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Montelukast effects on lymphocyte in asthmatic children

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Abstract

Asthma is a common disease in children with grief consequences on social and educational performance of sufferer. Montelueukas has been a mainstay drug for asthma attack controller medication. However, its effect on blood is not well defined. The main objective is to determine the effect of the drug on white blood cells. This case control study encompasses 72 children with confirmed asthma, 36 of them received 4mg of monteleukast granule daily for four months, the remaining half did not receive the drug. Complete Blood Count (CBC) was performed at the beginning of the study and then monthly till the end of the study. There was no statistically significant difference in the CBC parameters at beginning and during the first two months ($P>0.5$) between the two group. There was a trend toward a reduction in the lymphocyte count in the treated group in the third month in comparison to the control one. The last CBC measurement (4 months) showed statistically significant reduction in the lymphocyte count ($P<0.01$) in the treated group when compared to the control group. In conclusion: Monteleukast negatively influence the number of lymphocytes and caution should be exercised to avoid prescribing the drug in conditions known to reduce lymphocyte counts such as Covid-19 infection.

Keywords: Montelukast; Lymphocyte; Asthmatic children; Covid-19

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Introduction

Asthma is an inflammatory disorder of the airways, which involves multiple inflammatory cells and mediators that contribute to the characteristic clinical and pathophysiological changes [1]. It is characterized by wheezing, cough, and dyspnea.

Chronic inflammation and smooth muscle dysfunction are consistent features of asthma pathophysiology, responsible for disease progression and airway remodeling. The acute and

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chronic inflammation in asthma is the result of extensive infiltration of the airway by inflammatory cells including T cells, eosinophils, mast cells accompanied by the release of inflammatory mediators- cytokines and leukotriene (e.g., IL-4, -5, -9, and -13) from these cell and also release the bronchoconstrictor mediators such histamine, cysteinyl leukotrienes and prostaglandin D2 when activated [2, 3].

The secretory molecules of these cells promote eosinophil and mast cell influx, mucus hypersecretion, airway wall remodeling, and airway hyper-responsiveness (AHR), which underpin the clinical manifestations of mild to moderate disease [2, 3].

T lymphocytes present in increased numbers in asthmatic airways, T lymphocytes release specific cytokines, including interkeukins (IL) 4, 5, 9, and 13, which orchestrate eosinophilic inflammation and IgE production by B lymphocytes [4]. An increase in Th2 cell activity may be due, in part, to a reduction in the regulatory T cells that normally inhibit Th2 cells. In severe asthma, there is also an increase in innate type 2 T cells (ILC2), and also Th1 and Th17 cells. Dendritic cells take allergens from the airway surface and migrate to regional lymph nodes where they interact with regulatory T cells to ultimately stimulate production of Th2 cells from naive T cells [5]. Macrophages present in increased numbers in asthmatic airways, they may be activated by allergens through low-affinity IgE receptors to release inflammatory mediators and cytokines that amplify the inflammatory response, especially in severe asthma [6].

Childhood onset “allergic asthma” has been considered a Th2 disease for nearly 20 years, although proof in humans has been limited. The initial focus on this pathway began with identification of an adaptive immune response in a murine model characterized by the release of a distinct set of interleukins, including IL-4, IL-5, IL-9, and IL-13, from Th2-type (T helper) CD4+ cells, which mediate the pathogenesis of allergic asthma [7]. IL-4 and IL-13 are canonical Th2-type cytokines that play a key role in human allergic asthmatic responses. IL-4 promotes the differentiation and proliferation of Th2-type T cells and switching of B cells from IgG to IgE production, whereas IL-13 is an effector cytokine that mediates airway hyper-reactivity and mucus hyperproduction [8]. Th1 cells, which characteristically produce interferon-γ, have been thought to primarily play a role in clearance of intracellular infections and autoimmunity [9]. Th1 cells were also considered to have a protective effect in allergic asthma by inhibiting Th2 responses, however, recent data from murine and human studies suggest that Th1 responses may actually enhance allergy and airway hyper-reactivity in asthma [10, 11]. Th17 cells, which produce IL-17 with resultant neutrophilic inflammation, are another important type of T helper cell that has been shown to mediate steroid-resistance in a murine model of asthma [12].

Montelukast is a leukotriene D4 (LTD4) and a leukotriene E4 (LTE4) receptor antagonist. Inhibition of LTD4 and LTE4 reduces the bronchoconstriction and increased pulmonary vascular edema associated with an acute asthma attack. Montelukast is used chronically as a prophylactic agent for the treatment of asthma. Montelukast is not used to treat an acute asthma

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attack. It is administered orally. Its oral bioavailability is 64%, with 99% plasma protein binding. Montelukast and its metabolites are excreted primarily in bile.

Less than 0.2% of an administered dose of montelukast and its metabolites are found in urine [13]. Montelukast belongs to this new class of drugs, which has been proved effective in asthmatic children and its safety profile is comparable with that of placebo. The major advantages of this drug are its once-daily oral administration, which increases adherence to the therapeutic regimen; its long-term persistent efficacy in the prevention of exercise-induced bronchoconstriction; its possible preventive activity on viral-induced asthma exacerbations; and its complementary and additive effects when used with inhaled corticosteroids.

As established for all drugs commonly used in the treatment of asthma, there is an inter individual variability also in response to montelukast [13]. Therefore, it is important that caregivers evaluate treatment effect objectively in every asthmatic child to provide the single patient with a therapeutic regimen allowing the best quality of life [14]. Montelukast suppressed LPS-induced M2-related cytokines and chemokines in alternatively activated macrophages, and the effects might be mediated through the MAPK-p38 and NF-κB-p65 pathways [15].

The CysLT1 receptor is most highly expressed in spleen, peripheral blood leukocytes including eosinophils, and lung smooth muscle cells and interstitial lung macrophages. The CysLT2 receptor is most highly expressed in the heart, adrenal medulla, placenta and peripheral blood leukocytes. In the airways and lungs, leukotriene is released by neutrophils, eosinophils, macrophages, epithelial cells, and vascular endothelial cells, and is involved in smooth muscle contraction, blood vessel dilatation, mucus secretion, and eosinophil recruitment [16]. It has been shown that the cysLTR plays a more important role than cysteinyl leukotriene in the pathogenesis of allergic airway inflammation [17]. Previous studies have demonstrated that montelukast significantly improves airway inflammation, pulmonary function, and symptom score in asthmatic wheezing infants compared with those in a placebo group [18] and reduces asthma exacerbations in children with asthma [19, 20]. Most of the effects of cysteinyl-LTs relevant to the pathophysiology of asthma are mediated by activation of the CysLT1 receptor [21, 22] that is expressed in monocytes and macrophages, eosinophils, basophils, mast cells, neutrophils, T cells, B lymphocytes, pluripotent hemopoietic stem cells (CD 34+), airway smooth muscle cells, bronchial fibroblasts, and vascular endothelial cells [23, 24]. The CysLT2 receptor is expressed in human peripheral basophils, endothelial cells, cultured mast cells and in nasal eosinophils and mast cells in patients with active seasonal allergic rhinitis [25-28].

Subjects and Methods

This observational study encompasses thirty-six children with confirmed asthma who visited Azadi Teaching hospital out patient's clinic over the period from 10/10/2018 to 10/10/2019. The participant was of both sexes with age range between 2 - 12 years.

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The diagnosis of asthma was made by pediatricians according to the American Thoracic Society (ATS) guidelines.

Asthmatic children who met the following criteria were included in this work:

- Asthmatic children between ages of 2 years to 12 years
- Patient's responses to nebulizer beta-agonist.
- Presence of persistent wheezing, chest tightness and persistent cough at night and/or early morning (mild persistent asthma). These symptoms were confirmed by physical examination and spirometry (FEV1>80% and FVC ratio).

We excluded asthmatic children with the following conditions

- Patients under age of 2 years and more than 12 years.
- Presence with persistent moderate and sever of (FEV1 <80%).
- Patient with intermittent, moderate and sever symptoms of asthma.
- Patient with upper respiratory tract infections within three weeks that requires antibiotic therapy
- Children not responded to β- agonist.
- Presence of hepatic or renal disorder.
- Previous or family history of sensitivity to montelukast and ketotifen.
- Respiratory tract, cardiac and other disorders.

Patients who received drugs that include one or more of the following:

- Beta -agonists (oral or long-acting or anticholinergics) within 1 week.
- Corticosteroids within 1 month.

The thirty-six child whom diagnosed to have mild persistent asthma on the basis of history, pulmonary function test, physical examination was involved in the study that had follow up period of 16 weeks for each participant

The diagnosis was made according to the following criteria:

- Patients having airflow limitation and persistent respiratory symptoms such as wheezing, chest tightness, shortness of breath and coughing particularly at night or in the early morning. These with daytime symptoms represented more than 2 days per week, but less than 1 time per day and night time symptoms represented more than 2 nights per month.
- Patients who demonstrated FEV1>80%.

Parents of the children were informed about the aim of the study, medications used, treatment strategy including dose, timing, duration of treatment and the parameters that will be taken to assess the efficacy and safety of the treatment.

Each parent was instructed to visit the hospital with their child at monthly interval for four months (first, second, third and fourth visits). the parents were informed not to use any medication of

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asthma before informing us, other than β_2-agonist (salbutamol) in case they have attacked of acute bronchoconstriction. The patients received montelukast orally; each night for a period of sixteen weeks in age dependent dosage; children aged 2-5 years, 4mg granules in the evening was given and for those children aged 6-12 years, 5mg chewable tablet in the evening was given. The chewable tablets or granule are instructed to be taken after evening meal at regular interval (mostly at 9 p.m.). Chewable tablet to be taken directly with adequate water. Granules intake was either directly by mouth, or mixed with a spoonful of cold or room temperature soft food to be taken all within 15 minutes after opening the drug sachet.

Five milliliter of blood were obtained from peripheral veins from each patient before drug administration and every 4 weeks after drug administration with each planned visit. The blood samples were transferred to EDTA containing tubes and used for blood film preparation.

The blood film slides were labeled with pencil to include patient's full name, sex, and date of birth, and examined by two specialist hematologist and reported to include morphology and each white blood cell type number and percentage.

Data were analyzed using the statistical package of social sciences (SPSS) version 18.0 (Chicago, USA). Paired sample t-test was used to compare between mean values (of first visit 1) and the subsequent four visits (2-5). Analysis of variance (ANOVA) was used for comparing the mean of different parameters used for evaluation of treatments between the treated groups. Chi square t -test was used for categorical variance in this study. P value < 0.05 was considered statistically significant.

Results

We included 36 children in this observational study with age range 2-12 year with confirmed diagnosis of asthma according A. Almost two third of them were male (23 male, 63.88%) and 13 (36.11%) were female, with the age range of 2-5 years was slightly more than the half (55.55%) years, while the remaining were 6-12 years old (44.44%). Numerical details of the characteristics are shown in Table 1.

Table1.

Demographic data (*n* = 36) of children

Variable	n (%)
Total Number of patients	36
Male	23(63.88)
Female	13(36.11)
Age	
2 -5 yrs	20(55.55)
6-12 yrs	16(44.44)

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According to the data shown in Table 2. There was no significant difference between the first and second visit blood films with regard to lymphocyte count, the earlier count was higher than the number seen in matching healthy population.

Comparative between first and second visit of patients Table 2.

Counts comprise of visit first and two	Paired Differences							
				95% Confidence Interval of the Difference				
	Mean	Std. Deviation	Std. Error Mean	Lower	Upper	t	df	Sig. (2-tailed)
V1 - 2	4.9	16.35	3.57	2.54	12.36	1.37	20	.185

Considering first visit lymphocyte number as background(control), third visit count, had a trend toward a decrease in the lymphocyte number but without reaching statistical significance (P > 0.05) as shown in Table 3.

Comparative between first and third visit of patients Table 3

Counts comprise of visit first and three	Paired Differences							
				95% Confidence Interval of the Difference				
	Mean	Std. Deviation	Std. Error Mean	Lower	Upper	t	df	Sig. (2-tailed)
V1 - V3	6.0	12.86	2.31	1.28	10.71	2.597	30	.014

The decrease in lymphocyte count that was seen in the third visit, was more prominent in the fourth visit and reached high statistical significance (P <0.05), numerical details are shown in Table 4.

Comparative between first and fourth visit of patients Table 4.

Counts comprise of visit first and fourth	Paired Differences							
				95% Confidence Interval of the Difference				
	Mean	Std. Deviation	Std. Error Mean	Lower	Upper	t	df	Sig. (2-tailed)
V1- V4	9.59	14.45	2.68	4.089	15.08	3.57	28	.001

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Table 5 shows the last visit data and the reduction in the lymphocyte count was further amplified with a P value of less than 0.001

Comparative between first and fifth visit of patients Table 5.

Counts comprise of visit first and five	Paired Differences							
				95% Confidence Interval of the Difference				
	Mean	Std. Deviation	Std. Error Mean	Lower	Upper	t	df	Sig. (2-tailed)
V1 - V5	13.93	15.71	2.92	7.95	19.91	4.77	28	.001

Discussion

Asthma is a very common medical complain during childhood with its associated grief medical and social sequels. Many medication has been tried with variable success. The advance in understanding of asthma pathophysiology has shed some light on the vital role of cysLT1 pathway.

Monteleukast is a potent cysLT1 receptor antagonist, which selectively competes with the specific binding of [3H] LTD4 at the receptor site in human cells and which has been shown to be generally safe and well-tolerated in humans [29]. The receptors for the cysteinyl-leukotrienes (i.e. LTC4, LTD4 and LTE4) are termed CysLT1 and CysLT2 exhibit distinct expression patterns in human tissues, mediating, for example, smooth muscle cell contraction, regulation of vascular permeability, and leukocyte activation.

Cysteinyl-leukotrienes have also been suggested to signal through the P2Y12, GPR17 and GPR99 receptor [30]. In fact, contractions elicited in HB by either LTC4 or LTD4 are sensitive to the classic antagonists [31]. In addition, in human lung, Cys-LT2 receptors have been demonstrated to be present also on pulmonary veins which contract by both LTC4 and LTD4 [32]. Therefore, as in human bronchi, these receptors do not discriminate between LTD4 or LTC4. Moreover, endothelial cells of human pulmonary veins possess both a Cys-LT1 receptor population, which mediates contraction of the veins, and a Cys-LT2 population, mediating their relaxation [33].

T-lymphocytes are thought to play a pivotal role in the pathogenesis of asthma [34]. The ability of eosinophils to migrate from the blood through the vascular endothelium is markedly increased by exposure to inflammatory cytokines produced by T-lymphocytes such as tumor necrosis factor alpha (TNF-α), interleukin (IL)-4, IL-5, and IL-13. In particular, the CD4+ lymphocyte is an important source of these cytokines and possibly chemokines such as macrophage inflammatory protein-alpha (MIP-α), eotaxin, and regulated upon activation in normal T cells expressed and secreted (RANTES), all of which have possible roles in enhancing eosinophils' chemotaxis, survival, maturation, and activation [35].

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Lymphocytes are a type of white blood cell that play several roles in the immune system, including protection against bacteria, viruses, fungi, and parasites. Lymphocyte increased in response to infections or cancer.

It was interesting to find that there was progressive decrease in the lymphocyte count with the continuation of treatment, reaching normal number at the study endpoint after 16 weeks. This observation can be explained, partly, by the ability of the drug to improve airway patency and reduce sputum production, clinically seen as improvement in signs of wheezing and shortness of breath, both can reduce infection frequency and severity and consequently lymphocyte count. Other explanations might present.

However, in covid-19 infection the lymphocyte decreased. Levels of lymphocytes and lymphocyte subsets are of great importance to keep the immune system functional. Usually viral infection, immunodeficiency diseases, and other infectious diseases lead to abnormal changes in the levels of lymphocyte subsets [36, 37].

Lymphopania has been associated with increased disease severity in COVID-19 (44). As it might be hypothesised that repletion of lymphocytes could be key to recovery from COVID-19. Also showed that interleukin-6 (IL-6) concentrations differed significantly between survivors and non-survivors of COVID-19, with non-survivors having up to 1·7-times higher values.

The total number of WBC in the early stage of the disease (COVID-19) was normal or decreased, or the lymphocyte count was decreased. Confirmed cases need to have met one of the two conditions: (a) nucleic acid of SARSCoV-2 test in respiratory or blood samples is positive; or (b) the viral gene sequencing of respiratory or blood samples is highly homologous with the SARSCoV-2 [38]. This change clarifies the diagnosis of SARSCoV-2 infections in children, although a small number of cases need to be further assessed based on clinical dynamics.

Conclusion

Montelukast shows significant reduction in lymphocyte count which increased in asthmatic child, it may not be used in controlling asthmatic patient in endemic of covid-19.

Competing interests

The authors declare that they have no competing interests.

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