International Journal of Pediatric Otorhinolaryngology 77 (2013) 670–673

Contents lists available at SciVerse ScienceDirect

International Journal of Pediatric Otorhinolaryngology

journal homepage: www.elsevier.com/locate/ijporl

The role of OM-85 BV (Broncho-Vaxom) in preventing recurrent acute tonsillitis in children

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ARTICLE INFO

Article history:
Received 29 August 2012
Received in revised form 8 January 2013
Accepted 9 January 2013
Available online 4 February 2013

Keywords:
Bacterial lysates
Immunomodulators
Immunostimulants
Recurrent tonsillitis

ABSTRACT

Objective: To evaluate the efficacy of an immunostimulant (bacterial lysate) Broncho-Vaxom in the management of children with recurrent acute tonsillitis.
Methods: A 5-year retrospective cohort study of 177 children presenting with a diagnosis of recurrent acute tonsillitis. Patients' demographics and laboratory studies at presentation were retrieved. For patients given Broncho-Vaxom, we defined response as a decrease in the frequency of acute tonsillitis episodes after 3 months of therapy (partial: by $\leq$50% and total: by >50%). Patients showing response to Broncho-Vaxom were further followed until study-end or need for tonsillectomy.
Results: The median age of patients was 4.5 years (range: 1–15 years) with 63.8% being males. 131 (74%) patients received Broncho-Vaxom as initial therapy, and 99 (75.6%) showed response (51.2% total and 24.4% partial response). A normal ESR level was the only predictor of total compared with no response (OR: 3.53, 95% CI: 1.03–12.07); while both normal ESR (OR: 7.15-times, 95% CI: 1.18–43.39) and normal CRP (OR: 12.66, 95% CI: 1.43–111.86) levels were independent predictors of total over partial response. None of the patients showing total response required tonsillectomy on long-term follow up while in those with partial response 34.4% required subsequent tonsillectomy (median follow-up: 9 months).
Conclusions: A considerable proportion of children receiving Broncho-Vaxom for recurrent acute tonsillitis show a decrease in the frequency of episodes in the short term, and very few patients eventually require tonsillectomy on long-term follow up.

1. Introduction

Recurrent acute tonsillitis during childhood can result in considerable morbidity and school absenteeism [1]. Decades of experience using tonsillectomy for recurrent acute tonsillitis in children have led to consensus that it is effective. However, recent systematic reviews indicate that the level of evidence regarding the ability of tonsillectomy to reduce the number of episodes of sore throat is very low (modest size effect), except in children with severe symptoms, and the decision to undergo tonsillectomy should be clearly weighed against the potential harms including intraoperative and postoperative morbidity [2,3]. Whilst removing the tonsils will always prevent 'tonsillitis', the impact of the procedure on 'sore throats' is much less predictable [2,3]. Moreover, very few studies evaluated the effect of antibiotic therapy on recurrence rates [4]. Thus, the search for alternative interventions is ongoing.

Bacterial immunomodulators that contain killed bacteria, their lysate or components of bacterial cells were proved to increase efficiency of the immune system response, via both a specific as well as a non-specific effect on the cellular and humoral mechanisms [5]. Since the 1970s, when the concept of the bacteria-derived immunomodulators appeared, various products were developed and accepted mostly for the prevention of recurrent respiratory tract infections. The OM-85 BV (Broncho-Vaxom; OM Pharma, Geneva, Switzerland) preparation contains lysates of eight bacterial pathogens (in equal parts) of the most often encountered microorganisms in respiratory tract infections [6]. As a bacterial immunostimulator, Broncho-Vaxom was shown to affect both innate immunity influencing macrophages, neutrophils activity and proinflammatory cytokines production, as well as acquired immune responses regulated by lymphocytes and synthesis of immunoglobulins [7]. Results from a recent meta-analysis showed that children treated with Broncho-Vaxom experience significantly and consistently fewer cases of recurrent respiratory tract infections compared with controls (26.2% risk difference) [6]. In this study, we aimed to evaluate the efficacy of

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http://dx.doi.org/10.1016/j.ijporl.2013.01.009

Broncho-Vaxom in the management of children with recurrent acute tonsillitis in specific, and determine predictors of response to therapy.

2. Methods

This was a retrospective observational cohort study of children presenting to the Pediatric Otolaryngology Clinic at the American University of Beirut Medical Center, Beirut, Lebanon between January 1 2006 and December 31 2010. Inclusion criteria were age between 6 months and 18 years and a diagnosis of recurrent acute tonsillitis (more than *three* distinct episodes in the past 12 months [2]) on presentation to our clinic during the study period. Exclusion criteria were immune deficiency, obstructive tonsils necessitating tonsillectomy, and the use of immune modulators other than the study drug. Patients are seen at our clinic at least 10 days after the last acute episode. Highly recurrent acute tonsillitis was defined as seven or more episodes of acute tonsillitis in 1 year, five episodes per year for two consecutive years, or three episodes per year for three consecutive years [8]. Retrieved data at first presentation included age, sex, history of recurrent acute tonsillitis, and results of laboratory studies (not taken during acute illness): total hemoglobin level, white blood cell (WBC) count, erythrocyte sedimentation rate (ESR), c-reactive protein (CRP) level, urinalysis, antistrepolysin O (ASO) titer, and throat cultures. The treatment modality used was also recorded (Broncho-Vaxom, tonsillectomy, and antibiotics). For patients receiving Broncho-Vaxom, response to therapy was evaluated 3 months from the start of treatment (i.e. at the end of treatment course). Response was categorized as follows: *No response*, no change or increase in the frequency of acute tonsillitis episodes; *Partial response*, decrease in the frequency of acute tonsillitis episodes by $\leq$50%; and *Total response*, decrease in the frequency of acute tonsillitis episodes by >50%. All responders to Broncho-Vaxom were further followed beyond 3 months either at subsequent follow-up visits or through a telephone interview with the parents when follow-up visits were not available. Two long-term outcomes were evaluated: remaining with a recurrent infection rate of less than 3 times per year thus not requiring tonsillectomy, or having a recurrence rate of 3 or more times per year thus necessitating tonsillectomy.

2.1. Broncho-Vaxom

Each Broncho-Vaxom capsule contains 3.5 mg of lyophilized bacterial lysates of *Haemophilus influenzae*, *Diplococcus pneumoniae*, *Klebsiella pneumoniae* and *ozaenae*, *Staphylococcus aureus*, *Streptococcus pyogenes* and *viridans*, *Neisseria catarrhalis*. Excipients include modified corn starch, magnesium silicate, magnesium stearate, propyl gallate (E 310), sodium glutamate, mannitol, gelatine, indigotine, titanium dioxide. The typical treatment dosage is one capsule daily for 10 consecutive days per month for a total of 3 months. The capsule is opened and the content is dissolved in liquid (water, juice, or milk) and is given in the morning on an empty stomach. If the child is old enough to swallow the capsule then he/she will take it with a sip of water, milk, or juice also in the morning on an empty stomach. Concomitant antibiotic prophylaxis was undertaken for some patients during the first month of administration of Broncho-Vaxom in an attempt to temporary suppress recurrence of tonsillitis before getting the second (booster) course of Broncho-Vaxom. In such cases, penicillin was used in a suspension form (400 IU/5 ml) with an oral dose of 2.5 ml twice daily for children younger than 5 years of age and 5 ml twice daily for those 5 years and older.

2.2. Statistical analysis

Descriptive statistics are presented as medians (interquartile range [IQR]) or percentages. Bivariate correlations were done using the Mann–Whitney *U* test for continuous variables and the Fisher's exact test for categorical variables. Multivariate logistic regression analysis was used to retrieve the adjusted odds ratios (OR) and 95% confidence intervals (CI) for study variables of interest, with response to therapy being the dependent variable. All *p*-values are two-sided with the level of significance set at 0.05.

3. Results

A total of 177 patients presented with recurrent acute tonsillitis during the study period. The median age was 4.5 years (IQR: 3.0–6.3 years; min: 1 year; max: 15 years) including 113 (63.8%) boys and 64 (36.2%) girls. The initial treatment modality was Broncho-Vaxom in 131 (74%) patients while 38 (23.2%) had tonsillectomy within a median of 1 month from presentation (IQR: 1.0–2.5 months; min: 1 month; max: 15 months). One month of prophylactic antibiotics were concomitantly used in 80.5% of patients receiving Broncho-Vaxom. Patients receiving Broncho-Vaxom as the initial treatment modality had a similar age and sex distribution compared with those who underwent tonsillectomy (Table 1). Moreover, both groups of patients had a similar proportion of patients with abnormal laboratory studies, in most preformed tests (Table 1). However, the tonsillectomy group had a higher proportion of patients with highly recurrent acute tonsillitis ($p = 0.017$), a positive ASO titer ($p = 0.028$), or a positive throat culture ($p = 0.051$) (Table 1).

Table 1
Predictors for choice of initial treatment modality after study inclusion.

Parameter	Broncho-Vaxom $n = 131$	Tonsillectomy $n = 38$	*p*-value
Age in years, median (IQR)	4.0 (3.0–6.0)	5.0 (3.9–7.0)	0.174
Age <5 years, *n*/*N* (%)	73/131 (55.7)	17/38 (44.7)	0.232
Age ≥5 years, *n*/*N* (%)	58/131 (44.3)	21/38 (55.3)	0.232
Male, *n*/*N* (%)	85/131 (64.9)	21/38 (55.3)	0.341
Highly recurrent acute tonsillitis, *n*/*N* (%)	96/123 (78.0)	30/31 (96.8)	0.017
Positive ASO titer, *n*/*N* (%)	30/83 (36.1)	7/9 (77.8)	0.028
Elevated ESR level, *n*/*N* (%)	40/80 (50.0)	5/7 (71.4)	0.436
Elevated CRP level, *n*/*N* (%)	20/83 (24.1)	1/5 (20.0)	1.000
Elevated WBC count, *n*/*N* (%)	9/73 (12.3)	3/14 (21.4)	0.400
Anemia, *n*/*N* (%)	32/87 (36.8)	4/14 (28.6)	0.765
Abnormal urinalysis, *n*/*N* (%)	1/76 (1.3)	0/7 (0.0)	1.000
Positive throat culture, *n*/*N* (%)	10/33 (30.3)	4/5 (80.0)	0.052

URTI, upper respiratory tract infections; ASO, antistrepolysin O; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; WBC, white blood cell; IQR, interquartile range. *Laboratory definitions*: positive ASO titer: ≥200 IU/ml; elevated ESR level: >20 mm/h for females and >15 mm/h for males; elevated CRP level: >2.5 mg/l; elevated WBC: >11,000/cu mm; Anemia: hemoglobin level <12.0 g/dl; Abnormal urinalysis: any abnormality on visual exam, dipstick test, or microscopic exam.

Table 2
Predictors of response to Broncho-Vaxom therapy.

Parameter	No response $n=32$	Response		
		All patients $n=99$	Partial response $n=32$	Total response $n=67$
Age in years, median (IQR)	4 (3–6)	4 (3–6)	4 (3–5)	5 (4–7)
Age <5 years, *n*/*N* (%)	18/32 (56.2)	55/99 (55.6)	23/32 (71.9)	32/67 (47.8)
Age ≥5 years, *n*/*N* (%)	14/32 (43.8)	44/99 (44.4)	9/32 (28.1)	35/67 (52.2)
Male, *n*/*N* (%)	22/32 (68.8)	63/99 (63.6)	22/32 (31.2)	41/67 (38.8)
Highly recurrent acute tonsillitis, *n*/*N* (%)	24/30 (80.0)	72/93 (77.4)	22/29 (75.9)	50/64 (78.1)
Positive ASO titer, *n*/*N* (%)	7/23 (30.4)	23/60 (38.3)	6/18 (33.3)	17/42 (40.5)
Elevated ESR level, *n*/*N* (%)	14/21 (66.7)	26/59 (44.1)	13/18 (72.2)	13/41 (31.7)[*,††]
Elevated CRP level, *n*/*N* (%)	6/21 (28.6)	14/62 (22.6)	9/19 (47.7)	5/43 (11.6)[††]
Elevated WBC count, *n*/*N* (%)	4/20 (20.0)	5/53 (9.4)	4/16 (25.0)	1/37 (2.7)[*,†]
Anemia, *n*/*N* (%)	5/23 (21.7)	27/64 (42.2)	10/22 (45.5)	17/42 (40.5)
Abnormal urinalysis, *n*/*N* (%)	1/19 (5.3)	0/57 (0.0)	0/18 (0.0)	0/39 (0.0)
Positive throat culture, *n*/*N* (%)	3/10 (30.0)	7/23 (30.4)	3/9 (33.3)	4/14 (28.6)
Concomitant antibiotics, *n*/*N* (%)	25/28 (89.3)	58/75 (77.3)	21/26 (80.8)	37/49 (75.5)

URTI, upper respiratory tract infections; ASO, antistrepolysin O; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; WBC, white blood cell; IQR, interquartile range.
Laboratory definitions: positive ASO titer: ≥200 IU/ml; elevated ESR level: >20 mm/h for females and >15 mm/h for males; elevated CRP level: >2.5 mg/l; elevated WBC: >11,000/cu mm; anemia: hemoglobin level <12.0 g/dl; abnormal urinalysis: any abnormality on visual exam, dipstick test, or microscopic exam.
[*] $p<0.05$ compared with no response group.
[†] $p<0.05$.
[††] $p<0.01$ compared with partial response group.

3.1. Response to Broncho-Vaxom

Three months following Broncho-Vaxom administration, a total of 99 (75.6%) patients showed response to therapy: 67 (51.2%) patients showed total response while 32 (24.4%) showed partial response. The remaining 32 (24.4%) patients showed no response. Comparisons of study variables between the three response groups are outlined in Table 2. Patients who showed total response were less likely to have abnormal ESR compared with the partial response ($p = 0.005$) and no response ($p = 0.014$) groups. Moreover, they were less likely to have abnormal CRP levels compared with the partial response group ($p = 0.006$). Patients who showed total response were also less likely to have abnormal WBC count compared with the partial response ($p = 0.025$) and no response ($p = 0.047$) groups. On multivariate logistic regression analysis including WBC count, ESR, and CRP levels, a normal ESR level was the only predictor of total compared with no response (OR: 3.53, 95% CI: 1.03–12.07); while both normal ESR (OR: 7.15, 95% CI: 1.18–43.39) and normal CRP (OR: 12.66, 95% CI: 1.43–111.86) levels were independent predictors of total over partial response.

3.2. Long-term follow-up in responders

Patients showing total response were further followed-up for a median of 9 months (IQR: 3–27 months; min: 0 months; max: 45 months) and none required subsequent tonsillectomy. Patients showing partial response were further followed-up for a median of 9 months (IQR: 3–12 months; min: 0 months; max: 45 months) and 11 (34.4%) required subsequent tonsillectomy. The median time to the need for tonsillectomy in those patients was 9 months (range, 1–12 months).

4. Discussion

In this study, we demonstrated that a considerable proportion of children treated with Broncho-Vaxom for recurrent acute tonsillitis show a decrease in the frequency of episodes in the short term, and very few patients eventually required tonsillectomy on long-term follow up. Comparison between the results of our work and those from previous studies remains challenging, as different criteria are applied to define recurrent disease or response to therapy, and most available studies included a cohort of patients with varying upper respiratory tract infections. Nonetheless, our findings surely echo results from such clinical trials showing a relative risk reduction in the frequency of upper respiratory tract infections with Broncho-Vaxom therapy compared with placebo [6,9–13]. The benefit of Broncho-Vaxom in the primary prevention of upper respiratory tract infections has also been demonstrated [14]. It was also demonstrated that for children reporting at least three upper respiratory tract infections during the previous winter season, a 3-month preventive treatment with Broncho-Vaxom provides substantial economic benefits both for the insurers and for society in general [15].

Defects in the immune systems are well known to be linked with frequent respiratory tract infections. It has been shown that 57% of children with recurrent respiratory tract infections were deficient in one of the immunoglobulin (Ig) G subclasses and that 17% were IgA deficient [16]. This correlation between recurrent respiratory tract infections and immunological deficiencies represents the rationale for a nonspecific immunostimulating treatment for children suffering from recurrent infections. It may also justify how a bacterial immunostimulant might prevent viral infections, the most common cause of upper respiratory tract infections in children. In support of this, our study found no association between a positive ASO titer, a positive throat culture, or use of concomitant 1 month prophylactic antibiotics and response to Broncho-Vaxom therapy.

Previous studies have identified that the most notable predictors of response to Broncho-Vaxom therapy are age (younger children) and the frequency of previous acute episodes [6]. Our study did not observe such an association, which may be attributed to the small sample size upon stratification. However, we found a strong association between response to therapy and ESR or CRP levels at baseline, where children having normal levels were more likely to achieve response to therapy. The utilities of ESR and CRP in the diagnosis and follow-up of infections that occur in children have been the subject of many studies. Emphasis has mostly been placed on differentiating between acute bacterial and acute viral infections of the respiratory tract because of the obvious differences in patient management. CRP levels are generally higher in patients with streptococcal tonsillitis compared to patients with tonsillitis without group A streptococcus isolated from a throat swab; while ESR cannot reliably distinguish the microbial etiology [17]. In light of the lack of association between confirmed bacterial etiology and response to Broncho-Vaxom therapy in our study, the predictive ability of CRP or ESR levels

regarding the response rate cannot be interpreted in this direction, and further studies are needed to explain the observed finding. However, irrespective of the underlying mechanism, measurement of both markers may prove useful to outline patients that are more likely to show benefit; a strategy that could be of importance in developing countries with limited resources.

We tried to identify factors that may have influenced the physician's choice of performing a tonsillectomy rather than using a bacterial immunostimulant upon the child's initial presentation with a history of recurrent acute tonsillitis. It was noted that a suspicion of a bacterial etiology was the main factor favoring the choice of tonsillectomy. However, our study herein confirms that the etiology of tonsillitis does not affect response to Broncho-Vaxom. In all cases, we recommend that an individualized approach with a careful risk-benefit assessment should be applied.

The main limitation is that we conducted an observational study for a therapeutic intervention, which means that confounding by indication, patient characteristics, or use of antibiotics cannot be fully ruled. Such factors can only be addressed in a randomized controlled trial recruiting patients without any concomitant antibiotic use. Nonetheless, in our study patients received antibiotics (in a prophylactic dose) only during the first month of treatment with Broncho-Vaxom, to temporary suppress the recurrence of infections. Such short duration of prophylaxis is unlikely to affect the short (3 months) or long-term effects on response.

In conclusion, our study highlights the benefit of bacterial immunostimulant therapy with Broncho-Vaxom for the management of recurrent acute tonsillitis in childhood. Further randomized studies are needed to better identify which patients show the most favorable response, ideally using patient-related factors or laboratory markers that are commonly available at a relatively low cost.

Conflicts of interest

None declared.

Authors contributions

Conception and design: MAB, data collection: RS, data analysis and interpretation: MAB and RS, manuscript writing: MAB and RS. Both authors approved the final version prior to submission.

Acknowledgment

The study was supported by an unrestricted educational grant form OM Pharma. The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

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