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Review Article

Management of Inflammation in Chronic Obstructive Pulmonary Disease-Update

RC Barman[1], MT Alam[2], MMSU Islam[3], G Biswas[5], MAR Howlader[6], SA Fattah[7]

Abstract :

Chronic obstructive pulmonary disease (COPD) is a systemic inflammatory condition, the earliest manifestation of which is airway obstruction which is only partially reversible and the treatment rationales are provided accordingly. Research has shown that COPD-inflammation involves multiple inflammatory cells and mediators and the underlying pathology differs from asthma inflammation.For these reasons, therapeutic agents that are effective in asthma patients may not be optimal in COPD patients. COPD exacerbations are intensified inflammatory events compared with stable COPD. The clinical and systemic consequences believed to result from the chronic inflammation observed in COPD, suggest that inflammation intensity is a key factor in COPD and exacerbation severity and frequency. Although inhaled corticosteroids are commonly used and are essential in asthma management, their efficacy in COPD is limited, with only a modest effect at reducing exacerbations. The importance of inflammation in COPD needs to be better understood by clinicians, and the differences in inflammation in COPD versus asthma should be considered carefully to optimize the use of anti-inflammatory agents. Current COPD management focuses predominantly on symptom relief by optimizing bronchodilatation. The role of phosphodiesterase type 4 inhibitors (PDE4), statins, angiotensin converting enzyme inhibitors, theophylline and tumor necrosis factor inhibitors in COPD management will be reviewed. Targeting COPD inflammation with the goal of reducing exacerbations is a major focus of current clinical practice & outcome research.

Key words: COPD, GOLD, Spiromerty, Roflumilast, Bronchodilators.

Introduction :

Chronic obstructive pulmonary disease is a major cause of morbidity and mortality throughout the world. An estimated three million deaths worldwide in 2005 were attributed to chronic obstructive pulmonary disease (COPD)[1]. Studies have predicted that COPD will jump from the sixth to the third most common cause of death and morbidity worldwide between 1990 and 2020[2,3]. Cigarette smoking is by far the most common cause of COPD. However, other factors like extended exposure to air pollution and a hereditary deficiency of the anti-protease alpha -1 antitrypsin also contribute to the reduced lung function. COPD can be exacerbated by respiratory infections and is often associated with various comorbid conditions, including heart disease and lung cancer[4,5]. Much has been learned about COPD since the Global Initiative for Chronic Obstructive Lung Disease (GOLD) issued its first report, Global Strategy for the Diagnosis, Management and Prevention of COPD in 2001. Optimal management of COPD is crucial, as the costs incurred from this illness by society can be significant[6]. COPD is manifested by the presence of airflow limitation and systemic manifestations. Two different schools of thought relating to association of COPD found in the literature. One group thinks that a systemic spillover of inflammatory events occurring in the lungs is thought to happen in systemic manifestations. Another group believes that the effects represent a systemic inflammatory state as a part of common inflammatory genotype[7,8,9]. The disease impact can be minimized with smoking cessation, regular physical activity and available medications.

1. Dr. Rakhal Chandra Barman, MBBS, DTCD, Assistant Professor, Dept. of Respiratory Medicine, FMC, Faridpur.

2. Dr. Md. Towhid Alam, MBBS, FCPS (Medicine), Associate Professor, Dept. of Medicine, FMC, Faridpur.

3. DrM.M.Shahin-Ul-Islam, MBBS, FCPS (Medicine), MD (Gastroenterology), Assistant Professor, Dept. of Gastroenterology, FMC. Faridpur.

4. Dr. Sk. Abdul Momen Ahmed, MBBS, MD (Pathology), Lecturer, Dept. of Pathology, FMC, Faridpur.

5. Dr. Gonopati Biswas. DDS, Assistant Professor, Dept. of Dentristy, FMC, Faridpur.

6. Dr. Md. Anwar Rahman Howlader, FCPS (Medicine), Assistant Professor, Dept. of Medicine, FMC, Faridpur.

7. Dr. Sk. Abdul Fattah, DTCD, FCPS (Medicine), Associate Professor, Dept. of Medicine, FMC, Faridpur.

Address of correspondence :
Dr. Rakhal Chandra Barman, MBBS, DTCD, Assistant Professor. Dept. of Respiratory Medicine, FMC, Faridpur. Phone: +88-0171-8476748, Email: rakhalbarman@yahoo. com

Inflammation in Chronic Obstructive Pulmonary Disease

Patients with stable COPD have evidence of systemic inflammation, particularly when the disease is severe or during exacerbation. This is characterized by elevated circulating pro-inflammatory cytokines, acute phase reactants, and increased number of immune cells[10]. These components of inflammation can account for systemic manifestations of COPD and exacerbate comorbid conditions. Moreover systemic inflammation has been associated with a greater decline in lung function[11]. Cyokines are small-signaling protein molecules secreted by immune cells. Interleukin-6(IL-6) and plasma tumor necrosis factor (TNF) are increased in COPD, particularly during exacerbation[12]. Elevated IL-6 induces the release of acute phase reactants from the liver cell & may account for the increase in C- reactive protein (CRP) found in patients with COPD. Increased CRP levels have been associated with decreased lung function, increase disease severity& increased hospitalization[13,14]. Fibrinogen, another acute reactant that is synthesized in the liver in response to IL-6 has been found to be elevated in patients with COPD with frequent exacerbation[15]. IL-6 and other chemokines play an important role in neutrophil and monocyte recruitment in patients with COPD. These chemokines are said to be increased in patients with COPD[16]. Leucocytes and platelets are also released from bone marrow. A link between persistent pulmonary low grade inflammation and many comorbidities have been suggested, including deconditioning anaemia, cardiovascular disease and osteoporosis[17,18]. To manage this inflammation two different therapeutic management schemes may be required, one targeting disease in the lungs while other focuses on the systemic inflammatory state.

Diagnosis and Staging of Chronic Obstructive Pulmonary Disease

An important issue in the treatment of COPD is early diagnosis. COPD has a long subclinical phase leading to underdiagnosis and therefore delayed treatment[19,20]. Considering that various studies have demonstrated the potential long term benefit of early intervention[21,22]. A detailed assessment of smoking history and symptoms including dyspnoea, limitation of physical activity due to breathlessness, and chronic cough or sputum production, should lead to the suspicion of COPD. Once the disease is suspected, spirometry is essential for confirmation by demonstrating airflow limitation i.e. a ratio of forced expiratory volume in one second (FEV1) to forced vital capacity (FVC) that is not fully

The GOLD has categorized COPD into four stages according to the severity of the airflow obstruction: mild (FEV1/FVC< 0.70, FEV1>80% predicted), moderate (FEV1/FVC<0.70, FEV150%-80% predicted), severe (FEV1/FVC<0.70, FEV1 30%-50% predicted), very severe(FEV1/FVC<0.70, FEV1<30% predicted or FEV1<50% predicted plus chronic respiratory failure)[23].

Chronic Obstructive Pulmonary Disease Remains Underdiagnosed

Underdiagnosis of COPD may be the result of a number of problems. Factors contributing to the underdiagnosis of chronic obstructive pulmonary disease are [5,19]

* Many patients with chronic obstructive pulmonary disease do not present to their primary care physician until their symptoms are severe and they have moderately advanced airflow obstruction

* Patients adopt their lifestyle and physical activity to minimize their symptoms

* Spirometry remains underutilized in the primary care setting.

In the US, the National Health & Nutrition Examination Survey (NHANES III) estimated COPD prevalence at 24 million adults, yet only 10 million reported a diagnosis of the disease, meaning that at least half of the patients remain undiagnosed[20].

Pharmacologic Therapies for Chronic Obstructive Pulmonary Disease

Pharmacologic therapy is used to reduce symptoms, reduce the frequency and severity of exacerbation, improve health status and exercise tolerance, and also reduce the lung function decline. Each treatment regimen needs to be patient-specific as the relationship between the severity of symptoms and the severity of airflow limitation is influenced by other factors, such as the frequency and severity of exacerbations, the presence of respiratory failure, co-morbidities and general health status. Very few agents in the COPD therapy focus on decreasing the systemic inflammation seen in the chronic lung condition. This may explain why some patients with COPD continue to progression of disease and recurrent exacerbation despite optimal treatment with standard therapy. Therefore new therapeutic approaches are of increasing interest. Potential therapies targeting the inflammatory component of COPD will be discussed.

Corticosteroids

Oral corticosteroids are potent, relatively non-specific anti-inflammatory agents that are commonly used to treat acute exacerbation of COPD. Calverly et al have shown that treatment with oral corticosteroids decrease the time to resolution of exacerbation & relapse rate[24]. However, oral corticosteroids are associated with many side effects, and maintenance oral steroid therapy has been associated with increased mortality rates in patients with COPD[24].

Inhaled corticosteroids (ICS) have been shown to be beneficial in the treatment of COPD owing to the weaker corticosteroid-sensitive pattern of inflammation[25]. ICS reduce CRP & IL-6, inhibit the expression of certain inflammatory genes, leading to reduction of cytokine levels[26]. Several placebo-controls have shown that it reduces the rate of COPD exacerbation by approximately 25%[27].

ICS when combined with long-beta agonists (LABA) have greater effect[28,29.30]. In the TORCH trial, combination therapy reduced the rate of lung function decline, and delayed and reduced the numbers of exacerbations in patients, particularly those with moderate to severe COPD. However, there is no difference in mortality[31]. Therefore ICS immunotherapy is generally not recommended as a part of COPD management, but rather used in combination with LABAs in symptomatic patients with moderate to severe COPD and frequent exacerbations[32,33]. Despite recommendations from various authorities, studies have failed to demonstrate that ICS suppress inflammation, particularly in patients with COPD[34]. A randomized placebo-controlled, multicenter clinical trial that involving 11 centers in Canada failed to demonstrate any significant effect of ICS or combination therapy on systemic levels of CRP or IL-6 in patients with COPD. However, it showed a significant reduction in surfactant protein D levels and improved health status and lung function in patients with moderate to severe COPD over a four week period[35]. Studies have also failed to demonstrate that a ICS-LABA combination has any significant effect on neutrophilic inflammation of COPD patients[36,37].

Selective Phosphodiesterase-4 Inhibitors

GOLD recently added roflumilast, a selective PDE4 inhibitor, to its latest international treatment guidelines for COPD[38]. This once daily active therapy is recommended for patients with severe COPD or very severe COPD and history of exacerbations and chronic bronchitis[38]. Selective PDE4 inhibitors act as anti-inflammatory agents and have the ability to suppress the release of inflammatory mediators implicated in COPD[39,40]. Roflumilast also significantly reduces sputum neutrophil and eosinophil counts by 35.5 % and 50.0 % respectively compared with placebo[40]. Therefore, PDE4 inhibitors may present significant advantage over other drugs that primarily target single mediators or singe biochemical pathways.

PDE4 acts to degrade c-AMP, a secondary messenger involved in pro-inflammatory mediators. One of the principal effects of PDE4 inhibitors is their ability to increase c-AMP levels, subsequently activating protein kinase A. This in turn phosphorylates proteins, thereby inhibiting many inflammatory cells[41]. PDE4 inhibitors have been shown to target three important components of COPD: airway obstruction, inflammation & structural chages[34].

Millis et al conducted a multiple treatment meta-analysis to determine the relative effectiveness of LABAS, long acting anti-cholinergics (LAACs), PDE4 inhibitors, and ICS in various combinations in reducing the rate of COPD exacerbations. Adding roflumilast to LAACs had the most significant effects and the highest probability of being the best first- line treatment[42]. Roflumilast may cause gastrointestinal symptoms, weight loss and to a lesser extent headache and increased patient withdrawal[43]. Inans attempt to administer relatively high doses of PDE4 inhibitors to the lungs while reducing the potential for systemic side effects, inhaled PDE4 inhibitors are currently being developed[44]. Overall, roflumilast is considered safe and relatively well tolerated.

HMG-CoA Reductase Inhibitors

Statins, 3-hydroxy-3-methylglutaryl-coenzyme a (HMG-Coa) reductase inhibitors, are commonly used as cholesterol-lowering drugs and have been shown to decrease cardiovascular mortality[45]. Statins having anti-inflammatory and antioxidant properties have been found to be effective in management of COPD. Statins act by inhibiting mevalonic acid in alveolar

macrophages[46]. It also reduces neutrophil migration, cytokine production, adverse matrix remodeling, small airways inflammation, and apoptosis[47]. As such in neutrophil mediated COPD, statins attenuate persistent neutrophilic inflammation by reducing recruitment &/or activation of inflammatory cells in the lungs[48]. Statins reduced both cardiovascular and respiratory mortality seen in retrospective study[49]. Patients of COPD with high CRP levels may benefit from statin treatment seen in studies[50]. It is remarkable that the mortality benefit seen in patients with COPD on statins appears to be greater than that seen with ICS or ICS-LABA combinations[51].

Angiotensin-converting Enzyme Inhibitors (ACEI) and Angiotensin II Receptor Blockers (ARB)

It is widely accepted that ACEI have a significant therapeutic effect on major cardiovascular diseases. Inhibition of the renin-angiotensin system produces anti-inflammatory effect in patients with COPD[52]. Anti-inflammatory effect causes reduction in pro-inflammatory genes and other pro-inflammatory substances in patients with COPD[53,54]. This effect leads to significant immune-modulatory effects, resulting in reduction of systemic cytokine levels[55]. This lower ACE activity has been shown to improve pulmonary haemodynamic variables, reduce hypoxic pulmonary hypertension and pulmonary vascular remodeling[56-58]. Moreover ARB has been shown to significantly reduce hyperinflation in patients with COPD by an unknown mechanism[59].

Theophylline

Although theophylline has been used in the management of patients with COPD, its exact mechanism of action in the airway is still unclear. Theophylline is a week bronchodilator with some anti-inflammatory properties. It is unclear whether this anti-inflammatory effects influence the systemic inflammation in COPD. Theophylline has been shown to non-selectively inhibit several PDE isoforms in the airways[60]. Randomized controlled studies have shown that theophylline alone or in addition to bronchodilators and corticosteroids improves respiratory function, dyspnoea and exercise tolerance in patients with severe COPD[61,62].

Tumor Necrosis Factor-alpha Inhibitors

Studies have shown that patients with COPD have increased levels of TNF-alpha in their sputum, especially during acute exacerbations[63,64]. The levels are also elevated in the plasma, possibly due to an overspill from the inflamed lung[65]. The increase in systemic TNF-alpha has also been implicated in cachexia and skeletal muscle wasting in patients with severe COPD[66]. It has been postulated that inhibiting TNF-alpha may be beneficial in reducing inflammation[67]. Hence studies have evaluated the effectiveness of specific TNF-alpha inhibitor in patients with COPD. Surprisingly, TNF-alpha inhibitors have not been shown to significantly benefit patients with moderate to severe COPD in the short term[68,69]. Again, there were no improvements in symptom score, lung function, exercise capacity, dyspnoea and acute exacerbations over two years[69]. However, an observational study suggests that etanercept, systemic monoclonal antibody, may reduce COPD hospital admissions[70]. Lack of significant benefit from TNF agents may be explained by the fact that COPD is a highly complex inflammatory disease with many other cytokines and mediators. So more long-term trials are required to clearly identify or dismiss the effect of TNF-alpha inhibitors on COPD.

Conclusion

COPD is a disease resulting from abnormal inflammatory response of the lungs to irritant particles and gases. The disease is marked by airflow limitation as well as systemic inflammation. Once COPD has been diagnosed, current effective management should be based on an individualized assessment of current symptoms and future risks with a goal to relieve symptoms, improve exercise tolerance, improve health status, prevent disease exacerbation, prevent and treat exacerbations and reduce mortality. Despite evidence that there may be an exaggerated decline in patients with higher inflammatory markers, current treatment approach may not target the inflammation in COPD. Although patients on ICS & LABAs have shown clinical improvement and reduction of exacerbation rates, this treatment has failed to show any mortality benefit. Further studies demonstrate there is little reduction in inflammatory markers with this treatment. Selective PDE4 inhibitors decrease inflammation by inhibiting many inflammatory cells. These agents show promising results in patients with moderate to severe COPD. However, gastrointestinal tolerability & weight loss are not infrequently reported. Adding roflumilast to LAACs had the most significant treatment effects & the highest probability of being the best first line treatment. Overall, roflumilast is considered safe and relatively well tolerated. Theophylline has mild non-specific anti-inflammatory properties and patients receiving this treatment have shown clinical improvement. However,

side effects and potential drug interactions outweigh its everyday use. Other agents, including statins, ACE inhibitors/ARBs, and TNF-alpha inhibitors have been studied to reduce inflammation levels. However, further research is needed to elucidate their role in patients with COPD to have better treatment and thereby goal of therapy will be achieved.

References :

1. World Health Organization (WHO), Chronic Obstructive Pulmonary Disease, 2007. Available at www.who.int/respiratory/copd/(accessed july 31,2011)
2. Menezes AM, Perez-Padilla R, Jardim JR. Chronic Obstructive Pulmonary Disease in five Latin American cities (the PLATINO study): a prevalence study. Lancet 2005;366:1875-81.
3. Mannino DM, Gagnon RC, Petty TL. Obstructive Lung disease and low lung function in adults in the United States: data from the National Health and Nutition Examination Survey, 1988-1994. Arch Intern Med.2000;160: 1683-9.
4. Hoogendroom M, Feenstr TL,Hoogenveen RT. Long term effectiveness and cost- effectiveness of smoking cessation interventions in patients with COPD. Thorax 2010;65:711-8.
5. Yao H, Rahman I. Current concept on the role of inflammation in COPD and lung cancer, CurrOpin Pharmacol.2009;9:375-83.
6. Foster TS, Miller Jd, Marton JP. Assessment of the economic burden of COPD in the U.S: a reviewand synthesis of literature.2006;3(4)211-8.
7. FabbriLM, Rabe KF. From COPD to chronic systemic inflammatory syndrome? Lancet 2007;370(9589):797-9.
8. Yanbaeva DG,Dentener MA, Crutzberg EC. Systemic inflammation inCOPD: is genetic susceptibility a factor? COPD 2006;3:51-61.
9. Nicota JS, Robert AS. Systemic inflammation and comorbidity in COPD: a result of overspill of inflammatory mediators from the lungs: review of the evidence. Thorax 2010;65:930-6.
10. Gan WQ,Man SF, Senthilselvan A. Association between chronic obstructive pulmonary disease and systemic inflammation; a systemic review and a meta-analysis. Thorax 2004;59(7):574-80.
11. Donaldson GC, Seemungal TA, Patel IS. Airway and systemic inflammation and decline in lung function in patients with COPD. Chest2005;128(4):1995-2004.
12. Bhowmik A, Seemungal TA, Sapsford RJ. Relation of the sputum inflammatory markers to symptoms and lung function changes in COPD exacerbations. Thorax 2000;55(2):114-20.
13. Man SF,Connet E, Anthonisen NR. C-reactive protein in mild to moderate chronic obstructive pulmonary disease. Thorax 2006;61:849-53.
14. Franciosi LG, Page CP, Celli BR. Markers of disease severity in chronic obstructive pulmonary disease. PulmPharmacolTher.2006;19:189-99.
15. Dahl M, Tybjaerg-Hansen A, Vestbo J. elevated plasma fibrinogen associated reduced pulmonary function and increased risk of chronic obstructive pulmonary disease. Am J RespirCrit Care Med.2001;164(6):1008-11.
16. Spruit MA, Gosselink R, Troosters T. Muscle force during an acute exacerbation in hospitalized patients with COPD and its relationship with CXL8 and IGF-I. Thorax 2003;58:752-6.
17. Sevencaks MJ, Stockly RA. Chronic obstructive pulmonary disease, inflammation and co-morbidity-a common inflammatory phenotype?Respir Res.2006;7:70.
18. Fabbri LM, Luppi F, Beghe B. Complex chronic co-morbidities of COPD.EurRespir J.2008;31:204-12.
19. Talamo C, de Oca MM, Halbert R. Diagnostic leveling of COPD in five Latin American Cities.2007;131:60-7.
20. Damarla M, Celli BR, Mullerova HX. Discrepancy in the use of confirmatory testes in patients hospitalized with the diagnosis of chronic obstructive pulmonary disease or congestive heart failure.Respir Care.2006;51:1120-4.
21. Jenkins CR, Jones PW, Calverley PM. Efficacy of salmeterol/fluticasone propionate by GOLD stage of chronic obstructive pulmonary disease: analysis from the randomized placebo-controlled TORC study.Respir Res.2009;10:59.
22. Price D, Freeman D, Kaplan A. progressive breathlessness in COPD- the role of hyperinflation and its pharmacological management. Prim Care Respir J.2005;14:28593.
23. Rabe KF, Hurd S, Anzoeto A. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease. Am J RespirCrit Care Med.2007;176:532-55.
24. Calverley PM. The role of corticosteroids in chronic obstructive pulmonary disease.SeminRespirCrit Care Med.2005;26(2):235-45.
25. Calverley PM, Boonsawat W, Cseke Z. Maintenance therapy with budesonide and formeterol in chronic obstructive pulmonary disease.EurRespir J.2003;22(6):912-9.
26. Sin DD, Lacy P, York E. Effects of fluticasone on systemic markers of inflammation in chronic obstructive pulmonary disease. Am J RespirCrit Care Med.2004;170:760-5.
27. Burge PS, Calverley PM, Jones PW. Randomized double placebo, controlled study of fluticasone proprionate in patients with moderate to severe chronic obstructive pulmonary disease:the ISOLDE trial. BMJ 2000;320:1297-303.
28. Calverley PM, Anderson JA, Celli B.Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. N Engl J Med.2007;356:775-89.
29. Calverley PM, Boonsawat W, Cseke Z. Maintenance therapy with budesonide and formeterol in chronic obstructive pulmonary disease.EurRespir J.2003;22(6):912-9.
30. Szafranski W, Cukler A, Ramirez A. Efficacy and safety of budesonide/formeterol in the management of chronic obstructive pulmonary disease.EurRespir J.2003;21(11):74-81.
31. Vestbo J. Torch Study Group,The TORCH towards a revolution in COPD health survival study protocol. EurRespir J.2004;24:206-10.
32. Global Initiative for Chronic Obstructive Lung Disease (GOLD), Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease.2010. available at www. Goldcopd.com (accessed July 31,2011).
33. Young RP, Hopkins R, Eaton TE. Pharmacological actions of statins; potential utility in COPD.EurRespir Rev.2009;18(114):222-32.
34. Barnes PJ. Reduced histone deacetylase in COPD:clinical implications. Chest 2006;129:151-5.

35. Sin DD, Man SF, Marciniuk DD.The effects of fluticasone with or without salmeterol on systemic biomarkers of inflammation in chronic obstruvtive pulmonary disease. Am J RespirCrt Care Med.2008;177:1207-14.

36. Calverley PM, Anderson JA, Celli B.Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. N Engl J Med.2007;356:775-89.

37. Young RP, Hopkins R, Eaton TE.Potential benefits of statins on morbidity and mortality in chronic obstructive pulmonary disease: a review of the evidence. Postgrad Med J.2009:685:414-21.

38. Global Initiative for Chronic Obstructive Lung Disease (GOLD), Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease, 2010,available at www. Goldcopd.com (accessed July 31, 2011).

39. Rabe KF, Bateman ED, O'Donnell D. Roflumilast-an oral anti-inflammatory treatment for Chronic Obstructive Pulmonary Disease:arandomized controlled trial. Lancet 2005;366(9485);563-71.

40. Grootendorst DC, Gauw SA, Verhoosel RM. Reduction in sputum neutrophil and eosinophil numbers by the PDE4 inhibitor roflumilast in patients with COPD. Thorax 2007;62:1081-7.

41. Houslay MD.PDE4 CAMP-speceficphosphodiesterase.Prog Nucleic Acid Res Mol.2001;23:249-315.

42. Mills EJ, Druyts E, Ghement I. Pharmacotherapies for chronic obstructive pulmonary disease:amultiple treatment comparison meta-analysis.Clin Epidemol.2001;28:107-29.

43. Fabbri LM, Calverley PM, Izquierdo-Alonso JL.In moderate to severe chronic obstructive pulmonary disease treated with long acting bronchodilators:two randomized clinical trials. Lancet 2009;374:695-703.

44. Chapman RW, House A, Richard J. Pharmacology of a potent and selective inhibitor of PDE4 for inhaled administration.Eur j Pharmacol.2010;643:274-81.

45. Hothersol E, Mcsharry C, Thomson NC. Potential therapeutic role for statins in respiratory disease. Thorax 2006;61:729-34.

46. Marin L. Chronic Obstructive Pulmonary Disease: pathophysiology,current methods of treatment and potential for simvastatin in disease management. Expert Opin Drug Deliv.2011;8:1205-20.

47. Liao JK, Laufs U. Pleiotropic effects of statins.Annu Rev PharmacolToxicol. 2005;45:89-118.

48. Barnes PJ, Shapiro SD,Pauwels RA. Chronic obstructive pulmonary disease: molecular and cellular mechanisms. Eur Respir.2003;22:672-88.

49. Mortensen EM, Copeland LA, Pugh MJ. Impact of statins and ACE inhibitors on mortality after COPD exacerbations. EurRespir J.2009;3:40-5.

50. Mancini GB, Etminan M, Zhang B. Reduction of morbidity and mortality by statins, angiotensin converting enzyme inhibitors in patients with chronic obstructive pulmonary disease. J Am CollCardiol. 2006;47:2554-60.

51. Dobler CC, Wong KK, Marks GB. Associations between statins and COPD: a systemic review. BMC Pulm Med.2009;9:32.

52. Dandona P, DhindsaS, Ghanim J. Angiotensin II and inflammation: the effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockade.J Hum Hypertens.2007:21:20-7.

53. Guba M, Steinbauer M, Buchner M. Different effects of short term ACE and AT1 receptor inhibition on postischemic injury and leucocyte adherence in vivo and in vitro. Shock 2000;13:190-6.

54. Alkharfy KM, Kellum JA, Matzke GR. Unintended immunomodulation: part II, Effects of pharmacological agents on cytokine activity. Shock.2000;13:346-60.

55. Dandona P, DhindsaS, Ghanim J. Angiotensin II and inflammation: the effect of angiotensinconverting enzyme inhibition and angiotensin II receptor blockade. J Hum Hypertens.2007:21:20-7.

56. Kanazawa H, Hirata K, Yoshikawa J. Effects of captopril administration on pulmonary hemodynamics and tissue oxygenation during exercise in ACE gene subtypes in COPD patients: a preliminary study. Thorax 2003;58:629-331.

57. Nong Z, Stassen JM, Moons L. Inhibitionof tissue angiotensinconverting enzyme with quinapril reduces hypoxic pulmonary hypertension and pulmonary vascular remodeling. Circulation1996;94:1941-7.

58. Cargill RI, Lipworth BJ.Lisinopril attenuates acute hypoxic pulmonary vasoconstriction in humans. Chest1996;109:424-9.

59. Andreas S, HermannLC, Raupach T. Angiotensin II blockers in obstructive pulmonary disease: arandomized controlled trial.EurRespir J.2006;27:972-9.

60. Rabe KT,Magnussen H, Dent G. Theophylline and selective PDE4 inhibitors as bronchodilators and smooth muscle relaxants. EurRespir J.1995;8:637-42.

61. Mckay SE, Howe CA, ThomsonAH. Value of theophylline treatment in patients handicapped by chronic obstructive pulmonary disease. Thorax1993;48(3):227-32.

62. Murciano D, Auclair MH, Pariente R. A randomized controlled trial of theophylline in patients with severe chronic obstructive pulmonary disease. N Engl J Med.1989;320(23):1521-5.

63. Keatings VM, Collins PD, Scott DM. Differences in interleukin-8 and tumor necrosis factor-in induced sputum from patients with chronic obstructive pulmonary disease or asthma. Am J RespirCrit Care Med.1996;153:530-4.

64. Aaron SD, Angel JB, Lunau M. Granulocyte inflammatory markers and airway infection during acute exacerbation of chronic obstructive pulmonary disease. Am J RespirCrit Care MED.2001;163:349-55.

65. Barnes PJ. Unexpected failure of anti- tumor necrosis factor therapy in chronic obstructive pulmonary disease. Am J RespirCrit Care MED.2007;175(9):866-7.

66. Stewart CE, Newcomb PB, Holly JM. Multifaceted role of TNF in Myoblast destruction: amplitude of signal transduction pathways. J Cell Physiol.2004;198:237-47.

67. Barnes PJ. Unexpected failure of anti-tumor necrosis factor therapy in chronic obstructive pulmonary disease. Am J RespirCrit Care MED.2007;175(9):866-7.

68. Van der Vaart M, Oeter GH, Postma DS. First study of infliximab treatment in patients with chronic obstructive pulmonary disease. Am J RespirCrit Care MED.2005;172(4):465-9.

69. Ranmard SI, Fogarty C, Ketsen S. The safety and efficacy of infliximab in moderate to severe chronic obstructive pulmonary disease.Am J RespirCrit Care MED.2007;175:926-34.

70. Sullsa SI, Ernst P, Hudson M. TNF-alpha antagonists and the prevention of hospitalization for chronic obstructive pulmonary disease. Am J RespirCrit Care MED.2007;175:926-34.