Respiratory syncytial virus prophylaxis in preterm infants: a cost-effectiveness study from Turkey

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The main aim of this study was to evaluate the cost-effectiveness of respiratory syncytial virus (RSV) prophylaxis with palivizumab in Turkey, by comparing hospitalization rates and costs as well as results of risk analyses in preterm infants who were treated either with palivizumab or conservatively. This retrospective study was undertaken in two centers on infants born with a gestational age of ≤32 weeks during the 2010-2011 seasons. Patients were divided into two groups based on status of RSV prophylaxis. The records of 272 infants were included in the final analysis, 201 (73.9%) of which had received palivizumab (Group 1), while 71 (26.1%) were not given any form of RSV prophylaxis. The difference between groups in terms of demographic characteristics and risk factors for RSV infection was statistically insignificant (p>0.05). Thirteen patients (6.5%) in Group 1 and 5 patients (7%) in Group 2 were hospitalized for lower respiratory tract infections (LRTIs) (p>0.05). In newborns born at ≤28$^{6/7}$ weeks of gestation, RSV prophylaxis with palivizumab was associated with a 38.75% decrease in hospitalization rates due to LRTIs compared to the untreated group (8% in the untreated group vs. 4.9% in the palivizumab group; p=0.577). The hospitalization rate due to LRTIs for infants in Group 1 born after 29-32 weeks of gestation was 7.5% compared to a rate of 6.5% in Group 2, with a statistically insignificant difference (p=0.828). In infants with bronchopulmonary dysplasia (BPD) born at ≤28$^{6/7}$ weeks of gestation, treatment with palivizumab was associated with a 39.1% decrease in LRTI-related hospitalization rates (14.3% in the untreated group vs. 8.7% in the palivizumab group; p=0.677). This clinical study is the first of its kind from Turkey to evaluate the cost-effectiveness of palivizumab treatment as prophylaxis against RSV infections in preterm infants, where hospitalization rates and costs of patients treated with palivizumab were compared with those of infants who were treated conservatively. Our study results suggest that administration of palivizumab does not have any cost benefit, regardless of gestational age. However, a reduction in hospitalization rates in association with palivizumab treatment was observed in infants born at ≤28$^{6/7}$ weeks of gestation with or without BPD.

Key words: cost-effectiveness, respiratory syncytial virus infections, palivizumab, premature infants, hospitalization, Turkey.

The respiratory syncytial virus (RSV), a member of the Paramyxoviridae family, is an enveloped, non-segmented, negative-stranded RNA virus, which uses attachment (G) and fusion (F) surface glycoproteins that lack neuraminidase and hemagglutinin activities to infect cells[1]. RSV is considered the most common cause of lower respiratory tract infections (LRTIs) in infants worldwide[2].

Palivizumab (Synagis®) is a humanized murine monoclonal anti-F glycoprotein immunoglobulin with neutralizing and fusion inhibitory activity against RSV that is indicated

for the prevention of serious LRTIs due to the virus[3]. Current guidelines recommend the use of RSV prophylaxis for patients at high risk of developing severe RSV infections, including infants with prematurity, bronchopulmonary dysplasia (BPD) or congenital heart disease (CHD). Previously reported RSV-related hospitalization rates range from 3% to 37%[4-7]. Palivizumab has been shown to reduce the overall rate of hospitalization in premature infants and in children with BPD by 55%[8]. Several prospective, randomized, double-blind, placebo-controlled trials have shown RSV prophylaxis to reduce morbidity, with no benefit with regard to mortality[8-10].

Passive immunization against RSV, although safe and moderately effective, is quite expensive, and the significant costs associated with RSV prophylaxis have prompted the undertaking of several extensive studies investigating the cost-effectiveness of preventive treatments[11].

In Turkey, RSV prophylaxis with palivizumab is administered based on guidelines and recommendations that were designed for developed nations. *Recommendations for RSV prophylaxis in Turkey put forth by the Turkish Neonatology Society in 2007* are shown in Table *I*[12]. In recent years, several developing countries have completed cost-effectiveness studies in an attempt to formulate their own criteria for RSV prophylaxis[11,13-16]. The high cost of palivizumab for developing nations, such as Turkey, cannot be ignored.

The main aim of this study was to evaluate the cost-effectiveness of palivizumab prophylaxis by comparing hospitalization rates and costs as well as results of risk analyses in preterm infants who were treated either with palivizumab or conservatively.

Material and Methods

This retrospective study was undertaken in two centers (Zekai Tahir Burak Maternity Training Hospital and Etlik Zübeyde Hanım Maternity and Women's Health Academic and Research Hospital) with the approval of the local ethics committee. The medical records of infants born in the 2010-2011 season were systematically reviewed, and infants born with a gestational age (GA) of ≤32 weeks were divided into two groups based on prophylaxis status. Infants who received RSV prophylaxis with palivizumab were stratified into Group 1, whereas Group 2 consisted of newborns who did not receive palivizumab prophylaxis because of refusal of their parents.

Perinatal characteristics such as birth weight and GA as well as information regarding a medical history of respiratory distress syndrome (RDS), patent ductus arteriosus (PDA), proven or clinic sepsis, necrotizing enterocolitis (NEC), BPD, and retinopathy of prematurity (ROP) were recorded on pre-prepared forms. Other parameters that were noted include postnatal clinical parameters such as duration of mechanical ventilation and length of hospitalization. The diagnosis of BPD was based on criteria set by the United States (US) National Institutes of Health[17].

Respiratory syncytial virus (RSV) prophylaxis was administered taking into consideration the current recommendations of the Turkish Neonatology Society, which have been adapted from the recommendations of the American Academy of Pediatrics (AAP) and the European Palivizumab Study Group[12].

Patients who were hospitalized due to LRTIs were identified using the ICD10 coding system (J12, J16, J17, and J18 for pneumonia; J21 for acute bronchiolitis). Data on the hospitalization

Table I. Recommendations of Turkish Neonatology Society for RSV Prophylaxis

Recommendations
1. Infants born at 28 weeks' gestation or earlier during RSV season, whenever that occurs during the first 12 months of life.
2. Infants born at 29–32 weeks' gestation if they are younger than 6 months of age at the start of the RSV season.
3. Infants and children younger than 2 years who have been treated for BPD within 6 months of the start of the RSV season.
4. Infants and children younger than 2 years with cyanotic or complicated congenital heart disease.

rates and costs for the RSV season (between October and March) were obtained from the hospitals that admitted these infants. Results of cost analyses for the 2011 RSV season were provided in US dollars (USD) using the official exchange rate of the Central Bank of the Republic of Turkey. As per the manufacturer's instructions, palivizumab was administered intramuscularly at a standard dose of 15 mg/kg, repeated every 30 days. In Turkey, according to the records of the Turkish Pharmacist's Association, one 50 mg-vial of palivizumab costs 516 USD.

Statistical Analysis

All statistical analyses were carried out using MS-Excel 2007 and the Statistical Package for the Social Sciences for Microsoft Windows, version 15.0 (SPSS Inc., Chicago, IL, USA). Comparisons of categorical variables between groups were made using the chi-square test. For continuous numerical variables, either the independent samples t-test or the Mann-Whitney U test was used, depending on the normality of distribution, which was evaluated using the Shapiro-Wilk test. A p-value of <0.05 was considered indicative of statistical significance.

Total cost for each patient in the palivizumab group was the sum of hospitalization costs and cost of palivizumab treatment (number of doses x unit price per dose). For patients in Group 2, only hospitalization costs were taken into account when calculating total cost.

Results

The records of 272 infants were deemed sufficient for inclusion in the final analysis, 201 (73.9%) of which received palivizumab (Group 1), while 71 (26.1%) were not given any form of RSV prophylaxis (Group 2). The demographic and clinical characteristics of the study population are presented in Table II. The difference between groups in terms of demographic characteristics and risk factors for RSV infection was statistically insignificant ($p>0.05$).

Patients in Group 1 received an average of 3.8 vials of palivizumab per patient, while infants with LRTIs (n=13) received an average of 4.2 vials per patient. None of the patients in Group 1 developed a palivizumab-related adverse effect.

A review of the medical records revealed that 13 patients (6.5%) in Group 1 were hospitalized

Table II. Demographic and Clinical Characteristics of the Study Population

Characteristic	Group 1 (n=201)	Group 2 (n=71)	p-value
Gestational age, weeks[a]	28.7±1.9	29.1±2	0.091
Birth weight, g[a]	1219±308	1268±247	0.165
Male gender[b]	109 (54.2)	39 (54.9)	0.919
RDS[b]	142 (70.6)	56 (78.9)	0.181
PDA[b]	50 (24.9)	17 (23.9)	0.876
Proven or clinical sepsis[b]	40 (19.9)	18 (25.4)	0.335
NEC[b]	21 (10.4)	6 (8.5)	0.629
ROP[b]	45 (22.4)	14 (19.7)	0.639
Moderate-severe BPD[b]	28 (13.9)	10 (14.1)	0.974
Need for MV[b]	116 (57.7)	48 (67.6)	0.143
Duration of MV, day[a]	9.39±10.6	6.59±9.7	0.225
Length of hospitalization (NICU)[a]	45.7±20.6	43.9±20.3	0.355
LRTI-related hospitalization[b]	13 (6.5)	5 (7.0)	0.867

[a]Values provided as mean ± standard deviation

[b]Values provided as number and percentage of patients

RDS: Respiratory distress syndrome. PDA: Patent ductus arteriosus. NEC: Necrotizing enterocolitis. ROP: Retinopathy of prematurity. BPD: Bronchopulmonary dysplasia. MV: Mechanical ventilation. NICU: Neonatal intensive care unit. LRTI: Lower respiratory tract infection.

for LRTI compared to 5 patients (7%) in Group 2, with a statistically insignificant difference ($p>0.05$).

Patients were further subdivided into two groups based on GA, and in newborns born at $\leq 28^{6/7}$ weeks of gestation, RSV prophylaxis with palivizumab was associated with a 38.8% decrease in hospitalization rates due to LRTIs (8% in the untreated group and 4.9% in the palivizumab group), although this difference was deemed statistically insignificant ($p=0.577$). The hospitalization rates due to LRTIs for infants in Group 1 born after 29-32 weeks of gestation was 7.5% compared to a rate of 6.5% in Group 2. Treatment with palivizumab was not associated with a significant decrease in hospitalization rates in infants born with a GA of 29-32 weeks (Table III).

In infants with BPD born at $\leq 28^{6/7}$ weeks of gestation, treatment with palivizumab was associated with a 39.1% decrease in LRTI-related hospitalization rates (14.3% in the untreated group vs. 8.7% in the palivizumab group), although the difference between groups was again deemed statistically insignificant ($p=0.677$). An analysis on infants with a GA of 29-32 weeks and BPD could not be performed due to insufficient data.

General cost analysis revealed the total cost of hospitalization for the 71 infants who did not receive palivizumab (Group 2) was 9,670 USD, or 136.20 USD per infant. On the other hand, the total cost of hospitalization and palivizumab treatment for the 201 infants in Group 1 was 439,611 USD, or 2,187 USD per infant. Had the 201 infants in the palivizumab group not received RSV prophylaxis, the estimated cost of hospitalization according to calculations made for the 71 infants in Group 2 would have been 27,387 USD. Based on this assumption, treatment with palivizumab was associated with a total added cost of 412,223 USD in the 201 infants from Group 1 (Table IV).

A separate cost analysis performed for infants born at $\leq 28^{6/7}$ weeks of gestation revealed a total hospitalization cost of 1,665 USD for the 25 patients who did not receive palivizumab, which translated to a per infant cost of 66.50 USD. The cost of hospitalization and treatment for the 81 patients who received palivizumab was 192,301 USD, or a cost per infant of 2,374 USD. If the 81 patients who were given palivizumab had not been treated, the estimated cost of hospitalization would have been 5,393 USD, which corresponds to a loss of 186,908 USD associated with palivizumab treatment (Table V).

The *Number Needed to Treat* (NNT) for all infants born at $\leq 29^{6/7}$ weeks of gestation was 112, while for infants who also had BPD the calculated NNT was 59. Although the NNT for all infants born at $\leq 28^{6/7}$ weeks of gestation was 32, results of subgroup analysis revealed that infants with a GA of $\leq 28^{6/7}$ weeks who also had BPD were at the highest risk, with an NNT of 18.

Discussion

Recommendations regarding the use of palivizumab vary between countries. Variations in the RSV season for the northern and southern hemispheres, differences in the distribution of GA and birth weights of premature infants, differences in BPD rates that are affected by GA, the higher number of working mothers in the west that results in the introduction of children to daycare at an earlier age, the high cost of palivizumab treatment, and the differences in hospitalization costs between countries have all prompted nations

Table III. Lower Respiratory Tract Infection-Related Hospitalization Rates According to Gestational Age

Gestational age	Groups	LRTI-related hospitalization n (%)	p-value
$\leq 28^{6/7}$ weeks (n=106)	Group 1	4 (4.9%)	0.577
	Group 2	2 (8.0%)	
	Total	6 (5.7%)	
29-32 weeks (n=166)	Group 1	9 (7.5%)	0.828
	Group 2	3 (6.5%)	
	Total	12 (7.2%)	

LRTI: Lower respiratory tract infection.

Table IV. General Cost Analysis for Infants Treated (Group 1) or Not Treated (Group 2) with Palivizumab

Groups	LRTI-related hospitalization	N	Min. (USD)	Max. (USD)	Sum (USD)	Mean (USD)	Std. Deviation
Group 2 (n=71)	–	66	.0	.0	.0	.0	.0
	+	5	92.2	5216.7	9672.2	1934.4	1931
Group 1 (n=201)	–	188	516.3	2581.8	374361.9	1991.2	546
	+	13	1811	19282.1	65249.6	5019.2	4505

LRTI: Lower respiratory tract infection. USD: United States dollars.

to generate their own guidelines regarding palivizumab prophylaxis[11].

In 1998, the AAP initially recommended the use of palivizumab[1] in children aged <24 months who required treatment for BPD within six months of the RSV season,[2] in infants with a GA of <29 weeks up to 12 months of age,[3] in infants with a GA of 29-32 weeks up to 6 months of age, and[4] in infants with a GA of 32-35 weeks if they have additional risk factors[18]. These recommendations were revised in 2003 to include[1] infants with a GA of 32-35 weeks who have at least 2 of 5 additional factors, if under the age of 6 months, and[2] children with hemodynamically significant CHD if under the age of 24 months. It was also proposed that palivizumab could be considered in children with severe immunodeficiency[19]. The most current guidelines were last updated and published in 2009[20], and starting from November 1, 2009, palivizumab prophylaxis is now also recommended for infants with a GA 32-35 weeks who have 1 of 2 risk factors (in child care or >1 child <5 years of age in the household), if under 3 months of age. Other proposals include a dose cap of a maximum of 5 doses for patients with CHD, BPD or a GA of <32 weeks, and of 3 doses for infants with a GA of 32-35 weeks.

There remains a chasm between AAP recommendations and current clinical practice, mainly due to non-adherence to the proposed number of doses as well as other recommendations. Nevertheless, experts are all in agreement that treatment with palivizumab should be reserved for children who are most likely to benefit from RSV prophylaxis[21]. In a recent cost analysis study from the US on 159,790 children under the age of 2 years, RSV prophylaxis with palivizumab was found to be associated with significant reductions in hospitalization rates in infants at high risk for infection, while also proving cost-effective[22].

On the other hand, in Europe, where the healthcare system and associated costs are different, there has been a general trend towards limiting the use of palivizumab following the publication of recent data. In a cost-effectiveness analysis study from Germany on 1,103 premature infants, it was reported that treating all premature infants with palivizumab was very expensive and not cost-effective. Investigators therefore recommend RSV prophylaxis be given to a select group of infants with BPD who were considered to be at a higher risk for developing a severe RSV infection[13]. National guidelines in the Netherlands also recommend RSV prophylaxis to high-risk groups (GA of ≤28 weeks, male gender, infants born during the RSV season, and infants with BPD). Similarly, following the results of a comprehensive study involving 29 hospitals from the Netherlands, prophylaxis with palivizumab was only found to be cost-effective in patients with BPD when given during the RSV season[14]. In another study from Sweden in which the records of 3,801 infants from a period spanning from 1990-2005 were retrieved from the national database, it was observed that prophylaxis with palivizumab was cost-effective in premature infants with a GA of <29 weeks, but only when the risks of asthma or death were also taken into consideration[16].

In 2002, following a cost-effectiveness analysis from New Zealand, a joint decision was made to limit the indications of palivizumab treatment. Following a meeting also held in New Zealand, a consensus panel came up with the recommendation that infants with chronic lung disease discharged on home oxygen were the priority for palivizumab treatment, followed by premature infants with a GA of ≤28 weeks[23].

Table V. Cost Analysis for Each Group According to Gestational Age

Gestational age	Groups	LRTI-related hospitalization	N	Min. (USD)	Max. (USD)	Sum (USD)	Mean (USD)	Std. Deviation
≤28$^{6/7}$ weeks (n=106)	Group 2	–	23	.0	.0	.0	.0	.0
		+	2	92.2	1572.9	1665.1	832.5	1046.9
	Group 1	–	77	516.3	2581.8	172981	2246.5	416.8
		+	4	2846.7	7146.9	19320.7	4830.1	1958.3
29-32 weeks (n=166)	Group 2	–	43	.0	.0	.0	.0	.0
		+	3	1261.2	5216.7	8007	2669	2210.4
	Group 1	–	111	516.3	2581.8	201380.9	1814.2	556.4
		+	9	1811	19282.1	45928.9	5103.2	5383.1

LRTI: Lower respiratory tract infection. USD: United States dollars.

Administration of palivizumab prophylaxis based on AAP criteria (criteria for GA >32 weeks excluded) did not seem to have any benefit in our study population. Although palivizumab did seem to be associated with reductions in hospitalization rates of preterm infants with a GA of ≤28$^{6/7}$ weeks (39.1% decrease for patients with BPD, 38.8% decrease for patients without BPD), this reduction was deemed statistically insignificant. With a NNT of 18, infants born at ≤28$^{6/7}$ weeks of gestation with BPD were considered to have the highest risk. However, due to the high cost of treatment combined with the low cost of hospitalization, administration of palivizumab does not seem cost-effective for any GA. In our study, we estimated an added cost of 412,223 USD associated with the use of palivizumab compared to conservative treatment.

Several prospective studies have shown RSV prophylaxis to reduce morbidity, with no benefit with regard to mortality[8-10]. The effect of palivizumab treatment on mortality could not be evaluated in our study since none of the patients in either of the groups died.

Another area where the use of palivizumab remains unclear is for endemic nosocomial RSV. A nosocomial RSV infection is defined as the development of an RSV infection ≥5 days (3-7 days) after admission, confirmed by either laboratory tests or culture. Nosocomial RSV infections are known to have a more severe clinical course than community-acquired infections. An endemic is believed to occur following an outbreak of nosocomial RSV infections in a few cases.

The Spanish Neonatology Society defines a nosocomial RSV endemic as the presence of three or more cases (including the index case) of infections that developed after hospitalization[24]. During the RSV endemic in our neonatal intensive care unit (NICU) in January 2009, a total of 15 infants developed an RSV infection, 5 (33%) of whom died during follow-up. Implementation of tight measures of infection control and maintenance of stringent hygienic conditions, along with the administration of palivizumab prophylaxis, helped prevent the spread of the RSV epidemic to the remaining 37 preterm infants. This experience has prompted our recommendation of palivizumab prophylaxis to hospitalized preterm infants during an outbreak of RSV[25].

The retrospective nature of our study has its limitations, the most important of which being that infants hospitalized for LRTIs were not tested for RSV. Furthermore, the study group did not include any patients with CHD. Nevertheless, our study remains the only clinical study from Turkey to evaluate the cost-effectiveness of palivizumab by comparing LRTI-related hospitalization rates and cost of infants who were treated with palivizumab with those who did not receive RSV prophylaxis. Our results need to be confirmed by a prospective study on a larger group of patients to help determine hospitalization costs related to RSV infections.

Our study results suggest that administration of palivizumab does not have any cost benefit, regardless of GA. However, a reduction in hospitalization rates in association with palivizumab treatment was observed in infants

born at ≤28$^{6/7}$ weeks of gestation with or without BPD. Adapting RSV prophylaxis criteria designed for developed countries to developing countries, such as Turkey, would be expected to have a heavy toll on the cost of healthcare. Palivizumab prophylaxis as[1] for all infants with a GA of <29 weeks (28 weeks +6/7 days) who are younger than 1 year of age during the RSV season, regardless of the presence of BPD and[2] for infants younger than 2 years of age who receive BPD-specific treatment (oxygen supplementation, bronchodilators, diuretics, corticosteroid) within 6 months of the start of the RSV season may be considered to be useful for Turkey.

On the other hand, based on our previous report, in the presence of at least three concurrent cases of confirmed RSV infection in the NICU, prophylaxis may be commenced for all premature infants with a GA of <29 weeks or for those with BPD who are born after 29 weeks of gestation in the NICU.

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