Growth velocity in prepubertal children using both inhaled and intranasal corticosteroids

Lasmar, Laura; Brand, Paul L.P.; Lima, Anna Carolina Lustosa; Maciel, Maria Fernanda; Camargos, Paulo

Published in:
Annals of Allergy, Asthma and Immunology

DOI:
10.1016/j.anai.2016.01.011

Publication date:
2016

therefore increased immune suppression, viruses such as HHV6 can reactivate in an uncontrolled fashion.[5] After DRESS, T-reg cells were found to have lost their ability to inhibit cytokine production and proliferate effector T cells. T-reg cells might have become overloaded initially and in turn become refractory after DRESS, leading toward an immune imbalance.[5,6] This decrease in functional T-reg cells might, at least in part, have contributed to the autoimmunity.

In addition to deregulated T-reg cells, viral reactivation could play a role in post-DRESS autoimmunity. Viral reactivation has long been known to play a large role in DRESS pathogenesis so much so that HHV6 reactivation is often used as a criterion to diagnose DRESS.[5] Other viruses associated with DRESS include Epstein-Barr virus and cytomegalovirus.[6] Viral reactivation can be asymptomatic, cause reoccurrence of DRESS, or just cause organ-specific disease.[6] The combination of nonfunctional T-reg cells after DRESS and viral reactivation could work synergistically in promoting autoimmunity (organ specific or systemic).[5,6] Some studies have found that HHV6 in the thyroid is significantly higher in Hashimoto thyroiditis.[7] Patients with lupus have higher titers of antibodies against Epstein-Barr virus and increased viral copy numbers than in the general population.[6] The exact pathomechanism of how viruses contribute to post-DRESS autoimmunity needs further investigation.

Because only a subset of patients with DRESS develops autoimmunity, genetically predisposing HLA genes might be a factor. Because of the limited number of cases of autoimmune T1DM associated with DRESS, no specific HLA association has been discussed. Some studies have linked DQA1*0303, DQB1*0401, and HLAB62 with fulminant T1DM after DRESS.[8,9] In 1 of the other 2 case reports of autoimmune-induced T1DM, the HLA typing showed DQA1*0303, the reported HLA linked with those who developed fulminant T1DM.[3] Why this patient developed autoimmune diabetes rather than fulminant diabetes is unclear.

In addition to these contributors, the culprit drug could play a role. There have been reports of minocycline-induced autoimmunity without DRESS.[10] Minocycline can cause various symptoms including polyarthralgia, autoimmune hepatitis, lupus, and vasculitis.[10] Studies on minocycline have shown that it has immunomodulatory effects, despite unclear pathogenesis. Some hypothesize that it might work similarly to other drug-induced autoimmunity, such as hapten formation, unmasking neoantigens, molecular mimicry, or cross-reactivity with self-antigens. It is hypothesized that all the following can contribute to minocycline-induced autoimmunity: inherent immunomodulatory effect of minocycline, HLA subtype, T-reg cell deregulation, and latent viral infection.[10]

This interesting case has important takeaway points. Physicians need to be constantly vigilant about detrimental complications so they can weigh the benefits against the risks of prescribing medications. Furthermore, it is important for physicians to be aware of potential complications of DRESS to perform appropriate screenings and provide timely treatment. In this case, the patient's diabetes was found incidentally. Hence, clinically relevant laboratory studies should be considered for a timely diagnosis to prevent severe complications.

Jennifer Lan, MD*
Amit Lahoti, MD†
D. Betty Lew, MD*
*Division of Allergy and Immunology
†Division of Endocrinology
Department of Pediatrics
The University of Tennessee Health Science Center
Memphis, Tennessee
dlew@uthsc.edu

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Growth velocity in prepubertal children using both inhaled and intranasal corticosteroids

The concomitant use of inhaled and intranasal corticosteroids raises concerns in relation to the impairment of the growth velocity in the prepubertal period.[1] Regular use of inhaled corticosteroids (ICSs) at low or medium daily doses is associated with a mean reduction of 0.48 cm per year in linear growth velocity,[1] whereas most studies of intranasal corticosteroids (INCs) did not find clinically relevant growth suppressive effects in this age group.[2] Conversely, Skoner et al[3] found a reduction of 0.9 cm after 12 months in children aged 6 to 9 years receiving a mean of 336 μg of intranasal beclomethasone dipropionate daily. However, studies evaluating the adverse effect on growth of the concurrent and medium to long-term use of these 2 formulations in prepubertal children are scarce. The aim of the present study was to assess growth velocity in prepubertal children using different doses of beclomethasone dipropionate, with or without the concomitant use of an INC.

We performed a prospective, observational, real-life study in which we enrolled prepubertal asthmatic children (3–9 years of age for girls and 3–9.5 years of age for boys) from our asthma management program in Belo Horizonte city, Brasil.[4] All patients used beclomethasone dipropionate– chlorofluorocarbon, the standardized inhaled corticosteroid provided for free by the Municipal Health

Disclosures: Authors have nothing to disclose.
Funding Sources: Dr Camargos is supported by grant 303396/2012-1 from Conselho Nacional de Desenvolvimento Científico e Tecnológico and grant PPM0065-14 from the Fundação de Amparo à Pesquisa do Estado de Minas Gerais. These research agencies had no influence in the design and conduct of the study; in the collection, management, analysis, and data interpretation; in the writing, review, or approval of the manuscript; and in the decision to submit the paper for publication.

Authority, through a valved plastic spacer.[3] We categorized patients according to the daily prescribed beclomethasone dipropionate dose in 3 groups as follows: less than 500 μg/d, 500 to 750 μg/d, and more than 750 μg/d. Because the Municipal Health Authority prioritizes asthma management over allergic rhinitis management, children with allergic rhinitis were only prescribed an INC when available free of charge or affordable to the family (equivalent to up 200 μg of aqueous intranasal beclomethasone dipropionate). The dosages of beclomethasone dipropionate with or without an INC were adjusted during follow-up based on the level of asthma and rhinitis control achieved, following Global Initiative for Asthma and Allergic Rhinitis and its Impact on Asthma guideline recommendations.[5,6]

Predefined exclusion criteria were as follows: birth weight below 2,500 g, current malnutrition (weight lower than −2 *z* scores below the mean age value for weight),[7] other concurrent chronic diseases, and use of systemic corticosteroids for more than 2 weeks per year to treat asthma exacerbations.

Patients were followed up for at least 2 years. Height was assessed every 3 months as described by van't Hof et al.[8] The primary end point was the mean height gain in centimeters per year.

Eighty children with asthma (48 boys [60%]) were followed up for a mean (SD) period of 3.50 (1.39) years. Their mean (SD) age at admission was 4.29 (1.96) years. Sixty-four of them also had AR (80%), 19 of whom (29.7%) used INCs combined with beclomethasone dipropionate during follow-up. The mean (SD) height was 112.93 (12.58) cm at admission and 138.31 (14.54) cm at the end of follow-up. These values corresponded approximately to a mean *z* score equal to 0 for the 80 patients as a whole.[7] At admission and the end of the follow-up, the mean adherence rate for beclomethasone dipropionate and INCs were 79.4% and 66.7% and 66.7% and 54.8% of the prescribed dose according to fill-refill pharmacy records, respectively.

Figure 1 depicts the growth velocity (expressed as centimeters per year) curves according to the different doses of beclomethasone dipropionate, alone or combined with an INC: (a) less than 500 μg, no INC; (b) less than 500 μg, combined with an INC; (c) 500 to 750 μg, no INC; (d) 500 to 750 μg, combined with an INC; (e) higher than 750 μg, no INC; and (f) higher than 750 μg, combined with an INC.

Because daily dosages up to 500 μg of beclomethasone dipropionate are considered safe, this group (group a) was considered as the reference group against which growth velocity in all other groups was compared. In group a, the mean (SD) height gain was 6.11 (4.27) cm per year. Mean (SD) height growth in the other groups was 6.16 (4.84) cm per year in group b ($P = .96$ compared with group a), 6.92 (6.91) cm per year in group c ($P = .37$), 5.36 (3.45) cm per year in group d ($P = .69$), 7.94 (7.01) cm per year in group e ($P = .26$), and 4.74 (5.16) cm per year in group f ($P = .44$), respectively.

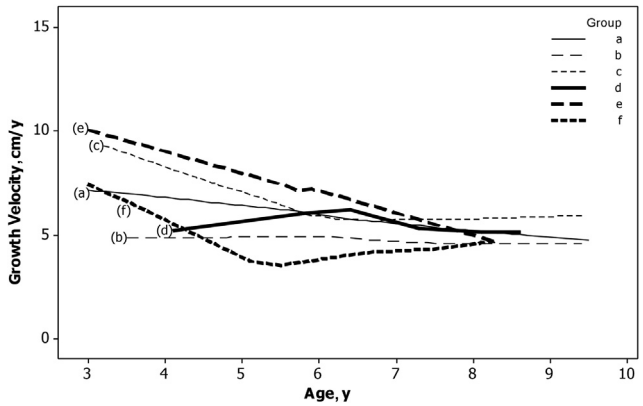

Figure 1. Growth velocity curves according to the different doses of beclomethasone dipropionate, alone or combined with an intranasal corticosteroid.

Overall, the prepubertal children in our study had a height gain of approximately 6 cm per year (corresponding to a change in *z* score equal to 0), which is the expected mean annual gain for the age group studied.[7] However, even though growth velocity was similar at the end of the observation period, children receiving INCs seemed to grow slower at the beginning.

Among the individuals who were prescribed more than 750 μg/d of beclomethasone dipropionate and an INC (group f), the slope of the curve demonstrated lower annual growth velocity from 3 to 5 years of age than that expected for healthy prepubertal children; however, this was followed by recovery of growth velocity, and height attained at the end of the follow-up period was comparable to both children receiving lower doses of beclomethasone dipropionate with or without INC (Fig 1) and with reference standards of healthy children.[5] At the end of follow-up, all studied patients had comparable height.

Our results are similar to those obtained in the only other real-life study that assessed growth parameters among prepubertal children with asthma and allergic rhinitis using both ICSs and INCs.[5] In this study, the authors did not find any effect on growth overall. However, their study had a retrospective design and no standardized protocol to measure height, and the median follow-up period was shorter than ours (ie, 2 years and 4 months).[9]

In conclusion, although we found an initial reduction of growth velocity related to daily use of inhaled beclomethasone dipropionate– chlorofluorocarbon in doses greater than 500 μg/d (or equivalent), particularly when it was used concomitantly with an INC, subsequent annual height gain resulted in recovery of height growth to the expected height and age reference standards. Because individual increased susceptibility to the growth-related adverse effects of ICSs and INCs cannot be predicted or excluded, careful height monitoring remains indicated in patients using these formulations, irrespective of the dose used.

Laura Lasmar, MD, PhD[*]
Paul L.P. Brand, MD, PhD[†,‡]
Anna Carolina Lustosa Lima, MSc[§]
Maria Fernanda Maciel, MD[*]
Paulo Camargos, MD, PhD[*]
[*]*Pediatric Pulmonology Unit*
University Hospital
Federal University of Minas Gerais
Belo Horizonte, Brazil
[†]*Princess Amalia Children's Centre*
Isala Hospital
Zwolle, The Netherlands
[‡]*Postgraduate School of Medicine*
University Medical Centre
University of Groningen
Groningen, The Netherlands
[§]*Department of Professional Masters on Information Technology*
Applied to Computational Biology
Inforium College of Technology
Belo Horizonte, Brazil
paulo.camargos@pq.cnpq.br

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Montelukast-induced metamorphopsia in a pediatric patient
A case report and a pharmacovigilance database analysis

Metamorphopsia is a type of optical illusion in which the size, shape, or angulation of objects is perceived as altered. Individuals typically see lines as wavy instead of straight and flat surfaces as curved. It is a rare manifestation of a central nervous system insult, mainly to the visual or vestibular systems.[1] It is a symptom caused by disorders of the retina or choroid and frequently observed in age-related macular degeneration.[1]

Metamorphopsia rarely occurs as an adverse drug reaction (ADR). An analysis of case reports from the National Registry of Drug-Induced Ocular Side Effects has identified bisphosphonates, cetirizine, retinoids, and topiramate as the drugs mostly involved in ocular ADRs. No cases of metamorphopsia were detected,[2] confirming the rarity of this ADR.

To date, the ocular ADRs are not included in the adverse effects reported in the summary of product characteristics of montelukast; the correlation between its use and the ocular event has not yet been investigated. Montelukast is used in the treatment of asthma and allergic rhinitis in children and adults. Although generally well tolerated, it may lead to clinical ADRs, such as upper respiratory tract infection, worsening asthma, and headache. Rare events of eosinophilic granulomatosis with polyangiitis have also been reported.[3]

We present the first case, to our knowledge, of montelukast linked to the onset of metamorphopsia. We propose a possible mechanism leading to its insurgence and provide an analysis of international pharmacovigilance databases to map its occurrence.

A 12-year-old girl with asthma was treated with montelukast at the therapeutic dose (5 mg/d). Approximately an hour after the first oral administration, the patient experienced headache and visual disturbance in which the perfectly straight lines appeared wavy and parts of the line appeared blank with flat surface bending. Approximately 15 minutes after the onset of the visual disturbance, she was hospitalized. Neurologic examination and electroencephalography revealed no abnormalities. Results of an Amsler test, a diagnostic tool used to detect the visual disturbances, were positive.[4]

The patient received no other concomitant drug or herbal treatment and had no personal or family history of ocular diseases. Considering the temporality between the drug intake and the appearance of the reaction, the treatment was discontinued, and a diagnosis of iatrogenic metamorphopsia was made. The ADR resolved after drug withdrawal in few days. The patient no longer experienced ocular disturbances and metamorphopsia during a 3-month follow-up.

Disclosures: Authors have nothing to disclose.
Funding Sources: This study was supported by the Italian Medicines Agency, the Centre of Pharmacovigilance of Regione Lombardia, and grant RC 2014 from the Italian Ministry of Health (Dr Clementi).
Drs Clementi and Radice jointly directed this work.

The positive dechallenge result and the temporal association between the drug's use and the onset of the reaction suggested a possible causal relationship between metamorphopsia and montelukast administration, which was also confirmed by the causality assessment scale of Naranjo et al,[5] the algorithm mostly used to identify the causality of ADR. Montelukast-associated metamorphopsia has not previously been reported in the literature, although the international pharmacovigilance databases contain several reports of ocular events associated with the drug.

We retrieved 719 reports of ocular ADRs in which montelukast was the suspected drug involved, inserted into the following pharmacovigilance databases: the Danish Health and Medicines Authority, the Health Canada Vigilance Adverse Reaction Online Database, the Netherlands Pharmacovigilance Centre Lareb Databank, the UK Medicines and Healthcare Products Regulatory Agency, the US Food and Drug Administration Adverse Event Reporting System, and the Australian Adverse Event Reporting System (Table 1). Of 719 ocular ADR reports, 4 of those in the Adverse Event Reporting System described metamorphopsia, representing 0.5% of the total ocular events retrieved in our analysis. Of these, one refers of a 13-year-old boy with multiple allergies in therapy with montelukast. Approximately 15 minutes after the administration, the patient experienced visual disturbance with metamorphopsia. The limit of this analysis is that the pharmacovigilance databases mostly receive reports of serious ADRs, resulting in an underestimation of the issue.

The ocular ADRs are scant in general and rare with montelukast. Previous studies have estimated that myopia and conjunctivitis can occur in patients taking montelukast, with an incidence of 2%; mydriasis is among the most frequent adverse effects with overdosage of the drug. The pathogenic causes of montelukast-associated metamorphopsia may be multiple and not necessarily mutually exclusive. Metamorphopsia is often the result of progressive accumulation of fluid in the rear area of the ocular fundus, leading to the perception of a deformed visual field.[1] It is therefore plausible that inflammation and peripheral edema play an important role in this visual disturbance.[6] Inflammatory processes and the increase in vascular permeability are indeed responsible for macular edema that results in metamorphopsia. The release of inflammatory mediators, such as histamine and products of arachidonic acid metabolism, has been demonstrated in the bronchoalveolar fluid of patients with asthma, and in some cases montelukast is able to cause periorbital edema.[7] In our case, a partial inefficacy of montelukast in reducing proinflammatory mediators combined with the onset of edema have probably triggered metamorphopsia. Another possibility is headache often associated with bizarre visual and spatial distortions.[8] Headache has been commonly reported (>1 per 100 to <1 per 10) in clinical studies that enrolled patients with asthma treated