calculated by dividing the volume by the defined section length. Details of the evaluation method can be found in Lukas

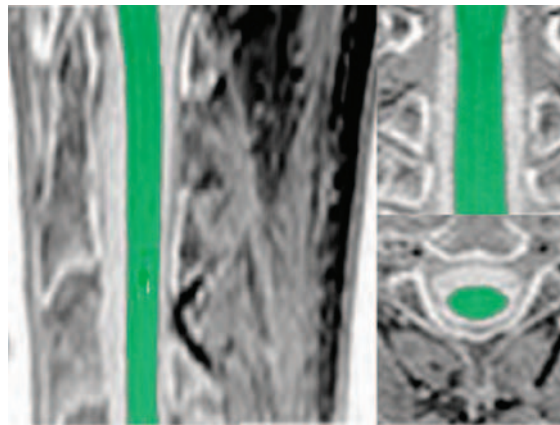


Figure 1. Spinal cord segmentation technique at the level C1 to C3.

Table 2. Walking distance and Expanded Disability Symptom Scale during triamcinolone acetate treatment.

	All patients (n=31)	SPMS (n=22)	PPMS (n=9)
WD before TCA (Mean [range])	194 m [10–800 m]	168 m [10–400 m]	257 m [40–800 m]
WD after TCA (Mean [range])	498 m [15–2000 m]	488 m [90–2000 m]	518 m [15–1200 m]
Significance <i>p</i>	<i>p</i> < 0.001	<i>p</i> = 0.001	<i>p</i> = 0.046
EDSS before TCA (Mean ± SD)	5.5 ± 0.9	5.5 ± 0.9	5.4 ± 1.0
EDSS after TCA (Mean ± SD)	4.9 ± 1.0	4.9 ± 0.9	4.8 ± 1.1
Significance <i>p</i>	<i>p</i> < 0.001	<i>p</i> = 0.001	<i>p</i> = 0.071
Number of TCA injections	3 inj. : 1 patient 6 inj. : 30 patients	6 inj. : 22 patients	3 inj. : 1 patient 6 inj. : 8 patients

Data are quoted as mean (±SD) [range], *n*, number of subjects; WD, walking distance; SPMS, secondary progressive MS; PPMS, primary progressive MS; *p*, statistical significance of differences between WD (respectively EDSS) after therapy in comparison with therapy start by Wilcoxon signed rank testing.

et al. [2008]. To correct for intra-individual variations due to gender, natural aging and head size, all cross-sectional area results were normalized by multiplying by the ratio of the mean intracranial cavity volume (ICC) of the total population to the ICC for each individual. This is a common procedure in morphometric studies of the central nervous system (CNS) [Whitwell *et al.* 2001], which in our study reduced the interindividual variability of the mean USC area in the healthy control group from 9.1% to 6.8% (mean USC area in the healthy control group, not normalized: $89.4 \pm 8.2 \text{ mm}^2$, normalized: $87.3 \pm 5.9 \text{ mm}^2$). Furthermore, after normalization the mean USC area in the healthy control group showed no significant correlation with age.

The intracranial volume was assessed on the basis of the volumetric T1-weighted 3D data by using a semi-automated volumetry method for brain volumetry which is identical to the method used in Lukas *et al.* [2004]. The histogram based volume computation approach employed therein is described in more detail in Hahn *et al.* [2004].

Statistical analysis

Statistical analyses were performed using the SPSS14 (SPSS Inc., Chicago, IL) software. Wilcoxon signed rank test for repeated measurements was used to examine changes of EDSS and maximum walking distance after treatment. Correlation between relative WD gain and the mean normalized cross-sectional spinal cord area in subjects were evaluated using Spearman's rank correlation. To examine the effects of mean USC area and initial maximum walking distance on the relative WD gain a multiple linear regression analysis was performed. Possible influences of the pretreatment at the beginning of the TCA therapy on the relative WD gain were assessed by an analysis of variance with the mean USC area as covariable and pretreatment (present/absent) as a fixed factor. Analysis between subgroups according to the rate of atrophy was done by Mann–Whitney U-testing.

Results

Mean walking distance for the whole group increased from 255 m at baseline to 566 m after TCA therapy. The mean EDSS of the whole patient group showed a slight decrease by 0.6. The differences between the mean walking distance and EDSS before and after TCA therapy were statistically highly significant with $p \leq 0.001$ for the whole patient group and SPMS subgroup

and significant for the mean walking distance in the PPMS subgroup ($p = 0.046$; see Table 2).

Treatment benefit was evaluated according to the relative gain in maximum walking distance: $rel. \text{ WD}_{gain} = (WD_{after \text{ TCA}} - WD_{before \text{ TCA}}) / WD_{before \text{ TCA}}$; range: 67% to +1900%. Correlation between the relative WD gain and the mean cross-sectional spinal cord area revealed a significant correlation with $r = 0.442$ and $p = 0.019$, indicating that treatment benefit tends to be higher for patients with less USC atrophy than for patients with marked atrophy of the USC. In the scatter plot (Figure 2) the distribution of the relative WD gain values in dependence on the mean USC area is presented for clarification. Presence or absence of pre-treatment showed no significant impact on the TCA benefit in this study group ($p = 0.937$).

Relative WD gain in subjects was significantly dependent on mean USC area and initial maximum walking distance indicating that higher treatment benefit prevails in patients with little USC atrophy but short maximum walking distance at the start of the TCA therapy (Table 3). To illustrate this effect further (Figure 3) the patients were grouped into those with no atrophy ($> 80 \text{ mm}^2$, $n = 14$), or atrophy ($\leq 80 \text{ mm}^2$, $n = 17$) on the basis of the mean USC area of the control group (mean: $87.1 \pm 5.8 \text{ mm}^2$). A further subdivision of the patients according to the initial maximum walking distance G_0 into groups: $G_0 \leq 150 \text{ m}$, $G_0: 150\text{--}400 \text{ m}$, $G_0 > 400 \text{ m}$ was performed. Although statistical

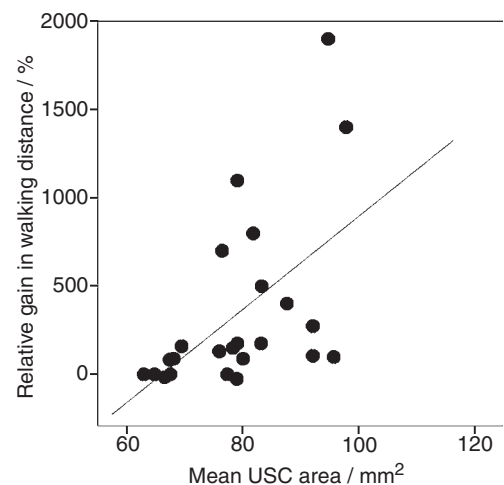


Figure 2. Scatter plot of relative walking distance improvement (treatment benefit) dependent of the mean upper spinal cord area.

testing between these subgroups did not reach significance, the box plots demonstrate that patients with an initial short maximum walking distance (≤ 150 m) and no atrophy exhibited greatest benefit in improved maximum walking distance (median $> 1000\%$) (Figure 3).

Discussion

Efficiency and safety of TCA therapy in progressive MS have been reported in a few studies so far [Hellwig *et al.* 2006a; Hoffmann *et al.* 2006, 2003]. Previous selection of patients has been based on clinical symptoms; for example, predominant spinal cord disability. Given the invasive character of this therapy, additional paraclinical findings such as the presence of cervical cord atrophy may be useful to preselect patients with good prospects to benefit from the treatment. We observed that patients with no or little atrophy in the upper spinal cord achieved the strongest treatment benefit especially when their initial walking abilities were impaired. Our findings are not surprising, but rather corroborate current pathophysiological models. The spinal cord is a clinically eloquent region and damage in this area has the potential to affect dramatically the functional outcome of MS patients. Damage can be due to acute lesions, which are often accompanied by cord swelling or result from degenerative processes, which lead to spinal cord atrophy. The latter seems to be the end state of tissue destruction resulting in an irreversible damage in which therapeutic treatment effects may be ineffective. Furthermore there is evidence that tissue damage in the cord is not restricted to MS lesions itself. By using magnetization-transfer histogram analysis subtle tissue damage can also be assessed outside MS cord lesions in the normal appearing white matter (NAWM) [Rovaris *et al.* 2001, 2000; Bozzali *et al.* 1999]. Besides the accumulation of macroscopic lesions and the severity of tissue destruction within those lesions, NAWM changes also contribute to the clinical status in MS patients [Rovaris *et al.* 2000]. In patients with no or little spinal cord atrophy subtle inflammation and patchy edema may play a relevant role in

functional disability. In the absence of Gd enhancement these processes may be beyond the resolution of conventional MRI techniques as shown by DTI and MTR studies [Agosta *et al.* 2005; Rovaris *et al.* 2001; Filippi *et al.* 2000]. It can be hypothesized that in this cohort anti-inflammatory drug treatment when given intrathecally may lead to a reduction of subacute inflammation and/or edema inducing an improvement of disability. In contrast to i.v. injection, intrathecal application of a small dosage of a slow-release steroid compound leads to higher concentrations at the origin of inflammation which has been demonstrated by Rohrbach *et al.* [1988]. This effect has also been hypothesized in a clinical TCA study in relapsing remitting MS patients with painful dysaesthesia due to acute spinal cord lesions in which prior treatment with i.v. steroids failed [Hellwig *et al.* 2006b].

In contrast, in patients with moderate to distinct atrophy subacute inflammation may play only a minor role and disability in these patients may result from pronounced irreversible tissue loss, which will not be affected by anti-inflammatory treatment approaches. However, even in the

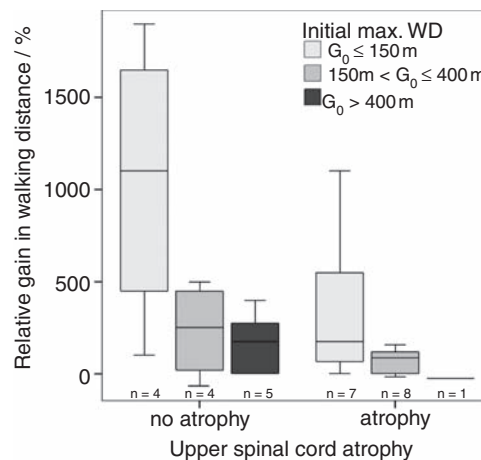


Figure 3. Relative gain in max. walking distance (WD) is highest for patients with short WD at therapy start and no USC atrophy (boxes depict median values and 25%/75% quartiles, error bars show ranges).

Table 3. Multiple linear regression of relative walking distance (WD) gain (treatment benefit) in dependency on mean upper spinal cord (USC) area and initial walking distance in MS patients.

R^2	Independent variable	Regression coefficient	Standard error	p value
0.308	Mean USC area	18.97	6.97	0.011
	Initial WD	-0.51	0.21	0.021

subgroup of patients with severe atrophy in the spinal cord, we observed cases of increase of the walking distance. One possible explanation for this contradictory finding can be that to some degree locomotor disability is a result of MS pathology in the brain. Intrathecal TCA therapy also acts upon inflammatory processes in the brain. Since we have not explicitly excluded acute or subacute brain inflammation by MRI, which is a major shortcoming of this study, in some patients the observed treatment profit can result from brain involvement. On the other hand, patients in this study have been selected on the basis of slow disease progression rather than on acute relapse. Thus, acute disease activity within the brain seems to be unlikely. Finally, it has to be mentioned that we cannot fully exclude prior effects on the development of spinal cord atrophy due to immunosuppressive or immunomodulatory treatment which might confound the results of this study.

When subdividing MS patients according to their disease subtype, results showed no significant EDSS changes after treatment in the PPMS group. However, these results must be kept with caution due to the small number of patients in this subgroup. Further MRI studies monitoring the long-term benefit of TCA and its impact on the evolution of spinal cord atrophy in a larger cohort of patients are currently ongoing and will also include brain MRI. In conclusion, absence of USC atrophy as measured by a volumetric MR-based strategy is a predictive marker for intrathecal TCA therapy outcome in progressive MS with predominant spinal symptoms.

Conflict of interest statement

None declared.

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