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Efficacy and safety of repeated intrathecal triamcinolone acetonide application in progressive multiple sclerosis patients

Volker Hoffmann, Sebastian Schimrigk, Saida Islamova, Kerstin Hellwig, Carsten Lukas, Nils Brune, Dieter Pöhlau, Horst Przuntek, Thomas Müller*

Department of Neurology, St. Josef-Hospital, Ruhr-University of Bochum, Gudrunstrasse 56, 44791 Bochum, Germany

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Abstract

Available immunomodulatory and conventional steroid treatment options for patients with progressive multiple sclerosis (MS) only provide limited symptomatic benefit. We performed an open trial on the short-term and long-term efficacy and safety of repeated intrathecal application of the sustained release steroid triamcinolone acetonide (TCA) in 36 progressive MS patients. Six TCA administrations, performed every third day, reduced the EDSS score (initial: 5.6 ± 0.93 [mean ± S.D.]; end: 4.9 ± 1.0; $p < 0.001$) and increased the walking distance (WD) (initial: 294 ± 314 m; end: 604 ± 540 m; $p < 0.001$). Twenty MS patients continued intrathecal TCA treatment with one TCA injection performed with a variable frequency ranging from 6 to 12 weeks. Both EDSS and walking distance remained stable in these patients until the end of the follow-up investigation period. No serious side effects occurred. We conclude that repeated intrathecal TCA injection provides substantial benefit for progressive MS patients with predominantly spinal symptoms.

Keywords: Progressive multiple sclerosis; Efficacy; Triamcinolone acetonide; Intrathecal

1. Introduction

To date, clinical trials on patients with progressive multiple sclerosis (MS) showed no clear evidence of an effective symptomatic treatment, which stabilized or reversed disability, particularly once the disease enters the progressive stage. Immunomodulatory compounds efficaciously reduce the rate of MS relapses, but do not convincingly, positively alter or even improve patients with progressive MS [1]. Numerous papers exist on the pros and cons and/or on the efficacy of intrathecal administration of different dosages of various conventional sustained release steroid compounds, i.e. methylprednisolone acetate, in the MS literature. Beneficial, though controversially discussed, effects appeared in progressive MS patients with predominantly spinal symptomatology according to case reports, open trials and one double-blind, controlled study with some steroid preparations, including the sustained release compound triamcinolone acetonide (TCA) [2–4]. However, a distinct superior clinical benefit of intraspinal TCA administration did not occur in an open study, which compared the efficacy of intravenous methylprednisolone administration with repeated intrathecal TCA injections, performed maximally three times within 3 weeks [3]. An increasing number of reports of serious side effects, i.e. adhesive arachnoiditis or sterile meningitis, nearly caused a cessation of further trials on the efficacy of intraspinal steroid application in MS. Putative hypothetical causes were the risks of lumbar puncture itself and/or the applied steroid, mostly methylprednisolone acetate, and its preservatives [4]. The revival of intrathecal steroid treatment started with the positive outcome of a trial on intractable postherpetic neuralgia, in which 89 patients received up to a maximum of four intraspinal methylprednisolone applications within 4 weeks without any serious side effects [5].

The objective of this open, prospective study in progressive MS patients was to show the short- and long-term efficacy and the tolerability of repeated intrathecal TCA treatment.

* Corresponding author. Tel./fax: +49-234-509-2426.
E-mail address: thomas.mueller@ruhr-uni-bochum.de (T. Müller).

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2. Subjects and methods

2.1. Subjects

We enrolled 36 MS patients (subtypes: 22 secondary-progressive; 14 primary-progressive; female: 24; male 12; Table 1) into this study [6]. We only included participants with an EDSS score of ≤ 7.5. Subjects did not receive steroids and were on a stable immunomodulatory drug treatment for at least 4 weeks before study entry. They had to experience distinct MS symptom progression, which corresponded to at least one point on the EDSS scale, in the last 2 years before study entry, but had to be stable for at least 4 weeks before inclusion. The trial design did not allow for participants with a history of seizures, subdural hematoma and/or severe post-lumbar puncture syndrome.

2.2. TCA administration

We used an atraumatic (Sprotte®) needle for intrathecal treatment in order to reduce the risk for onset of post-lumbar puncture syndrome [7]. We took 5–7 ml of cerebrospinal fluid (CSF) for cell count and protein analysis for safety reasons. Then we dissolved 40 mg (= 1 ml) TCA in 9 ml of sterile saline solution (0.9%) under sterile conditions and slowly injected this mixture over a period of approximately 5 min. Then patients had to stay in the supine position for at least 2 h.

2.3. Clinical evaluation

We performed EDSS scoring before the first injection ($EDSS_{initial}$) and on the day after the last TCA application ($EDSS_{TCA\ course}$) with simultaneous estimation of walking distance (WD) [8]. We offered patients who showed an improvement of their EDSS score of at least one point or a distinct increase of their WD after their first six TCA applications further treatment on a regular basis with one TCA application of individually varying frequency of every 6–12 weeks based on the treating physician's clinical impression and the patient's judgement. We also simultaneously scored these patients with the EDSS ($EDSS_{follow\text{-}up}$) and measured the WD ($WD_{follow\text{-}up}$) before each TCA injection in this follow-up period.

Table 1
Data of all participants

	All ($n=36$)	Six TCA injections ($n=16$)	Follow-up ($n=20$)
Age	44.8 ± 10.5, 25–61	48.63 ± 8.45, 29–61	41.75 ± 11.19, 25–59
Duration of MS	10.7 ± 7.0, 2–26	11.56 ± 8.33, 2–26	10 ± 5.92, 4–24
$EDSS_{initial}$	5.6 ± 0.93, 4–7.5	5.72 ± 1.08, 4–7.5	5.55 ± 0.81, 4.5–7
$EDSS_{TCA\ course}$	4.9 ± 1.0, 3.5–7.5	5.13 ± 1.27, 3.5–7.5	4.7 ± 0.73, 4–6
$EDSS_{follow\text{-}up}$			5.0 ± 0.7, 4–6.5
$WD_{initial}$	294 ± 314, 0–1200	245.13 ± 303.55, 0–1200	333.4 ± 325.25, 2–1200
$WD_{TCA\ course}$	604 ± 540, 0–2500	443.81 ± 353.39, 0–1200	733 ± 633.5, 80–2500
$WD_{follow\text{-}up}$			782 ± 548, 20–2200

Values represent mean ± standard deviation, minimum–maximum, age and duration of disease is given in years, walking distance (WD) is given in meters, n = number of subjects, TCA = triamcinolone acetonide, TCA course = values after six TCA injections within 3 weeks, TCA follow-up = values of further TCA treatment as described in the methods section.

2.4. Ethics

Each subject gave informed written consent. The local ethics committee approved this study.

2.5. Statistical analysis

Data showed a normal distribution according to the Kolmogorow–Smirnow test. As a result, we only performed parametric tests. We used ANCOVA with repeated measure design for comparison of EDSS scores and walking distance before and after the course of six TCA injections. We set age, MS subtypes and duration of disease as covariates. An additional ANCOVA analysis was performed in the follow-up patient group. We set the number of TCA applications, the follow-up treatment duration in months, age, and duration of MS and MS subtypes as covariates. We employed the Tukeys Honest Significance Difference Test for post hoc comparisons.

3. Results

3.1. Efficacy of the initial six TCA injections

EDSS scores significantly (ANCOVA $F_{(df\ 1,\ 35)}=63.55$, $p=2.23e-09$) decreased (Table 1). WD significantly (ANCOVA $F_{(df\ 1,\ 35)}=32.32$, $p=2.02e-06$) increased (Table 1). Neither the EDSS score nor the WD worsened in any patient.

Sixteen patients (subtypes: 10 secondary-progressive; 6 primary-progressive) stopped further TCA treatment, five of them (subtypes: 2 secondary-progressive; 3 primary-progressive) had no benefit concerning their EDSS score and their WD, one further primary-progressive MS patient only experienced an EDSS improvement from 6.5 to 6.0. The remaining 10 MS patients did not want to participate for various reasons and were lost for standardized follow-up evaluations. Nevertheless, statistical analysis in these 16 patients revealed a significant reduction of the EDSS score (ANCOVA $F_{(df\ 1,\ 15)}=18.36$, $p=0.00065$) and a significant WD increase (ANCOVA $F_{(df\ 1,\ 15)}=12.94$, $p=0.003$).

Twenty patients (subtypes: 12 secondary-progressive; 8 primary-progressive) wished to receive further TCA applications due to their positive response and therefore entered the follow-up study.

3.2. Efficacy of further TCA injections

The duration of follow-up treatment was 13.1 ± 6.22, 3–23 [mean $\pm$ S.D., range] months with 6.35 ± 3.91, 2–15 TCA injections. The post hoc analysis shows that the significant EDSS reduction occurred after the initial six TCA applications and then remained stable (ANCOVA $F_{(df\ 2,\ 38)}=18.31$, $p=2.7e-06$, post hoc analysis: $EDSS_{initial}$ versus $EDSS_{TCA\ course}$: $p=0.00012$; $EDSS_{initial}$ versus $EDSS_{follow\text{-}up}$: $p=0.0009$; $EDSS_{TCA\ course}$ versus $EDSS_{follow\text{-}up}$: $p=0.15$, Table 1).

Correspondingly, the same outcome was evident concerning the estimation of WD despite a further insignificant increase (ANCOVA $F_{(df\ 2,\ 38)}=16.07$, $p=8.76e-06$; post hoc analysis: $WD_{initial}$ versus $WD_{TCA\ course}$: $p=0.0002$; $WD_{initial}$ versus $WD_{follow\text{-}up}$: $p=0.0001$; $WD_{TCA\ course}$ versus $WD_{follow\text{-}up}$: $p=0.84$; Table 1).

There was no significant impact of covariates in the statistical analysis (data not shown).

3.3. Side effects

We performed a total of 340 lumbar punctures in this trial. We occasionally observed a transitory increase of CSF protein above 500 mg/l (total: 14). A temporary rise of CSF cells occurred (total: 17), but this did not induce clinical symptoms in any case. The maximum cell count was 38/μl. Five patients developed headache after lumbar puncture (total: 13), but they did not stop further TCA treatment. We once observed onset of transitory tinnitus in combination with temporary pain in the lower extremities in one patient. Deep vein thrombosis, ovarian cancer, and traumatic bone fracture occurred in the follow-up period. All of them were not related TCA therapy.

4. Discussion

Our results demonstrate the efficacy and safety of repeated intraspinal TCA application in progressive MS patients with spinal symptoms. Our application rate with six TCA injections within 3 weeks was distinctly higher compared with earlier trials [9]. Our analysis also strongly indicates that most primary- and secondary-progressive, even very advanced, MS patients improve from this therapeutic approach with six TCA injections. However, our study design and performance does not allow any conclusion concerning the duration of the achieved benefit. Our long-term results did not show a further statistically significant additional benefit on MS symptoms, and we cannot draw any conclusions on the impact of TCA treatment on progression of MS. Therefore, there is an urgent need for further confirmatory trials to additionally address all these issues. However, concerning long-term steroid therapy and progression of MS, we stress that there are positive outcomes of trials with intravenous methylprednisolone administration in various application rates and dosages on long-term disease progression and/or on brain atrophy in secondary-progressive and, respectively, relapsing–remitting MS patients [10,11]. In contrast to studies on intravenous oral steroid treatment, we did not observe the typical side effects of systemic high-dosage steroid administration. Onset of side effects of lumbar puncture were negligible since we used an atraumatic needle [7].

In conclusion, our data demonstrate the efficacy and safety of repeated intrathecal TCA application on the symptoms in progressive MS patients, which markedly improved. We point out that only MS specialists with broad experience of intraspinal TCA application should perform this kind of therapy after careful information and risk-benefit evaluation in cooperation with the patient. Further trials on the efficacy and safety of intrathecal TCA treatment and comparisons to systemic high-dosage steroid treatment are urgently needed in progressive MS.

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