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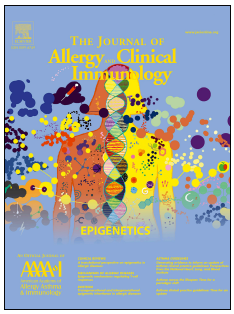

Primary prevention of severe lower respiratory illnesses in at-risk infants using the immunomodulator OM85

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Primary prevention of severe lower respiratory illnesses in at-risk infants using the immunomodulator OM85.

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Capsule summary: Severe lower respiratory illnesses (sLRI) during infancy increase the risk of asthma. The immunomodulator BronchVaxom® can increase the time to the first sLRI and reduce the cumulative burden of sLRI in "at risk" infants.

To the Editor,

Severe lower respiratory illnesses (sLRI) during infancy, i.e. those associated with fever (>38°C) and/or wheeze, increase the likelihood of subsequent asthma in at-risk subjects[1-5]. Moreover, time-to-first-sLRI after birth appears significantly reduced in children who develop persistent wheeze[5], suggesting that early infancy may be a period of particularly high vulnerability to the "asthmatogenic" effects of these infections. Significant interest exists in primary prevention of asthma and we have previously postulated that this may be achievable by protection against sLRI during infancy[6]. However, progress in testing this hypothesis has been limited by the availability of appropriate therapeutics which are approved for use in this age group. In this regard, the immunomodulator, OM85 (BronchoVaxom®), has been used in Europe to prevent recurrent upper respiratory infections (URI) in children[7] and to reduce the frequency and severity of wheeze episodes in asthmatic children[8]. OM85 is a lyophilized extract derived from a mixture of bacterial respiratory pathogens containing multiple TLR-like ligands, with a long history of safe use in children. However, it has not been tested previously in the specific context of sLRI prevention in at-risk infants.

We accordingly conducted a randomized clinical trial (BV2012/15, ACTRN12612000518864) where at-risk infants, by virtue of a parental history of asthma and allergies, were randomized to OM85 (3.5mg) or identical placebo for the first ten days of April through August; one month before and during the months of the winter viral seasons in Brisbane, Australia. Infants were 3-9 months of age when recruited, treated for their first two winter seasons and followed off treatment for a third year. The primary outcome variable was the frequency of sLRI over the first two winters of the child's life (see Supplemental data for clinical definitions). An *a priori* decision was taken to complete all secondary analyses for which data were available. All analyses were performed as intention-to-treat. All children who received at least one dose of study treatment were included in the safety analyses. As no previous study had used OM85 in primary prevention of sLRI, we used the data published by Razi et al.[8] showing a 30-40% reduction in wheeze episodes (OM85

3.57±1.61, placebo 5.75±2.71) in asthmatic children to determine sample size, which showed that 26 children per group would be required to give 80% power (α=0.05) to detect a 38% difference in sLRI between the groups. We therefore aimed to recruit 30 children per group. Those who withdrew or dropped out were not replaced, primarily due to resource limitations.

Fifty nine children, aged 5.8±1.9 months were recruited and randomized; 29 to OM85 and 30 to placebo. There were no differences in demographic characteristics (Supplemental Table 1). One child from each group withdrew before taking any study medication. Twenty five children randomized to OM85 had evaluable data at the end of the first winter, 24 at the end of the second winters and 23 completed the study. More children in the placebo group were lost to follow-up. Evaluable data were available at the end of the first winter for 27 children, for 22 children at the end of the second winter and 18 finished the study.

There was no significant difference in the frequency of sLRI over the first two winters between the groups. Within the OM85 group 17/24 (70.8%) recorded 37 sLRI [median 1.0 (25%-75% 0.0, 2.0)] and 14/22 (63.6%) recorded 47 sLRI [1.0 (0.0, 4.0)] in the placebo group (p=0.84 Mann-Whitney). The time to the first sLRI was significantly longer for children receiving OM85 than for those receiving placebo [median 442.0 (25%, 75% >853.0, 124.0) days vs median 85.0 (25%, 75% 386.0, 54.0) days, p=0.006 Kaplan-Meier survival analysis with Gehan-Breslow test] (Figure 1A). In this analysis, children who did not experience a sLRI during the study were censored on the date that they left the study (withdrew or competed). While there was a tendency for a reduction in the number of children who had any LRI, the number of LRI per child and the time to first LRI, there were no statistically significant differences between groups (Supplemental data, Supplemental Tables 2 &3).

OM85 appeared to be more effective at preventing sLRI in the first winter. Fewer children in the OM85 group had a sLRI than those in the placebo group [6/25 (24.0%) vs 14/27 (51.9%), p=0.05 Fisher Exact). Similarly, children receiving OM85 had fewer sLRI [7 infections, median 0.0 (0.0, 0.75)] than those in the placebo group [18 infections, median 1.0 (0.0, 1.0)] but this did not reach

statistical significance (p=0.052). For those children who did have sLRI, there was no difference in duration for those in the active and control groups [10.3 (8.3, 25.8) days vs 20.0 (7.0, 23.3) days, p=0.61].

There did not appear to be any carry over protection for the rest of the first year of the study once children stopped taking OM85 [OM85 on 6/25 (24.0%), off 11/25 (44.4%), placebo on 12/27 (44.4%), off 4/27 (14.8%), p=0.046 Chi Square]. A similar pattern was seen for the number of sLRI during the first study year [OM85 on: median 0.00 (0.00, 0.75); off: 0.50 (0.00, 1.00); placebo on: 0.00 (0.00, 1.00); off: 0.00 (0.00, 0.00) p=0.062].

By definition sLRI are LRI accompanied by fever (fLRI) and/or wheeze (wLRI). Examining the individual components showed similar effects of OM85 at decreasing the number of fLRI and wLRI and the proportion of children experiencing them. However, lack of study power for these secondary analyses meant that most comparisons did not reach statistical significance (Supplemental Tables 4 & 5).

Fewer children receiving OM85 had an URI in the first winter season than in the placebo group (45.8% v 88.5%, p=0.002). The number of URI was also lower in those receiving OM85 than placebo [median 0.00 (0.00, 1.00) vs 2.00 (1.00, 3.00) p=0.002). There was no difference in the time to first URI [41.3 (9.4) days vs 50.7 (18.9) days, p=0.69].

The cumulative frequency of sLRI was greater in the placebo group (total 75, median 1.00 (25%, 75% 1.00, 5.00) than in those receiving OM85 [total 58, median 2.00 (25%, 75% 0.00, 3.00)] (Supplemental Tables 6 &7), Figure 1B, p<0.001). Throughout the study period children in the placebo group had more days of sLRI [total 838, median 589 (25%, 75% 428, 749) days] than those randomized to OM85 [total 656, median 439 (25%, 75% 212, 545) days] (Supplemental Tables 8 & 9, Figure 1C, p<0.001), and these group differences were greatest in early infancy.

Giving OM85 to infants three to nine months of age was safe and tolerable. Parents opened the capsule and dissolved the contents in a small amount of liquid (water, breast milk, or formula). The

most commonly reported adverse events were gastrointestinal disorders, skin conditions, ear infections and general disorders, with no significant differences between groups (Supplemental Table 10).

The study did not achieve its primary outcome, in that the overall frequency of sLRI over the first 2 winters in children receiving OM85 and receiving placebo did not differ significantly. However, the time to first sLRI, was significantly longer for those receiving OM85 than those receiving placebo. This is encouraging as early sLRI[3,4], and in particular reduced time to first sLRI after birth[5], increases the risk of persistent asthma in at-risk children. Moreover, the cumulative frequency of sLRI, and the number of days with sLRI symptoms, were also significantly lower in those receiving OM85, suggesting a reduction in the overall inflammatory burden in the lower airways during this crucial period of early lung growth. We acknowledge that this proposed mechanism for OM85 is speculative and requires mechanistic studies. In contrast, while there was a tendency for reduced overall frequency of LRI in the group receiving OM85, this did not reach statistical significance during any study period. The implication of these data is that OM85 was more effective at preventing sLRI than milder LRI.

The effects of OM85 were strongest in the first winter season, with a trend for fewer children in the OM85 group to have sLRI and URI. There was no evidence of a carry-over protective effect after treatment had stopped in the first study year. This suggests that infants and young children may require treatment all year round to maintain the early benefit of OM85. This lack of carry-over effect differs from the findings of Razi et al.[8]. However, they studied older children, not infants, and the differences in maturational stage of immune development between respective study populations may play an influence here. In this context we have recently shown that susceptibility to fLRI in infancy is highest in infants at the lower end of the innate immune development spectrum[6].

Despite the study being underpowered, some important lessons have been learned. 1) OM85 appears to be is safe and can be given to infants as young as 3 months of age. 2) OM85 can be used for primary prevention of sLRI in the high-vulnerability period of infancy, but may not be effective

in prevent milder LRI. 3) The treatment regimen giving OM85 for the first 10 days of the winter months may not be adequate to provide sufficient protection of at-risk infants against sLRI occurring while off treatment. In this regard, animal studies[9] with OM85 suggest that protection against respiratory viral infection is maximal if treatment is ongoing during the infection period. Further studies, with greater power, and possibly employing alternative treatment regimens, are warranted to determine whether OM85 can prevent asthma in at-risk infants and young children.

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179 **Figure Legend**

180 **Figure 1: Severe Lower Respiratory Illness (sLRI) during the study period.** Panel A: Time to
181 first sLRI, panel B: cumulative frequency of sLRI, panel C: cumulative number of days with sLRI.
182 Solid line = OM85 group, dashed line = Control group.

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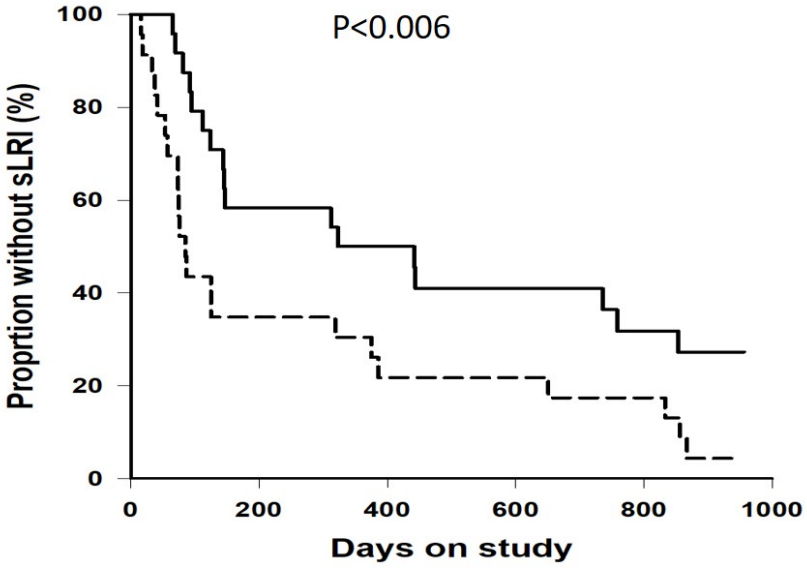
A



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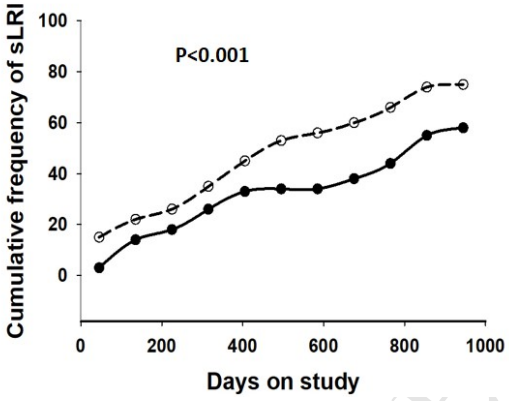

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