




Hypersensitivity pneumonitis: Lessons from a randomized controlled trial in children

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Abstract

Introduction: Hypersensitivity pneumonitis (HP) in children is a severe interstitial lung disease and potentially, a chronic condition, if not treated appropriately. No evidence-based guidelines are available; in particular, the role of systemic glucocorticoid therapy is unclear.

Methods: The aim of this randomized, double-blind, placebo-controlled, parallel-group, multi-center, phase II trial in pediatric HP was to assess the outcome of HP in children after 6 months of treatment and to compare 3 months of treatment with oral prednisolone or placebo.

Results: After 1.5 years and the inclusion of only four children, we terminated the study prematurely. Two of the children randomized to prednisolone did not achieve the predefined response of FVC to normal. One child treated with placebo recovered to normal, similar to another child treated with prednisolone. All children treated with steroids developed drug-related side effects.

Discussion: This uncompleted study illustrates the urgent medical need for evidence-based treatment protocols for this condition. We discuss the hurdles which were specific for completion of this trial in a rare condition. Among other options, we suggest the inclusion of children into an all-age study of HP, as in adults the same questions are unanswered.

KEYWORDS

clinical trials, interstitial lung disease (ILD)

Martin Wetzke and Elias Seidl shared the last authorship.

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1 | INTRODUCTION

Hypersensitivity pneumonitis (HP), also called exogenous (extrinsic) allergic alveolitis, is a complex pulmonary disorder caused by IgG-mediated inflammation against various inhaled allergens to which individuals have previously been sensitized.^{1,2} Due to narrow age range and limited environmental exposures, that is, bird and fungus antigens, the disease is less frequent in children which makes the diagnostic effort even more challenging than in adults.³⁻⁶ Particularly, if diagnosis and treatment are delayed, the disease may become chronic, progressive, and sometimes fatal (29% at 5 years).⁷⁻⁹ Removing the patient from the suspected etiologic exposure is essential but cumbersome and may frequently be incomplete. Often, high levels of bird antigens can be detected in the domestic environment over a prolonged period even though the antigen has been removed and the environment has been cleaned.¹⁰ Chronic exposure can lead to progressive respiratory failure requiring lung transplantation early in life.¹¹

Treatment of HP is solely empirical and primarily based on allergen elimination and anti-inflammatory treatments.² There is only one randomized clinical trial in 36 adult patients with acute HP¹² which demonstrated that the initial recovery of the diffusion capacity but not FEV1 or FVC, was somewhat more rapid with systemic corticosteroids, whereas recurrent attacks were more frequent. A huge disadvantage of glucocorticosteroids or other immunosuppressive treatments is that reduced and persistent allergen exposure can be masked and thus, if undiscovered, may drive allergic inflammation and slow but continuous development of lung fibrosis, whereas symptoms and lung function are improved.

In children beyond the age of 2 years, more than half of all the new cases of interstitial lung diseases in Germany were due to HP.¹³ Among the 23 children with confirmed pediatric HP identified over a 3-year surveillance epidemiologic study, 7 of them have already developed a chronic disease state at the initial presentation including clubbing.³ Despite treatment with prolonged courses of systemic steroids, outcome was not favorable in all children.

Based on the knowledge of HP in children and because at least 50% of the children with newly diagnosed HP are not diagnosed appropriately and a majority is treated in a non-standardized manner with oral glucocorticosteroids,³ we proposed a randomized study design closely linked to current clinical needs.¹⁴ The primary objective was to evaluate the outcome of HP at 6 months, comparing oral treatment with systemic steroids or placebo. Secondary objectives included evaluating allergen elimination, safety of the treatments, and several outcome variables never assessed in chILD trials before.

We initiated this trial in the frame of the chILD-EU project (FP7-305653). Objective of one of its work packages was to identify areas of most urgent need for clinical studies, to suggest appropriate trial designs, and to put them into practice as much as possible. This should establish the basis to obtain additional funding by demonstrating feasibility. Because the goal of the work package was already achieved and no additional funding was acquired in time, the study was concluded prematurely. Whereas we did not achieve whole completion of the study and its goals, nevertheless, very important data were obtained and are reported by this study. In addition, we summarize our experience made with this investigator-initiated trial in a rare condition.

2 | METHODS

2.1 | Trial design and participants

This study was a prospective, multicenter, 1:1 randomized, double-blind, placebo-controlled parallel-group study (Figure 1). Subjects included patients aged 3–25 years with (1) newly diagnosed HP, (2) unchanged inhaled steroids if on; if off, no plans to introduce them in the following 6 months, and (3) agreement to home visit by an independent study physician. HP was diagnosed (and independently confirmed by an expert panel) in the presence of at least four of the following seven criteria: (a) history of appropriate allergen exposure, (b) restrictive lung function testing (FVC < 80% predicted for age and FVC/FEV1 < 1)(usually > 5 years), (c) positive serum precipitins for bird, fungus, (d) lymphocytosis (>20%) in BAL, (e) HRCT with characteristic nodular, linear or reticular opacities, ground-glass pattern with increased attenuation, (f) lung biopsy demonstrating lymphocytic alveolitis, bronchiolitis, and non-caseating histiocytic granulomatous, (g) controlled allergen exposure followed by characteristic reaction, including fever, coughing, restriction on lung function, hypoxemia/desaturation at rest or with exercise. The study was set up at the European Management Platform for Childhood Interstitial Lung Disease (www.childeu.net).¹⁵ Seven Pediatric Pulmonology Departments of University Children's hospitals participated (Munich, Hannover, Essen, Frankfurt, Giessen, Bochum, and Leipzig).

Antigens responsible for HP were carefully identified (both, detection of allergen in home and demonstration of appropriate precipitins in serum) and eliminated with the help of a detailed ground plan of the property where the family lived. A trained member of the study team used a structured checklist to identify all possible allergen sources in the environment and a complete allergen

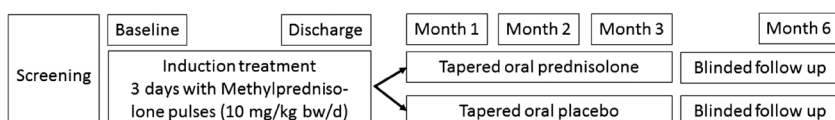


FIGURE 1 Schematic trial design

elimination was done while the patient was hospitalized. Success of antigen elimination was controlled by an independent home visit by the study team (trial Day 56 [49–63]).

After inclusion into the study and baseline measurements, all patients received an induction treatment with 10 mg/kg body weight (max. 1 g) methylprednisolone intravenously on three consecutive days. Then, patients were randomized to prednisolone (0.5 (Month 1), 0.25 (Month 2), 0.125 (Month 3) mg/kg body weight) or placebo, packaged as capsules containing tablets prepared by the Pharmacy University Medical Center, Mainz, Germany. Open rescue treatment (0.5 mg/kg body weight/day oral prednisolone) was allowed until the patient's lung function improved at the discretion of the treating physician.

The primary endpoint was the relative change of forced vital capacity (FVC) from baseline through Month 6 compared to change from placebo. For secondary endpoints, the patients were classified as responder (FVC value after 6 months \geq 93% of normal¹⁶) or as nonresponder. Further endpoints included desaturation with standardized exercise test for children, Borg scale, weight, usage of rescue glucocorticosteroids, and validated patient-reported outcomes regarding health economics and quality of life at enrollment, after 3 and 6 months of treatment.^{17,18}

Power calculations were performed by means of a *t*-test with a correlation to the baseline value of .4 and were based on a one-sided level of significance of $\alpha = .05$. With 40 patients evaluable per protocol, the study would have a power of 58% to detect non-inferiority of the placebo arm versus the prednisolone arm with a non-inferiority bound of 7% (SAS, Version 9.2). Due to the small sample size by the end of the study, no statistical calculations were done and individual results were given.

The study was approved by the competent authorities (BfArM), the lead Ethics committee of the University Hospital Munich (99-14fed), and all local ethics committees. All subjects included gave their written informed consent, were randomized, and had received trial treatment.

3 | RESULTS

During the study period from January 2015 to July 2016, seven centers were open and screened for eligible patients. These sites cared for an estimated 25% of the 12 million children in the age group between 3 and 18 years in Germany and in need of specialized pediatric pneumology services. Four children with acute HSP were diagnosed and willing to participate in the trial. All four met the inclusion and exclusion criteria, were randomized, and completed the trial (Figure 1).

Table 1 gives the baseline characteristics of the subjects. Of interest, subjects P1 and P2 were from the same family and simultaneously exposed to down feathers in their beds. The older boy was initially a little bit more compromised, having low baseline saturation, exercise intolerance, so that exercise testing could not be done. His younger sister desaturated significantly with exercise. All

subjects had severe restrictive lung function impairment (Table 1, Figure 1). Subject P2 was randomized to placebo, subjects P1, P3, and P4 to verum.

No summary results were calculated, but analysis of the individual data yielded deep insights into the biology of the responses. The primary efficacy variable was FVC and its change from baseline through Month 6, compared between placebo and verum (Figure 2). P3 and P4 had a poor response and did not reach normal lung function after 6 months, despite treated with verum (Figure 3). This was supported by our pre-specified classification as a responder or nonresponder. Both patients were nonresponder (Table 1).

Assessment of other response variables included desaturation on standardized exercising 6 min walking test, and quality-of-life questionnaire (Table 1, Figure S1). All changes observed were consistent between the variables. None of the patients used additional rescue glucocorticosteroids.

All subjects treated with prednisolone over the 3 month period developed treatment-related side effects, in particular subjects P3 and P4 (Table 1). These patients had poorer adherence to medication, possibly in connection with these adverse events. Adherence to treatment in P1 and P2 was excellent (Table 1).

Health economic analysis demonstrated that the majority of costs arose from the initial hospital treatment with allergen removal and pulsed steroid treatment. Between enrollment and 3 months, additional costs arose in P1 for antibiotic treatment, in P2 for pulse oximetry surveillance between 3 and 6 months, and P4 was treated in hospital for 2 days for surveillance of a respiratory tract infection.

4 | DISCUSSION

The major limitation of this blinded and randomized trial was its premature closure and the small number of patients included. This was due to several reasons: the study design was developed as work package within a limited research project. Additionally, the anticipated enrollment was lower than expected and there was a lack of structuring the clinical trial to carry on for many years in view of low incidences in rare conditions in general. Nevertheless, one should keep in mind that the database is very small, we obtained many valuable insights into pediatric HP. Furthermore, we generated several resources for further trials in chILD making them publicly available.

4.1 | Clinical aspects of the trial

There is a long-standing debate for the indication of glucocorticosteroids in the treatment of HP.¹ The seminal randomized trial of prednisolone versus placebo in 36 adults with HP by Kokkarinen et al.¹² set the stage for this unresolved question.¹² Whereas the proponents of medical treatment add additional medicines such as azathioprine or rituximab to the armamentarium,¹ a strong argument is made not just for petty antigen identification and elimination but

TABLE 1 Baseline demographics and clinical course of the study subjects

Subject	P1	P2	P3	P4
Randomized to/gender	Prednisolone/male	Placebo/female	Prednisolone/female	Prednisolone
Age at study inclusion (years)	8.4	6.6	10.6	12.9
Antigens identified responsible for HP	Down feathers in bed	Down feathers in bed	Birds	Birds
FVC (% predicted)				
Screening	35	55	47	59
Baseline	35	55	n.d.	59
Discharge	85	90	63	58
After 1 month	112	91	73	77
After 2 months	117	81	81	76
After 3 months	114 ^a	95 ^a	85	76
After 6 months	126 ^a	103 ^a	84	65
O₂ sat (%) at rest after exercise				
Screening	90 not done	98 84	98 n.a.	99 92
Baseline	90	98	100	97
Discharge	99	98	98	97
After 1 month	99	98	98	97
After 2 months	99	97	98	95
After 3 months	99 95	99 100	98 n.a.	98 90
After 6 months	99 99	98 99	99 98	99 91
6 min walk distance (m)(% pred.)				
Screening	Not done, resp. insuf.	465 (79)	n.d.	460 (72)
After 3 months	540 (91)	510 (87)	n.d.	475 (74)
After 6 months	580 (97)	570 (97)	670 (105)	490 (77)
Exposure (Compliance all visits) (%)				
Compliance at months 1 (%)	100	99	88	81
Compliance at months 2 (%)	103	103	92	68
Compliance at months 3 (%)	100	100	n.a.	n.a.
Compliance at months 6 (%)	96	93	83	94
Adverse events				
	Fever after diagnostic BAL, oral candidiasis, conjunctivitis, hematoma	Headache, tiredness, weight gain, conjunctivitis	Cushing habitus, increased hair growth	Gastritis, lower respiratory tract infection, arterial hypertension
Quality of life (parents) Physical Psychosocial health^b				
Baseline	29 51	25 59	46 69	79 84
Month 3	100 97	96 96	100 98	n.a.
Month 6	100 92	96 99	100 100	71 81
Length of initial admission to hospital (days)				
	8	8	6	5

Abbreviations: FVC, forced vital capacity; HP, hypersensitivity pneumonitis.

^aResponder, if FVC value after 3 or 6 months more than or equal to 93% of the norm values tabulated by Quanjer et al.¹⁶

^bResults are given as arbitrary scores between 100 (best) and 0.

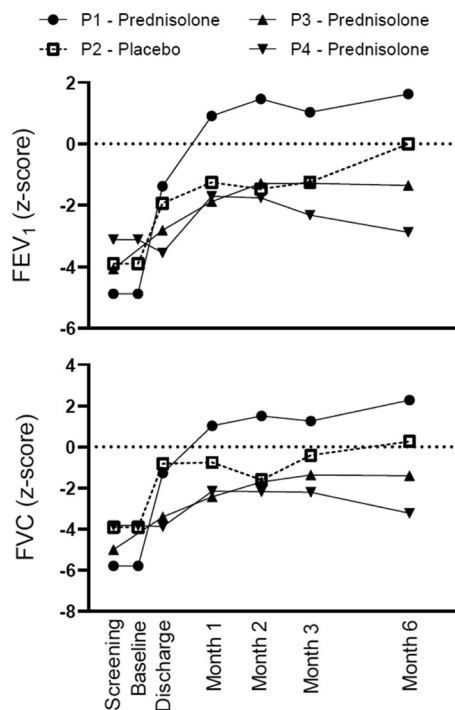


FIGURE 2 Lung function values of individual subjects expressed as z-scores. Closed symbols verum, open symbols placebo treatment following discharge

also for a detailed observation of lung function recovery, at least in acute and subacute cases. An unsurpassable proof of complete antigen elimination is the recovery of lung function without long-term corticosteroids, as it is illustrated in our patient P2. On the other hand, even with treatment leading to significant steroid side effects, a full recovery may not be achieved (P3, P4). Although, antigen removal in these two patients was checked, by the study team during the home visits, as bird antigens are known to be very persistent in the home environment.¹⁰ Our current practice is observation of lung function recovery in the absence of steroid treatment and repetitive rounds of antigen search and elimination; sometimes, in case of fungi, relocation may become necessary, too.

We considered the initial hospitalization of children with severe lung function impairment as inevitable to allow the removal of domestic antigens throughout their absence and to provide an antigen-free environment. We introduced the initial 3-day boost of steroids during the Delphi discussion of the positive experience of some centers.⁵ It led to a rapid improvement in only two of the four children, suggesting to be of limited value, when considering its costs and potential side effects. On the other hand, the design to treat all children initially with a boost of steroids may confound and it may be difficult to assess the sole effect of allergen removal. The direct medical costs were solely driven by the in-patient treatment. The psychological value of emphasizing the importance of keeping the child out of an allergen containing home environment is an important argument

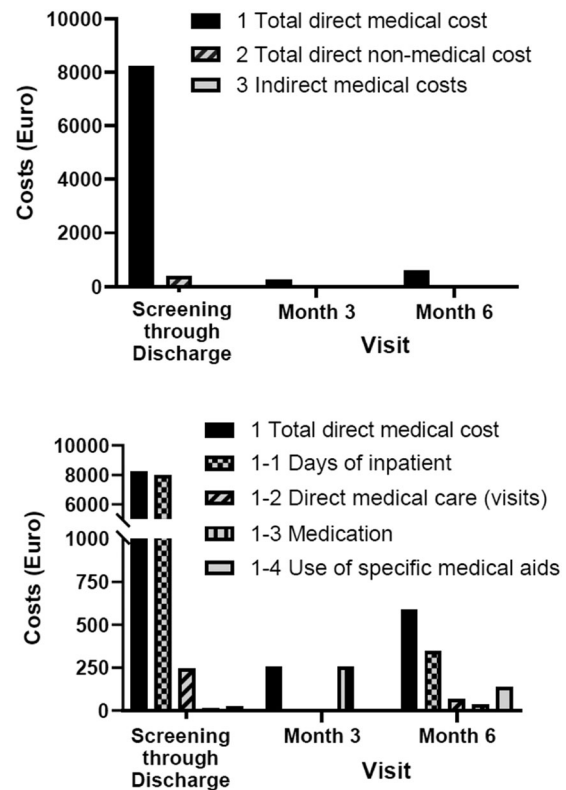


FIGURE 3 Mean of direct medical cost, direct nonmedical cost, and indirect cost (€) of the four subjects at enrollment, after 3 months and 6 months. In the lower panel allocation of total direct costs (days of inpatient, direct medical care, medication, and use of specific aids)

for the initial admission; alternatively, accommodation with suitable relatives may be an option for saving costs, too.

Although few cases, this is the first randomized controlled trial published in children's interstitial lung diseases, a large family of rare conditions. We implemented successfully relevant clinical variables in a standardized fashion, investigated their applicability in a pediatric ILD trial setting, and made these protocols available (Supporting Information). Of note, broadly established reference values for the 6-min walk test are still lacking. The quality-of-life questionnaire which we previously validated for children's interstitial lung disease¹⁸ worked well and may be used as patient-reported outcome, in particular with regard to the respiratory domain (Figure S1).

In a previous population-based observational study, we determined an incidence of 23 cases of EAA over a 3-year period.¹³ This is in accordance with the incidence observed during this trial, that is, about 11 children per year (four cases over 1.5 years in a population of about 3 million children, equal to about 0.9/million children, Germany has about 13 million children). These data suggest that any study conducted in areas of rare pediatric conditions have to include many countries to achieve sufficient numbers of patients. While conducting studies on rare diseases which continue from childhood into adulthood, we recommend considering a joint program with adults and a guaranteed contingent of children.

4.2 | Trial conduction aspects in rare pediatric disorders

Beyond the anticipatory actions and obstacles,¹⁹ we focused on two areas for a successful trial; the structural background of trial conduction and a realistic appraisal of patient numbers recruited into a trial. Regarding the latter point, one has to acknowledge that only a fraction of incident cases can actually be recruited into a trial. Although in specialized center care, the recruitment fraction may be significantly higher than on average, there are retarding factors beyond the control of the center. Indeed, in our study, 100% of the affected patients were included in the active study centers. In agreement with the incidence of 11 patients per year, estimated in our preceding study,^{3,13} the other patients were incident at sites not participating in the trial (oral communication, cases identified via the child-EU register). However, these patients were not referred into the trial, despite the previous announcement by most sites. Thus it is not realistic to take referrals reliably into account and any recruitment estimation cannot be conservative enough.

Further important lessons for conducting an investigator-initiated trial in rare diseases concern the structural setting of the lead and trial sites. For such studies, all centers invited to participate should operate an up-to-date clinical trial unit with appropriate administrative and clinical staff. In addition, standard operating procedures for clinical trials should be in place, independent of the intended rare disease trial, and centers that do not have such structures should be avoided. An excellent structural backbone, that is, staff available and busy running other studies, can accommodate few incident annual patients over a period of several years. Only the actual patient and the staff would need to perform the tasks whenever necessary and would be paid for that particular time. In investigator-initiated trials, it is impossible to pay for having staff available at any time a patient might arrive. The need of having a small budget for a prolonged time period, often years, has to be negotiated with the sponsoring foundations. In our experience, this is frequently not understood and rather difficult to achieve.

A viable option to study pediatric aspects of rare conditions, though nowadays uncommonly put into practice, is the inclusion of children into trials that are also or primarily run in adults. Obviously, this is dependent on the medication whichever is studied and not appropriate for novel drugs never used in children. However, in all other instances such as repurposing or investigating nondrug approaches to diagnostics, including a quota of children is an option rarely realized. Such an approach could help to increase high-quality trials for children with rare diseases manifesting through lifetime. Instead, split pediatric investigational plans are postponed or just not realized because of all the many hurdles already listed above. In this context, we demonstrated successfully for children's interstitial lung diseases, that many clinical variables including lung function measurements, walking tests, patient-reported outcome measure, and tools of economic burden, can be assessed reliably in a standardized fashion in any trial, allowing the same measurements in patients within a broad age range.

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AUTHOR CONTRIBUTIONS

Matthias Griese: Conceptualization (equal); data curation (equal); formal analysis (equal); funding acquisition (equal); investigation (equal); methodology (equal); project administration (equal); resources (equal); supervision (equal); validation (equal); visualization (equal); writing – original draft (equal); writing – review & editing (equal). **Florian Stehling:** Investigation (equal); resources (equal); writing – review & editing (equal). **Nicolaus Schwerk:** Investigation (equal); resources (equal); writing – review & editing (equal). **Martin Rosewich:** Investigation (equal); resources (equal); writing – review & editing (equal). **Hans Rock:** Software (equal); writing – review & editing (equal). **Christian Ruckes:** Formal analysis (equal); supervision (equal); writing – review & editing (equal). **Kai Kronfeld:** Supervision (equal); writing – review & editing (equal). **Daniela Sebah:** Project administration (equal); supervision (equal). **Martin Wetzke:** Investigation (equal); resources (equal); writing – review & editing (equal). **Elias Seidl:** Data curation (equal); formal analysis (equal); investigation (equal); methodology (equal); resources (equal); writing – review & editing (equal).

DATA AVAILABILITY STATEMENT

Data available on request from the authors. Additional documents and guidelines (investigational product dossier (IMPD), information concerning drug preparation, standard operating procedures) are shared on reasonable request by contacting the lead investigator.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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