Tolerability and efficacy of Bioaron C® syrup in treatment of upper respiratory tract infections in children. Results of a post-marketing surveillance study in Poland

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Summary

A post-marketing surveillance study (PMSS) was carried out in Poland with 313 children aged 3-10, predisposed to upper respiratory tract infections. The study participants received Bioaron C® syrup, containing aqueous extract of *Aloë arborescens* leaves, juice of *Aronia melanocarpa* fruit and ascorbic acid. The main object of the present study was to investigate its tolerability and influence on the course of an acute URTI in children. Among the study participants 14% received Bioaron C® as a single medication and 86% of the patients received concomitant medications. The efficacy of the treatment was measured according to a validated symptom score. The best results were obtained for symptoms related to rhinitis and bronchitis but there was no major effect seen on pain and fever. Within the subscores rhinitis and bronchitis Bioaron C® alone was able to lead to an improvement and could contribute to a reduction in particular of the single symptoms blocked and runny nose, cough and hoarseness. Treatment with Bioaron C® resulted in a significant improvement of the symptomology of URTI. Bioaron C® was tolerated very well.

Key words: Aloë arborescens extract, Aronia melanocarpa extract, upper respiratory tract infections, Post Marketing Surveillance Study

INTRODUCTION

Bioaron C® syrup is a herbal medicinal product containing aqueous extract of Aloe (*Aloë arborescens* Mill.) leaves, juice of chokeberry (*Aronia melanocarpa* Elliot.) fruits and ascorbic acid. In Poland, it has been used for a long time in prophylaxis and treatment of common cold and recurrent upper respiratory tract infections in children.

It has been reported that Bioaron C® inhibits an antigen-specific immunological response and is a potent intracellular antagonist of hydroxyl radicals, which can be considered as a beneficial effect in the prevention of chronic disorders [1].

Phytochemical investigations on *A. arborescens* have shown the presence of glycoproteins (lectins), mineral compounds and a carboxypeptidase-class enzyme with bradykinase activity.

It has been also reported that *A. arborescens* extracts are rich in poly- and monosaccharides, including glucose, galactose, mannose and arabinose [2, 3, 4]. There are very few scientific publications on pharmacological actions of *A. arborescens*, and the existing ones provide evidence for their anti-inflammatory and chemopreventive effects (prevents BOP-induced pancreatic neoplasia in hamsters) [5, 6].

In vitro and *in vivo* studies on human lymphoid cells indicate the immunomodulatory activity of aloctin A, a glycoprotein isolated from the leafs of *A. arborescens*. The immunomodulatory effect was achieved via mitogenic stimulation of lymphocytes, binding of human alpha2-macroglobuline, complement activation via alternative pathway and antiinflammatory activity [7].

It has also been demonstrated that water extracts of *A. arborescens* inhibited the histamine release from mast cells induced by antigen in a concentration-dependent manner and it is suggested that such extracts may be useful in the treatment of type I immediate allergic disorders [8].

The extract of *A. melanocarpa*, one of the active product ingredients of Bioaron C®, is known to possess significant antioxidant properties. The role of free radicals in many disease conditions has been well established. The reactive oxygen species generated by several biochemical reactions in human organism are capable of damaging cells and provoking mutagenic and finally carcinogenic effects [9]. The relevance in other pathological situations was reported [9]. Cellular constituents sometimes cannot scavenge it effectively. *A. melanocarpa* berries are rich in polyphenols and anthocyanins which act as free radical scavengers (such as hydroxyl, alkoxyl or peroxyl) [10, 11] and have cytoprotective effect, as well as exhibit a strong antimutagenic activity against the action of a mutagen [12].

The mechanism of action of Bioaron C® syrup is only partially understood. The clinical efficacy is supposed to be caused by polymeric compounds like glycoproteins, which react with α_2-macroglobulines and activate component C-3 and proactivator C-3 of the human serum complement system.

The activated component C-3 influences the production of antibodies by B- lymphocytes and stimulates lymphocyte mitosis [1, 13].

The *in vivo* study in mice indicates an effect of Bioaron C® on several effectors of humoral and cellular immunity. It stimulated to a lower extent a spontaneous proliferation and to a higher extent the proliferation induced by suboptimal and optimal mitogen concentrations [1].

The *in vitro* studies in a human cell model with Bioaron C® showed also a dose–dependent inhibition of LPS-induced IL-6, TNF-α and IL-1β release [14].

Thus, Bioaron C® seems to be a promising as an anti-inflammatory and antiphlogistic herbal medicinal product for symptomatic treatment of common cold or other upper respiratory tract infections.

The results of an Open Label Study in Poland with Bioaron C® in the treatment of upper respiratory tract infections are presented.

MATERIALS AND METHODS

Study design and participants

The study was designed as a post-marketing surveillance study (PMSS) and children predisposed to upper respiratory tract infections were included. Children aged 3-10 were recruited from 62 pediatric centers in Poland, which were spontaneously attended because of symptoms of upper respiratory tract infection (URTI).

Children with asthma bronchiale, chronic obstructive pulmonary disease (COPD), tuberculosis, leukemia, collagenosis, multiple sclerosis, HIV infection, autoimmune diseases, organ transplantation, inflammatory gastrointestinal disease or known impairment of absorbtion were excluded from the study. Other exclusion criteria were: use of immunosuppressing, immunostimulating or immunomodulating medication, allergy tests or vaccination during the PMSS, cytostatic therapy during 6 months before baseline. A total of 313 children were recruited: 45% were males and 55% females. The average age of the patients was 5.3 years in the female and 5.4 years in the male group.

The total study period was about 14 weeks. Three doctor's visits were evaluated: a baseline visit 1, a follow-up visit after 14 days (visit 2) and and a long-term follow-up visit 3, which occurred 12 weeks after visit 2. Demographic information as sex, age, weight, height and history of upper respiratory tract inflammations in the past 12 months were collected at baseline. At the first baseline visit the participants received Bioaron C® as a single medication or as add-on therapy either with an expectorant, mucolytic, antipyretic, antiphlogistic, antibiotic or a combination of them. At visit 2 patients were examined by the physicians and asked to take Bioaron C® as a prophylactic between visit 2 and visit 3 if necessary.

Objective

The primary objective of this PMSS was to investigate the tolerability and the influence of Bioaron C®, either given alone or in combinations with other drugs, on the course of an acute URTI in children.

Outcome criteria/analysis

Treatment efficacy was measured according to a validated symptom score [15]. The physicians involved in the study were asked to evaluate the URTI symptoms (Table 1) and the severity, tolerability and safety of Bioaron C® for each patient in a CRF and to report any adverse event occurring during the study period.

Table 1.

The subscore groups and the single symptoms: rhinitis, bronchitis, pain, fever.

subscore	single symptoms
"rhinitis"	- blocked nose
	- runny nose
	- sniffing
	- handkerchief use
	- sneezing
"bronchitis"	- hoarseness
	- expectoration
	- chest pain
	- shortness of breath
	- cough
"pain"	- sore throat
	- headache
	- joint aches
	- dizziness
	- difficult swallowing
"fever"	- night sweats
	- sweating during the day
	- chills

The following score was used for assessment of severity: 1=none, 2=mild, 3=moderate and 4= severe).

Changes in subscores and symptoms between baseline and visit 2 were evaluated as categorised variable (no change/worsening; slight improvement; 'strong improvement' defined as a score reduction of at least 2 compared to baseline).

For the categorized subscore evaluation, patients were divided into the following 3 groups: single medication users (only Bioaron C® n=43), users of Bioaron C® together with one additional medication (n=28) and users Bioaron C® in combination with more than one medication (n=242) (Table 2).

Table 2.

Concomitant medication.

groups	n	%	female	male
Bioaron C® as single medication	43	14	25	18
Bioaron C® plus one concomitant medication	28	9	13	15
Bioaron C® plus two or more concomitant medications	242	77	134	108

RESULTS AND DISCUSSION

313 patients were enrolled into the study with a median number of 5 URTIs within the past 12 months. Among the participants 14% received Bioaron C® as a single medication and 86% of the patients received concomitant medications (Table 2). A wide range of different drugs was used as concomitant medications. As expected, according to the indications investigated, most frequently antibiotics were given to 46% of the patients, followed by antipyretics to 43%, expectorants to 42%, antiphlogistics to 37% and mucolytics to 34% of the patients.

The following tables show the results of URTI treatment with Bioaron C®. With regard to the subscores and the single symptoms, the best results were obtained for symptoms related to rhinitis and bronchitis. Not surprisingly, there was no major effect seen on pain and fever, which may be a domain for additional treatment with analgesics and/or antiphlogistics.

As shown in the tables, within the subscores rhinitis and bronchitis Bioaron C® alone was able to lead to an improvement and could contribute to a reduction in particular of the single symptoms blocked and runny nose, cough and hoarseness (Tables 3-8). With regard to other single symptoms, in particular in the subscores "pain" and "fever", there were no relevant changes seen, neither towards improvement nor worsening. One observation may be of interest: it is well known that children with infections do not eat very well. Within this study, an improvement of the children's appetite was seen in about 65%–68% of the patients in all subgroups (Table 9). The underlying mechanism for that phenomenon is not yet clear. But this finding is well in accordance with knowledge about the practical experience with Bioaron C® for the past 15 years of marketing: Bioaron C® can be used as a single medication in children with URTIs and, in addition, may improve the children's appetite. Compared to that, the additional benefit of concomitant medication may be limited to children with mild URTIs.

Table 3.

Change of subscore "rhinitis" from baseline to Visit 2.

change of subscore "rhinitis"	single medication		Bioaron C + one medication		Bioaron C + more than one medication		total	
	N	%	N	%	N	%	N	%
strong improvement	4	9.3	1	3.6	27	11.2	32	10.2
slight improvement	29	67.4	23	82.1	173	71.5	225	71.9
no change/worsening	10	23.3	4	14.3	42	17.4	56	17.9
total	43	100.0	28	100.0	242	100.0	313	100.0

Table 4.

Change of symptom "blocked nose" from baseline to Visit 2.

change of symptom "blocked nose"	single medication		Bioaron C + one medication		Bioaron C + more than one medication		total	
	N	%	N	%	N	%	N	%
strong improvement	9	20.9	9	33.3	81	33.9	99	32.0
slight improvement	18	41.9	9	33.3	65	27.2	92	29.8
no change/worsening	16	37.2	9	33.3	93	38.9	118	38.2
total	43	100	27	100	239	100	309	100

Table 5.

Change of symptom "runny nose" from baseline to Visit 2.

change of symptom "runny nose"	single medication		Bioaron C + one medication		Bioaron C + more than one medication		total	
	N	%	N	%	N	%	N	%
strong improvement	13	30.2	4	14.3	83	35.2	100	32.6
slight improvement	11	25.6	10	35.7	65	27.5	86	28.0
no change/worsening	19	44.2	14	50.0	88	37.3	121	39.4
total	43	100	28	100	236	100	307	100

Table 6.

Change of subscore "bronchitis" from baseline to Visit 2.

change of subscore bronchitis	single medication		Bioaron C + one medication		Bioaron C + more than one medication		total	
	N	%	N	%	N	%	N	%
strong improvement	0	0	0	0	0	0	0	0
slight improvement	29	67.4	19	67.9	202	83.5	250	79.9
no change/worsening	14	32.6	9	32.1	40	16.5	63	20.1
total	43	100.0	28	100.0	242	100.0	313	100.0

Table 7.

Change of symptom "cough" from baseline to Visit 2.

change of symptom "cough"	single medication		Bioaron C + one medication		Bioaron C + more than one medication		total	
	N	%	N	%	N	%	N	%
strong improvement	12	27.9	7	25	107	44.2	126	40.3
slight improvement	16	37.2	10	35.7	77	31.8	103	32.9
no change/worsening	15	34.9	11	39.3	58	24.0	84	26.8
total	43	100	28	100	242	100	313	100

Table 8.

Change of symptom "hoarseness" from baseline to Visit 2.

change of symptom "hoarseness"	single medication		Bioaron C + one medication		Bioaron C + more than one medication		total	
	N	%	N	%	N	%	N	%
strong improvement	4	9.3	2	7.1	62	25.6	68	21.7
slight improvement	13	30.2	8	28.6	79	32.6	100	31.9
no change/worsening	26	60.5	18	64.3	101	41.7	145	46.3
total	43	100	28	100	242	100	313	100

Table 9.

Change of single symptom "lack of appetite" from baseline to Visit 2.

change of symptom "lack of appetite"	single medication		Bioaron C + one medication		Bioaron C + more than one medication		total	
	N	%	N	%	N	%	N	%
strong improvement	13	30.2	5	17.9	68	28.3	86	27.7
slight improvement	15	34.9	13	46.4	96	40.0	124	39.9
no change/worsening	15	34.9	10	35.7	76	31.7	101	32.5
total	43	100.0	28	100.0	240	100.0	313	100.0

Out of 313 patients 264 continued therapy with Bioaron C® after the second visit. 95% of these patients received Bioaron C® as immunostimulant to reduce recurrence of an acute upper respiratory tract inflammation. Between visit 2 and visit 3 (period of 12 weeks) 39% of the children did not experience a new episode of inflammation, 33% of the children had one new episode, 16% two and 9% three episodes.

In the group of patients treated by Bioaron C® as a single medication, 77% of physicians assessed Bioaron C® as very efficient and 23% as efficient. In the group of patients who took concomitant medications with Bioaron C®, 45% physicians assessed Bioaron C® as very efficient, 50% efficient and 5% less than efficient.

One must take into account that it was an observational, non-interventional study thus not using a control group: pediatricians involved into this study applied their usual therapeutic regimens. The fact that the majority of patients took one or even more than two concomitant medications was due to the normal therapeutical behaviour of the pediatricians.

TOLERABILITY AND SAFETY

86% of the physicians stated that the patients tolerated Bioaron C® very well, 14% indicated that the patients tolerated Bioaron C® well, and none of them stated that the patients tolerated Bioaron C® poorly.

Similarly, for 86% of the patients the physicians indicated that Bioaron C® was very safe, 14% stated that it was safe and none of them evaluated Bioaron C® as less safe. No adverse events or serious adverse events were reported throughout the study.

CONCLUSION

The results of this trial are well in accordance with the long known experience that symptoms of upper respiratory tract infections, in particular symptoms of rhinitis and bronchitis, can be treated successfully with Bioaron C® alone, in particular in mild to moderate cases. The benefits of concomitant medication used in this study did not increase the response much more.

The result of the present study supports the well-known benefits of Bioaron C® in the symptomatic treatment of URTIs. It can be considered as an effective and well-tolerated remedy in the treatment of upper respiratory tract infections in children. However, a controlled study will be necessary to confirm these results.

In summary, treatment with Bioaron C® clearly reduced the severity of symptoms of upper respiratory tract inflammations in children and was tolerated very well.

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TOLERANCJA I SKUTECZNOŚĆ SYROPU BIOARON C® W LECZENIU INFEKCJI GÓRNYCH DRÓG ODDECHOWYCH U DZIECI. WYNIKI POSTMARKETINGOWYCH BADAŃ OBSERWACYJNYCH W POLSCE

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Streszczenie

Przeprowadzono w Polsce postmarketingowe badania obserwacyjne u 313 dzieci w wieku od 3-10 lat ze skłonnością do infekcji górnych dróg oddechowych. Uczestnicy badania otrzymywali syrop Bioaron C®, zawierający wyciąg z liści aloesu drzewiastego (Aloë arborescens Mill.), sok z owoców aronii (*Aronia melanocarpa* Elliot.) i witaminę C. Przedmiotem oceny prezentowanych badań była tolerancja syropu oraz jego wpływ na przebieg ostrych infekcji górnych dróg oddechowych u dzieci. Spośród uczestników badania 14% otrzymywało tylko Bioaron C®, a 86% pacjentów oprócz Bioaronu C® dodatkowe środki. Skuteczność terapii oceniano zgodnie ze zwalidowaną skalą objawów. Najlepsze wyniki osiągnięto w leczeniu objawów nieżytu nosa i zapalenia oskrzeli, nie obserwowano natomiast wpływu na ból czy gorączkę. Monoterapia Bioaronem C® okazała się najlepsza w leczeniu objawów nieżytu nosa i zapalenia oskrzeli, w szczególności takich składowych jak zatkany i cieknący nos, kaszel i chrypka. Terapia Bioaronem C® w stopniu znaczącym wpływała na poprawę symptomów infekcji górnych dróg oddechowych. Syrop Bioaron C® był bardzo dobrze tolerowany.

Słowa kluczowe: wyciąg z aloesu drzewiastego, wyciąg z aronii czarnoowocowej, infekcje górnych dróg oddechowych, postmarketingowe badania obserwacyjne