Double-blind Crossover Trial of Trimethoprim-Sulfamethoxazole in Spinocerebellar Ataxia Type 3/Machado-Joseph Disease

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Design: Placebo-controlled, double-blind crossover trial in 22 patients with genetically confirmed SCA3/MJD. Study phases of 6 months were separated by a washout period of 4 weeks. Dosages were a combination of trimethoprim, 160 mg, and sulfamethoxazole, 800 mg, twice daily for 2 weeks, followed by a combination of trimethoprim, 80 mg, and sulfamethoxazole, 400 mg, twice daily for 5.5 months.

Setting: Outpatient department of the Neurological Clinic, Ruhr-University, Bochum, Germany.

Main Outcome Measures: Ataxia ranking scale, self-assessment score, static posturography, and results of motor performance testing. Effects on the visual system were studied using the achromatic Vision Contrast Test System and the Farnsworth-Munsell 100-hue test for color discrimination. Physical and mental health were documented using the Medical Outcomes Study 36-Item Short-Form Health Survey. Subgroup analyses assessed the influence of age, sex, age at onset, duration of the disease, phenotype, and CAG repeat length on test performance.

Results: Twenty of 22 patients completed the study. Dropouts were due to a rash (placebo phase) and an attempted suicide in a family conflict. Trimethoprim-sulfamethoxazole therapy had no significant effect in SCA3/MJD patients in the short-term analysis (2 weeks) or in the long-term interval (6 months).

Conclusions: In contrast to previous reports that studied smaller groups of patients, treatment with trimethoprim-sulfamethoxazole did not improve the diverse and complex movement disorders caused by SCA3/MJD. Trimethoprim-sulfamethoxazole had no effect on the visual system and cannot be recommended as a continuous treatment for SCA3/MJD patients.

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**S**pinocerebellar ataxia type 3 or Machado-Joseph disease (SCA3/MJD) is the most frequent form of autosomal dominant cerebellar ataxia in France, Germany, Japan, Portugal, and the United States.1-5 The disease-causing mutation is an expanded CAG trinucleotide repeat in a novel gene MJD1 on chromosome 14q32.6,7 The CAG repeat codes for a polyglutamine stretch in the gene product ataxin-3, which is expanded in patients with SCA3/MJD (SCA3/MJD patients). The MJD1 gene is widely expressed in neuronal and nonneuronal tissues. Whereas normal ataxin-3 has a cytosolic distribution, it shows additional nuclear location in SCA3/MJD patients. Here, fragments of ataxin-3 containing the expanded polyglutamine stretch form nuclear inclusions that are the pathological hallmark of SCA3/MJD.8,9 Nuclear inclusions occur especially in brain regions that are substantially prone to degeneration in SCA3/MJD, eg, the dentate nucleus, substantia nigra, globus pallidus, pontine nuclei, anterior horn cells, and Clarke columns.10,11 Similar inclusions are found in transgenic animal models, where they occur before the onset of symptoms.11,12 Despite the improved understanding of the underlying pathologic features, major steps in the pathogenesis remain to be elucidated, and therapy is still symptomatic, eg, antiparkinsonian and antispastic drugs and physiotherapy.

Four independent studies reported improvement of neurologic dysfunction in SCA3/MJD with a combination of trimethoprim and sulfamethoxazole.13-16 Trimethoprim-sulfamethoxazole was thought to ameliorate spasticity or to increase biotin and homovanillic acid levels, which were decreased in the cerebrospinal fluid...
PATIENTS AND METHODS

PATIENTS

We studied 22 patients (12 men and 10 women; mean age, 44.7 ± 11.0 years) with genetically confirmed SCA3/MJD, representing 15 families. Informed consent was obtained from all patients after the nature of the trial had been fully explained. The study was approved by the ethics committee of the Ruhr-University, Bochum, Germany. In addition to sociodemographic variables, extensive clinical and disease information (duration of disease, CAG repeat length, and phenotypic variables, eg, cerebellar symptoms, pyramidal signs, peripheral neuropathy, and extrapyramidal motor signs) was assessed in each patient. Disability was measured using gait disturbance as the key symptom. Each patient was categorized in 1 of the following 3 distinct categories: patients who were able to walk 10 m unassisted; those who needed support, such as from a stick or a stroller; and those who were confined to a wheelchair (Table 1). All patients included in this study were able to stand without assistance.

METHODS

Patients were randomly assigned to receive trimethoprim-sulfamethoxazole or placebo during the first trial phase. In the second phase, treatment crossed over to the alternate preparation. Complete evaluation of all study items was performed at the beginning, after 2 weeks, and at the end of each 6-month phase, constituting 6 study visits for each patient. The 2 treatment phases were separated by a washout period of 4 weeks (Figure 1).

Trimethoprim-sulfamethoxazole tablets and similar lactose placebo tablets were provided by Glaxo-Wellcome (Hamburg, Germany). Trimethoprim-sulfamethoxazole dosages were trimethoprim, 160 mg, and sulfamethoxazole, 800 mg, twice daily for the first 2 weeks and a combination of trimethoprim, 80 mg, and sulfamethoxazole, 400 mg, twice daily for the remainder of the 6-month phase.

At the beginning of each treatment phase, a urine sample was examined to exclude urinary tract infection. Blood cell counts and routine blood chemistry analysis were performed at the baseline and end point of each study phase.

Clinical rating included the modified ataxia score of Klockgether et al., expanded to include items to assess non-cerebellar effects of SCA3/MJD, eg, dysphagia, visual impairment, peripheral neuropathy, spasticity, incontinence, and sleep disorders (Table 2). For all items, higher scores indicated worse functioning. A score of 0 indicated normal performance or absence of symptoms. All examinations were performed in a standardized manner, in the same sequence, and were supervised by the same investigator (L.S.).

Ataxia of stance was documented and quantified by means of static posturography using a force-measuring platform monitored by a computer. The subject was asked to stand still with both eyes open, looking at a target placed at 50 cm in front of the eyes. The data from the 3 components of the force acting on the platform were converted from analog to digital and entered into a computer. A program calculated the changes in position of the resultant vector, from which the average center of foot pressure was obtained. Calculation of the sway path of the center of foot pressure (in millimeters per second) was performed as described by Diener et al. Recording time was 32 seconds.

Dexterity was quantified with the motor performance test of Schoppe, using the subtest plugging.

### Table 1. Demographic Data of 22 Patients With SCA3/MJD *

<table>
<thead>
<tr>
<th>Patient No./ Sex/Age, y</th>
<th>Age at Onset, y</th>
<th>Disease Duration, y</th>
<th>No. of CAG Repeats</th>
<th>Cerebellar Symptoms</th>
<th>Pyramidal Signs</th>
<th>PNP</th>
<th>EPMS</th>
<th>Disability</th>
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<tr>
<td>1/M/32</td>
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<td>+</td>
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<td>2/F/55</td>
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<td>74</td>
<td>+</td>
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<td>6</td>
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<td>18/M/41</td>
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<td>70</td>
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<td>19/F/43</td>
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<td>73</td>
<td>+</td>
<td>+</td>
<td>−</td>
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</tbody>
</table>

*SCA3/MJD indicates spinocerebellar ataxia type 3/Machado-Joseph disease; PNP, peripheral neuropathy; EPMS, extrapyramidal motor signs; plus sign, present; minus sign, absent; 1, walks without support; 2, needs a stick or a stroller; and 3, confined to a wheelchair.
of SCA3/MJD patients. 

All 4 studies included only a small number of patients and had short, if any, placebo-controlled periods. Therefore, we conducted a double-blind, placebo-controlled crossover trial to test the effect of trimethoprim-sulfamethoxazole therapy in 22 patients with genetically confirmed SCA3/MJD (Figure 1). We analyzed short- and long-term effects and performed posturography and a computer-based dexterity test, and obtained achromatic contrast sensitivity, color discrimination, and clinical scores. Subgroup analyses using clinical and genetic variables were performed to search for subtypes of SCA3/MJD responding to trimethoprim-sulfamethoxazole.

Twenty of 22 patients completed the study. Dropouts were due to a rash after 3 weeks in the placebo phase and an attempted suicide in a family conflict after 4 months in the trimethoprim-sulfamethoxazole phase. Except for minor gastrointestinal problems in some patients, no relevant adverse effects were noted with long-term administration of trimethoprim-sulfamethoxazole in SCA3/MJD patients. Likewise, there were no changes in blood cell counts or results of blood chemistry studies.

Trimethoprim-sulfamethoxazole had no significant effect in SCA3/MJD patients in the short-term analysis (2 weeks) or in the long-term interval (6 months). Detailed data are presented in Table 3. The ataxia sum score improved slightly after 14 days, albeit in both the trimethoprim-sulfamethoxazole and placebo phases and without significant differences. Also, no trend was observed in clinical scores in patients receiving trimethoprim-sulfamethoxazole or placebo (Figure 2). In particular, spasticity, which was reported to improve throughout the previous reports, showed no alterations during trimethoprim-sulfamethoxazole treatment (Table 3).

Sway path in posturographic analyses did not differ significantly at baseline between treatment groups. Neither placebo nor trimethoprim-sulfamethoxazole had a significant effect on sway path after 2 weeks or 6 months of treatment. Dexterity in the motor performance test improved minimally but not significantly (repeated measures analysis of variance; right, \( P = .62 \); left, \( P = .75 \)). Similarly, a tendency toward improved color discrimination in the Farnsworth-Munsell 100-hue test was observed for short- and long-term evaluation. However, these minor effects occurred with trimethoprim-sulfamethoxazole as well as with placebo (Table 3). No relevant alterations were found in the achromatic Vision Contrast Test System. The SF-36 did not show relevant changes in the subscores for general or mental health or for physical functioning.

STATISTICS

Differences in clinical scores between baseline and second (after 2 weeks) and third visits (after 6 months) were tested for each treatment arm separately using non-parametric tests (Kruskal-Wallis test and Cuzick test for trend). Results of diagnostic examination were transformed if not normally distributed and tested using repeated-measures analysis of variance within each treatment arm separately. Differences between treatment arms at baseline and follow-up visits 1 and 2 were tested using Wilcoxon rank sum test for clinical scores and \( t \) test for the results of diagnostic examinations. This was also done for the 3 subgroups defined above. In addition, we calculated relative changes in cerebellar score and color discrimination between follow-ups 1 and 2 and tested their differences to evaluate whether the relative magnitude was different between treatments. For this analysis we used the Wilcoxon signed rank test (cerebellar score) and \( t \) test (color discrimination). Finally, quality-of-life scores (medians) were tested between the placebo and treatment groups using the Wilcoxon rank sum test.
<table>
<thead>
<tr>
<th>Symptom</th>
<th>Symptom Score, Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cerebellar Symptoms</strong></td>
<td></td>
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</tbody>
</table>
| Ataxia of gait | 1. Slight ataxia only visible when walking in tandem or without visual feedback  
2. Moderate ataxia visible in normal walking; difficulties when walking in tandem  
3. Broad-based or staggering gait; unable to walk in tandem  
4. Unable to walk without support; use of a stick or a stroller  
5. Wheelchair bound; bedridden |
| Ataxia of stance | 1. Slight swaying only present without visual feedback  
2. Moderate swaying; still able to stand with feet together  
3. Marked swaying; unable to stand with feet together  
4. Unable to stand without support  
5. Wheelchair bound; bedridden |
| Upper limb ataxia | 1. Slight hypermetria in fast arm movements  
2. Hypermetria and decomposition of movements only in fast arm movements  
3. Marked hypermetria and decomposition of arm movements leading to moderate disturbances in everyday life  
4. Pronounced hypermetria and decomposition of movement heavily interfering with everyday life  
5. Inability to perform coordinated arm movements |
| Lower limb ataxia | 1. Hypermetria in heel-to-shin test  
2. Hypermetria and slight ataxic performance in heel-to-shin test  
3. Marked hypermetria and ataxic performance in heel-to-shin test  
4. Pronounced ataxia in performing heel-to-shin test  
5. Unable to perform heel-to-shin test |
| Truncal ataxia | 1. Sitting with thighs together and arms folded with slight oscillations of the trunk  
2. Sitting with moderate oscillations of the trunk  
3. Sitting with oscillations of the trunk and legs  
4. Sitting with severe dysequilibrium  
5. Sitting without support impossible |
| Dysdiadochokinesia | 1. Minimal slowness of alternating movements  
2. Marked slowness of alternating movements  
3. Slowness and irregular performance of alternating movements  
4. Severe irregularity of alternating movements  
5. Inability to perform alternating movements |
| Intention tremor | 1. Slight terminal tremor  
2. Marked terminal tremor  
3. Kinetic tremor throughout intended arm movements  
4. Severe kinetic tremor heavily interfering with everyday life  
5. Maximal form of kinetic tremor making intended movements impossible |
| Dysarthria | 1. Disturbances only in special test items  
2. Moderate disturbance  
3. Marked disturbances; speech still intelligible  
4. Considerable difficulties in understanding  
5. Unintelligible speech |
| **Noncerebellar Symptoms** | |
| Dysphagia | 1. Gag reflex alteration without dysphagia  
2. Rare dysphagia ≤1/wk  
3. Occasional dysphagia ≤1/d  
4. Frequent dysphagia or severe aspiration  
5. Oral intake insufficient; feeding by means of gastrostomy |
| Visual impairment | 1. Diplopia or blurred vision only when tired or relaxed  
2. Intermittent diplopia or blurred vision well compensated by prism glasses  
3. Frequent diplopia; at most, partially compensated by prism glasses  
4. Reading or watching television impaired  
5. Permanent visual impairment affecting activities of daily living |
| Peripheral neuropathy | 1. Asymptomatic loss of tendon reflexes, muscle wasting, or impaired sensory tests  
2. Weakness, not affecting walking capacities or mild paresthesia  
3. Weakness expanding to the arms or teasing dysesthesia  
4. Weakness prohibits walking without support  
5. Weakness prohibits walking |
| Incontinence | 1. Urinary frequency or nocturia  
2. Urinary urgency or rare incontinence (<1/wk)  
3. Frequent urge incontinence (<1/d)  
4. Incontinence requires napkins or intermittent condom catheters  
5. Incontinence requires permanent catheterization or diapers |
| Spasticity | 1. Increased tendon reflexes, abnormal plantar response, or spasticity not affecting gait  
2. Mild spastic gait component, spinal automatisms, or clonus  
3. Gait mildly impaired by spasticity  
4. Spasticity prohibits walking  
5. Spastic contractures |
| Sleep disorder | 1. Prolonged sleep latency, frequent arousals, or impaired restorative properties of sleep (<1/wk)  
2. Impaired sleep ≥1/wk  
3. Disabling sleep disturbance responding to medication  
4. Chronic use of sleep medication with moderate success  
5. Drug-resistant insomnia |

*Score of 0 would indicate normal test performance or absence of symptoms.*
Subgroup analyses did not reveal an effect of age, sex, age at onset, or duration of the disease on the study performance. Furthermore, CAG repeat length did not correlate with test results. Even more important, no clinical subgroup defined by peripheral neuropathy, spasticity, or extrapyramidal motor signs could be identified that improved during trimethoprim-sulfamethoxazole therapy.

In this placebo-controlled, double-blind crossover trial, we did not find a therapeutic effect of trimethoprim-sulfamethoxazole in SCA3/MJD. In contrast, 4 previous studies claimed positive effects of trimethoprim-sulfamethoxazole in SCA3/MJD. We could not confirm the positive effects of trimethoprim-sulfamethoxazole

**Table 3. Performance of Patients With SCA3/MJD on Different Tests**

<table>
<thead>
<tr>
<th>Test</th>
<th>Trimethoprim-Sulfamethoxazole Phase</th>
<th>Placebo Phase</th>
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<tr>
<td></td>
<td>Baseline</td>
<td>2-wk Evaluation</td>
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<tr>
<td>Ataxia rating scale</td>
<td>15.3 ± 5.1</td>
<td>14.0 ± 4.7</td>
</tr>
<tr>
<td>Ataxia of gait</td>
<td>2.8 ± 1.0</td>
<td>2.5 ± 1.0</td>
</tr>
<tr>
<td>Ataxia of stance</td>
<td>2.4 ± 0.7</td>
<td>2.1 ± 0.7</td>
</tr>
<tr>
<td>Upper limb ataxia</td>
<td>2.1 ± 0.9</td>
<td>2.0 ± 0.9</td>
</tr>
<tr>
<td>Lower limb ataxia</td>
<td>1.6 ± 0.9</td>
<td>1.6 ± 1.1</td>
</tr>
<tr>
<td>Truncal ataxia</td>
<td>2.0 ± 1.2</td>
<td>1.8 ± 1.2</td>
</tr>
<tr>
<td>Dysdiadochokinesia</td>
<td>2.1 ± 1.3</td>
<td>2.1 ± 1.3</td>
</tr>
<tr>
<td>Intention tremor</td>
<td>0.2 ± 0.4</td>
<td>0.2 ± 0.4</td>
</tr>
<tr>
<td>Dysarthria</td>
<td>2.0 ± 0.5</td>
<td>2.0 ± 0.5</td>
</tr>
</tbody>
</table>

**Additional symptoms**

| Dysphagia                | 2.3 ± 1.4 | 2.2 ± 1.4 | 2.3 ± 1.4 | 2.2 ± 1.3 | 2.1 ± 1.2 | 2.4 ± 1.3 |
| Seeing impairment        | 1.7 ± 1.0 | 1.7 ± 1.1 | 1.6 ± 0.8 | 1.6 ± 0.9 | 1.5 ± 0.8 | 1.5 ± 1.0 |
| Peripheral neuropathy    | 1.1 ± 1.1 | 1.0 ± 0.8 | 1.2 ± 0.9 | 1.1 ± 0.8 | 1.1 ± 0.8 | 1.0 ± 1.1 |
| Incontinence             | 1.1 ± 1.1 | 1.0 ± 1.1 | 1.2 ± 1.1 | 1.0 ± 1.1 | 0.9 ± 1.1 | 1.0 ± 1.2 |
| Spasticity               | 1.2 ± 0.9 | 1.2 ± 0.9 | 1.2 ± 1.0 | 1.5 ± 0.9 | 1.3 ± 1.0 | 1.2 ± 1.0 |
| Insomnia                 | 1.5 ± 1.6 | 1.4 ± 1.7 | 1.7 ± 1.6 | 1.5 ± 1.1 | 1.5 ± 1.7 | 1.5 ± 1.2 |
| Sway path, mm/s          | 61.2 ± 17.2 | 63.4 ± 21.4 | 60.5 ± 11.0 | 61.9 ± 11.0 | 60.8 ± 9.9 | 64.1 ± 15.5 |
| MLS, left hand, s        | 725 ± 147 | 686 ± 77 | 681 ± 75 | 695 ± 217 | 678 ± 197 | 700 ± 227 |
| MLS, right hand, s       | 664 ± 147 | 623 ± 105 | 638 ± 82 | 643 ± 189 | 619 ± 175 | 646 ± 182 |
| FM100, TES               | 79.6 ± 67.3 | 77.3 ± 62.2 | 65.9 ± 43.7 | 75.8 ± 54.8 | 68.6 ± 47.9 | 64.3 ± 43.1 |
| VCTS, cycles per degree  | 5.7 ± 0.9 | 5.8 ± 0.5 | 5.8 ± 0.6 | 5.7 ± 0.6 | 5.9 ± 0.7 | 6.0 ± 0.6 |
| 1.5                      | 6.1 ± 0.7 | 6.1 ± 0.6 | 6.2 ± 0.5 | 6.0 ± 0.8 | 6.1 ± 0.9 | 6.0 ± 1.0 |
| 6                        | 4.2 ± 0.9 | 4.5 ± 1.4 | 4.7 ± 1.0 | 4.6 ± 1.1 | 4.6 ± 1.2 | 4.6 ± 1.4 |
| 12                       | 2.2 ± 1.6 | 2.8 ± 1.4 | 2.6 ± 1.0 | 2.1 ± 1.3 | 2.8 ± 1.5 | 2.4 ± 1.2 |
| 18                       | 0.5 ± 1.0 | 1.0 ± 1.5 | 1.2 ± 1.2 | 0.5 ± 0.7 | 0.3 ± 1.3 | 0.7 ± 1.3 |
| SF-36                    | 60 ± 28   | 45 ± 27   | 39 ± 20   | 49 ± 18   | 50 ± 23   | 43 ± 18   |
| General health           | 64 ± 25   | 64 ± 24   | 52 ± 13   | 52 ± 22   | 54 ± 15   | 39 ± 9    |
| Mental health            | 26 ± 18   | 22 ± 15   | 20 ± 13   | 25 ± 14   | 22 ± 11   | 19 ± 12   |

*Data given as mean ± SD score unless otherwise indicated. MLS indicates motor performance test of Schoppe; FM100, Farnsworth-Munsell 100-hue test; TES, total error score; VCTS, Vision Contrast Test System; and SF-36, Medical Outcomes Study 36-item Short-Form Health Survey.*
on gait disturbance, spasticity, hyperreflexia, and/or contrast sensitivity as published previously.

This discrepancy may be caused by 3 major problems shared by all previous studies. First, all were performed in isolated cases or in a small group of at most 8 patients. Only in the study of Sakai et al were diagnoses genetically confirmed. Second, all had only short, if any, placebo-controlled periods, lasting a maximum of 4 weeks. Third, quantitative methods to measure the course of the disease during the trial were rare or missing. Only Sakai et al and Mello and Abott used timed motor activities as an objective measurement in addition to clinical rating scores.

This is the first trial that included 22 patients (more than all previous studies together) with genetically confirmed SCA3/MJD in a placebo-controlled crossover study. We evaluated short- and long-term effects of trimethoprim-sulfamethoxazole therapy for SCA3/MJD. In addition to clinical rating scales and a self-assessment questionnaire, we introduced objective variables, eg, posturography, the motor performance test of Schoppe, the Farnsworth-Munsell 100-hue test, and the Vision Contrast Test System. Even with these well-elaborated and comprehensive methods, we found no significant effects of trimethoprim-sulfamethoxazole in SCA3/MJD patients. Since previous studies investigated only small groups of patients, positive effects of trimethoprim-sulfamethoxazole might have been confined to individual patients or subtypes of SCA3/MJD. Therefore, we performed subgroup analyses to evaluate effects of age, sex, age at onset, duration of the disease, and CAG repeat length on test performance. No clinical subgroup (defined by peripheral neuropathy, spasticity, and extrapyramidal motor signs) improved with trimethoprim-sulfamethoxazole therapy. This point is especially important, because discrepancies between this and previous studies may be attributed to different phenotypes of SCA3 and MJD. Positive effects of trimethoprim-sulfamethoxazole in previous studies were seen for symptoms like spasticity and contrast sensitivity, which SCA3 and MJD have in common. We also included patients with extrapyramidal affection, faciolingual fasciculationlike movements, and (mild) pseudoxephalmelos. These symptoms define the main differences between SCA3 and MJD.

We observed short-term (14-day) effects in a few patients receiving trimethoprim-sulfamethoxazole, but we found similar effects in patients receiving placebo, demonstrating the magnitude of placebo effects in ataxia trials. No patient had concordant improvement throughout the tasks for a treatment period of 6 months.

Sakai and colleagues set up a hypothesis about how trimethoprim-sulfamethoxazole operates in SCA3/MJD. They found biotinier levels to be reduced in cerebrospinal fluid of SCA3/MJD patients. According to results of animal studies, trimethoprim-sulfamethoxazole raises the levels of brain biotinier, which secondarily leads to increased levels of dopamine, norepinephrine, and serotonin. According to Sakai and coworkers, trimethoprim-sulfamethoxazole may exhibit an effect in SCA3/MJD due to these neurotransmitter changes. However, the same authors showed in a later study that the biotinier effect after 10 days in 5 SCA3/MJD patients was substantially worse compared with patients in their trimethoprim-sulfamethoxazole study. The effect did not differ significantly from that of placebo.

This trimethoprim-sulfamethoxazole study is one of the first ataxia treatment trials that takes the genetic nature of the diseases into account. Former investigations mostly examined groups of patients with ataxia and undefined or heterogeneous genetic backgrounds. This may be one reason why an effective therapy for most forms of ataxia is still lacking.

CONCLUSIONS

Using a placebo-controlled, double-blind crossover design, a study period of 6 months, and a homogeneous, genetically determined study population, we concluded that trimethoprim-sulfamethoxazole is not an effective treatment for SCA3/MJD. Recent research tremendously improved our insight into the pathogenesis of ataxia disorders. Since pathogenic pathways differ between forms of ataxia, future drug trials should consider the genetic background of these diseases. Because of the small numbers of patients, placebo-controlled crossover designs should be applied to reduce confounding. With respect to the slowly progressive nature of the disease, long-term studies are necessary to detect effects on the course of the disease. For the same reason, surrogate markers should be found to reflect disease activity or pathogenic factors influencing disease progression.

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REFERENCES


