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.

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

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 contraindication 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 (FIO2) × support + medications, where FIO2 is the actual or effective (for a nasal cannula) FIO2; support...
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 ligature; 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.

### 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 Control | 25.0 | 580 | Male | 1.6 | Alive | Died on day 92 | Pulmonary and cardiac failure |
| 2 Patient Control | 25.0 | 610 | Female | 0.7 | Died on day 112 | Pulmonary and cardiac failure, SIRS |
| 3 Patient Control | 23.9 | 850 | Male | 1.6 | Alive | Died on day 168 | Pulmonary and cardiac failure, SIRS |
| 4 Patient Control | 25.7 | 570 | Female | 1.6 | Alive | Died on day 296 | Pulmonary and cardiac failure |
| 5 Patient Control | 25.1 | 625 | Male | 1.7 | Alive | Died on day 224 | Pulmonary and cardiac failure, SIRS |
| 6 Patient Control | 24.0 | 605 | Female | 1.6 | Alive | Died on day 112 | Pulmonary and cardiac failure, SIRS |
| 7 Patient Control | 25.3 | 670 | Male | 1.6 | Alive | Died on day 270 | Pulmonary and cardiac failure, SIRS |
| 8 Patient Control | 27.0 | 550 | Female | 1.4 | Died on day 327 | Septic shock following surgery |
| 9 Patient Control | 23.0 | 640 | Male | 1.6 | Alive | Died on day 296 | Pulmonary and cardiac failure |
| 10 Patient Control | 23.3 | 471 | Female | 1.6 | Alive | Died on day 296 | Pulmonary and cardiac failure |
| 11 Patient Control | 25.9 | 900 | Female | 1.7 | Alive | Died on day 270 | Pulmonary and cardiac failure |

### 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.
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 (systemic 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.
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 neonologist, fulfills 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 clinical 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.

References
1. Doyle LW, Brion LP et al; COIN Trial Investigators: Nasal CPAP or intubation at birth for very preterm infants. N Engl J Med 2008;358:700–708.
2. Baraldi E, Filippone M: Chronic lung disease after premature birth. N Engl J Med 2007;357:1946–1955.
3. Kwinta P, Pietrzyk JJ: Preterm birth and respiratory disease in later life. Expert Rev Respir Med 2010;4:593–604.
4. Eber E, Zach MS: Long term sequelae of bronchopulmonary dysplasia (chronic lung disease of infancy). Thorax 2001;56:317–323.
5. Groneck, P, Speer CP: Inflammatory mediators and bronchopulmonary dysplasia. Arch Dis Child Fetal Neonatal Ed 1995;73:1–3.
6. Ogden BE, Murphy SA, Saunders GC, Pathak D, Johnson JD: Neonatal lung neutrophils and elastase/proteinase inhibitor imbalance. Am Rev Respir Dis 1984;130:817–821.
7. Stemmark KR, Eyzaguirre M, Westcott JY, Henson PM, Murphy RC: Potential role of eicosanoids and PAF in the pathophysiology of bronchopulmonary dysplasia. Am Rev Respir Dis 1987;136:770–772.
8. Mirro R, Armstead W, Lefler C: Increased airway leukotriene levels in infants with severe bronchopulmonary dysplasia. Am J Dis Child 1990;144:160–161.
9. Groneck P, Götz-Speer B, Oppermann M, Eiffert H, Speer CP: Association of pulmonary inflammation and increased microvascular permeability during the development of bronchopulmonary dysplasia: a sequential analysis of inflammatory mediators in respiratory fluids of high-risk preterm neonates. Pediatrics 1994;93:712–718.
10. Kotecha S, Chan B, Azam N, Silverman M, Shaw RJ: Increase in interleukin-8 and soluble intercellular adhesion molecule-1 in bronchoalveolar lavage fluid from premature infants who develop chronic lung disease. Arch Dis Child Fetal Neonatal Ed 1995;72:90–96.
11. Dahlén SE, Björk J, Hedqvist P et al: Leukotrienes promote plasma leakage and leukocyte adhesion in postcapillary venules: in vivo effects with relevance to the acute inflammatory response. Proc Natl Acad Sci USA 1981;78:3887–3891.
12. Marom Z, Sheltaner JH, Bach MK, Morton DR, Kaliner M: Slow-reacting substances, leukotrienes C4 and D4, increase the release of mucus from human airways in vitro. Am Rev Respir Dis 1982;126:449–451.
13. Davidson D, Drafft D, Wilkens BA: Elevated urinary leukotriene E4 in chronic lung disease of extreme prematurity. Am J Respir Crit Care Med 1995;151:841–845.
14. Ladha F, Bonnet S, Eaton F, Hashimoto K, Korbutt G, Thébaud B: Sildenafil improves alveolar growth and pulmonary hypertension in hyperoxia-induced lung injury. Am J Respir Crit Care Med 2005;172:750–756.
15. Ardhanareswaran K, Mirotsou M: Lung stem and progenitor cells. Respiration 2013;85:89–95.
16. Evans CH, Ildstad ST (eds): Committee on Strategies for Small-Number-Participant Clinical Research Trials, Board on Health Sciences Policy Small Clinical Trials: Issues and Challenges. Institute of Medicine, National Academy Press, Washington, 2001.
17. Madan A, Brozanski BS, Cole CH, Oden NL, Cohen G, Phelps DL: A pulmonary score for assessing the severity of neonatal chronic lung disease. Pediatrics 2005;115:450–457.
18. Spicer CC: Some new closed sequential designs for clinical trials. Biometrics 1962;18:203–211.
19. Kears GL, Lu S, Maganti L, Li XS, Migoya E, Ahmed T, Knorr B, Reiss TF: Pharmacokinetics and safety of montelukast oral granules in children 1 to 3 months of age with bronchiolitis. J Clin Pharmacol 2008;48:502–511.
20. Eichenwald EC, Stark AR: Management and outcomes of very low birth weight. N Engl J Med 2008;358:1700–1711.
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:

|         | 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. \( p = 0.02 \), 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.