

Influence of measles vaccination on the progression of atopic dermatitis in infants

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Atopic dermatitis (AD) is a chronic inflammatory skin disease, affecting 10–20% of children. Measles vaccination has been reported to have contradictory effects on incidence of AD in children. Therefore, we performed the first prospective, double-blind, placebo-controlled study to analyze the evolution of AD in infants after measles vaccination. The study included 12 infants (10–14 months old) with AD, randomly assigned to two groups: while the first group received a single dose of a standard measles vaccine ROUVAX, the second was treated with placebo (vehicle). Infants were followed-up for 6 months after administration of ROUVAX/placebo for the clinical signs associated with AD, by determination of SCORAD index. In addition, serum was taken before vaccination and 1 month later to determine the presence of seroconversion and to analyze the progression of serum levels of CCL18 (PARC) and E-selectin, known to be distinct serum markers that reflect clinical features of AD. In the vaccinated group, five of six children seroconverted 1 month after treatment and one infant showed a 50% improvement of SCORAD. Serum levels of CCL18 were significantly decreased in two treated infants (of four analyzed for this group) and E-selectin slightly decreased in one infant (of three analyzed by this test). In placebo-treated group the SCORAD improved in one patient and serum levels of CCL18 and E-selectin did not change. These data suggest that measles vaccination not only does not aggravate AD, but may also improve some of the immunological parameters of this allergic disease. Inclusion of a higher number of patients in a similar study should give a more comprehensive overview of the benefit of measles vaccination on the clinical evolution of AD patients, and potentially open new avenues to the clinical application of the anti-inflammatory effect of measles virus proteins.

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Atopic dermatitis (AD) is a chronic inflammatory skin disease characterized by eczematous skin lesions. This allergic reaction presents a skin manifestation of atopy, affecting 10–20% of children and 1–3% of adults. It is often the first step in the atopic march, which leads to asthma and allergic rhinitis in the majority of afflicted patients. AD usually starts during early infancy and childhood, but it can persist into or start in adulthood and has increased two to threefold during the past three decades in industrialized

countries (1). AD corresponds to T-cell mediated delayed type hypersensitivity reaction and is associated to the generation of memory T cells of Th2 type, expressing the skin homing receptor, cutaneous lymphocyte-associated antigen (CLA) (2). Severity of the disease, both in adults and children, is associated to the serum level of the soluble E-selectin (3, 4) a leukocytes adhesion molecule, which serves as a ligand for CLA and allows lymphocyte extravasation in the tissue. In addition, increase in CCL18 (PARC, pulmonary

and activation-regulated chemokine) both in serum and lesional skin of AD patients have recently been demonstrated (5, 6). This chemokine is produced by antigen-presenting cells, binds to CLA⁺ T cells in the peripheral blood and induces their migration into skin, playing an important role in the pathogenesis of AD (5).

Measles virus (MV) is among the most contagious pathogens for humans, still infecting over 40 million people and causing the death of close to 1 million persons each year mainly in the developing world (7). In addition, sporadic outbreaks of acute measles still occur in industrialized countries, provoked by low vaccination coverage, often related to parental concerns over vaccination safety (8). Complete elimination of measles is one of priorities of World Health Organization, which requires high vaccination coverage throughout the world. Therefore, vaccination with the live-attenuated MV has been introduced as a part of public health program in most of the countries. Measles infection and measles vaccination have been associated with the AD in children by rather contradictory results, reported by different authors. One recent retrospective study in the cohort of 3–15-yr-old Danish children has demonstrated that the incidence of AD augmented after measles, mumps and rubella (MMR) vaccination and measles infection, suggesting that measles vaccination could increase the risk of AD (9). In accord to these results, the other retrospective analysis of 6-yr-old Finish children showed that naturally acquired measles infection was associated with increased prevalence of asthma and AD (10). In contrast to these observations, a cross-sectional study of Scottish schoolchildren suggested that MV infection could reduce the risk of atopic diseases (11) and exposure to MMR-infections or MMR vaccination in childhood did not increase a risk of sensitization to common allergens and to allergic respiratory diseases (12). In addition, a study of the relationship between MV infection and subsequent atopy in a village of Guinea-Bissau, West Africa suggested that measles infection might prevent the development of atopy in African children (13). Moreover, a marked improvement in symptoms of patients with AD during natural measles has been observed by different authors (14, 15).

To better understand the potential association of measles vaccination with the progression of AD in infants, we have performed the first prospective, randomized, double-blind, placebo-controlled investigation. This study has aimed to analyze the clinical evolution of AD and modulation of physiopathological parameters in a

small group of infants after measles vaccination. We report here the absence of any negative effects of MV vaccination on the progression of AD and even amelioration of tested immunological parameters in some of analyzed children.

Material and methods

Patients

The study was performed between June 2003 and December 2004 and included 12 infants (eight boys and four girls) between 10 and 14 months of age. All infants suffered from AD, based on the criteria of Hanifin and Rajka (16). None of the patients were treated with systemic steroids or received measles vaccine previously. Long-term concomitant treatment of children included fluoride and/or vitamin D supplements. Treatment of AD was limited to local emollient (ATODERM[®]) and in the case of worsening of disease, topical corticosteroid ointment Desonide (LOCAPRED[®]), provided by the study team. The study protocol was approved by the local ethics committee and parents gave written informed consent.

Measles vaccination

Measles vaccination was performed using vaccine ROUVAX (attenuated MV, vaccine strain Schwartz (≥1000 DICC 50), Laboratory Aventis-Pasteur MSD, Lyon, France), given subcutaneously, in one dose. Vaccine was generally very well tolerated and in only two infants the augmentation of temperature by 39°C was observed. Randomly chosen patients received placebo, composed 0.5 ml of physiological serum, given subcutaneously and these infants were vaccinated at the end of the study. The randomization file was generated by computer, using a permuted-block algorithm, with participants stratified according to AD severity. Concealed allocation was performed after baseline data collection by the study nurse, by calling the coordination centre. All placebo-treated children received measles vaccine after the completion of the study.

Severity scoring of AD

Severity of AD was determined using SCORAD (17), taking into account the total affected skin area, intensity of skin lesions and subjective symptoms including pruritus and sleep loss. The maximal score this method could give is 103 points. This test was performed twice before the

inclusion of patients in the study and vaccination, and repeated 1, 3 and 6 months later.

Laboratory analysis

Serum was taken before and 1 month after the vaccination and tested for measles-specific IgG and IgM antibodies by commercial ELISA (EnzygnostR Anti-Masern-Virus, DADE Behring, Deerfield, IL, USA). CCL18 and E-selectin were quantified in the serum using sensitive commercial ELISA, following the instructions of the manufacturer (R&D Systems, Minneapolis, MN, USA).

Statistical analysis

Statistical analysis was performed using standard statistical tests. Student's paired *t*-test and Wilcoxon signed rank test to estimate the significance levels of the differences between groups.

Results

Progression of clinical parameters of AD after measles vaccination

Infants suffering from AD were randomly divided into two groups (four boys and two girls in each group) and received either measles vaccine or placebo. The baseline SCORAD was similar in two study groups: 21.46 (s.d. 10.28) in the ROUVAX group and 16.36 (s.d. 12.55) in the placebo group. The SCORAD evolution was determined before vaccination and 1, 3 and 6 months later (Fig. 1). In both groups symptoms of AD were significantly improved in one patient, 1 month after vaccination and SCORAD index stayed low by the end of study. In the other patients, having lower SCORAD index at the beginning of the study, no important changes in the clinical progression of AD were observed.

Changes in the serum level of CCL18 and E-selectin

All infants were seronegative for measles-specific antibodies at the moment of the inclusion into study. In one patient (ROL) seroconversion was not observed after measles vaccination, possibly because of the vaccine failure. In contrast, one infant (FRA) seroconverted after receiving a placebo. These two infants were followed for clinical progression of AD but were not analyzed for immunological parameters.

Two distinct serum factors were followed in analyzed patients: CCL18 and E-selectin. Both biomarkers were shown previously to follow

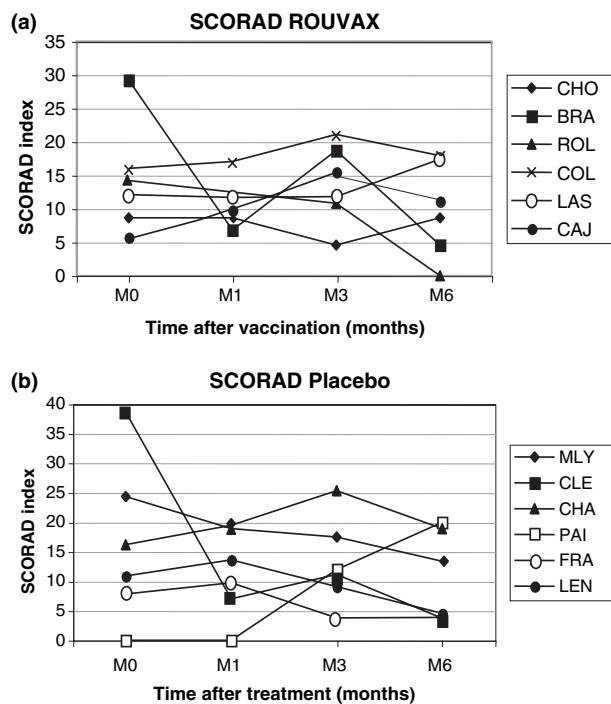


Fig. 1. Severity of eczema after measles vaccine (a) or placebo (b) treatment, evaluated using SCORAD index. Randomly chosen six infants in each group were followed during 6 months.

clinical features of AD (3–5) and there are no reports on their association with measles vaccination or infection. In all analyzed infants the serum level of CCL18 and E-selectin were highly elevated, similarly to what has been reported previously in AD patients. Due to the small quantity of obtained serum only four vaccinated patients were analyzed for the serum level of CCL18, and in two of them the CCL18 level was significantly decreased (Fig. 2a). In contrast, no changes were observed in placebo-treated infants. Remaining serum of five infants was then tested for the level of E-selectin. Only moderate decrease of E-selectin was observed in one patient (LAS) after vaccination (Fig. 2b).

Discussion

Prevalence of atopic diseases, including AD is constantly increasing in industrialized countries in last few decades. As there is still no causal therapy, better understanding of risk factors and prevention of AD are especially important. Vaccination may interfere with the pathogenesis of AD and the exacerbation of AD after BCG vaccination (18) or smallpox vaccination (19) has been reported. Some recent retrospective studies suggested an increased risk of AD after measles

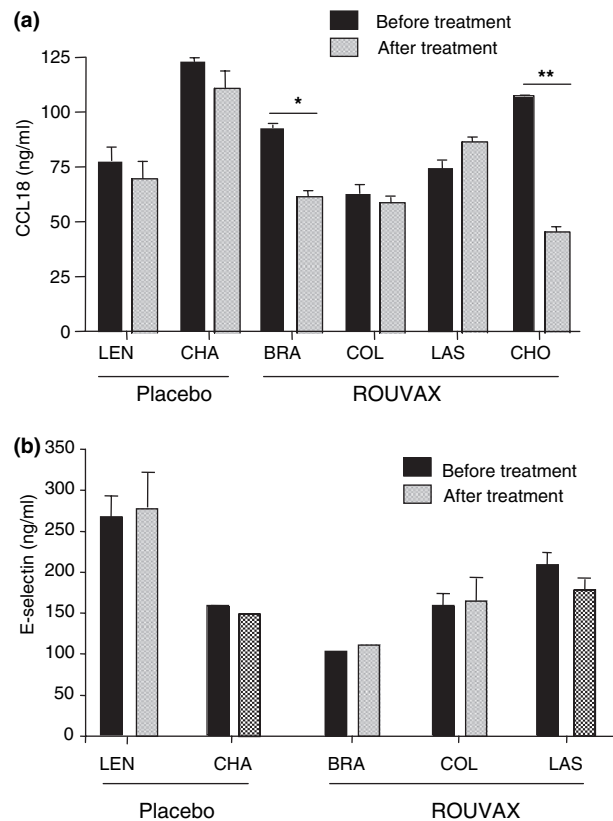


Fig. 2. Serum levels of soluble CCL18 (a) and E-selectin (b) in infants with atopic dermatitis before and after treatment with measles vaccine ROUVAX and placebo (* $p = 0.0183$; ** $p = 0.0011$, Student test). Normal serum values obtained with the same ELISA kit for E-selectin were between 29.1 and 63.4 ng/ml (mean value: 46.3).

vaccination or infection (9, 10). Therefore, we performed a prospective study to evaluate the influence of broadly used measles vaccination on the progression of AD in infants. We report here that measles vaccination did not aggravate either clinical signs of AD or tested immunological parameters in any of analyzed infants during the period of 6 months after vaccination. Nevertheless, in two of four tested patients, AD prognostic marker CCL18, decreased significantly after vaccination, suggesting that measles vaccination may even have some favorable effect in stabilizing certain biomarkers characteristic for AD. Although these results were obtained with the small number of patients, due to the difficulties in the recruitment of this specific age group, they go along with some other observations of reduced atopy after MV infection (11, 13) and even complete disappearance of AD in some children after measles (14, 15). Contrasting results obtained by different authors may reflect different life style of analyzed population and climate conditions, as increased risk to AD after MV

vaccination was observed overall in Scandinavian countries. In addition, our study does not provide information on the long-term outcome of vaccinated patients, which rest to be analyzed.

The potential beneficial effect of measles vaccination may be related to the induction of temporary immunosuppression. MV infection has been known for a long time to be followed by disappearance of delayed-type hypersensitivity responses to tuberculin (20) and impaired *in vitro* proliferation of peripheral blood lymphocytes (21). Many immunological alterations observed during measles infection also occur at lesser magnitude after vaccination of children using attenuated MV (22, 23). Anti-measles vaccination induces predominant Th1 type response, with IFN- γ being a principal cytokine produced in vaccinated children (24) and both IL-2 and IFN- γ in *in vitro* infected lymphocytes (25), may interfere with predominant Th2 response in AD. In addition, we have recently shown using preclinical model of skin hypersensitivity reaction in mice that MV proteins could generate a systemic immunosuppression of T-cell mediated inflammation (26). Furthermore, it has been shown using human *in vitro* system that MV receptor CD46 is involved in the generation of T-regulatory cells (27) and importance of T-regulatory cells in the pathogenesis of AD has recently been demonstrated (28). Finally, the engagement of the second MV receptor, human molecule CD150 (SLAMF, for signaling lymphocytic activation molecule), was shown to induce the reversal of human allergic Th2 type lymphocytes, isolated from skin biopsies of patient with AD, into Th1 profile (29). Taken together, these results provide additional arguments in favor of a beneficial effect of anti-measles vaccination in allergic inflammatory processes mediated by T lymphocytes.

Disease suppression with topical steroids is the current conventional treatment for AD and new therapeutic approaches are needed in this domain. In that context, administration of a killed *Mycobacterium* has been shown to improve AD in children, by modifying immune balance towards Th1 profile (30, 31), and BCG vaccination reduced the risk from asthma and atopic diseases in adolescence (32), although BCG vaccination had only weak protective effect against atopic diseases in infants (33). As anti-measles vaccination is widely applied and well tolerated, a moderate immunosuppression of cellular immune response induced by this vaccination could be used to improve clinical signs of patients with AD. Furthermore, anti-measles

vaccination induces a transitory immunosuppression in vaccinated seropositive adults, suggesting that presence of anti-measles immunity does not interfere with immunosuppressive effect of vaccination (34). Inclusion of a higher number of patients in a study similar to the one described in this report, should give a more comprehensive overview of the benefit of measles vaccination on the clinical evolution of AD patients, and potentially open new avenues to the therapeutic application of the anti-inflammatory effect of MV proteins.

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