Leukotriene Receptor Blockade as a Life-Saving Treatment in Severe Bronchopulmonary Dysplasia

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Key Words

Pediatrics · Neonatology · Bronchopulmonary dysplasia · Montelukast

Abstract

Background: Bronchopulmonary dysplasia (BPD) is a major cause of mortality and morbidity in infants with an extremely low birth weight. Because there is no effective therapy, the mortality of this condition in severely affected patients is high. Therapeutic blocking of the leukotriene system seems to be a logical approach due to the known pathophysiology of BPD. **Objectives:** The aim of this study was to examine the therapeutic effect of montelukast in preterm children suffering from severe BPD. **Methods:** We performed an unblinded, prospective trial including infants born between 23 and 27 weeks of gestation suffering from severe BPD. The study drug was montelukast (1 mg/kg of body weight as a single dose daily in the 1st week of therapy, increasing to 1.5 mg/kg of body weight in the 2nd week and finally to 2 mg/kg of body weight in the 3rd week). Treatment was continued until the radiological signs and the clinical symptoms of BPD disappeared or the patient was discharged from the hospital. Each patient included in this study was matched for gestational age, birth weight, and pulmonary severity score to a control. **Results:** Until March 2014, a total of 22 infants were

enrolled into the study. The rates of the primary outcome differed significantly between the montelukast-treated group and the control group. All but 1 of the children in the treatment group survived (91%), whereas 7 of the 11 children in the control group died (survival rate 36%; $p = 0.002$ using Fisher's exact test). The mean mechanical ventilation time (41.2 ± 25.3 vs. 103.7 ± 90.6 days) was significantly shorter and the mean preterm complication score (3.0 ± 1.7 vs. 5.6 ± 1.4) was significantly lower in treated patients compared to the control group. ($p = 0.05$ for both items; Wilcoxon's matched-pairs test). **Conclusion:** Based on the clinical observations, the statistical results, and the relatively low risk of the study drug montelukast, we recommend using this treatment in severe cases of BPD for infants facing a high risk of death.

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Background

Bronchopulmonary dysplasia (BPD) is a major cause of mortality and morbidity in preterm infants [1]. Despite the increased use of antenatal corticosteroids, postnatal

Trial registration: German Clinical Trials Register DRKS00004763.

surfactant therapy, and improved ventilation techniques, including high-frequency oscillation and early nasal CPAP [1], the incidence has not decreased. Clinically, the number of cases has increased due to the increasing survival of very preterm infants. Because there is no effective therapy to date, the mortality caused by this condition in severely affected preterm infants is high. In many of the survivors, severe respiratory symptoms and functional abnormalities persist into adolescence and early adulthood [2], resulting in lifelong consequences. BPD has a high and still rising incidence of 1–1.8 per thousand newborns in Germany [3, 4]. The pathogenesis of BPD has not been completely understood until now; several mechanisms seem to be involved. In addition to the histologically evident traumatic injury to the lungs due to mechanical ventilation, barotrauma biochemical studies have shown a high impact on the disease due to inflammatory processes in the airways [5]. Known pathogenetic mechanisms are a result of an imbalance of protease/antiprotease production [6], increased lipid inflammation mediators [platelet-activating factor and leukotrienes (LT)] [7–10], elevated cytokine production, and the immature status of the antioxidant system [8, 11, 14].

These abnormally upregulated inflammatory signal pathways seem to impede normal lung development, resulting in a lack of alveolarization and a delay in pulmonary microvascular maturation.

Approximately 15 years ago, 3 research groups found elevated levels of cysteinyl-LT in tracheal fluid and urine from preterm infants with bronchopulmonary disease [7, 8, 13]. Cysteinyl-LT have potent proinflammatory properties including bronchoconstriction, mucus secretion, airway hyperreactivity, and increased vascular permeability [11, 12]. In adults, the LT inflammation reaction is modulated by natural LT antagonists from mesenchymal stem cells, resulting in much lower LT levels during inflammatory lung disease [15], an observation which suggests a lack of these natural LT antagonists in preterms.

Based on these facts, we hypothesized that an LT-blocking drug may provide a therapeutic option for the disease.

Surprisingly, no clinical studies have been reported as of yet on LT antagonists in severe BPD. Therefore, we decided to perform an explorative study in life-threatened infants. Montelukast was chosen as the drug to be tested in this study. Montelukast is an orally active and selective LT receptor antagonist that inhibits the cysteinyl LT CysLT1 receptor. Montelukast has a large dose range, and published reports suggest that, given in pregnancy beyond the 24th week of gestation, montelukast has no fetal side effects. Off-

label use is common in children older than 1 month suffering from recurrent wheezing. In a clinical trial, a dose of 1–2 mg/kg of body weight was given to full-term born infants at 1 month of age with no side effects [19].

Methods

The dosage of montelukast was set to 1 mg/kg of body weight (single dose, daily) in the 1st week of therapy, increasing to 1.5 mg/kg of body weight in the 2nd week and finally to 2 mg/kg of body weight in the 3rd week.

Montelukast was given to the patients in this study in addition to their conventional therapy regimen.

Preterm infants with life-threatening BPD were chosen as the study group, with a probability of survival rated equal to or less than 50% by the attending physician. Further inclusion criteria for this study were a gestational age of less than 32 weeks, a birth weight of less than 1,500 g, and the need for mechanical ventilation support at day 28 after birth. Because a classical randomized blinded study design was rejected (with respect to the low therapeutic risk and the high mortality rate) for our patients by the local ethics committee, an open study design was chosen and carried out (Ethics Committee of the University of Erlangen-Nuremberg vote No. 3978).

Following this design, therapy was offered to all study patients, and the control group consisted of children in whom the planned therapy scheme was not possible due to existing or arising contraindications for the study drug (4 children) without significance for the outcome (phenobarbital therapy in controls 6, 7, 10, and 11; table 1), and children whose parents provided informed consent for participation in this study (as a control group patient) but not for administration of the medication montelukast (controls 1–5, 8, and 9; table 1).

The general exclusion criteria for the study and control groups were congenital metabolism disorders and severe congenital malformations (e.g. congenital heart disease and severe congenital immunodeficiency). The recommended initiation of therapy was defined as the period between days 28 and 45 of life and as early as possible.

Each included patient was matched as soon as possible (with a maximum delay of less than 48 h) for gestational age, birth weight, and pulmonary severity score (PSC) [17] to an included control infant. The study drug was given during the time of oxygen dependence/mechanical ventilation due to BPD.

The primary endpoint of this study was defined as the time of discharge from the hospital or death. The aim of this study was to compare the survival of patients versus controls at the primary endpoint.

The secondary endpoints were defined as the duration of mechanical ventilation, the severity of the pulmonary disease, and complications.

Statistical analysis was performed using the Wilcoxon matched-pairs signed-rank test and Fisher's exact test [16, 18]. For the complex situation of determining the severity of the pulmonary disease, a published score was used as mentioned above [17].

The score is defined empirically as PSC, which is equal to the fraction of inspired oxygen (FIO_2) $\times$ support + medications, where FIO_2 is the actual or effective (for a nasal cannula) FIO_2 ; support

Table 1. Clinical characteristics of the 11 treated patients and the controls

Pair No.		Gestational age at birth, weeks	Birth weight, g	Sex	PSC on day 28	Outcome	Cause of death
1	Patient	25.0	580	Male	1.6	Alive	
	Control	25.0	610	Female	0.7	Died on day 92	Pulmonary and cardiac failure
2	Patient	25.0	850	Male	1.6	Alive	
	Control	25.3	570	Female	1.6	Died on day 168	Pulmonary and cardiac failure, SIRS
3	Patient	23.9	570	Male	1.6	Alive	
	Control	24.1	625	Female	1.8	Died on day 112	Pulmonary and cardiac failure
4	Patient	25.7	605	Male	1.7	Alive	
	Control	25.1	595	Male	1.6	Died on day 296	Pulmonary and cardiac failure
5	Patient	24.0	605	Male	1.6	Alive	
	Control	25.6	670	Male	1.6	Died on day 224	Pulmonary and cardiac failure, SIRS
6	Patient	25.6	540	Female	1.2	Alive	
	Control	26.3	840	Male	1.2	Alive	
7	Patient	28.6	760	Female	1.6	Alive	
	Control	27.3	660	Female	1.4	Died on day 270	Pulmonary and cardiac failure, SIRS
8	Patient	27.0	550	Female	1.5	Died on day 327	Septic shock following surgery
	Control	27.3	640	Male	1.6	Alive	
9	Patient	23.0	640	Male	1.6	Alive	
	Control	23.3	471	Female	1.6	Died on day 89	Pulmonary and cardiac failure
10	Patient	24.1	580	Male	1.6	Alive	
	Control	27.3	460	Female	1.6	Alive	
11	Patient	25.9	960	Female	1.7	Alive	
	Control	26.4	900	Female	0.9	Alive	

is 2.5 for a ventilator, 1.5 for nasal continuous positive airway pressure, or 1.0 for a nasal cannula or hood oxygen, and medications is 0.20 for systemic steroids for BPD, 0.10 each for regular diuretics or inhaled steroids, and 0.05 each for methylxanthines or intermittent diuretics. The score can range from 0.21 to 2.95.

Another scoring system was used for the complications in our preterm patients. The preterm complication score was defined as the sum of persistent ductus arteriosus + retinopathy of prematurity + intraventricular bleeding + periventricular leukomalacia + necrotizing enterocolitis + pneumothorax, where persistent ductus arteriosus is 0 for none, 1 for yes, and 2 for surgical ligation; retinopathy of prematurity is 0 for none and 1–4 according to the maximum grade; intraventricular bleeding is 0–4 according to the maximum grade; periventricular leukomalacia is 0 for none and 1 for yes; necrotizing enterocolitis is 0 for none, 1 for yes, and 2 for necrotizing enterocolitis requiring surgery, and pneumothorax is 0 for none, 1 for single, and 2 for repeated. The score ranges from 0 to 15.

Severe cases of BPD as in the study group selected here occur seldom in a single neonatal intensive care unit; therefore, a multicenter study design including 5 tertiary neonatal intensive care units was chosen.

Results

From January 2010 until March 2014, 11 patients and 11 controls could be completely analyzed, and 1 additional study patient was doing well under therapy at the time of reporting.

No statistically significant differences were observed when analyzing gestational age (25.3 ± 1.6 vs. 25.6 ± 1.3 weeks), body weight at birth (658 ± 138 vs. 624 ± 144 g), and PSC on day 28 after birth (1.54 ± 0.13 vs. 1.41 ± 0.35) between the patients and the controls, respectively (Wilcoxon's matched-pairs signed-rank test). The therapy group consisted of 4 girls and 7 boys, and the control group included 4 girls and 7 boys (table 1).

The mean montelukast treatment time was 111 ± 53 days in the study group and 1.6 ± 3.7 days in the 4 treated controls (controls 6, 7, 10, and 11; table 1).

No drug-associated adverse events were observed in our patients.

Fig. 1. Radiological evidence of the effect of therapy. **a** The initial chest radiograph features (28th day of life) in a study patient (born in the 24th week of gestation, birth weight 605 g) consist of numerous circular bubbles (example marked by the dotted arrow), often termed type I bubbles and thought to be dilated terminal bronchioles and alveolar ductuli, and more linear structured bubbles (arrow), termed type II bubbles and known to be a sign of interstitial emphysema. The left lower field shows a greater zone of hyperinflation, signs of emphysema, and the beginning of parenchyma

destruction. **d** The chest X-ray on day 28 in the control infant (born in the 25th week, weight 670 g) demonstrates qualitatively the same findings but these are slightly less pronounced. **b** After 4 weeks of treatment, the patient showed a slight improvement, whereas the control infant's lungs had worsened (**e**). **c** Finally, after 6 months, the patient's lung appeared better overall, whereas the X-ray from the control (**f**) 1 day before the child died due to heart failure (aged 5 months), in addition to the persistent severe findings of BPD, showed a strong degree of interstitial edema.

Table 2. Survival according to treatment

	Nonsurvivors	Survivors
Patients	1	10
Controls	7	4

All but one of the infants in the treatment group (patients) survived, whereas 7 of the 11 infants in the control group died. $p = 0.002$, Fisher's exact test.

All infants had varying concomitant medications administered (e.g. methylxanthines, steroids, and diuretics).

Survival

Table 2 shows the study results for survival.

Four of the 7 nonsurvivors in the control group died because of respiratory failure and (right ventricular) cardiac failure, and in 3 of those cases cardiac failure combined with pulmonary failure triggered septicemia (sys-

temic inflammatory response syndrome; SIRS). The one nonsurvivor in the therapy group died due to septic shock after surgery for necrotizing enterocolitis.

Radiological and Clinical Findings

Montelukast-treated infants showed clear radiological improvement based on the pulmonary findings that became evident in the 4th week of treatment in most cases. In contrast, the controls showed an increasing degree of lung destruction. Radiology showed an increasing number of fibrotic areas. Figure 1 demonstrates 2 typical radiological series.

The PSC decreased significantly in the montelukast-treated infants after 4 weeks and was significantly lower compared to that of the controls. This difference was even more pronounced at the final assessment of the score (the study endpoint), which was performed as late as possible (e.g. if the control died or at discharge from the clinic or at the end of the montelukast therapy, based on whichever event occurred last). The PSC findings are summarized in figure 2.

Fig. 2. Mean PSC as defined in Methods. Initially, at the start of therapy, there was no difference between the patients and the controls (time 1). After 4 weeks of therapy, the score was significantly lower in the patients compared to the controls (time 2). This difference was even more pronounced at the study endpoint (time 3). Wilcoxon's matched-pairs signed-rank test, $p = 0.01$ for time 2 and time 3; the error bars indicate the single standard deviation.

The mean mechanical ventilation time (41.2 ± 25.3 vs. 103.7 ± 90.6 days) was significantly shorter and the mean preterm complication score (3.0 ± 1.7 vs. 5.6 ± 1.4) was significantly lower in patients versus controls (for both, $p = 0.02$; Wilcoxon's matched-pairs signed-rank test).

Discussion

Considering the study design, it is evident that a classical double-blinded approach in a larger study group would have been preferable from a statistical point of view [16, 18].

However, given the very poor prognosis of the patients and the small potential risk of the therapy, such a design was judged unethical by our group and the local ethics committee. Such a situation is not uncommon in neonatology [20].

Another limiting factor for clinical trials in this special field (neonatology) is the low incidence of the diseases. Severe BPD, albeit a common problem for the neonatologist, fulfils all of the criteria of an orphan disease [16]. It is well accepted by us that the clinical approval of orphan drugs (e.g. by the FDA) is based on small, unblinded clin-

ical studies, often without a control group if the prognosis *quoad vitam* is very poor. These factors may partly justify such (quite common) study designs in the field of neonatology.

Statistical testing is difficult in small study groups; nevertheless, our treatment group experienced a significantly increased survival (91 vs. 36%; $p = 0.02$), and the duration of the necessary mechanical ventilation was significantly shorter in the montelukast-treated infants.

Probably due to the 'milder' and shortened mechanical ventilation, represented by the significantly reduced PSC after 4 weeks of montelukast, complications (necrotizing enterocolitis, retinopathy of prematurity, intraventricular bleeding, periventricular ischemic damage, and persistent ductus arteriosus) occurred significantly less often in the study group compared to the control group. Closer investigation of each of these complications was not possible due to the small size of the study group.

However, the statistics in the study should not be overestimated. The power of the applied test may be relatively low due to the small number of included infants in this study.

Apart from the statistics, it is remarkable that in a patient group in which every child was judged by his or her attending neonatologist to have a chance of survival equal to or less than 50% only 1 patient died. In the control group, in which this risk was judged equally, the mortality was 63%.

Conclusions

Finally, from our clinical observations also based upon the statistical results and the relatively low risk of treatment with montelukast, we recommend consideration of such a treatment (as a compassionate approach) in severe cases of BPD in patients facing a high risk of death (ideally as participants of a clinical study). The definition of high risk in this context should be the task of the attending neonatologists.

For all not-life-threatening disease stages, a further (blinded and randomized) clinical trial has to be performed before such a therapy can be recommended.

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Financial Disclosure and Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Erratum

The authors of the article entitled 'Leukotriene receptor blockade as a life-saving treatment in severe bronchopulmonary dysplasia' [Respiration 2014;88:285-290, DOI:10.1159/000365488] wish to publish the following two corrections.

On page 288, table 2, the correct p value is 0.02, see below:

Table 2. Survival according to treatment

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Controls	7	4

All but one of the infants in the treatment group (patients) survived, whereas 7 of the 11 infants in the control group died. $p = 0.02$, Fisher's exact test.

On page 290, left column, the text should read:

This study was partly funded by an unrestricted grant from the Oberfrankenstiftung and the Orchesterakademie, Bayreuth, Germany, which had no influence on the design, collection, analysis, or interpretation of data or publication.