Prospective, Randomized Comparison of OM-85 BV and a Prophylactic Antibiotic in Children with Recurrent Infections and Immunoglobulin A and/or G Subclass Deficiency

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ABSTRACT

Background: Patients with immunoglobulin (Ig)A and/or IgG subclass deficiency may be asymptomatic or may have recurrent, mainly respiratory infections.

Objective: This study compared the clinical efficacy and tolerability of prophylactic therapy with either the oral immunomodulator bacterial extract OM-85 BV or benzathine penicillin G (BPG) in the prevention of recurrent infections in symptomatic patients.

Methods: In this 26-month, prospective, randomized study conducted at the Department of Pediatric Immunology, Ege University (Izmir, Turkey), children aged 1 to 12 years with recurrent infections and IgA and/or IgG subclass deficiency were enrolled. After an initial 12-month control period, patients were randomized to receive OM-85 BV or BPG. OM-85 BV (3.5-mg capsule) was given once daily for the first 10 days of each month for the first 3 months of the study. IM injections of BPG were given at a dose of 1.2 million units (for patients with body weight >27 kg) or at a half-dose (for patients with body weight ≤27 kg) every 3 weeks for 12 months. In nonresponders (ie, those who continued to have recurrent infections at 12-month follow-up), IV immunoglobulin (IVIG) replacement therapy at 400 mg/kg body weight was given every 4 weeks for an additional 12 months. The results of IVIG therapy were assessed by the authors using clinical observation. Adverse effects and adverse drug reactions were documented by the authors for each vaccine, prophylactic therapy, and IVIG.

Results: A total of 91 children (56 boys, 35 girls; mean [SD] age at the start of the control period, 46.4 [31.0] months) were enrolled. Of these, 44 were

randomized to the OM-85 BV group and 47 to the BPG group. The year before prophylactic therapy, the mean (SD) number of reported infections was 10.7 (3.6) and the mean (SD) number of antibiotic courses was 9.7 (3.6) (OM-85 BV group: mean [SD] number of reported infections, 10.5 [3.3]; mean (SD) number of antibiotic courses, 9.3 [3.3]; BPG group: mean [SD] number of reported infections, 10.8 [3.9], mean (SD) number of antibiotic courses, 10.1 [3.9]). At 12 months, the number of infections and antibiotic courses decreased significantly in the entire study population, but the between-group difference was not significant. Five patients in each group (OM-85 BV group, 11.4%; BPG group, 10.6%) were considered nonresponders and received IVIG treatment. Compared with responders, nonresponders were significantly younger (mean [SD] age, 34.40 [21.70] months vs 52.65 [30.52] months; $P = 0.036$) and had lower serum IgG ($P < 0.001$), IgG1 ($P = 0.006$), IgG2 ($P = 0.003$), IgG3 ($P = 0.035$), and IgM ($P = 0.008$) levels and antibody responses to tetanus toxoid and *Haemophilus influenzae* type b (Hib) vaccines ($P = 0.036$ and 0.013, respectively). At 12-month follow-up, a protective effect of the prophylactic IVIG therapy was seen, with a statistically significant reduction in the number of infections to 3.3 (2.4) and in the number of antibiotic courses to 2.7 (2.5) (both $P = 0.005$).

Conclusions: In this study population of children with recurrent infections and IgA and/or IgG subclass deficiency, prophylactic therapy with either OM-85 BV or an antibiotic significantly decreased the number of infections per year. In addition, nonresponders benefited from IVIG replacement therapy. (*Curr Ther Res Clin Exp.* 2003;64:600–615) Copyright © 2003 Excerpta Medica, Inc.

Key words: IgA deficiency, IgG subclass deficiency, prophylactic therapy, intravenous immunoglobulin.

INTRODUCTION

Patients with immunoglobulin (Ig)A and/or IgG subclass deficiencies may be asymptomatic or have recurrent infections. Prophylactic treatment should be considered for patients whose clinical symptoms recur. In these patients, first-line treatment includes antibiotic therapy early in the course of the infection, supportive symptomatic therapy, vaccination with conjugate vaccines, and prophylactic antibiotics.^{1–3} Gandhi et al⁴ reported that prophylactic antibiotics were an effective treatment modality in children with chronic sinusitis, even in those with selective immune abnormalities. Patients who have recurrent infections and are poorly responsive to medical management are candidates for IV immunoglobulin (IVIG) replacement therapy.^{5–7} Patients with IgA and/or IgG subclass deficiency have frequent infections with pneumococci and *Haemophilus influenzae*. It is important to measure specific antibodies against these microorganisms before and after vaccination with the polysaccharide or conjugate vaccines now commercially available.^{8,9}

OM-85 BV is an immunostimulating extract of 8 bacterial pathogens of the upper respiratory tract (*H influenzae*, *Streptococcus pneumoniae*, *Klebsiella pneumoniae*, *Klebsiella ozaenae*, *Staphylococcus aureus*, *Streptococcus pyogenes*, *Streptococcus viridans*, and *Branhamella catarrhalis*). OM-85 BV, which works through mucosa-associated tissue, activates and regulates various components of the immune system. Several randomized clinical trials¹⁰⁻¹³ have shown that OM-85 BV can reduce the number of acute respiratory tract infections (RTIs) by 25% to 50% compared with placebo in adults and children with a history of recurrence.

Aksit et al¹⁴ have reported that IM benzathine penicillin G (BPG) prophylaxis is effective in preventing group A beta-hemolytic streptococcal pharyngitis in children. Gunzenhauser et al¹⁵ studied the effect of BPG in the prevention of febrile acute respiratory disease among US Army trainers. The reduction in the annual admission for febrile acute respiratory disease was 64.2% with prophylaxis. Throat culture results supported the hypothesis that BPG has a broad effect in the prevention of febrile acute RTI that extends beyond the simple elimination of group A streptococcal infection.

We assessed the clinical efficacy and tolerability of oral prophylactic therapy with either OM-85 BV or BPG in the prevention of recurrent infections in children with IgA and/or IgG subclass deficiency.

PATIENTS AND METHODS

This 26-month, prospective, randomized study was conducted at the Department of Pediatric Immunology, Ege University (Izmir, Turkey) from September 2000 to November 2002. The study was approved by the local ethics committee.

Patients

Children aged 1 to 12 years with recurrent infections and IgA and/or IgG subclass deficiency documented by laboratory analyses were enrolled. An IgA level <5 mg/dL was considered *complete IgA deficiency*. Levels >5 mg/dL but <2 SD below the age-related mean level were considered *partial IgA deficiency*. IgG subclass levels <2 SD below the age-related mean level were considered *IgG subclass deficiency*.^{16,17} *Recurrent infection* was defined as the presence of ≥6 episodes of infection during the previous 12 months. Children with anatomic abnormalities of the respiratory tract, chronic respiratory disease, autoimmune disease, liver or kidney failure, malnutrition, or cancer, and those receiving corticosteroids, immunosuppressants, immunostimulants, γ -globulin, or anti-convulsive drugs were excluded. Parents or guardians provided written informed consent prior to the study.

Methods

The 12-month period before the administration of prophylactic therapy was used as the control period for each child. At the end of that period, the following

data were collected from the patients' medical records obtained from their referring physician at study entry: age at onset of recurrence, number of infections, number of antibiotic courses, infection type, and number of hospitalizations. Some patients also were observed for 3 to 6 months to confirm that they experienced recurrent infections.

The risk factors for recurrent infections (eg, gestational age at birth, birth weight, history of allergy, duration of breastfeeding, number of children living at home, number of persons living at home, attendance of the child or a sibling at a day-care center or school, and number of persons smoking in the home) also were recorded at study entry.

Serum IgA, IgG and IgG subclass, and IgM levels were determined by immunonephelometry (BNTM II Nephelometer, Dade Behring Inc., Deerfield, Illinois) before prophylactic therapy and at 3- and 12-month follow-up.

In some patients, IgG antibody levels to tetanus toxoid were measured using Euroimmun Microplate enzyme-linked immunosorbent assay (ELISA) (EUROIMMUN AG, Lübeck, Germany) because all 91 patients had been previously immunized with this protein antigen (because of the limited availability and high cost of commercial kits in our laboratory at the time of the study, not all patients underwent IgG antibody measurement). Antibody levels ≥ 0.1 IU/mL were considered protective.¹⁸ For patients with serum levels of anti-tetanus antibody < 0.1 IU/mL (unprotective levels), repeat vaccination was provided using IM injection of 0.5 mL of tetanus toxoid vaccine. Four weeks later, antibody levels were measured again. Children whose levels were not protective were considered tetanus toxoid vaccine failures.

At study entry (before prophylactic therapy), some children were immunized using an IM injection of 0.5 mL of the conjugated *H influenzae* type b (Hib) vaccine (because of the limited availability and high cost of commercial kits in our laboratory at the time of the study, not all patients underwent Hib vaccination). Sera were obtained before and 4 weeks after vaccination and were stored at -20°C . In patients with a history of having received the conjugated Hib vaccine, postimmunization antibody titers were measured directly. IgG antibodies against Hib were quantitated using the Binding Site[®] ELISA kit (The Binding Site Ltd., Birmingham, United Kingdom). An antibody level ≥ 1 $\mu\text{g/mL}$ as measured using ELISA was considered protective.¹⁹ Children whose level was < 1.0 $\mu\text{g/mL}$ underwent repeat vaccination. Four weeks later, children with unprotective levels were considered conjugated Hib vaccine failures.

After the control period, patients were randomized to receive prophylactic therapy with either OM-85 BV or BPG. The names of the participants were sorted alphabetically, and patients were assigned to treatment according to a random list in blocks of 5. In the OM-85 BV group, patients were given 1 capsule of OM-85 BV* (3.5 mg) daily for the first 10 days of each month for the first 3

*Trademark: Broncho-Vaxom[®] (OM PHARMA, Geneva, Switzerland).

months of the study and then received no treatment for the subsequent 9 months of the study. Patients in the BPG group were treated every 3 weeks with a single IM injection of 1.2 million units (for patients with body weight >27 kg) or a half-dose (for patients with body weight ≤27 kg) for 12 months. All patients were followed up for 12 months at 3-month intervals and each time they had symptoms of infection. All physical examinations and drug prescriptions were performed by the authors.

Efficacy Assessment

During the 12 months of the trial, the type and number of infections and the number of antibiotic treatments and hospitalizations were recorded. A diagnosis of acute upper RTI was made in the presence of rhinorrhea and/or sore throat or cough without signs of acute lower RTI for ≥48 hours. Otitis media was diagnosed by otoscopic examination. Pulmonary infection was diagnosed when 1 or more of the following clinical findings were present: fever, cough, rhonchi, and/or rales. The diagnosis was confirmed using chest radiography. The diagnosis of a urinary tract infection was based on clinical symptoms, urinalysis (pyuria), and confirmed by a urine culture. Gastrointestinal infection was diagnosed by the presence of watery or bloody diarrhea more than 6 times a day and stool specimen examinations. Sinusitis was diagnosed on the basis of radiographic examination of the sinuses prompted by the presence of cough, halitosis, and purulent nasal discharge. Because only a few viral investigations (eg, cytomegalovirus and Epstein-Barr virus) could be performed by the Department of Microbiology at Ege University, we could not distinguish infections according to etiologic agent (bacterial or viral).

If the number of infections at 12-month follow-up decreased <25% compared with the control period in any patient, that patient was considered a non-responder to prophylactic therapy. In these patients, prophylactic IVIG replacement therapy at 400 mg/kg body weight was given every 4 weeks for an additional 12 months. During the IVIG treatment period, patients were followed up every 4 weeks and each time they had symptoms of infection. The type and number of infections and the number of antibiotic treatments were recorded.

IVIG was administered by a pediatric immunologist or nurse. The results of IVIG therapy were assessed by the authors using clinical observation during the 12-month follow-up.

Tolerability Assessment

Adverse effects and adverse drug reactions were documented by the authors at each follow-up visit, using patient interview, for each vaccine, prophylactic therapy, and IVIG.

Statistical Analysis

The Statistical Package for Social Sciences version 6.0 (SPSS Inc., Chicago, Illinois) was used for all analyses. The comparisons between groups were made

using appropriate statistical methods (chi-square test, Fisher exact test for categorical analyses, and Student *t* test and Mann-Whitney *U* test for continuous variables). Antibody values were expressed as geometric means and comparisons of preimmunization and postimmunization antibody titers and comparisons of pre-treatment and posttreatment variables; comparisons of follow-up immunoglobulin levels were made by the paired *t* test. $P < 0.05$ was considered significant.

RESULTS

Ninety-one patients (56 boys, 35 girls) were enrolled (44 in the OM-85 BV group and 47 in the BPG group). On enrollment, the mean (SD) age was 46.4 (31.0) months, and at the beginning of the prophylactic therapy the mean age was 50.6 (30.1) months. All participants completed the trial.

Selective IgA deficiency was the most common condition (32 patients [35.2%]); 7 patients (7.7%) had complete IgA deficiency and 25 patients (27.5%) had partial IgA deficiency. The other immunologic abnormalities were as follows: IgG3 deficiency (25 patients [27.5%]), IgA + IgG3 deficiency (20 patients [22.0%]), IgG2 deficiency (5 patients [5.5%]), IgA + IgG2 + IgG3 deficiency (4 patients [4.4%]), IgA + IgG2 deficiency (3 patients [3.3%]), and IgG2 + IgG3 deficiency (2 patients [2.2%]). At the start of the control period, the mean (SD) number of reported infections was 10.7 (3.6) and the number of antibiotic courses was 9.7 (3.6) (OM-85 BV group: mean [SD] number of reported infections, 10.5 [3.3]; mean (SD) number of antibiotic courses, 9.3 [3.3]; BPG group: mean [SD] number of reported infections, 10.8 [3.9]; mean (SD) number of antibiotic courses, 10.1 [3.9]). Most patients had documented recurrent episodes of acute upper RTIs (88 patients [96.7%]) and/or otitis media (33 patients [36.3%]), and 30 patients (33.0%) had episodes of pulmonary infection that were documented using chest radiography. Urinary tract infections, gastrointestinal infections, and sinusitis were seen in 16 (17.6%), 15 (16.5%), and 11 (12.1%) patients, respectively.

All patients had received tetanus toxoid vaccine; antitetanus antibody level was measured in 65 patients (71.4%). Of those 65 patients, 8 (12.3%) were considered vaccine failures (3 patients [4.6%] with IgA deficiency and 5 patients [7.7%] with IgA + IgG3 deficiency). However, all 8 (100.0%) produced protective antibody responses to repeat tetanus toxoid vaccination.

Nineteen children (20.9%) had received the Hib vaccine, and an additional 37 (40.7%) received it in our study. On investigation of the occurrence of conjugated Hib and tetanus toxoid vaccine failures, we found that after immunization the geometric mean titer of anti-Hib was significantly increased ($P < 0.001$) (Table I). Nine of the 37 patients (24.3%) receiving the Hib vaccine had high anti-Hib preimmunization levels that were attributed to previous infections; 1 of the 37 patients (2.7%) receiving the Hib vaccine with IgA + IgG3 deficiency failed to respond to conjugated Hib vaccine (before immunization, 0.13 µg/mL; after immunization, 0.65 µg/mL). Conversely, 3 of the 19 patients (15.8%) who

Table I. Antibody titers in study patients (N = 91).

Antibody	Geometric Mean	Range
Antitetanus antibody level after immunization, IU/mL (n = 65)	1.16	0.12–6.32
Anti-Hib antibody level, µg/mL		
Before immunization (n = 37)	0.44	0.11–12.30
After immunization (n = 56)	6.98*	0.65–26.44

Hib = *Haemophilus influenzae* type b.

* $P < 0.001$ versus before immunization (paired t test).

had received the Hib vaccine had low anti-Hib levels and responded to repeat vaccination (2 patients [10.5%] with IgA + IgG3 deficiency and 1 patient [5.3%] with IgA deficiency).

Efficacy

Both prophylactic therapy groups had similar baseline demographic and clinical characteristics at the beginning of the trial (Table II). The risk factors for recurrent infections, hematologic values, serum immunoglobulin levels, IgG subclasses, and specific antibody responses to conjugated Hib and tetanus toxoid vaccine also were similar in the 2 groups.

When the numbers of infections and antibiotic courses in each group at 12 months were compared with the numbers in the medical records 12 months before the trial, significant reductions were detected in both groups during prophylactic therapy (both $P < 0.05$). The mean (SD) rates of infection were significantly reduced, by 56.6% (23.2%) in the OM-85 BV group and 54.1% (22.4%) in the BPG group (both $P < 0.05$). No significant between-group differences were found.

Mean (SD) values of immunoglobulin and IgG subclasses in the OM-85 BV and BPG groups before and after immunization are shown in Tables III and IV, respectively. Although after 3 months of treatment IgA, IgG, and IgM levels were similar to pretreatment levels in both groups, at 12-month follow-up the levels had increased significantly (except the IgM level in the OM-85 BV group) ($P < 0.05$). At 3-month follow-up, the IgG1 levels in the OM-85 BV group and the IgG2 levels in the BPG group were significantly higher than pretreatment levels (both $P < 0.05$). At 12 months, IgG1 and IgG2 levels were significantly increased in both groups and IgG3 levels were significantly increased in the OM-85 BV group (all $P < 0.05$).

In the entire study population, the rate of hospitalization decreased significantly at 12 months compared with before treatment, from 17.6% (16/91) to 1.1% (1/91) ($P = 0.029$). At 12 months, the numbers of infections and antibiotic treatments were reduced significantly in the entire study population, by 55.8%

Table II. Baseline demographic and clinical characteristics of study patients (N = 91) before prophylactic therapy, and the effects of the prophylactic therapeutic regimens during the trial compared with the previous year. (Values are expressed as mean [SD] unless otherwise indicated.)*

Characteristic	OM-85 BV Group (n = 44)	BPG Group (n = 47)
Age, mo	44.2 (27.6)	56.5 (31.4)
Sex, no. (%)		
Boys	28 (63.6)	28 (59.6)
Girls	16 (36.4)	19 (40.4)
Age of onset of recurrent infection, mo	9.9 (8.4)	14.1 (12.4)
Before prophylactic therapy		
No. (%) of hospitalized patients	10 (22.7)	6 (12.8)
No. of infections	10.5 (3.3)	10.8 (3.9)
No. of antibiotic courses	9.3 (3.3)	10.1 (3.9)
After prophylactic therapy		
No. (%) of hospitalized patients	1 (2.3) [†]	0 (0.0) [†]
No. of infections	4.4 (2.5) [†]	4.8 (2.9) [†]
Reduction rate of the infections, %	56.6 (23.2)	54.1 (22.4)
No. of antibiotic courses	4.0 (2.6) [†]	4.0 (2.8) [†]
Reduction rate of antibiotic courses, %	55.2 (27.2)	56.4 (28.0)
No. (%) of nonresponders	5 (11.4)	5 (10.6)

BPG = benzathine penicillin G.

*No significant between-group differences were found.

[†] $P < 0.05$ versus before prophylactic therapy (paired t test).

and 55.3%, respectively (both $P < 0.05$). Fifty-nine of the 91 children (64.8%) had a $\geq 50.0\%$ reduction in the number of infections during the trial compared with the previous year and 22 (24.2%) had a 25.0% to 49.0% reduction. In contrast, 10 patients (11.0%; 5 patients each from the OM-85 BV group [11.4%] and the BPG group [10.6%]; 5 [5.5%] with IgG3 deficiency, 2 [2.2%] with IgA + IgG2 deficiency, 2 [2.2%] with IgG2 + IgG3 deficiency, 1 [1.1%] with IgA + IgG3 deficiency) had poor outcomes ($< 25.0\%$ reduction in the mean [SD] number of infections) during prophylactic therapy (from 11.1 [3.2] to 9.20 [2.78] infections per year). These patients were considered nonresponders and were treated with IVIG replacement therapy. Compared with responders, nonresponders were significantly younger (mean [SD] age, 34.40 [21.70] months vs 52.65 [30.52] months; $P = 0.036$). They also had lower serum IgG ($P < 0.001$), IgG1 ($P = 0.006$), IgG2 ($P = 0.003$), IgG3 ($P = 0.035$), and IgM ($P = 0.008$) levels (Table V), as well as significantly lower postimmunization antibody responses to tetanus toxoid ($P = 0.036$) and conjugated Hib vaccine ($P = 0.013$) (Table VI). The outcome of the prophylactic treatment was inversely correlated with age; serum IgG, IgG1, IgG2, IgG3, and IgM levels; and antibody responses to conjugate Hib and tetanus toxoid vaccines.

Table III. Mean (SD) immunoglobulin (Ig) levels before and after treatment in the OM-85 BV group (n = 44).

Immunoglobulin	Before Treatment	After Treatment	
		Month 3	Month 12
IgA, mg/dL	44.5 (34.0)	48.5 (31.8)	52.6 (31.4)*
IgG, mg/dL	760.6 (267.4)	795.9 (230.5)	836.2 (237.9)*†
IgG1, g/L	5.58 (1.63)	6.23 (1.78)*	6.51 (1.73)*†
IgG2, g/L	1.21 (0.64)	1.33 (0.72)	1.41 (0.72)*†
IgG3, g/L	0.20 (0.11)	0.19 (0.09)	0.23 (0.25)*
IgG4, g/L	0.32 (0.31)	0.30 (0.22)	0.30 (0.26)
IgM, mg/dL	96.9 (39.4)	94.5 (37.5)	92.8 (36.8)

* $P < 0.05$ versus before treatment (paired t test).† $P < 0.05$ versus month 3 (paired t test).

The 10 nonresponders were treated with IVIG. After 12 months of IVIG therapy, a significant protective effect of the IVIG replacement therapy was observed, with a significant reduction in the mean (SD) number of infections (from 11.1 [3.2] to 3.3 [2.4] infections per year; $P = 0.005$) and in the number of antibiotic courses (from 10.4 [2.4] to 2.7 [2.5] courses per year; $P = 0.005$).

Tolerability

No treatment-related adverse effects were documented during treatment with either prophylactic regimen or during vaccinations. However, mild systemic adverse drug reactions (fever, headache, nausea) were documented in 2 of

Table IV. Mean (SD) immunoglobulin (Ig) levels before and after treatment in the benzathine penicillin G group (n = 47).

Immunoglobulin	Before Treatment	After Treatment	
		Month 3	Month 12
IgA, mg/dL	39.7 (30.6)	43.6 (30.7)	47.3 (32.3)*†
IgG, mg/dL	836.6 (306.0)	831.9 (293.0)	887.6 (335.3)*†
IgG1, g/L	6.64 (2.21)	6.63 (2.11)	6.94 (2.45)*†
IgG2, g/L	1.52 (0.87)	1.71 (0.87)*	1.85 (0.93)*†
IgG3, g/L	0.24 (0.17)	0.24 (0.16)	0.24 (0.16)
IgG4, g/L	0.28 (0.30)	0.35 (0.64)	0.32 (0.33)
IgM, mg/dL	92.9 (35.0)	91.9 (38.3)	97.3 (39.4)*†

* $P < 0.05$ versus before treatment (paired t test).† $P < 0.05$ versus month 3 (paired t test).

Table V. Mean (SD) serum immunoglobulin (Ig) levels in responders and nonresponders to prophylactic therapy.

Immunoglobulin	Responders (n = 81)*	Nonresponders (n = 10) [†]	P
IgA, mg/dL	41.68 (33.39)	45.16 (21.10)	0.320
IgG, mg/dL	824.0 (288.0)	557.0 (90.0)	<0.001
IgG1, g/L	6.31 (2.02)	4.58 (1.10)	0.006
IgG2, g/L	1.42 (0.75)	0.85 (0.84)	0.003
IgG3, g/L	0.23 (0.13)	0.19 (0.22)	0.035
IgG4, g/L	0.31 (0.31)	0.17 (0.12)	0.144
IgM, mg/dL	98.1 (36.0)	67.2 (22.0)	0.008

*Responders = patients in whom the number of infections during the 12-month follow-up period decreased $\geq 25\%$ compared with the previous year.

[†]Nonresponders = patients in whom the number of infections during the 12-month follow-up period decreased $< 25\%$ compared with the previous year.

the 10 patients (20.0%) who received IVIG therapy during the first infusion. These patients responded well to premedication with antihistamines for the later infusions.

DISCUSSION

In IgA and/or IgG subclass deficiency, assessing the patient's specific antibody responses is of crucial importance. Titers should be monitored after immunization with conjugate vaccines because booster doses may be required to elicit a protective antibody level.^{8-9,20} In our study, all of the vaccine failures responded to repeat vaccination.

Table VI. Antibody titers in responders and nonresponders to prophylactic therapy. (Values are expressed as geometric mean.)

Antibody	Responders*	Nonresponders [†]	P
Antitetanus antibody level after immunization, IU/mL	1.25 (n = 60)	0.44 (n = 5)	0.036
Anti-Hib antibody level, $\mu\text{g/mL}$			
Before immunization	0.44 (n = 33)	0.27 (n = 4)	0.851
After immunization	7.58 (n = 51)	1.62 (n = 5)	0.013

Hib = *Haemophilus influenzae* type b.

*Responders = patients in whom the number of infections during the 12-month follow-up period decreased $\geq 25\%$ compared with the previous year.

[†]Nonresponders = patients in whom the number of infections during the 12-month follow-up period decreased $< 25\%$ compared with the previous year.

Some patients with IgA and/or IgG subclass deficiency are prone to recurrent infections affecting their activities of daily living. Prophylactic antimicrobial therapy is beneficial in many of these patients. In our study, at 12 months, the patients in the BPG group had fewer infections compared with pretreatment and required fewer antibiotic treatments compared with the previous year.

Studies^{21–24} have shown that OM-85 BV increases the expression of adhesion molecules at the surface of polymorphonuclear leukocytes and enhances natural killer cell activity and the production of tumor necrosis factor alpha, interleukin (IL)-1, IL-2, and interferon gamma by human peripheral blood mononuclear cells. OM-85 BV also has been shown to stimulate the phagocytic and metabolic activity of macrophages and to induce B-lymphocyte proliferation.^{25,26} Bessler et al²⁷ found that OM-85 BV exhibits adjuvant properties when used with antigens, such as influenza vaccine. An in vitro experiment²⁸ indicated that OM-85 BV exerts immunomodulatory action on the signal transducer gp130 and gp130-binding cytokines, such as IL-6, IL-11, and IL-12. Oral administration of OM-85 BV also led to enhanced salivary and lung IgA levels in humans.²⁹ Emmerich et al³⁰ reported that after treatment with OM-85 BV in adult patients with non-obstructive chronic bronchitis, bronchoalveolar lavage (BAL) fluid CD4⁺/CD8⁺ lymphocyte ratio and BAL interferon gamma levels were increased. Furthermore, alveolar macrophage activity normalized and the BAL fluid IgA level increased. These findings indicate that OM-85 BV is capable of stimulating both cellular and humoral components of the immune response, resulting in enhancement of defense mechanisms against RTIs.

Several double-blind, placebo-controlled clinical trials^{13,31–33} demonstrated that adults and children treated with OM-85 BV experienced fewer recurrences of infections, were absent from work or school less frequently, and required fewer antibiotic treatments. In a randomized, double-blind, placebo-controlled study, Gutierrez-Tarango and Berber³⁴ assessed the protective effect of 2 courses of OM-85 BV for 12 months. The mean (SD) number of acute RTIs was 5.04 (1.99) in the OM-85 BV group versus 8.0 (2.55) in the placebo group ($P < 0.001$). The number of antibiotic courses and the total duration of infections also were reduced significantly. Reduction in the number of infections was 41.18% in the children aged <6 years ($P < 0.001$). According to a MEDLINE search of articles published from 1980 to 2003 and including the key terms *IgA deficiency*, *IgG subclass deficiency*, *antibiotic prophylaxis*, and *OM-85 BV*, studies of OM-85 BV in children with immune system defects are few. Also, the number of patients enrolled in this study was limited. Quezada et al³⁵ reported that in 14 children with recurrent infections and hypogammaglobulinemia, OM-85 BV improved the clinical condition and elevated the serum levels of IgG and IgA compared with placebo. In another study³⁶ in 11 patients with common variable immunodeficiency, a significant increase in serum IgA level was observed after OM-85 BV treatment, although no significant improvement was found in the clinical state. In several pediatric studies,^{12,31,34} the therapeutic regimen was OM-85 BV 3.5 mg/d for the first 10 consecutive days of each month for 3 consecutive months,

then daily for 30 days, followed by a repeat course of 10 consecutive days of therapy per month for 3 months. In our study, we preferred the first regimen, and we found that the number of infections and antibiotic courses was reduced significantly. Our study demonstrated that OM-85 BV was an effective treatment modality for children with IgA and/or IgG subclass deficiency who were experiencing recurrent infections. For all variables assessed, the effects of the 2 prophylactic therapy regimens were similar. According to our MEDLINE search, this is the first study comparing the efficacy of OM-85 BV versus antibiotic prophylaxis in children with IgA and/or IgG subclass deficiency.

Several clinical studies^{29,30} found that oral OM-85 BV therapy can locally modify nonspecific cellular defenses, but the ability to affect specific immune components, such as lymphocyte subsets and immunoglobulin, was controversial. Puigdollers et al³⁷ showed that OM-85 BV increased the levels of serum immunoglobulin and the level of IgA in saliva. Lusuardi et al²⁹ demonstrated that OM-85 BV increased IgA levels in the respiratory tracts of patients with chronic bronchitis without altering systemic immunity. In our study, serum immunoglobulin levels were similar to pretreatment levels at 3 months of treatment in both groups but were increased significantly at 12 months, except the IgM level in the OM-85 BV group. However, the pre- and posttreatment differences in serum immunoglobulin levels were attributed to the normal variation of immunoglobulin levels with age, because the increases in both groups were similar. Therefore, we concluded that the therapeutic action of OM-85 BV resulted from enhanced immune defenses in the respiratory tract.

IVIG replacement therapy should be given to patients who are not responsive to prophylactic therapeutic regimens or who have been shown to have impaired responses to the protein and polysaccharide antigens with which they have been immunized.^{6,38,39} Silk et al⁴⁰ reported that in children with IgG2 subclass and specific antibody deficiency who failed to improve after a 12-month period of prophylactic antibiotic therapy with trimethoprim-sulfamethoxazole, IVIG therapy significantly decreased the number of episodes of recurrent sinopulmonary infections. Similarly, Bernatowska-Matuszkiewicz et al³⁹ demonstrated the clinical efficacy of IVIG in pediatric patients with severe pulmonary inflammatory disease and IgG3 subclass deficiency by decreasing the duration of hospitalization and use of antibiotics and steroids. The mode of action cannot be attributed to replacement of respective isotypes, but it is probably due to replacement of specific antibodies.

In our study, the basis for IVIG therapy was the failure to demonstrate improvement with prophylactic therapies. Five patients from each prophylactic regimen had a poor outcome (<25.0% reduction in the number of infections). These patients were considered nonresponders and were treated with IVIG replacement therapy for an additional year. The outcome of the prophylactic treatment was inversely correlated with age; serum IgG, IgG1, IgG2, IgG3, and IgM levels; and antibody responses to conjugate Hib and tetanus toxoid vaccines. After immunization, the geometric mean serum IgG antibody levels to

Hib were 4-fold and to tetanus toxoid 3-fold higher in responders than in nonresponders to prophylactic therapy. IVIG therapy was associated with clinical improvement in all patients who had failed to improve with prophylactic therapy, and resulted in a significant reduction in the number of infections.

For IVIG therapy, the necessity for and the high cost of hospital visits are important negative factors. IVIG is also a limited resource, and although it has a long safety record, this therapy carries some risk of transferring disease. Our results indicate that the patients with IgA and/or IgG subclass deficiency should first be assessed for immunoglobulin levels and specific antibody responses. Prophylactic therapy with OM-85 BV or BPG may be a first step before IVIG in mildly and moderately affected patients. IVIG replacement therapy should be reserved for patients with low immunoglobulin levels and impaired responses to specific antigens and for patients not responsive to prophylactic antibiotics or OM-85 BV.

Adverse events due to OM-85 BV (mainly gastrointestinal disturbances, skin disturbances, headache, and dizziness^{12,31}) have been reported in 2.0% to 4.8% of patients treated with OM-85 BV.^{12,31} Adverse reactions to IVIG therapy are usually minor and occur in $\leq 15\%$ of patients.⁵ Generalized reactions, such as myalgia, fever, headache, nausea, and vomiting, are the most common type of reaction to IVIG. Reduction of the infusion rate of IVIG and premedication with hydrocortisone or antihistamines should be considered.⁵ In our study, no adverse events were documented during therapy with OM-85 BV or BPG. However, 2 of the 10 patients (20.0%) who received IVIG showed mild generalized reactions and responded well to premedication.

CONCLUSIONS

In this study population of children with recurrent infections and IgA and/or IgG subclass deficiency, prophylactic therapy with either OM-85 BV or an antibiotic significantly decreased the number of infections per year. In addition, nonresponders benefited from IVIG replacement therapy.

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