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Case Report

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Palivizumab in Neonatal RSV Infection

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Introduction

Palivizumab (Synagis; MedImmune Inc.) a humanized monoclonal antibody against the F-protein of Respira-tory Syncytial Virus (RSV) available for prophylaxis in high-risk infants, effectively reduces rates and severity of RSV lower respiratory tract infections. Premature infants because of their immunodeficiency, are particularly vulnerable to severe RSV infection early in life [1]. It is especially true when a disease develops as a nosocomial infection within the first weeks of life, while the infant is treated in neonatal intensive care unit. There is no spe-cific therapy for acute bronchiolitis caused by RSV other than supportive, which includes primarily the oxygen supplementation and mechanical ventilation. Surfactant administration and helium-oxygen combination were described as possibly effective for the most severe cases [2]. Ribavirin is the only option currently available for treatment of RSV infection but evidence suggests that it is not fully effective [3]. About 10 years ago, Chavez-Bueno S, et al. [4] found the treatment of RSV-infected high-risk children with intravenous palivizumab was well tolerated and associated with decreased mortality compared with previous reports. Recently, Torres JP et al. [5] suggested that early administration of intravenous palivizumab might be useful in selected patients with severe immunosuppression. Authors report three prematurely delivered infants (one born at 29th and twins born at 31st week of pregnancy) that developed contemporary serious nosocomial infections caused by respiratory syncytial virus (RSV) in the fourth and second week of their lives. Infection was probably transmitted from the parents who presented mild symptoms of upper respiratory tract infection. To establish the diagnosis, the swab specimens from patient's nostril and pharynx were taken. Fast Track Diagnostics Respiratory pathogens 21 test (Fast Track Diagnostics Luxemburg) was used to diagnose infection. Intramuscular injection of palivizumab was administered as a rescue therapy after obtaining the parental approval.

Patient 1

The female infant was delivered vaginally at 29 weeks of gestation. Two doses of betamethasone were given prenatally five days before birth. The birthweight was 1300g and the Apgar score was 5 at 1 min and 6 at 5 min. The infant breathed spontaneously at birth, but needed respiratory support because of grunting respiration and increased oxygen requirement. Nasal CPAP (Infant Flow Driver) was applied in delivery room and pressure of 5 cm H2O was used initially. During the first hour after birth the infant required a fraction of inspired oxygen (FiO2) - 0.35. However, the oxygen requirement tended to decrease and on the 10th day after birth, the infant became oxygen-independent and was weaned from nasal CPAP. From the 15th day of life, the infant was fed exclusively with breast milk and gained weight regularly. At 27th day of age, an increase in respiratory effort was observed and infant required 35% supplementary oxygen. Also, the ventilatory support with n-CPAP (Infant Flow Driver) was introduced. A chest X-ray film revealed a non-characteristic haziness of the upper lobes of both lungs, which suggested a mild pneumonia caused by aspiration. We decided to start treatment with penicil-lin and aminoglycoside (Tobramycin). The evaluation of plasma C-reactive protein and procalcitonin levels showed normal range values. Also, the leukocytes count was within the normal range. Blood sample and tra-cheal aspirates culture examinations showed negative results. Since we suspected viral infection, the swab spec-imens from nostril and pharynx were examined in Fast Track Diagnostics Respiratory pathogens 21 test and confirmed diagnosis of RSV infection. Within the next 48 h, breathing difficulty arose and when PaCO2 reached the value of 65 mmHg, the infant was intubated. In addition to conventional mechanical ventilation, the oxy-gen requirement was being continuously increased, so as to maintain Pa02 value above 50 mmHg we needed to ventilate infant with 100% of oxygen supply (Oxygenation Index = 31). Administration of surfactant (Curo-surf) was introduced but no improvement in oxygenation was observed. Since the infant was unable to maintain oxygen saturation above 88% while breathing 100% oxygen, we introduced inhaled nitric oxide with an initial dose of 10 ppm. However, the oxygen and ventilatory requirements did not tend to decrease sufficiently (FiO2 = 0.9; Oxygenation Index = 26) and we decided on the intramuscular injection of palivizumab (Synagis) in a dosage of 15 mg per kg on the third day of therapy. During the next two successive days, a spectacular improvement in clini-

cal condition was observed. Inhaled nitric oxide was discontinued and significant reduction in FiO2 value was observed (from 0.9 to 0.45). Patient was weaned from ventilator to n-CPAP within the next four days and its oxygen requirements (Fi02) were reduced to 0.25. On the 8th day after palivizumab administra-tion, infant was able to maintain oxygen saturation above 90% while breathing room air. There were no symp-toms of the recurrent RSV infection observed until patient was discharged. Also, no signs of chronic lung disease were found for 6 consecutive months of the follow-up observational study.

Patients: 2 and 3

The male and female infants (Twins) were delivered by cesarean section at 31st week of gestation. There were steroids given three days before the delivery. The birth weights were 1750g and 1880g respectively. Apgar score was 7 and 7 at 1 min and 8 and 7 at 5 min. At birth, both infants breathed room air spontaneously without any signs of respiratory insufficiency. From the 12th day of life, both infants were exclusively with breast milk and gained weights regularly. On the 15th day after birth, clinical symptoms of increased respiratory effort were ob-served and the infants required 25 - 30% supplementary oxygen and ventilatory support with n-CPAP. A chest X-ray film revealed non-characteristic changes in the upper lobes of the lungs. They were similar to those found in patient 1. We routinely started treatment with penicillin and aminoglycoside (Tobramycin). The plasma concentration of C - reactive protein and procalcitonin, as well as the leukocytes count were within the normal range. Within the next 24 hrs., breathing difficulty arose and when PaCO2 reached the value of 65 mmHg the infants were intubated. The oxygen requirement markedly increased, so as to maintain oxygen saturation above 88%, we needed to ventilate the infants with 90% and 75% of oxygen supply, respectively. Administra-tion of surfactant (Curosurf) was introduced with a slight improvement in oxygenation (FiO2 decreased from 0.9 to 0.75 and from 0.75 to 0.7 respectively). Since the symptoms of disease were similar to those found in the previous patient, we decided to perform a Fast Track Diagnostics Respiratory pathogens 21 test, which con-firmed the diagnosis of RSV infection in both infants. As the oxygen requirement showed no tendency to de-crease, intramuscular injection of palivizumab (Synagis) in a dosage of 15 mg per kg was introduced on the third day of therapy. During the next 96 hrs. both patients were weaned from ventilator to n-CPAP and the ox-ygen requirements were reduced to 0.25. On the 6th day after palivizumab administration, infants were able to maintain oxygen saturation above 90% while breathing room air without any ventilatory support. There were also no symptoms of the recurrent RSV infection observed until the infants were discharged. As with patient 1, there were also no signs of chronic lung disease found in the patient 2 and 3 for the six consecutive months of the follow-up observational study.

Discussion

Palivizumab, a humanized monoclonal antibody specific for RSV is approved for prophylaxis of RSV infection in high-risk prematurely born infants, but there is a little experience with its use for treatment of acute RSV in-fection in these patients. Two placebo-controlled studies evaluated treatment with intravenous palivizumab in children with RSV infection [6,7]. According to our knowledge, there is no previous report describing the use of palivizumab in the treatment of nosocomial RSV infection in premature infants occurring in the first month of life. Administration of a single dose of palivizumab, spectacularly decreased respiratory insufficiency and sig-nificantly reduced oxygen requirements, without any adverse clinical side-effects. The improvement in clinical conditions of all treated infants was already observed within the several hours after humanized monoclonal antibody was injected intramuscularly. The decision on therapeutic palivizumab injection was based on the results of previously published data suggesting the reduction of respiratory syncytial virus loads in tracheal aspi-rates in intubated infants after administration of humanized monoclonal antibody to RSV F protein [7]. Re-cently, also Torres JP, et al. [5] observed similar effects of intravenous palivizumab administration in children. On the other hand, implementation of RSV prophylactic treatment with palivizumab was shown to be safe and decrease morbidity and hospitalization [8, 9]. We emphasize the most important factor that influenced decision on therapeutic use of palivizumab in presented patients was continuous deterioration of their clinical condi-tions. We realize that retrospective analysis in the absence of control group of untreated patients is far from providing clinical efficacy in terms of mortality and morbidity. However, it cannot be ruled out that such a ben-eficial effect on the clinical course of respiratory insufficiency might have occurred due to palivizumab intra-muscular administration. Whether we should start the injection of palivizumab earlier, immediately after the diagnosis of RSV infection was confirmed, it may be explained and clarified in the further clinical investiga-tions.

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