Title: Recombinant human deoxyribonuclease for the treatment of acute asthma in children

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Running title: rhDNase in acute childhood asthma

Word count manuscript: 3224
Word count abstract: 261
Key Words: asthma exacerbation, treatment, dornase alfa, controlled clinical trial, pediatric

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ABSTRACT

Background: Airway obstruction in acute asthma is the result of airway smooth muscle contraction, inflammation and mucus plugging. Case reports suggest that mucolytic therapy might be beneficial in acute asthma. The aim of this study was to determine the efficacy of the mucolytic drug recombinant human deoxyribonuclease (rhDNase) in addition to standard treatment at the emergency department in children with an asthma exacerbation.

Methods: In a multicenter randomized double-blind controlled clinical trial, 121 children brought to the emergency room for a moderate-to-severe asthma exacerbation were randomly assigned to receive either a single dose of 5 mg nebulized rhDNase or placebo following the second dose of bronchodilators. An asthma score (scale 5 to 15) was assessed at baseline and at 1, 2, 6, 12 and 24 hours. The primary outcome variable was the asthma score 1 hour after the study medication.

Results: One hour after the study medication, the asthma score in the rhDNase group showed a 1.0 (0.5 to 1.6) points adjusted mean decrease from baseline (95%CI), vs. 0.7 (0.3 to 1.2) points in the placebo group; mean difference (95% CI)= 0.4 (-0.2 to 1.0) points; P=0.23. The asthma score over the study period of 24 hours also did not significantly differ between the rhDNase and placebo group (mean difference = 0.2 (-0.3 to 0.7) points, P=0.40). Duration of oxygen supplementation and number of bronchodilator treatments in the first 24 hours were similar in both groups.

Conclusion: Adding a single dose of nebulized rhDNase to standard treatment in the emergency room has no beneficial effects in children with moderate-to-severe acute asthma. (Controlled-trials.com number, ISRCTN81874766)

INTRODUCTION

The standard treatment for children with acute asthma consists of frequent nebulization of bronchodilators and early systemic corticosteroid therapy. [1] Since airway obstruction by viscous mucus is one of the pathophysiological features of acute asthma, [2-4] a logical approach to therapy might be to use a mucolytic agent. It is the DNA present in mucous plugs following lysis of inflammatory cells that contributes to increased viscosity and adhesiveness of the mucus, [5] and free DNA was indeed noted in mucus of subjects with acute asthma. [6] Such mucus can be liquefied by recombinant human deoxyribonuclease (rhDNase=dornase alfa), which cleaves extracellular DNA. [7, 8] The efficacy of rhDNase has been well documented in patients with cystic fibrosis, [9] and several publications suggest it is also effective in children with severe acute asthma with [10-12] or without atelectasis. [11, 13] We performed a randomized, controlled trial to determine whether nebulized rhDNase added to standard treatment would improve symptoms in children with moderate-to-severe acute asthma.
METHODS

Patients
Eligible subjects for this study were children aged 2-18 years with symptoms of acute asthma whose asthma score (Table 1) at arrival in the emergency room was $\geq 8$ and who required at least 2 nebulizing treatments with bronchodilators. We did not include children with another cause of dyspnoe, with a chronic cardiopulmonary disease other than asthma, or with a neurological condition.

Table 1. Methods of calculating the Asthma Score and the severity of asthma*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Asthma Scoring</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 point</td>
</tr>
<tr>
<td>Respiratory rate</td>
<td></td>
</tr>
<tr>
<td>(breaths/min)</td>
<td></td>
</tr>
<tr>
<td>2 – 3 yr</td>
<td>$\leq$ 34</td>
</tr>
<tr>
<td>4 – 5 yr</td>
<td>$\leq$ 30</td>
</tr>
<tr>
<td>6 – 12 yr</td>
<td>$\leq$ 26</td>
</tr>
<tr>
<td>$&gt; 12$ yr</td>
<td>$\leq$ 23</td>
</tr>
<tr>
<td>Haemoglobin saturation</td>
<td></td>
</tr>
<tr>
<td>(%)</td>
<td>$&gt; 95$ with room air</td>
</tr>
<tr>
<td>Auscultation</td>
<td>Normal breathing or end-expiratory wheezing</td>
</tr>
<tr>
<td>Retractions</td>
<td>None or intercostal</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>Speaks in sentences or coos and babbles</td>
</tr>
</tbody>
</table>

Severity of Asthma

<table>
<thead>
<tr>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma Score</td>
<td>5 – 7</td>
<td>8 – 11</td>
</tr>
</tbody>
</table>

* The overall asthma score (scale, 5 to 15 points) was calculated by adding the scores for each of five variables: respiratory rate, haemoglobin saturation, auscultation, retractions, and dyspnea. [14]

Study design
This was a multicenter, double-blind, parallel-group randomized study comparing the effect of inhaled rhDNase with placebo on the asthma score in children aged 2-18 years with symptoms of acute asthma. Setting: emergency rooms of eight participating hospitals in the Netherlands. Time period: between September 2005 and October 2006. The study was approved by the ethics review boards of all eight centers and written parental informed consent was obtained for each child.
All children at arrival received a dose of nebulized bronchodilators (< 4 years old: 2.5 mg Salbutamol, 0.25 mg Ipratropium; ≥ 4 years old: 5 mg Salbutamol, 0.5 mg Ipratropium). After parental consent, patients were randomly assigned to receive a single nebulization of 5 mg rhDNase (5 ml solution of 1mg/ml rhDNase, Roche Basel Switzerland) or 5 mg placebo (5 ml sodium chloride 0.9%) following the second nebulization of bronchodilators (Fig. 1). We opted for a dose of 5 mg in anticipation of the expected suboptimal lung deposition in young children with airways obstruction due to asthma. Study medication was prepared by the hospital pharmacists and had identical appearance and aroma. The vials with study medication were stored in a refrigerator located on the emergency department.

Study medication was administered with the use of a jet nebulizer using a mouthpiece when possible or through a firmly applied facemask at a constant oxygen supply rate of 6-8 liters per minute from a wall outlet. The same nebulizing equipment (Pari LC Star®, Pari GmbH, Germany) was used in all participants.

Randomization was carried out in the hospital pharmacies of the participating hospitals, using a random table sample with blocks of four numbers prepared by the study statistician. Throughout the study, physicians, nurses, parents and the trial coordinator remained unaware of the treatment assignment.

The dosing interval of nebulized bronchodilators was determined by the attending physician based on symptoms severity and clinical improvement rate.

Systemic corticosteroids (1 mg of prednisolone per kg of body weight as a starting dose, and subsequently 1-2 mg / kg /day for 5 to 7 days, to a maximal dose of 60 mg/day) were given after the second dose of bronchodilators, according to Dutch national asthma guidelines.

On the child’s arrival at the emergency department (TA), the attending physician recorded the clinical history, including previous admissions for asthma, duration and possible triggers of the current symptoms, and medication use.

Vital signs, the need for supplemental oxygen and the asthma score were assessed as well at TA, and next just before the nebulization of the 2nd dose of bronchodilators that was followed by the single dose of study medication (T0). The asthma score was subsequently assessed at 1 ± 0.25 hour (=T1), 2 ±0.5 (=T2), 6 ± 1 (=T6), 12 ± 2 (=T12) and 24 ±2 hours (=T24) after nebulization of the study medication (see Fig.1).

Supplemental oxygen was started when haemoglobin saturation was consistently lower than 93 percent, and was stopped when saturation was consistently above 92 percent.

Total number of nebulizer treatments in the first 24 hours after the study medication, time until discharge and duration of oxygen supplementation were recorded.

The decision to admit or discharge the child was up to the discretion of the treating physician. If the child was discharged home from the emergency department or within 24 hours after admission, the researcher three to five days later informed whether any subsequent visits had been made to a medical facility within 72 hours after the initial presentation.

Efficacy endpoints
The primary outcome measure was the asthma score 1 hour after the study medication. We used the asthma score developed by Qureshi and colleagues [14] in which respiratory rate, haemoglobin saturation, auscultatory findings, retractions and dyspnea are scored on a three-point scale, yielding a total score ranging from 5 (mild) to 15 (severe) (Table 1). A previous study showed good interrater reliability of this asthma score (Pearson correlation statistic, 0.92). [14] The asthma score had
been introduced as a clinical tool in all participating centers before the start of the study, so all participating physicians were experienced in using the score. The secondary outcome measures were the mean asthma scores at 2, 6, 12 and 24 hours after the study medication, the need for hospital admission, the duration of admission, the duration of supplemental oxygen and the number of nebulizer treatments in the first 24 hours.

**Estimate of sample size**
In a pilot study of 26 children, the asthma score decreased (mean (SD)) 0.8 (1.4) points between the time points T0 (before 2nd dose of bronchodilators) and T1 (1 hour after the 2nd dose bronchodilators). To demonstrate an additional 0.8-point decrease at T1 at a 5% significance level for a two-sided test with 80% power, this would require 100 patients, with 50 children in each group.

**Statistical analysis**
Data were analyzed on an intention-to-treat basis. Differences between baseline group characteristics and secondary outcome measures were assessed by chi-square or Fisher’s exact test and the Mann-Whitney test, as appropriate. Main analyses of between-group comparisons regarding asthma score changes were performed by repeated-measures of analysis of variance (RmANOVA), with baseline (T0) asthma score, age, sex and study center as covariates. In calculating mean values of the asthma score, the individual asthma score after discharge was arbitrarily set at 5 points. Linear interpolation of the asthma score was used if scores had been assessed outside the pre-specified time range. Linear interpolation was also used when the item ‘dyspnea’ could not be assessed accurately because the child was asleep at the time of observation. The analysis was performed with SPSS software (version 11.5) and SAS PROC MIXED. For all the analyses, a two-tailed P values of less than 0.05 was considered to indicate statistical significance.

**RESULTS**
A total of 121 children were enrolled and randomly assigned to treatment groups: 62 to rhDNase and 59 to placebo (Fig. 2). Demographic and baseline clinical characteristics of the two groups showed no significant differences (Table 2). At arrival, all children were treated with a dose of nebulized bronchodilators. Overall, the asthma score decreased after this first nebulizer treatment with (mean (95% CI)) 1.55 (1.32 to 1.79) points (Fig. 3). The study medication in the rhDNase group was given (median (IQR)) 1.3 (1.0 to 2.0) hours after arrival and in the placebo group after 1.3 (1.0 to 1.8) hours (P=0.95).
Table 2. Baseline characteristics of the children on arrival at the emergency department

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>RhDNase (N=61)*</th>
<th>Placebo (N=59)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex – M/F</td>
<td>40 / 21</td>
<td>37 / 22</td>
</tr>
<tr>
<td>Age (years)</td>
<td>4.4 (2.0 – 16.3)</td>
<td>4.5 (2.1 – 15.4)</td>
</tr>
<tr>
<td>Duration of symptoms – no. of patients (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 12 hours</td>
<td>19 (31)</td>
<td>19 (32)</td>
</tr>
<tr>
<td>12 - 24 hours</td>
<td>29 (48)</td>
<td>29 (49)</td>
</tr>
<tr>
<td>&gt; 24 hours</td>
<td>13 (21)</td>
<td>11 (19)</td>
</tr>
<tr>
<td>Asthma medication, current use – no. of patients (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No medication</td>
<td>17 (28)</td>
<td>11 (19)</td>
</tr>
<tr>
<td>Short-acting beta2-agonist only</td>
<td>19 (31)</td>
<td>25 (42)</td>
</tr>
<tr>
<td>Corticosteroid</td>
<td>24 (39)</td>
<td>22 (37)</td>
</tr>
<tr>
<td>Combination (steroid + long-acting beta2-agonist)</td>
<td>7 (11)</td>
<td>6 (10)</td>
</tr>
<tr>
<td>Leukotriene antagonist</td>
<td>3 (5)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Systemic corticosteroid</td>
<td>2 (3)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Asthma score (scale 5 – 15)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arrival at hospital (TA)</td>
<td>12 (8 – 15)</td>
<td>12 (8 – 15)</td>
</tr>
<tr>
<td>Baseline (T0)</td>
<td>10 (5 – 14)</td>
<td>10 (7 – 15)</td>
</tr>
<tr>
<td>Severity of asthma – no. of patients (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TA: Severe (score 12 – 15)</td>
<td>37 (61)</td>
<td>33 (57)#</td>
</tr>
<tr>
<td>Moderate (score 8 – 11)</td>
<td>24 (39)</td>
<td>25 (43)#</td>
</tr>
<tr>
<td>T0: Severe (score 12 – 15)</td>
<td>18 (30)</td>
<td>17 (29)</td>
</tr>
<tr>
<td>Moderate (score 8 – 11)</td>
<td>38 (62)</td>
<td>38 (64)</td>
</tr>
<tr>
<td>Mild (score 5 – 7)</td>
<td>5 (8)</td>
<td>4 (7)</td>
</tr>
</tbody>
</table>

Data expressed as median (range), unless otherwise specified.
TA = arrival at the emergency department; T0 = before nebulization of the 2nd dose of bronchodilators and the subsequent single dose of study medication.
* Study data were not available for one out of 62 patients in the rhDNase group.
# The asthma score at arrival (TA) was missing in 1 patient in the placebo group.

**Primary endpoint**

Both groups showed a similar improvement in the asthma score during the first 24 hours (Fig. 3). At baseline, the mean asthma score was 10.2 in the rhDNase-treated group vs. 10.4 in the placebo group. One hour after nebulization of the study medication the asthma score in the rhDNase group showed a 1.0 (0.5 to 1.6) point
adjusted mean decrease from baseline (95%CI) vs. 0.7 (0.3 to 1.2) points in the placebo group; mean difference = 0.4 (-0.2 to 1.0) points; P=0.23.
Overall, compared to baseline the asthma score one hour after the study medication had improved in 72 children (37 in the rhDNase group, 35 in the placebo group), had not changed in 21 (12 rhDNase, 9 placebo) and had worsened in 27 children (12 rhDNase, 15 placebo); P=0.68.

Repeated-measures analysis of variance showed no significant difference between the groups in the asthma score over the whole period of 24 hours: the adjusted mean decrease (95%CI) was 4.1 (3.6 to 4.6) points in the rhDNase group and 3.9 (3.3 to 4.5) points in the placebo group; mean difference = 0.2 (-0.3 to 0.7) points; P=0.40.
The item ‘dyspnea’ of the asthma score could not be assessed accurately in some children asleep at the time of observation. In these cases, linear interpolation of the item ‘dyspnea’ was used in order to obtain a total asthma score. An analysis in which the interpolated asthma scores of sleeping children were not included, showed similar results (data not shown).

Subgroup analyses
There was no significant effect modification by baseline asthma score, age, or the use of anti-inflammatory medication prior to the asthma attack (P=0.06; P=0.94; P=0.84, respectively). A separate analysis of the subgroup of children with a severe asthma score (≥ 12) at baseline (n=35) also showed no significant difference in the asthma score over time between the rhDNase group and the placebo group (mean difference (95% CI) = -0.1 (-1.3 to 1.1); P=0.85).

Secondary endpoints
Need for hospital admission
Most of the children (88%) were admitted to hospital. Only 14 children (6 in the rhDNase group, 8 in the placebo group) were discharged home from the emergency department. Four of the admitted children (4%) required intensive care (2 in the rhDNase group, 2 in the placebo group).
Thirty-one children were discharged within 24 hours after study entry (14 in the rhDNase group, 17 in the placebo group). Three of those in the placebo group were readmitted to the hospital within 72 hours of discharge, because symptoms had worsened (1 child after one day, 2 children within 1.5 hours after discharge) vs. none of those in the rhDNase group (P=0.23).

Time until discharge
Time until discharge did not differ between the rhDNase group and the placebo group (geometric mean (SE): 36.9 (1.2) vs. 33.9 (1.2) hours; mean difference (95%CI) = 0.92 (0.55 to1.54) hours, P=0.75.)

Duration of oxygen supplementation
Proportions of children requiring oxygen supplementation to maintain an haemoglobin saturation ≥93 % were similar in both groups over time (Fig. 4). The geometric mean (SE) time of oxygen supplementation did not differ; for both groups it was 28.3 (1.2) hours, P=0.99.
Co-interventions
Overall, there was no difference between both groups in the number of treatments with nebulized bronchodilators given in the first 24 hours during hospital stay. Children in the rhDNase group received a median (IQR) number of 7 (5.5 to 11.0) nebulizer treatments compared to 8 (6.0 to 10.0) in the placebo group (P=0.81). In the subgroup of children who were discharged within 24 hours (n=30), the number of nebulizer treatments did not differ between the rhDNase and placebo group (2 (0.0 to 5.3) and 2.5 (0.0 to 7.0) respectively, P=0.40). Prednisolon was administered to 90% of all children (55 of 59 in the placebo group and 53 of 61 in the RhDNase group). Twelve patients did not receive a course of systemic steroids (5 were discharged home from the emergency department after their symptoms had resolved following the dose of study medication).

Safety data
One child had a transient desaturation with an increase in dyspnea and tachypnea directly after the initiation of the nebulization with rhDNase, which resolved quickly after the nebulization was stopped. Hoarseness was reported in two children (1 in each group). Asthma scores for 27 children were higher (worsened) one hour after nebulization of the study medication as compared to baseline (12 children in the rhDNase group vs. 15 in the placebo group, P=0.47).

DISCUSSION
We report the first randomized double-blind controlled trial of nebulized rhDNase in children (aged 2-18 years) with an acute asthma exacerbation. The findings show no evidence to suggest that nebulization with the mucolytic rhDNase alleviates symptoms in children brought to the emergency room for moderate-to-severe acute asthma. We thus must reject our hypothesis that rhDNase is an effective additional treatment for children with acute asthma. This was based on the important role of mucus plugs in the pathophysiology of acute asthma, [2, 3] and the finding that DNA content is increased in mucus of patients with acute asthma. [6]

Up till now, only case reports have suggested benefit from rhDNase in children with a status asthmaticus unresponsive to conventional therapy [10-13] and in children with acute severe asthma treated at the emergency department. [11] Intervention with rhDNase, administered endotracheally or by means of a bronchoscope, was safe and improved ventilator settings, [12, 13] arterial blood gas values, [13] and resolved atelectasis [10, 12] in the children receiving intensive care. Nebulization of rhDNase in 3 children brought to the emergency department improved lung function parameters, the effectiveness of coughing and resolved atelectasis. [11] There may be several explanations for the lack of effect of rhDNase in our study. Firstly, children might have had relatively mild disease, with too little mucus plugging for rhDNase to be effective. Indeed, although all selected children had a moderate-to-severe asthma exacerbation and required at least two doses of bronchodilators, only four children required intensive care treatment. However, a subgroup analysis of children with an asthma score of at least 12 points after their first bronchodilator dose, also could not demonstrate an effect of rhDNase. Because this analysis is underpowered (n=35), definite conclusions about the effect of rhDNase in severe acute asthma cannot be drawn. We cannot exclude that rhDNase might have been effective in children with a more severe asthma exacerbation and/or atelectasis, or in
those requiring intensive care admission. Answering this question would require a separate study.

In earlier case reports, rhDNase was administered to children with a severe asthma exacerbation who also had atelectasis. We had no information about the presence or severity of atelectasis in our population, because it was not considered necessary or ethical to perform two chest radiographs during treatment at the emergency department.

A second explanation might be that the amount of DNA present in the mucus was too low for rhDNase to be effective. The average DNA content of mucus in patients with stable asthma is higher than that in healthy controls (7.1 versus 3.6 µg/ml). [15] Even higher levels were found in patients with an asthma exacerbation (0.5 mg/ml). [6] Mucus DNA content in asthma patients is much lower, however, than in cystic fibrosis patients (3-14 mg/ml) [16] in whom beneficial effects of rhDNase have clearly been documented. [9]

A third explanation could be suboptimal lung deposition of rhDNase in children with bronchial obstruction, resulting in deposition of rhDNase mainly in the more central airways, [17] and not reaching the peripheral airways. To compensate for suboptimal deposition, patients received a dose of 5 mg – twice the dose that cystic fibrosis patients use as maintenance treatment. Arguably, it could have been more effective to administer study medication directly at arrival or following the first dose of bronchodilators rather than after the second dose, or to use repeated nebulizations of study medication instead of one. However, we think that other timing or dosing frequency would not change the results, since neither the symptom scores at all time points, nor any of the secondary endpoints differed between the groups. Moreover, a single dose of rhDNase has an effect of many hours. [18]

Finally, as diagnosing asthma in preschool children is difficult, part of our study population might have had ‘exclusive viral wheeze’ and not asthma. The exact role of mucus plugging in the pathophysiology of airway obstruction in children with ‘exclusive viral wheeze’ has not been investigated to the best of our knowledge. Our study focused on current emergency clinical practice, which does not take into account the child’s asthma phenotype.

Most of the participating hospitals routinely admitted children with an acute asthma exacerbation who required at least two doses of nebulized bronchodilators. Therefore it was not meaningful to assess the effect of rhDNase on the admission rate. Even if longer observation in the emergency room would have been possible, we likely would not have found a positive effect of rhDNase on the admission rate, seeing that the decision to admit a child is based on the symptoms and that we found no significant effect of rhDNase on the asthma score over time.

In this study, the administration of rhDNase in acute asthma appeared to be safe. It was stopped in one case of temporary desaturation with an increase in dyspnea and tachypnea directly after start of the nebulization. The mechanism of this desaturation is unclear, but we speculate it might have been caused by the child’s inability to clear mucus effectively after quick liquefaction by rhDNase.

Because our study population reflects the population of children with acute asthma treated in the emergency rooms of district and tertiary care hospitals, our results can be generalized to the large majority of children with a moderate-to-severe acute asthma exacerbation. Further studies on the effect of rhDNase in children with acute asthma requiring intensive care or with large atelectasis are still needed.
In conclusion, our study shows that a single dose of nebulized rhDNase in addition to nebulized bronchodilators and systemic steroids is not effective in the treatment of children with moderate-to-severe acute asthma.

Acknowledgment
The authors thank the children, their parents, and the staff of the eight participating centers.

Funding:
Roche B.V., the Netherlands provided an unrestricted grant for this study, and financed the study medication. Pari GmbH, Germany donated the nebulizing equipment. The study sponsors were not involved in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Figure Legends

Figure 1. Study design

Figure 2. Enrolment, random assignment, follow-up, and analysis

Figure 3. Mean Asthma Scores during study
TA = arrival at the emergency department; T0 = before the 2nd dose of bronchodilators and the subsequent single dose of study medication. Study medication was administered after a median of 0.5 hours after the assessment of the asthma score at T0. The asthma scores at T1, T2, T6, T12 and T24 were assessed at 1, 2, 6, 12 and 24 hours after nebulization of the study medication, respectively. Data given are ANOVA estimates (with standard errors). At all time points, the number of patients in each treatment group for whom an asthma score was available is noted above the horizontal axis. P-values for differences between study arms at the various time points are all >0.20.

Figure 4. Need for supplemental oxygen during the first 24 hours
Patients (% of total) requiring supplemental oxygen to maintain an haemoglobin saturation of ≥ 93%. TA = arrival at the emergency department; T0 = before nebulization of the 2nd dose of bronchodilators and the subsequent single dose of study medication; T1, T2, T6, T12 and T24: 1, 2, 6, 12 and 24 hours after nebulization of the study medication, respectively.
REFERENCES

Placebo group

RhDNase group

**Arrival at hospital (TA)**
- Asthma Score
- Consent

**Baseline (T0)**
- Asthma Score

<table>
<thead>
<tr>
<th>Time (T)</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>T = 1 hour</td>
<td>Asthma Score</td>
</tr>
<tr>
<td>T = 2 hours</td>
<td>Asthma Score</td>
</tr>
<tr>
<td>T = 6 hours</td>
<td>Asthma Score</td>
</tr>
<tr>
<td>T = 12 hours</td>
<td>Asthma Score</td>
</tr>
<tr>
<td>T = 24 hours</td>
<td>Asthma Score</td>
</tr>
</tbody>
</table>

**Bronchodilators and systemic steroids according to treatment guidelines**

**1st dose bronchodilator**
- Randomization:
  - 1 dose of study medication

**2nd dose bronchodilator**
121 patients randomly assigned to study groups

59 Assigned to control
   59 Received study medication
      59 Included in intention-to-treat analysis

62 Assigned to rhDNase
   62 Received study medication
      1 No study data available
      61 Included in intention-to-treat analysis
Recombinant human deoxyribonuclease for the treatment of acute asthma in children

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