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A randomized, double-blind study to assess the efficacy of addition of tetracycline to triamcinolone acetonide in the treatment of moderate to severe atopic dermatitis

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Keywords
atopic dermatitis, corticosteroid, Staphylococcus aureus, tetracycline

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Abstract

Objective To assess the efficacy of tetracycline in triamcinolone acetonide ointment compared with triamcinolone acetonide ointment in patients with moderate to severe atopic dermatitis.

Design Randomised, double-blind parallel group study of 8 weeks’ duration.

Setting Outpatient clinic in a university hospital.

Participants Forty-four adult patients with moderate to severe atopic dermatitis (objective SCORAD > 25).

Interventions Initial phase (2 weeks): 3% tetracycline 0.1% triamcinolone acetonide vs. 0.1% triamcinolone acetonide twice daily all over the body. Maintenance phase (6 weeks) 0.1% triamcinolone acetonide once daily for 2 weeks, followed by every other day for 2 weeks. In the last 2 weeks, two applications a week were done. An emollient was used additionally once daily.

Main outcome measures Primary outcomes were the disease severity scores assessed by objective SCORAD and SASSAD at week 2. Secondary outcomes were the objective SCORAD and SASSAD at weeks 4 and 8, and Staphylococcus aureus colonization at weeks 0 and 2.

Results No significant differences in disease severity outcomes were found between the two groups. Both groups showed clinically relevant improvements in disease severity compared with baseline at weeks 2 and 4. At week 8, there was some worsening in disease severity in both groups, but the disease severity was still significantly lower than at the beginning of the study. Improvement of bacterial colonization was seen in 14 (63.6%) out of the 22 patients in the 3% tetracycline 0.1% triamcinolone acetonide group and in 5 (22.7%) out of the 22 patients in the 0.1% triamcinolone acetonide group.

Conclusion The addition of tetracycline was effective on skin colonization by S. aureus but did in our patients with atopic dermatitis not result in a significantly different improvement compared with the group treated without tetracycline.

Introduction

In patients with atopic dermatitis (AD), Staphylococcus aureus can be isolated from 90% of skin lesions and about 75% of clinically uninvolved areas. The presence of S. aureus on the skin can give colonization or induce infection. Williams et al. showed a linear relationship between the density of colonization of S. aureus and the severity of any particular patch of eczema. In AD skin, a deficiency has been shown in the expression of antimicrobial peptides, which are components of the innate immune system needed for efficient and rapid host defense against...
bacteria, fungi and viruses in the skin. This may account for the susceptibility to S. aureus of patients with AD. An exacerbation of AD caused by S. aureus is not limited to the effects of pyogenic infection alone; S. aureus secretes toxins, such as staphylococcal enterotoxin A and B (SEA, SEB) and toxic shock syndrome toxin-1 (TSST-1), at the skin surface, which may act as so-called superantigens in AD. These toxins can contribute to the inflammation of AD by causing continued T-cell activation and release of pro-inflammatory mediators. Exotoxins released from S. aureus can modulate disease severity and dermal T-cell infiltration. More than half of the individuals with AD have specific IgE antibodies to SEA and/or SEB in the serum, which may play a role in exacerbation and prolongation by an IgE-dependent immunoreaction.

Treatment with topical steroids alone will reduce S. aureus levels. Nilsson et al. achieved reduction or elimination of S. aureus only when a high potency steroid was used. For the treatment of AD, lower potency and medium potency preparations are preferred, and combinations with anti-staphylococcal therapy seem desirable. Several studies of a combination of topical antibiotics with corticosteroids clearly showed effectiveness in eradicating bacterial pathogens, but did not show a corresponding difference in clinical response. A comparison between steroid/tetracycline and steroid alone in AD has not yet been published. The aim of this study is to investigate the comparative advantage of adding tetracycline to a standard triamcinolone ointment. The rationale for our choice of tetracycline is that a positive effect of the addition of tetracycline may not only be due to its antibiotic effect but also its anti-inflammatory effect. Dermatological diseases that can be treated with tetracyclines because of its anti-inflammatory or auto-immune aetiology are, for example, bullous pemphigoid and panniculitis. Tetracycline inhibits polymorphonuclear cell and eosinophil chemotaxis, in vivo topically administered tetracycline does suppress neutrophil migration and has an anti-inflammatory effect by suppression of neutrophil chemotaxis.

Methods

Study design

This was a randomised, double-blind parallel group comparison of 8 weeks' duration.

Participants

Participants were all outpatients from Groningen University Medical Center, the Netherlands. We enrolled patients aged 18 years or over with a clinical diagnosis of atopic eczema as defined by Hanifin and Rajka. We included patients that had moderate to severe atopic eczema, disease severity of at least 25 by the objective SCORAD. Exclusion criteria were clinical infection, visible purulent lesions, use of investigational drugs, non-steroidal immunosuppressants, phototherapy, systemic corticosteroids, systemic or topical antibiotics within the past 4 weeks. Other exclusion criteria were topical ultrapotent corticosteroids or tar used in the previous 7 days, known hypersensitivity to any of the study medications, pregnant or breast-feeding women.

The protocol was approved by the local research ethics committee, and written informed consent was obtained from all participants.

Interventions

Initial phase (2 weeks)

We randomised participants to one of the two treatment groups as described in the paragraph on randomization. Participants received either 3% tetracycline 0.1% triamcinolone acetonide in oculentum simplex FNA (ointment base containing cetostearylalcohol, lanolin, vaseline and paraffin) twice daily or 0.1% triamcinolone acetonide in oculentum simplex FNA, twice daily all over the body up to 2 weeks in a double blind setting. No emollients were allowed during these two weeks. Bath oil was provided and used during and after bath/shower (once a week).

Maintenance phase (6 weeks)

All patients entered the maintenance phase. They received 0.1% triamcinolone acetonide ointment (i.e. without tetracycline). Study medication was applied to all sites that were known to have been affected previously. At first, this was applied once daily in the evening for 2 weeks (i.e. weeks 3 and 4 of the study). In weeks 5 and 6, treatment was continued with triamcinolone ointment every other day. In weeks 7 and 8, treatment was continued with two applications a week. Emollient was used once daily during this maintenance phase. Bath oil was continued during/after shower once a week.

Clinical assessments

Patients were seen at 0, 2, 4 and 8 weeks. At each visit, the disease severity was assessed by the objective SCORAD by an observer who was blinded to the treatment allocation. Extent is calculated by using the rule of nine and expresses the skin surface area involved. Intensity items are erythema, oedema/papulation, oozing/crusts, excoriations, lichenification and dryness of uninvolved
Triamcinolone plus tetracycline for atopic dermatitis

Schuttelaar and Coenraads

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skin (0–3 points for each item). The final score is then calculated by the following equation: A/5 + 7B/2. The objective SCORAD index range lies between 0 and 83.

At each visit, disease severity was also assessed by the Six Area, Six Sign Atopic Dermatitis (SASSAD) severity score. This score is obtained by grading six signs (erythema, exudation, excoriation, dryness, cracking and lichenification), each on a scale of 0 (absent), 1 (mild), 2 (moderate), or 3 (severe), at six sites: arms, hands, legs, feet, head and neck, and trunk. The final score is calculated by the sum. The range lies between 0 and 108.

All adverse events observed by the investigator or reported by the patient were recorded.

Bacteriological assessments

On entry and after 2 weeks, a swab was taken of a lesion and sent to a central laboratory (University Medical Center Groningen) for culture. Only *S. aureus* and beta-haemolytic streptococci were considered as pathogens. All swabs yielding a growth of 10 or fewer colonies were regarded as negative.

Outcomes

Primary outcomes were objective SCORAD and SASSAD at week 2.

Secondary outcomes were objective SCORAD and SASSAD at weeks 4 and 8. Another secondary outcome parameter was the bacterial load at week 2. Bacterial efficacy was defined as ‘successful’ if the pretreatment pathogen was eradicated, as ‘failure’ if the pretreatment pathogen persisted.

Sample size

For sample size calculation, we used the results of a pilot study15 carried out at our hospital; this pilot was a randomised study of 4 weeks’ duration in 18 patients comparing triamcinolone ointment with or without 3% tetracycllin, twice daily, for 2 weeks, followed by 2-week triamcinolone only. For the present study to detect a difference of at least 15 points (objective SCORAD) between the two groups, using a two sample *t*-test with a 0.05 two-sided significance level and 80% power, we would need a sample size of 22 participants in each group.

Randomization and blinding

Randomization was computer generated in blocks of four. The list was produced and stored by the clinical trials pharmacist. Treatment packs were prepared and labelled at the pharmacy. Allocation to the treatment groups was concealed to the researcher who used consecutively numbered packs. Participants and assessor were blinded to group assignment during collection of data. Colorant chinoline yellow CI 47005 (0.2%) and AZO rubine red E122 (0.000375%) were used to achieve adequate blinding by making the two ointments exactly similar in appearance.

Statistics

With the Komolgorov-Smirnov test, we checked whether our outcomes had normal distributions. Changes in scores were analysed by the two sample *t*-test. Differences in proportions were tested by the chi-squared test. All tests were two tailed, and *P* ≤ 0.05 was considered as significant. The 95% confidence interval (95% CI) for difference was used to interpret the results.

Results

Study population

The age of the 44 patients evaluated (13 males and 31 females) was 18 to 71 years (mean age, 33.9 years). The patients were randomly allocated to receive either tetracycline-triamcinolone (TT) ointment or triamcinolone (T) ointment. There were 22 patients in the TT group (8 males and 14 females; mean age, 37 ± 18 years). In the T group, there were 22 patients (5 males and 17 females; mean age, 32 ± 9 years).

The objective SCORAD mean (± SD) in the TT Group was 44 ± 13 and in the T group was 48 ± 13. The SASSAD mean (± SD) in the TT Group was 35 ± 13 and in the T group was 37 ± 13.

The two groups were comparable for age and disease severity, but there were more males in the TT group. All 44 patients completed the initial phase (2 weeks) of the study. In the maintenance phase, there were four dropouts (fig. 1). At week 4, there were two dropouts, both out of the T group. The first dropout used a topical antibacterial agent because of folliculitis, and the second had to be withdrawn because he/she received oral corticosteroids for an exacerbation of asthma. These two participants were excluded from the statistical analyses at week 4 (*N* = 42: TT, 22; T, 20).

At week 8, there were another two dropouts: one out of the T group who needed oral antibiotics because of folliculitis and one drop-out out of the TT group who needed oral antibiotics and a potent steroid because of an exacerbation of eczema mainly at the hands. These two patients were excluded from the statistical analyses at week 8 (*N* = 40: TT, 21; T, 19).
Primary outcomes

Clinical efficacy

The initial objective SCORAD (mean ± SD) at week 0 was 46.0 ± 13.0 (TT: 44.4 ± 12.8, T: 47.6 ± 13.3). As shown in fig. 2, after 2 weeks of treatment, the objective SCORAD (mean ± SD) significantly decreased in both treatment groups to 18.5 ± 13.3 (TT: 18.1 ± 13.9, T: 18.8 ± 13.1).

The initial SASSAD (mean ± SD) at week 0 was 36.0 ± 12.9 (TT: 35.1 ± 12.6, T: 36.9 ± 13.4). As shown in fig. 3, after 2 weeks of treatment, the SASSAD significantly decreased in both treatment groups to 12.7 ± 9.3 (TT: 12.5 ± 9.4, T: 12.9 ± 9.5).

Both for the objective SCORAD and for the SASSAD, there was no significant difference between the two treatment groups at week 2.

Secondary outcomes

Clinical efficacy

In total, 42 participants were analysed at week 4 (TT: 22, T: 20). The objective SCORAD (mean ± SD) at week 4 had significantly decreased in both of the two treatment groups to 12.1 ± 9.2 (TT: 11.3 ± 8.5, T: 13.0 ± 10.1). The SASSAD (mean ± SD) at week 4 had significantly decreased in both of the two treatment groups to 10.0 ± 7.9 (TT: 10.5 ± 8.0, T: 9.4 ± 8.0). The difference between the two groups in terms of change from baseline in objective SCORAD or SASSAD was not statistically significant at week 4.

In total, 40 participants were analysed at week 8 (TT: 21, T: 19). The objective SCORAD (mean ± SD) at week 8 had slightly increased in both of the two treatment groups to 16.4 ± 15.3 (TT: 15.7 ± 14.8, T: 17.2 ± 16.1). The SASSAD (mean ± SD) at week 8 had slightly increased in the total
group 10.9 ± 9.9 (TT: 9.7 ± 8.8, T: 12.3 ± 11.1). The SASSAD at week 8 slightly increased in the T group, but not in the TT group. The difference in change in SASSAD between the two treatment groups at week 8 was not significant. At week 8, there was some worsening in disease severity in the total group, but the disease severity was still significantly lower than at the beginning of the study.

The difference between the TT group and the T group in change in objective SCORAD or SASSAD was not statistically significant at the end of the treatment period (figs 2 and 3).

**Bacteriological efficacy**

Swabs for culture were taken from 44 patients at baseline: 22 in the TT group and 22 in the T group. Pathogens were isolated from baseline swabs of 40 patients: 20 (91%) in the TT group and 20 (91%) in the T group. In all isolates, the pathogen was *S. aureus*. At the end of week 2 (initial phase) in the TT group, 6 (27%) out of 22 patients had *S. aureus* present. In the T group, 15 (68%) out of 22 patients evaluated had *S. aureus* present. Bacterial efficacy was assessed as successful in 14 (64%) out of 22 patients who had received TT, all of whom had a proven colonization at baseline. In the T group, 5 (23%) out of 22 patients had the bacterial efficacy assessed as successful.

The difference in bacteriological efficacy, tested by the chi-squared test, was significant between the two treatment groups (*P* = 0.004).

### Table 1: Adverse events

<table>
<thead>
<tr>
<th></th>
<th>TT No. patients (%)</th>
<th>T No. patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total assessed</td>
<td>22</td>
<td>22</td>
</tr>
<tr>
<td>With adverse events</td>
<td>4 (18)</td>
<td>14 (64)</td>
</tr>
<tr>
<td>Adverse events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate/severe folliculitis</td>
<td>3 (14)</td>
<td>11 (50)</td>
</tr>
<tr>
<td>With <em>S. aureus</em></td>
<td>3 (14)</td>
<td>9 (41)</td>
</tr>
<tr>
<td>Negative bacterial swab</td>
<td>0</td>
<td>1 (4.5)</td>
</tr>
<tr>
<td>No bacterial analysis</td>
<td>0</td>
<td>1 (4.5)</td>
</tr>
<tr>
<td>Very mild folliculitis</td>
<td>1 (4.5)</td>
<td>3 (14)</td>
</tr>
<tr>
<td>With <em>S. aureus</em></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Negative bacterial swab</td>
<td>1 (4.5)</td>
<td>3 (14)</td>
</tr>
<tr>
<td>No bacterial analysis</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**Usage of ointment**

In the first 2 weeks, the mean use of ointment was 462 g in the TT group and 349 g in the T group. This difference was not statistically significant.

**Adverse events**

Table 1 presents the adverse events reported during the trial. In the total group, 18 out of 44 patients reported folliculitis. Fourteen out of 18 patients had moderate to severe folliculitis, whereas 4 out of 18 patients revealed very mild folliculitis (some pustules). Three out of 14 patients with moderate to severe folliculitis belonged to the TT group; 11 out of 14 patients were from the T group. From the three patients with folliculitis in the TT group, all three had *S. aureus* in the bacterial swab. From the 11 patients with folliculitis in the T group, nine patients had *S. aureus* in the bacterial swab; 1 patient had a negative swab; and in 1 patient, no bacterial analysis was done. The 4 out of 18 patients with a very mild folliculitis had all a negative bacterial swab. One of the four was from the TT group, three out of the four from the T group.

In both the TT and T groups, adverse events were probably related to treatment. Adverse events (folliculitis) was a reason for dropout in one patient from the TT group and one patient from the T group.

**Discussion**

Several studies have investigated whether anti-staphylococcal therapy has an influence on the activity of AD. Systematic reviews on antibiotic/steroid combinations are published by Hoare in 2000 and by Williams in 2003. They both concluded that there is lack of evidence...
that topical steroid/antibiotic combinations are more effective than topical steroids alone in improving clinical signs and symptoms of AD. Williams differentiated clinically infected atopic eczema and non-clinically infected eczema and reported that there was no evidence for both. However, in these studies, there was no clear definition for infected and non-infected AD. Nevertheless, if there is obvious clinical infection with pustular lesions, anti-staphylococcal therapy in addition to the normal AD treatment is common practice.

The present study is the first study on the topical treatment with a combination of tetracycline and triamcinolone in patients with AD. There are many advantages of a topical route for antibacterial therapy: one advantage is the delivery of a higher concentration of an antibacterial agent to the skin than by systemic therapy. Topical use also avoids systemic reactions. Disadvantages of topical antibiotics are the potential of sensitization. The topical antibacterials neomycin, fusidic acid and mupirocin have shown to cause allergic contact dermatitis. Another disadvantage is the potential for development of resistant organisms; this has been published for fusidic acid and for mupuricine. We used tetracycline as a topical antibacterial, not only because of the anti-inflammatory effect but also because it has a low risk for sensitization. Systemic resorption of tetracycline is negligible.

The principal aim of the present study was to study the efficacy of a 2-week treatment with tetracycline-triamcinolone ointment in patients with moderate to severe AD without overt signs of infection (pustular lesions). We were also able to investigate a maintenance phase during the subsequent 6-week follow-up period in which no topical tetracycline was used. Overall, both treatments were similarly very effective as judged by the different clinical severity parameters. We conclude that the benefit of anti-staphylococcal treatment in colonized patients without overt signs of infection is not shown. This study had an 8-week duration with low-intermittent steroid dose only in the last 2 weeks. A possible effect of antibiotics on prevention of relapse after these 8 weeks cannot be excluded.

Bacteriological evaluation was significantly in favour of TT \((P = 0.004)\), which indicates that tetracycline is effective on skin colonization with \(S. aureus\). Nevertheless, this did not lead to a difference in disease severity between the two treatment groups at 2, 4 and 8 weeks. We did not include patients with clinically infected eczema visible by pustular lesions; if we had enrolled only patients with overtly infected AD, we might have detected a difference in disease severity between the two groups.

In our study, the majority of adverse events was moderate folliculitis in the T group, most probably associated with treatment. Although folliculitis was an important adverse event in the T group, it did not result in a difference in disease severity. In this study, a high amount of corticosteroid ointment was used all over the body in the first 2 weeks \((TT: 462 \text{ g}, T: 349 \text{ g})\). Possibly, there was some occlusive effect of the ointment leading to a lot of folliculitis in the T group.

A possible explanation for the absence of a difference in disease severity is the total amount of ointment used in the first 2 weeks. Probably, the high topical dose of corticosteroid had a very good effect on disease activity; apparently, the role of the staphylococcal component was too marginal to cause a difference in clinical effect or the staphylococcal component was overruled by the high dose of topical corticosteroids. Maybe, bacterial clearance is not critical for substantial clinical improvement, and maybe, the importance of bacterial mechanisms is questionable in the context of anti-inflammatory treatment with topical steroids.

**References**


