e-ISSN: 0975-1556, p-ISSN:2820-2643

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2023; 15(6);816-824

Original Research Article

Relation between *Helicobacter pylori* Infection and Clinical and Functional Severity of Bronchial Asthma

Dr. Manohar V Reddy[1], Dr. Prasad K Manden[2]

[1]Internal Medicine Specialist, NMC Specialty Hospital, Abu Dhabi, UAE
[2]Pulmonologist, NMC Specialty Hospital in Abu Dhabi, UAE

Received: 28-08-2022 / Revised: 24-10-2022 / Accepted: 30-05-2023
Corresponding author: Dr. Manohar V Reddy
Conflict of interest: Nil

Abstract

Background: Helicobacter pylori (H. pylori) causes Gastritis in humans and prevalent in more than 50% of the world's populations. Apart from infecting the gastric mucosa it can cause extra-intestinal diseases like Allergic Asthma, Multiple sclerosis, Diabetes Mellitus.

Aim of the study: To study the relation between Pylori infection of the gastric mucosa and severity of Bronchial Asthma.

Methods: A prospective Analytical Study was undertaken at a Tertiary care Hospital in Abu Dhabi, UAE between 2019 and 2022. Totally 132 patients of Bronchial Asthma were included. Asthma was graded as per GINA grading. Laboratory investigations and radiological tests to confirm were done. Spirometry, H. Pylori tests were done to study the relation between the H. Pylori infection and severity of B. Asthma.

Results: There was no significant statistical difference between the incidence of Asthma and the age, gender and family history of Asthma of the patients in the study. But there was statistical significance in the Asthma patients with history of smoking and GERD incidence of B. No statistical significance noted in regards to the incidence of grades of Asthma in relation to their status of control. There was statistically significance of inverse relation between positive H. Pylori Ag and Positive Ig G of H. Pylori in blood in the patients with B. Asthma.

Conclusions: There was an infrequent association between Helicobacter Pylori infection and Bronchial Asthma in patients with an evident inverse relation in terms of grading of Asthma and its status of control. Hence the H. Pylori infection was positively related with the control of the disease. To understand the exact mechanism a larger scale studies are needed since it was not clear.

Keywords: H. Pylori, Allergy, Asthma, Gastritis and Immunology.

Introduction

Gastric infection producing organism were identified 30 years ago and named as Helicobacter Pylori (H. Pylori) with potential factors to produce disease.[1] H. Pylori organism has mucinous activity and contains adherence factors enabling them to penetrate the mucus membrane of the stomach. [2]This property allows them to colonize in gastric mucosa and release hydrolytic enzymes causing gastritis which is associated with infiltration of inflammatory cells. [3] Chronicity of this infection results in peptic ulcer disease, gastric cancer and gastric mucosa-associated lymphoid tissue lymphoma. Nearly 50% of the world's populations are

infected with H. Pylori. [4]H. Pylori are spiral, flagellated, motile, Gram –ve bacteria and producing urease enzyme for its survival in the Stomach mucosa. [5] According to European studies the prevalence of H. Pylori in the stomach mucosa is varying from 07% to 33%. [6] H. pylori are acquired in the childhood before 10 years in the developing countries; whereas the age of acquiring H. Pylori was higher in the developed countries. [7] Different pro-inflammatory substances like cytokines and eicosanoids are shown to be released from the gastric mucosa where H. pylori are colonized [8]; suggesting the pathogenic link between the bacterial infection and the diseases produced characterized by activation of inflammatory mediators and/or induction of autoimmunity might exist [9]. H. pylori have a capability of producing extra-intestinal organs producing diseases like liver and bile tract disease, ear and eye diseases, cardiovascular diseases, neurological disorders like multiple sclerosis and dementia, diabetes mellitus, immunological diseases like allergy, asthma and respiratory diseases and haematological disorders, gynaecological and pulmonary pathologies [8]. The international Agency of Research on Cancer officially recognized the H. Pylori as the causative organism to produce group I gastric cancer carcinogen. [3] Recently there is a decrease in the prevalence of H. Pylori infection in the developed countries which could be attributed to improved sanitation and increased use of antibiotics; the main parameters for this decrease. [9]But the decreased H. Pylori infection rate was associated with increased prevalence of increased prevalence of Allergic diseases like Bronchial Asthma, Atopy and allergic rhinitis. (10, 11]Existence of H. pylori infection is done by detecting IgG antibodies to H. pylori in blood, urea breath test by drinking 13C-labeled or 14C-labelled urea [10], H. pylori–specific antigens in stool [11] and endoscopic biopsy from the pre-pyloric region of the gastric mucosa by many techniques [12]. The relation of inversely proportional prevalence between H. Pylori infection of the gastric mucosa and Allergic diseases was reported by many studies. [13, 14, 15] But there is a great dispute regarding the design of these studies especially in the adult age groups. [16] The benefit of H. Pylori infection in reducing the prevalence of Allergic diseases is thought to be through a pivotal influence in the immunological response especially in asthma. The present study aims to evaluate the prevalence of *H. pylori* infection in the patients attending the Medical centres specialized for respiratory diseases.

Materials and Methods: A cross-sectional Analytical study was carried out on randomly selected 132 patients attending the Chest department of a Tertiary care Hospital, Abu Dhabi, UAE during the period from February 2019 to January 2022. All the patients were diagnosed as Bronchial Asthma. The study was conducted in accordance with relevant guidelines and regulations of the Hospital. A Hospital approved consent form and proforma were used.

Inclusion Criteria: Patients aged above 18 years and below 67 years were included. Patients of both genders were included. Patients diagnosed as Bronchial Asthma with different grades of severity on assessment with spirometry according to Global Initiative to Asthma (GINA, 2015), (17) were included. Patients willing to participate in the study were included. **Exclusion Criteria:** Patients aged below 18 years and above 67 years were excluded. Patients not willing to join the study group were excluded. Patients with co-morbidities which are associated with high incidence of H. pylori like coronary Heart Disease (CHD), Hypertension, Patients with Chronic Hepatic Disorders, Pulmonary Tuberculosis and Diabetes Mellitus were excluded**.** All the patients were subjected to thorough history taking,

clinical examination, radiological investigations; oxygen saturation at room temperature was recorded. Spirometry was done and the grading of the Bronchial Asthma was done according to (GINA, 2015).

Patients presenting with Medical history: Symptoms:

1. History of wheeze.
2. Shortness of breath.
3. Tightness in the chest (in adults).

More than one symptom mentioned above, Symptoms, (in adults), Symptoms present in the night or in the early morning, change of symptoms in time or intensity, symptoms aggravated by viral URTI, exercise, exposure to allergens, car fumes, toxic gases, weather changes, wheeze exaggerated by laughing or coughing and strong smells or smoke were taken as criteria to include in the study.

Ventilatory functions assessed by Spirometry: Spirometry was done in all the patients: Limitation of air flow was considered when: when FEV1/FVC ratio was less than 0.8. Bronchial asthma was considered when: Reversibility in FEV1 was more than 12% (or more than 200 ml) from pre-bronchodilator status to 15 minutes after inhalation of 200ug of Salbutamol. (Normal values based on the age taken in this study were: FEV_1/FVC: 8–19 yr: 85%, 20–39 yr: 80%, 40–59 yr: 75%, 60–80 yr: 70%). Bronchial Asthma was graded as

Intermittent: symptoms were occurring from less than 2 days/ week with Normal FEV1 between exacerbations, FEV1 more than 80% predicted and FEV1/FVC ratio-normal.

Persistent:

Mild: Symptoms more than 2 days in a week with FEV1 more than 80% predicted and FEV1/FVC ratio is normal.

Moderate: Symptoms occurring daily withFEV1 more than 60% but less than 80% predicted and FEV1/FVC reduced to 05%.

Severe: Symptoms occurring throughout the day Often 7 days in a week and sometimes occurring many times in a day, with FEV1 less than 60% predicted and FEV1/FVC ratio reduced to less than 05%. The diagnosis of Gastroesophageal reflux disease (GERD) was based upon a questionnaire filled up by the patients which consisted of 06 items (04- positive predictors and 02- negative predictors).

Positive predictors:

1. Heartburn.
2. Regurgitation.
3. Sleep disturbance due to reflux.
4. Use of over-the-counter medications.

Negative predictors:

1. Epigastric pain.
2. Nausea.

Estimation of serum antibody for H. pylori: A qualitative test was done in all the patients by a Rapid Anti H. pylori test to detect the antibodies in human serum, plasma or whole blood (Immune chromatography- with results within 15 minutes).

Results

1. **Positive:** Purplish red test and control bands were present on the membrane (when the concentration of antibody is low, the result is weak test band).
2. **Negative:** Purplish red control band alone appears on the membrane and test band absent.
3. **Invalid:** Absent control band in the control region. Stool antigen test for H. pylori was done in all the patients.

Statistical Analysis:

All the data was analyzed using the standard statistical methods using SPSS version 20.0. The variables were presented as numbers and percentage or mean ± standard deviation (SD). To test the level of differences for significance student t –

test and Chi Square (x2) test were used. The p value was taken as less than 0.05 to consider level of significance.

Results

Among the 132 subjects in the study there were 89 (67.42%) males and 43 (32.57%) females with a male to female ratio of 2.88:1. 23 (17.42%) of the patients were aged between 18 and 27 years, 23 (17.42%) of the patients were aged between 28 and 37 years, 37 (28.03%) of the patients were aged between 38 and 47 years, 41 (31.06%) of the patients were aged between 48 and 57 years and 13 (09.84%) of the patients were aged between 57 and 68 years. (Table 1) History of smoking was present in 73 (55.30%) of the patients and not present in 59 (44.69%) of the patients. History of GERD was present in 90 (68.18%), and not present in 42 (31.81%) of the patients. (Table 1) No statistically significant difference was observed in regards to the incidence of Asthma in relation to Age, gender and family history of Asthma in the study; (p value was less than 0.05%). But there was statistically significance in the patients with history of smoking and GERD incidence of B. Asthma in the study (p value was <0.05), (Table 1).

Table 1: Shows the demographic data of the subjects (n-132)

Observation	Number	Percentage	P value
Age groups			
18 to 27	23	17.42	
28 to 37	37	28.03	0.128
38 to 47	41	31.06	
48 to 57	18	13.63	
58 to 67	13	09.84	
Gender			
Male	89	67.42	0.113
Female	43	32.57	
Family H/O of Asthma			
Yes	57	43.18	0.147
No	75	56.81	
Smoking			
Yes	31	23.48	**0.041**
No	91	68.93	
GERD			
Present	42	31.81	
Absent	90	68.18	**0.037**

As per grading of GINA B. Asthma was graded in this study and found that there were 42 (31.81%) patients with mild B. Asthma. Among them 15/42 (35.71%) were with Asthma under control, 16/42 (38.09%) were under partial control and 11/42 (26.19%) were having uncontrolled Asthma. 51 (38.63%) patients were with moderate grade Asthma. Among them 15/51 (21.56%) were with Asthma under control, 16/51 (31.37%) were under partial control and 11/51 (21.56%) were having uncontrolled Asthma. 39 (29.54%) with severe grade of Asthma. (Table 2) Among them 15/39 (38.46%) were with Asthma under control, 16/39 (41.02%) were under partial control and 11/39 (28.20%) were having uncontrolled Asthma. No statistically significant difference was observed in regards to the incidence of grades of Asthma in relation to their status of control (p value less than 0.05).

Table 2: Shows the grading, status of control of Asthma as per GINA grading (n-132)

Observation	Number	Percentage	P value
Grading of Asthma (GINA)- 132			
Mild	**42**	**(31.81%)**	
Controlled	15	35.71	
Partially controlled	16	38.09	
Uncontrolled	11	26.19	
Moderate	**51**	**(38.63%)**	
Controlled	18	35.29	
Partially controlled	21	41.17	0.251
uncontrolled	12	23.52	
Severe	**39**	**(29.54%)**	
Controlled	10	25.64	
Partially controlled	19	48.71	
uncontrolled	20	51.28	
H. Pylori Antigen in Stool and Blood			
Positive	69	52.27	0.133
Negative	53	40.15	

In mild cases of B. Asthma H. Pylori Ag in stools was present in 19/42 (45.23%); (absent in 23/42 (54.76%). In moderate cases of B. Asthma H. Pylori Ag in stools was present in 13/51 (32.5%), (absent in 38 (74.50%). and in severe cases of B. Asthma H. Pylori Ag in stools was present in 08/39 (20.51%) cases (absent in 31/39 (79.48%), (Table 3). In mild cases of B. Asthma Ig G of H. Pylori in blood was present in 17/42 (40.47%); (absent in 25/42 (59.52%). In moderate cases Ig G of H. Pylori was present in the blood in 13/51 (absent in 38 (74.50%). and in severe cases of B. Asthma H. Pylori Ag in stools was present in 08/39 (20.51%) cases (absent in 31/39 (79.48%), (Table 3). There was statistically significance of inverse relation between positive H. Pylori Ag and Positive Ig G of H. Pylori in blood in the patients with B. Asthma. (p value was <0.05), (Table 3).

Table 3: Shows the positive H. Pylori AG in stool and IgG in Blood versus severity of B, Asthma (n-132)

Observation	H. Pylori in stool		H. Pylori IgG in Blood		P value
	Present 40 (30.30%)	**Absent 92 (69.69%)**	**Present 32 (24.24%)**	**Absent 100 (100%)**	
B. Asthma					
Mild- 42	19 (45.23%)	23 (54.76%)	17 (40.47%)	25 (59.52%)	**0.031**
Moderate- 51	13 (32.5%)	38 (74.50%)	11 (21.56%)	40 (78.43%)	
Severe- 39	08 (20.51%)	31 (79.48%)	04 (10.25%)	35 (89.74%)	

Among the 32 patients with positive Ig G of H. Pylori in blood 02 were negative for Ag in the stool. Similarly among the 100 patients with negative Ig G of H. Pylori in blood 10 were positive for Ag in the stool. The Specificity of these tests was 93.12% and the sensitivity of the tests was 71.55%. There was statistical significant difference between positive and negative H. pylori cases diagnosed by stool antigen and

serum IgG level (P value less than 0.05). It was found that most of the negative H. pylori cases diagnosed by serum IgG were negative by stool antigen test also (Table 4).

Table 4: Shows the specificity and sensitivity of lab investigations for H. Pylori (n-132).

Observation	Positive Stool Ag	Negative Stool Ag	Specificity	Sensitivity
Positive H. Pylori Ig G in Blood- 32	30	02	**93.12%**	**71.55%**
Negative H. Pylori Ag in Blood- 100	10	90		

Discussion

The present study was conducted to analyze the findings related to inverse relation between the H. Pylori infection of the gastric mucosa and the grading severity of the B. Asthma. 132 subjects with B. Asthma were included and spirometry, H. Pylori lab investigations of the stools and Blood Ig G were estimated in various severities of B. Asthma in them. Presently B. Asthma is one of the commonest chronic inflammatory pulmonary diseases initiated by allergy. The prevalence is approximately 1–18% of populations all over the world. The prevalence of Asthma was found to be shifting in urban areas due to migration of people from the rural areas to urban areas. [18] The hypothetical reason behind increased prevalence of atopic and allergic diseases was the reduced exposure to orofecal organisms. [19] But other authors opined that a conflict of multiple organisms' theory was playing the role. [20] It was reported in the literature that the incidence of *H. pylori* infection was found to be decreasing in adults and children especially in the developed countries. But this phenomenon is exactly opposite to the increased incidence of asthma and other allergic disorders in children. [21] In a study by Melby KK, Carlsen KL et al [22] it was reported that 16.4 percent of children, negative for *H. pylori* at the ages between of 2 and 10 years had Asthma at the age of 16. Hence it was suggested that exposure to orofecal contamination (H. Pylori) at the age of 12 would prevent development of Asthma. [23] In the present study 132 subjects in the age groups of 18 to 67 years were included with varying grades of Asthma and in varying status of control. In this group, there was statistically significance of inverse relation between positive H. Pylori Ag and Positive Ig G of H. Pylori in blood in the patients with B. Asthma; (p value was <0.05).Fouda et al. [23] using ELISA method to estimate the *H. pylori* IgG in the plasma of the Asthma patients and healthy children. Their results showed the titer of IgG was inversely related to the degree of asthma. The above results were similar to the results encountered in this study. From a Greek study by Tsigalou C, Konstantinidis TG et al, it was concluded that the infection of *H. pylori,* especially with the strains of CagA-positive *H. pylori*, was inversely correlated with the development of Asthma. [24] There were other cross-sectional studies also which supported the view that *H. pylori* infection was showing a protective role on the severity of Asthma patients. [25, 26. 27, 28]On the other hand there are studies which do not agree upon the mechanism and suggest further research in this aspect. [29, 30, 31, 32, 33] Certain researchers detected *H. pylori* exotoxin VacA the lung biopsies of humans which stimulated pulmonary airway epithelial cells to secrete inflammatory cytokines in vitro. [34] H. Pylori was discovered in the pulmonary tissues of patients with COPD. [35] Further more studies also confirmed that the existence of *H. pylori* infection provided protective effects against Asthma patients its eradication may have a

negative impact. [35, 36] The immune pathogenesis is very complex for B. Asthma as studies have proved that Toll-like receptors (TLRs), dendritic cells (DCs), helper T cells 1/2 (Th1/Th2), Th17, regulatory T cells (Tregs), etc. play their roles in a complex interaction network between cells and receptors. [37, 38, 39] The false negative results of Ag in stools and Ig G antibody of H. Pylori could also be due to age related factors; hence the actual correlation between the prevalence of H. Pylori infection and severity of Asthma might have been so accurate.

Conclusions

There was an infrequent association between Helicobacter Pylori infection and Bronchial Asthma in patients with an evident inverse relation in terms of grading of Asthma and its status of control. Hence the H. Pylori infection was positively related with the control of the disease. To understand the exact mechanism a larger scale studies are needed since it was not clear. Treatment of GERD symptoms in Asthmatic patients, regardless the presence of H. pylori infection helps in managing the asthma effectively. Detection of H. Pylori Ag in stools and IG G of H. Pylori in the plasma of Asthma patients are highly sensitive and the specificity is more than 95%.

References

1. Warren JR, Marshall B. Unidentified curved bacilli on gastric epithelium in active chronic gastritis. Lancet. 1983; 1:1273–5.
2. Murray PR. Medical microbiology. St Louis, MO, USA: Mosby; 1994.
3. Møller H, Heseltine E, Vainio H. Working group report on schistosomes, liver flukes and Helicobacter pylori.Int J Cancer. 1995; 60:587–9.
4. M. Buckley, C. O'Morain, Helicobacter biology – discovery, Br. Med. Bull. 1998;54(1): 7–16.
5. B.J. Egan, H.J. O'Connor, O' Morain C.A., extremely high prevalence of Helicobacter pylori infection in Bhutan, World J. Gastroenterol. 2008; 193: 2806.
6. J. Lopes, Helicobacter pylori infection: update on diagnosis and management, JAAPA. 2010; 23 (7): 20–37.
7. Ford, T.R. Axon, Epidemiology of Helicobacter pylori infection and public health implications, Helicobacter.2010;15: 1–6.
8. V. Tan, B. Wong, Helicobacter pylori and gastritis: untangling a complex relationship 27 years, J. Gastroenterol. Hepatol. 2011; 26: 42–45.
9. McCaig LF, Besser RE, Hughes JM. Trends in antimicrobial prescribing rates for children and adolescents. JAMA. 2002; 287:3096–102.
10. Anderson HR. Prevalence of asthma. BMJ. 2005; 330:1037–8.
11. Eder W, Ege MJ, von Mutius E. The asthma epidemic. N Engl J Med. 2006; 355:2226–35.
12. Lim JH, Kim N, Lim SH, et al. Inverse relationship between Helicobacter pylori infection and asthma among adults younger than 40 years: a cross-sectional study. Medicine (Baltimore). 2016;95: e2609.
13. Miftahussurur M, Nusi IA, Graham DY, Yamaoka Y. Helicobacter, hygiene, atopy, and asthma. Front Microbiol.2017; 8:1034.
14. Amberbir A, Medhin G, Erku W, et al. Effects of Helicobacter pylori, geohelminth infection and selected commensal bacteria on the risk of allergic disease and sensitization in 3-year-old Ethiopian children. Clin Exp Allergy. 2011; 41:1422–30.
15. den Hollander WJ, Sonnenschein-van der Voort AM, Holster IL, et al. Helicobacter pylori in children with asthmatic conditions at school age, and their mothers. AlimentPharmacolTher.2016; 43:933–43.
16. Global initiative for asthma (GINA), Global Strategy for Asthma

Management and Prevention. updated 2015.
17. World Health Organization. ‘‘WHO” Asthma. 2007. Int/mediacentre/factsheets/fs307/en/accepted at 29/12/2007.
18. Int/mediacentre/factsheets/fs307/en/accepted at 29/12/2007.
19. C.D. Ramesy, J.C. Celedon, The hygiene hypothesis and asthma, Curr. Opin. Pulm. Med. 2005; 11:14–20.
20. T.U. Kosunen, A. Aromaa, P. Knekt, et al., Helicobacter antibodies in 1973 and 1994 in the adult population of Vammala, Finland, Epidemiol. Infect. 1997;119: 29–34.
21. Melby KK, Carlsen KL, Håland G, Samdal HH, Carlsen KH. Helicobacter pylori in early childhood and asthma in adolescence. BMC Res Notes.2020;13(1):79.
22. Fouda EM, Kamel TB, Nabih ES, Abdelazem AA. Helicobacter pylori seropositivity protects against childhood asthma and inversely correlates to its clinical and functional severity. AllergolImmunopathol. 2018; 46(1):76–81.
23. Tsigalou C, Konstantinidis TG, Cassimos D, Karvelas A, Grapsa A, Tsalkidis A, et al. Inverse association between Helicobacter pylori infection and childhood asthma in Greece: a case-control study. Germs.2019;9(4):182–7.
24. Kato H, Pattison R, Bhandari S. Inverse relationship between Helicobacter pylori infection and asthma in US adults with peptic ulcer disease. Indian J Gastroenterol.2017;36(2):158–9.
25. Chen C, Xun P, Tsinovoi C, He K. Accumulated evidence on Helicobacter pylori infection and the risk of asthma: a meta-analysis. Ann Allergy Asthma Immunol. 2017;119(2):137–45. e2.
26. Lim JH, Kim N, Lim SH, Kwon JW, Shin CM, Chang YS, et al. Inverse relationship between Helicobacter pylori infection and asthma among adults younger than 40 years: a cross-sectional study. Medicine.2016;95(8): e2609.
27. Iizasa H, Ishihara S, Richardo T, Kanehiro Y, Yoshiyama H. Dysbiotic infection in the stomach. World J Gastroenterol. 2015;21(40):11450–7.
28. Wang YC, Lin TY, Shang ST, Chen HJ, Kao CH, Wu CC, et al. Helicobacter pylori infection increases the risk of adult-onset asthma: a nationwide cohort study. Eur J Clin Microbiol Infect Dis.2017;36(9):1587–94.
29. Molina-Infante J, Gutierrez-Junquera C, Savarino E, Penagini R, Modolell I, Bartolo O, et al. Helicobacter pylori infection does not protect against eosinophilic esophagitis: results from a large multicenter, case-control, study. Am. J. Gastroenterol.2018;113(7):972–9.
30. Holster IL, Vila AM, Caudri D, den Hoed CM, Perez-Perez GI, Blaser MJ, et al. The impact of Helicobacter pylori on atopic disorders in childhood. Helicobacter. 2012;17(3):232–7.
31. Wang Q, Yu C, Sun Y. The association between asthma and Helicobacter pylori: a meta-analysis. Helicobacter. 2013;18(1):41–53.
32. Wang Y, Bi Y, Zhang L, Wang C. Is Helicobacter pylori infection associated with asthma risk? A meta-analysis based on 770 cases and 785 controls. Int J Med Sci.2012;9(7):603–10.
33. Karimi A, Fakhimi-Derakhshan K, Imanzadeh F, Rezaei M, Cavoshzadeh Z, Maham S. Helicobacter pylori infection and pediatric asthma. Iran J Microbiol.2013;5(2):132–5.
34. Taye B, Enquselassie F, Tsegaye A, Amberbir A, Medhin G, Fogarty A, et al. Association between infection with Helicobacter pylori and atopy in young Ethiopian children: a longitudinal study. Clin Exp Allergy. 2017;47 (10):1299–308.

35. Popescu D, Andronescu D, Babes PA. The association between Helicobacter pylori infection and liver and biliary tract disorders. Curr Health Sci J.2018;44(2):186–91.
36. Lin CL, Hsiao G, Wang CC, Lee YL. Imperatorin exerts antiallergic effects in Th2-mediated allergic asthma via induction of IL-10-producing regulatory T cells by modulating the function of dendritic cells. Pharmacol Res. 2016; 110:111–21.
37. Abdelaziz MH, Abdelwahab SF, Wan J, Cai W, Huixuan W, Jianjun C, et al. Alternatively activated macrophages; a double-edged sword in allergic asthma. J Transl Med. 2020;18(1):58.
38. Puggioni F, Alves-Correia M, Mohamed MF, Stomeo N, Mager R, Marinoni M, et al. Immunostimulants in respiratory diseases: focus on Pidotimod. Multidiscip Respir Med. 2019; 14:31.