Advances In Therapy® | *Volume 18 No. 4*
July/August 2001

Efficacy of a Polyvalent Bacterial Lysate in Children With Recurrent Respiratory Tract Infections

Samuel Bentes Ruah, M.D.
Carlos Ruah, M.D.
Universidade Nova
Lisbon, Portugal

Antje van Aubel, M.D.
Stephan Abel, M.D.
Ulrich Elsasser
Sankyo Pharma GmbH
Munich, Germany

ABSTRACT

Respiratory tract infections (RTIs) are the most frequent infections in humans, particularly in children. In addition to intervention, increasing interest is focusing on immunomodulatory therapy for recurrent RTIs, which indicate a reduced defense capacity of the respiratory mucosa. LW 50020, an oral immunomodulator that contains the antigens of seven bacteria common in RTIs, has reduced the number, duration, and severity of RTIs in children and adults. This 56-week placebo-controlled, double-blind study in 188 children investigated whether the efficacy of the standard schedule (immunization cycle + one booster cycle) would be enhanced by additional booster cycles. Efficacy and safety over the long term were also assessed. The rate of infection was reduced by 50% with the standard schedule and could not be further decreased by two consecutive booster cycles. With both schedules, this reduction was sustained during a 28-week treatment-free observation period that followed the 28-week treatment period. The number of adverse drug reactions was low, and all were transient, expected, and nonserious. These results confirm that LW 50020 is an effective and safe strategy for RTIs.

Keywords: respiratory tract infections; oral immunomodulator; bacterial lysate; mucosa-associated; lymphoid tissue

0636

Address reprint requests to
Antje van Aubel, M.D.
Sankyo Pharma GmbH
Zielstattstr. 9
Munich, Germany

INTRODUCTION

Respiratory tract infections (RTIs) are extremely common in children and constitute a major challenge for general practitioners and pediatricians, as the reasons for increased susceptibility depend on the child's age. The role of health-care professionals has expanded from treating patients to maintaining health and preventing disease. To that end, physicians should first determine whether the recurrent infections are due to host-derived factors or are a result of environmental exposure. Host-derived factors may be nonimmunologic or related to immunodeficiency.[1] Specialist assessment is warranted in children with features suggesting an underlying major immunologic disorder.[2] Although antibody deficiencies are a significant cause of recurrent infections,[3] primary immunodeficiency or other alterations are rare in children.[4]

In young children, the leading cause of recurrent RTI is environmental exposure in day-care centers or nursery schools.[1] This increased risk has been demonstrated in children up to 5 years old.[5] Exposure to severe RTI before age 5 raised the risk of asthma in childhood and adolescence.[6,7] Other predisposing factors for recurrent RTI in children are atopy, including a family history, underlying respiratory diseases, or indoor and outdoor air pollution.[2,8-10]

Interest in allergy is growing.[11] In children, the prevalence of allergic sensitization and atopic diseases increases with rising socioeconomic status. The frequency of bronchitis, tonsillitis, and otitis media has been correlated with high social status, whereas an inverse social gradient was found for the frequency of febrile colds. Health inequalities thus exist in immune reactions and respiratory infections in children from different social classes.[12] The reasons are controversial.

Many studies show that indoor air pollution caused by cigarette smoke is associated with a heightened risk of acute RTIs and respiratory symptoms.[13] In a Swiss study in 4470 children between 6 and 14 years of age, almost half were exposed to environmental tobacco smoke and had an increased risk of RTIs.[14]

An investigation conducted in Poland in 9-year-old children exposed congenitally and postnatally to environmental tobacco smoke revealed not only an increased risk of RTI but also a nearly threefold higher risk of acute respiratory illness when tobacco smoke was combined with allergy.[15]

Susceptibility to acute RTI is also significantly related to body mass index (BMI).[9] Children with a BMI of 20 or more had a risk of acute RTI twice as high as those with a low BMI. Psychological stress as well may deplete local immune protection against viral invasion or bacterial colonization of the upper respiratory tract, thereby enhancing susceptibility to colds and flu. Alternatively, psychological disturbances may appear in response to frequent illness.[16]

Among available treatment strategies, enhancement of the host response to prevent recurrence is attracting interest. LW 50020 (Luivac®, Paspat®*), an oral immunomodulatory agent containing the antigens of seven bacteria common in RTIs, has been developed for this purpose.

The preparation induces nonspecific and specific immunity in the mucous membranes by antigenic priming of gut-associated lymphoid tissue, instigating prolifer-

*Registered trademarks of Sankyo Pharma GmbH, Munich, Germany: Luivac® in Germany, Austria, and Switzerland; Paspat® in Italy; Paspat® oral in Portugal.

ation and differentiation of immune cells and thereby exerting a protective effect against infections.[17-21] Enhanced inhibition of bacterial adherence was shown,[22] which is expected to inactivate pathogens in the respiratory mucosa.

A clinically relevant reduction of RTI by LW 50020 has already been demonstrated in controlled clinical trials that used the standard treatment schedule of immunization plus a booster cycle of 4 weeks each.[23,24]

The present study evaluated whether two additional booster cycles would further increase efficacy. The treatment period was followed by a 28-week observation period to uncover any difference in duration of efficacy between the two treatment groups.

PATIENTS AND METHODS

This was a prospective, placebo-controlled, randomized, double-blind study with parallel-group comparison. The study was approved by an ethics committee and carried out in 11 centers in Portugal according to the revised Declaration of Helsinki and the Good Clinical Practice guidelines. The guardians of all children provided written informed consent.

The study duration was 56 weeks. During the 28 weeks of treatment, group A received four active-treatment cycles; group B received two active-treatment cycles and two placebo cycles. Each cycle lasted 4 weeks and was interrupted by a treatment-free interval of the same duration. The treatment period was followed by an observation period of 28 weeks. Examination visits (E1–E8) occurred every 4 weeks during treatment. Visits during the follow-up period (weeks 29–56) were scheduled at the beginning of weeks 37, 45, and 53. The final visit (E9) was at the end of week 56.

Parents were asked to inform the physician of acute infections, each of which was documented separately.

Study Population

The study enrolled 188 boys and girls between 4 and 12 years of age with a history of recurrent RTIs (rhinitis, sinusitis, otitis, pharyngitis, laryngitis, bronchitis, and mixed forms) that met one or both of the following criteria: during the past 12 months, at least 10 infections in children 4 to 6 years old and at least 8 in children 7 to 12 years old, or, in either group, at least 4 severe infections (lasting >2 weeks).

Excluded were patients whose infections over the past 8 weeks had lasted longer than 6 weeks, those with continuous infections (eg, cystic fibrosis), and patients with severe diseases of internal organs, acute enteritis at the beginning of the study, or chronic inflammatory conditions of the gastrointestinal tract. Other reasons for exclusion were malignant tumors, severe immunodeficiency (including human immunodeficiency virus seropositivity), severe organic diseases of the respiratory tract (eg, malformations), allergy to bacterial lysates or excipients, steroid treatment for respiratory tract diseases during the past year (except occasional aerosol therapy), immunosuppressant treatment (eg, corticosteroids, cytostatics), and administration of immunomodulating/immunostimulating drugs (including immunoglobulins) in the previous few months, except for immunotherapy for hyposensitization.

Patients who withdrew prematurely were not replaced.

Study Medication

Each LW 50020 tablet contained 3 mg of a bacterial lysate mixture obtained from seven different American Tissue Culture Collection strains (*Klebsiella pneumoniae, Haemophilus influenzae, Branhamella catarrhalis, Streptococcus pneumoniae, Streptococcus pyogenes, Streptococcus mitis, Staphylococcus aureus;* at least 10^9 microorganisms of each strain) plus excipients (mannitol, microcrystalline cellulose, sodium starch, glycolate, magnesium stearate, colloidal anhydrous silica). The placebo tablets contained only the excipients of the LW 50020 tablets but were the same shape and size in order to maintain double-blinding.

The dosage of one tablet daily and the treatment schedule were identical in both groups.

Efficacy and Safety Endpoints

The primary endpoint was the frequency of RTIs. The investigator had to document each RTI at the regular visits and at additional visits in case of infection. An infection involving the upper or lower respiratory tract or ear was documented if at least one of the following was observed: fever (axillary temperature >38°C), purulent secretion from the nose, ear, or pharynx, complete reddening or capillary hyperemia of the tympanic membrane, swollen or painful ear canal or throat, and rales or marked breathing sounds.

Secondary endpoints were duration, severity, and clinical score of infections.

The duration of RTI was evaluated as the difference in days between the onset of infection and its end, defined as recovery with no or mild symptoms and general well-being. New symptoms of infection occurring after 2 symptom-free days were recorded as a new infection.

Using a three-point scale (mild = 1, moderate = 2, severe = 3), the physician assessed severity after the infection ended. Rating criteria were as follows: mild = little impairment of general well-being, the child able to attend school or kindergarten, with transiently elevated temperature above 38°C and no appetite; moderate = moderate impairment of general well-being, absence from school or kindergarten, increased need for sleep, axillary temperature above 38°C, no appetite; severe = severe impairment of general well-being, bed rest for several days, apathy, fever lasting several hours.

The severity score for a defined study period was calculated as the sum of all infections in this period; 0 was used if no infection was present.

The clinical score for RTI was the weighted product of overall severity with the duration of infection in days. Weighting factors for overall severity were mild = 1, moderate = 2, severe = 3.

Acute therapeutic interventions were documented for each infection.

The safety evaluation comprised results of laboratory analyses, documentation of adverse events, and the physicians' overall assessment of tolerability. The following laboratory values were ascertained: hemoglobin, hematocrit, erythrocytes, leukocytes, differential blood count (including pathologic forms), platelets, sodium, potassium, urea, creatinine, total bilirubin, uric acid, alkaline phosphatase, aspartate and alanine aminotransferases, gamma-glutamyl transpeptidase, and serum immunoglobulins (A,E,G,M). Blood samples were taken at baseline (E1), after the end of treatment (E8), and after the follow-up period (E9).

Adverse events were elicited by nonleading questions to the patient at every visit. The physician used a verbal rating scale (very good, good, moderate, poor) to derive a subjective overall assessment of tolerability at the end of treatment.

Determination of Sample Size and Statistical Methods

On the basis of a type I error probability of $\alpha = 10\%$ and a power of $1\text{-}\beta = 80\%$, a 30% difference in the frequency of infections would be regarded as statistically significant with at least 82 patients per group, if the number of infections is considered to follow the Poisson distribution.

The main endpoint for efficacy comparisons between the two groups was the rate of infections, ie, the number of newly diagnosed infections per unit of time. A newly diagnosed infection was assigned to a defined study period if its date of onset was within that period. The rate of infections per patient was estimated for a 4-week period to account for different lengths of the study periods.

The efficacy analysis, based on the per-protocol population, was divided into two parts: (1) confirmatory analysis of treatment differences in infection rates during E5–E8 (weeks 17–28) to test the efficacy of two additional treatment cycles; and (2) exploratory analysis of treatment differences in infection rates during follow-up E8–E9 (weeks 29–56) to investigate the long-term efficacy of two versus four treatment cycles.

The confirmatory analysis was performed with an exact test for comparing two means for Poisson distribution. The exploratory analysis was used for secondary variables of efficacy (duration, severity, clinical score, number of treatments per infection). Nonparametric procedures for between-group (Wilcoxon two-sample test) and within-group (Wilcoxon signed rank test) comparisons were applied.

Patients with missing data during follow-up could not be evaluated for long-term efficacy, as there was no last-value option for efficacy parameters. Thus, no intention-to-treat analysis was planned.

Analysis of safety was based on the safety population. The overall tolerability assessment, laboratory data, and adverse events were analyzed descriptively and casuistically.

RESULTS

Demographic and Baseline Features

One hundred eighty-eight patients (group A, 95; group B, 93) were randomized (safety population). Five patients (group A, 4; group B, 1) were withdrawn before treatment started because of violation of inclusion or exclusion criteria.

Thirteen patients (group A, 7; group B, 6) withdrew from the study prematurely between E1 and E8. Reasons for withdrawal were nonmedical in 10 patients (5 in each group) and medical in 3 (group A, 2; group B, 1); causal relationship to the study medication was suspected in 1 group A patient. Sixteen patients used unpermitted concomitant medication and were excluded from the per-protocol analysis. Patients who deviated from the study schedule were not excluded from this per-protocol analysis, which was therefore based on 154 patients (group A, 73; group B, 81).

Demographic characteristics in the two groups were comparable (Table), as were allergies/risk factors for RTIs (Fig 1).

Demographic Characteristics in the Per-Protocol Sample

	Group A	Group B
Sex, M/F, no (%)	45/28 (62/38)	44/37 (54/46)
Mean age, y	5.8	6.2
Mean height, cm	117	119
Mean weight, kg	24	25
Attending kindergarten/school, %	48/48	38/56
Elevated IgE level, %	51	44
RTIs during past 12 mos, mean no.	10.3	10.5
Severe RTIs*	2.3	2.2
Lower RTIs	3.0	3.5
RTI present on enrollment, %	16	5

*Duration >14 days.

Primary Endpoint

Rate of Infection

During the E5–E8 period (two additional booster cycles or two placebo cycles), the rate of infection was significantly reduced by about half, although the between-group comparison (confirmatory analysis) showed no significant difference (Fig 2). A further slight decrease was seen during E8–E9. The observed reduction in the infection rate of .13 per 4 weeks corresponds to 1.7 infections per year.

Thus, the reduction seen after the standard regimen (immunization + one booster cycle) remained stable or increased, and the two additional booster cycles did not further improve the results.

Fig 1. Percentage of patients with allergies/risk factors for RTI.

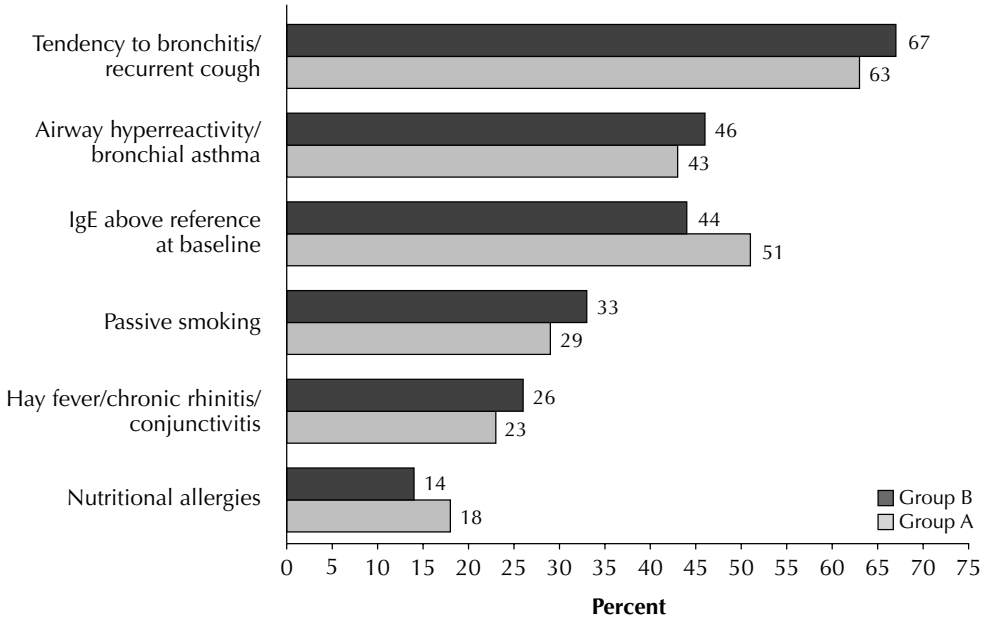
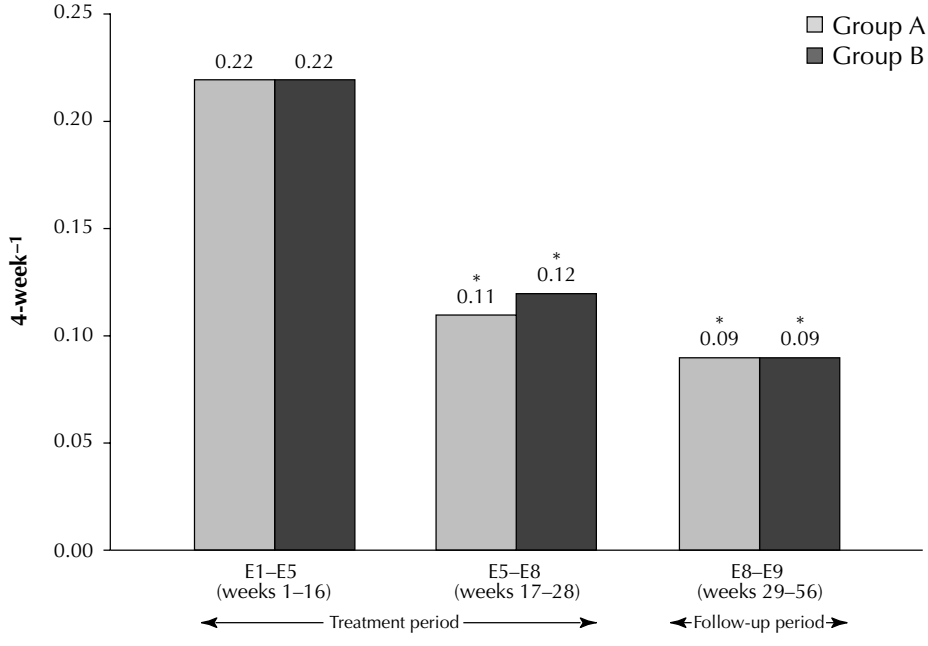


Fig 2. Rate of RTIs per patient per 4 weeks, stratified by study period.



*Within-group comparisons vs rate during E1–E5, $P<.01$.

Secondary Endpoints

No statistically significant differences were evident in the between-group comparisons for any secondary endpoint.

Duration

The mean number of days with RTI per patient per 4 weeks was .95 for group A and .84 for group B in the E1–E5 period. The mean during E5–E8 was reduced to .42 in group A and to .47 in group B (significant difference within groups). A further decrease—.32 in group A and .34 in group B—was seen on follow-up (E8–E9), corresponding to a reduction of 8.2 (group A) and 6.5 (group B) days with RTI per year.

Severity

Early in treatment (E1–E5), the mean severity of RTI per patient per 4 weeks was estimated at .32 in group A and .31 in group B. During E5–E8, this decreased by about 50% to .16 in both groups (significant difference within groups) and still further to a slight degree during follow-up. The mean severity rating was .11 in group A and .13 in group B.

Clinical Score

The mean clinical score per patient during E1–E5 was approximately 1.5 in group A and 1.3 in group B. As would be expected from the reduced number of infections during E5–E8, the mean decreased, respectively, to .6 and .7 (significantly different within groups). At the follow-up evaluation, the mean score was .4 in group A and .5 in group B.

Antibiotic Treatment

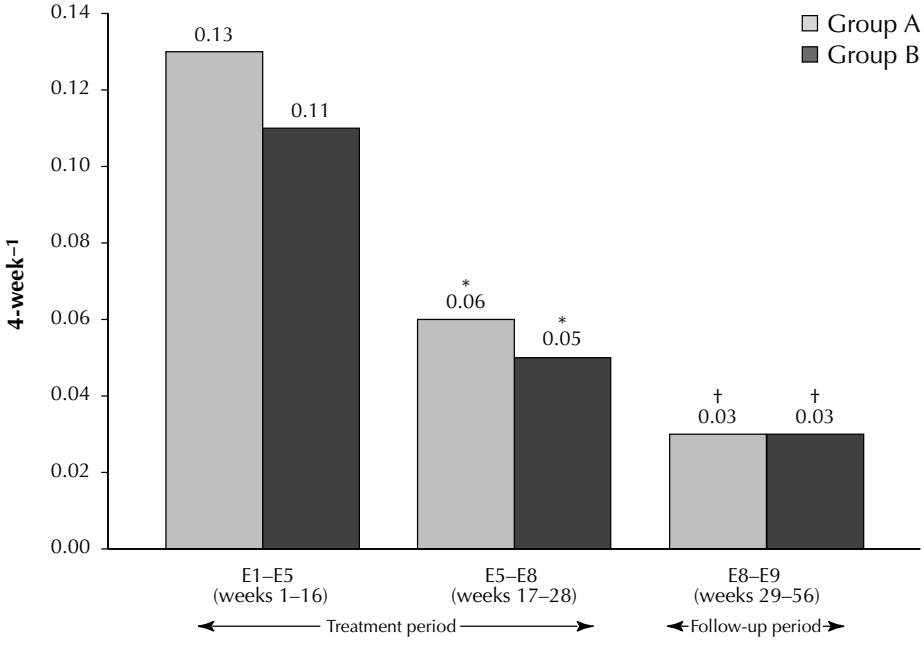
Antibiotic use decreased significantly by more than 70% in both groups during E5–E9 compared with E1–E5 (Fig 3). The mean rate of antibiotic treatments per patient per 4 weeks was estimated to be .13 in group A and .11 in group B during E1–E5 and .06 and .05 during E5–E8. A further decrease to .03 in both groups was seen during follow-up. The reduction corresponds to about one antibiotic treatment per year (group A, 1.3; group B, 1.0).

Safety

Tolerability was assessed as very good or good in 98.7% of the patients and as moderate in 1.3%. Eight adverse events were documented for six patients. A causal relationship with the study drug was felt to be possible or probable (moderate diarrhea, vomiting, mild abdominal pain) in two group A patients (three adverse events) and in one group B patient (one adverse event).

Laboratory values obtained at the examinations E1 (group A, 87; group B, 87), E8 (83, 85), and E9 (79, 81) showed only minor changes of no clinical relevance and no difference between groups.

Fig 3. Rate of antibiotic treatment per patient per 4 weeks, stratified by study period.



*Within-group comparisons vs E1–E5, $P<.05$.
†Within-group comparisons vs E1–E5, $P = .0001$.

DISCUSSION

Despite improving socioeconomic conditions, the frequency of RTIs in children and problems with treatment have not decreased in developed countries. RTIs, particularly otitis media and sinusitis, are more likely to involve sequelae in this population and must be treated rapidly to avoid serious morbidity.[25] Antibiotics are therefore of undeniable importance for many conditions. In uncomplicated viral infections, however, antibiotic treatment is irrational and sometimes harmful and may contribute to the development of resistant strains. Symptomatic treatment should be preferred.[26]

Regardless of the choice of drugs for the immediate treatment of RTIs, a multifaceted approach with additional immunomodulatory therapy is recommended in susceptible patients to enhance host immune response and prevent recurrence.[26,27] Because mucosal surfaces provide a portal of entry for most infectious viral and bacterial pathogens,[28] it is logical to attempt to prevent such diseases by inducing mucosal protection against the microorganisms.[29] The immunomodulator LW 50020 activates the specific and nonspecific immune system, enhancing the defense mechanisms of the mucosal immune system.[17-21]

As with other immunomodulators, the dosage and schedule of LW 50020 selected for clinical use are based on empiric data from basic research with oral immunomodulators and vaccines. The recommended schedule of two treatment periods separated by a treatment-free period is justified by the need for prolonged contact of orally administered antigens to achieve a satisfactory mucosal immune response.[30] The clinical efficacy of the preparation administered under the proposed dose schedule was proved in several placebo-controlled, double-blind studies in children and adults that evaluated number, duration, and severity of RTIs.[23,24] The aim of this study was to determine whether further treatment would increase clinical efficacy. Therefore, a placebo control was used to assess the value of additional booster cycles.

Over 56 weeks, LW 50020 showed a long-lasting and stable effect on the infection rate and related variables, which were reduced by about 50% in both patient groups after the immunization and booster cycle, compared with values obtained during the immunization and booster phase. The frequency of antibiotic use decreased by as much as 70%. These results demonstrate that full efficacy is achieved with the standard treatment schedule and, as with vaccines, cannot be enhanced by subsequent additional booster cycles.

The frequency of infections required by the inclusion criteria clearly exceeded that in a normal population.[31] In the year preceding the study, the children had suffered an average of 10 infections, compared with about eight upper RTIs per year in preschool children.[32] More than nine infections in preschool children and six infections in schoolchildren are regarded as pathologically increased.[33] Such infections cause absence from kindergarten and school and undoubtedly have adverse effects on existing lung disease.[26]

The reduction of RTIs in this study was maintained over the entire observation period. The estimated decrease in the number of infections per year (1.7 infections) and the saving of antibiotics (approximately one treatment) are of great clinical relevance and agree with calculations derived from a large multinational study.[34] Substantial savings in medical and drug costs are to be expected, as was also demonstrated in a German sample.[35]

Many children in this study had underlying respiratory symptoms and disease, such as tendency to bronchitis/recurrent cough (65%) or airway hyperreactivity/bronchial asthma (44%). In a large multinational study,[34] 77% of the 5000 enrolled patients had a similar history of risk factors for RTI. The immunomodulator LW 50020 proved to be effective and safe in all these patients. It can therefore be concluded that no restrictions are needed for risk groups studied. This is confirmed by the assessment of tolerability, which was good or very good in 98.8% of patients, and by the absence of relevant laboratory changes.

CONCLUSIONS

LW 50020, administered in the standard regimen of one immunization cycle and one booster cycle, is effective in children with recurrent RTIs, reducing the frequency, severity, and duration of infections by about 50%. Additional booster applications do not further improve efficacy. The reduction in the variables of infection was observed for about 9 months and was accompanied by a substantial decrease in antibiotic consumption of up to more than 70%, demonstrating that LW 50020 has long-lasting effects.

REFERENCES

1. Bellanti JA. Recurrent respiratory tract infections in pediatric patients. *Drugs.* 1997;54:1-4.
2. Towns S, Wong M. Assessment of the child with recurrent respiratory infections. *Aust Fam Physician*. 2000;29:741-746.
3. Wassermann RL, Sorensen RU. Evaluating children with respiratory tract infections: the role of immunization with bacterial polysaccharide vaccine. *Pediatr Infect Dis J.* 1999;18:157-163.
4. Korppi M. Recurrent respiratory infections in children: a practical approach for clinical work. *Pediatr Pulmonol.* 1997;16:144-145.
5. Nafstad P, Hagen JA, Oie L, Magnus P, Jaakkola JJK. Day care centers and respiratory health. *Pediatrics.* 1999;103:753-758.
6. Ferrari M, Tardivo S, Zanolin ME, et al. Serious childhood respiratory infections and asthma in adult life. A population based study. *Ann Allergy Asthma Immunol.* 1999;83:391-396.
7. Paoletti P, Prediletto R, Carrozzi L, et al. Effects of childhood and adolescence-adulthood respiratory infections in a general population. *Eur Respir J.* 1989;2:428-436.
8. Celedon JC, Litonjua AA, Weiss ST, Gold DR. Day care attendance in the first year of life and illnesses of the upper and lower respiratory tract in children with a familial history of atopy. *Pediatrics.* 1999;104:495-500.
9. Jedrychowski W, Maugeri U, Flak E, Mroz E, Bianchi I. Predisposition to acute respiratory infections among overweight preadolescent children: an epidemiologic study in Poland. *Public Health.* 1998;112:189-195.
10. Van Cauwenberge PB, Belussi L, Maw AR, Paradise JL, Solow B. The adenoid as a key factor in upper airway infections. *Int J Pediatr Otorhinolaryngol.* 1995;32(suppl.):71-80.
11. Lundbäck B. Epidemiology of rhinitis and asthma. *Clin Exp Allergy.* 1998;28:3-10.
12. Bolte G, Mielck A, Meyer I, Stiller-Winkler R, Heinrich J. Inverse social gradient of secondary immune response parameters in children. *Rev Environ Health.* 1999;14:135-143.
13. Shapiro ED. Epidemiology of acute respiratory infections. *Semin Pediatr Infect Dis.* 1998;9:31-36.
14. Latal Hajnal B, Braun-Fahrländer C, Grize L, et al. Effect of environmental tobacco smoke exposure on respiratory symptoms in children. *Schweiz Med Wochenschr.* 1999;129:723-730.
15. Jedrychowski W, Flak E. Maternal smoking during pregnancy and postnatal exposure to environmental tobacco smoke as predisposition factors to acute respiratory infections. *Environ Health Perspect.* 1997;105:302-306.
16. Drummond PD, Hewson-Bower B. Increased psychological stress and decreased mucosal immunity in children with recurrent upper respiratory tract infections. *J Psychosom Res.* 1997; 43:271-278.
17. Helmberg A, Böck G, Wolf H, Wick G. An orally administered bacterial immunomodulator primes rabbit neutrophils for increased oxidative burst in response to opsonized zymosan infection. *Immunology*. 1989;57:3576-3580.
18. Ruedl CH, Albin B, Böck G, Wick G, Wolf H. Oral administration of a bacterial immunomodulator enhances murine intestinal lamina propria and Peyer's patch lymphocyte traffic to the lung: possible implications for infectious disease prophylaxis and therapy. *Int Immunol.* 1993;5:29-36.
19. Ruedl CH, Frühwirt M, Wick G, Wolf H. Immune response in the lungs following oral immunization with bacterial lysates of respiratory pathogens. *Clin Diagn Lab Immunol.* 1994;1:150-154.
20. Van Daal GJ, Beusenberg FD, So KL, et al. Protection against influenza virus infection in mice by oral immunization with a polyvalent bacterial lysate. *Int J Immunol.* 1991;13:831-840.
21. Van Daal GJ, van't Veen A, So KL, et al. Oral immunization with polyvalent bacterial lysate and infection with *Streptococcus pneumoniae:* influence on interferon-gamma and PMN-elastase concentrations in murine bronchoalveolar lavage fluid. *Int Immunol.* 1993;5:29-36.

22. Wichels R, Wolfschaffner F, Guggenbichler JP. Prophylaxis of infections. *TW Pädiatrie.* 1996;9: 421-423.

23. Riedl-Seifert RJ, van Aubel A, Kämmereit A, et al. Recurrent infections during childhood: are they still a "crux medicorum"? [in German]. *J Pharmacol Ther.* 1992;2:108-117.

24. Rutishauser M, Pitzke P, van Aubel A, Elsasser U, Grevers G, Kämmereit A. Use of a polyvalent bacterial lysate in patients with recurrent respiratory tract infections. *Adv Ther.* 1998;15:330-341.

25. Gooch WM. Potential infectious disease complications of upper respiratory tract infections. *Pediatr Infect Dis J.* 1998;17:79-82.

26. Openshaw PJ, Lemanske RF. Respiratory viruses and asthma: can the effects be prevented? *Eur Respir J.* 1998;12(suppl 27):35S-39S.

27. Mushatt DM. Advances in antimicrobial therapy for respiratory tract infections. *Curr Opin Pulm Med.* 2000;6:250-253.

28. Staats HF, McGhee JR. Application of basic principles of mucosal immunity to vaccine development. In: Kiyono H, Ogra PL, McGhee JR, eds. *Mucosal Vaccines.* San Diego, Calif: Academic Press; 1996: 17-39.

29. Stead RH, Bienenstock J. Development of new oral vaccines and immunomodulators. In: Riedl-Seifert RJ, ed. *Mucosal Immunology.* Munich: Zuckschwerdt Verlag; 1998:119-128.

30. Walker RI. New strategies for using mucosal vaccination to achieve more effective immunization. *Vaccine.* 1994;12:387-400.

31. Monto AS, Sullivan KM. Acute respiratory illness in the community. Frequency of illness and the agents involved. *Epidemiol Infect.* 1993;110:145-160.

32. Jones NS. Current concepts in the management of pediatric rhinosinusitis. *J Laryngol Otol.* 1999; 113:1-9.

33. Stögmann W. Das infektanfällige Kind. *Tägl Pract.* 1992;3:283-294.

34. Grevers G, Aldrey O, Rodriguez B, Abel S, van Aubel A. Treatment of recurrent respiratory tract infections with a polyvalent bacterial lysate: results of an open, prospective, multinational study. *Adv Ther.* 2000;7:103-116.

35. Büchner KR. *Treatment of Out-Patients With Recurrent Respiratory Tract Infections.* Bayreuth, Germany: PCO Publisher; 1994.