Biomarkers in real-life COPD management

Valorisation Addendum

Valorisation is defined as the process of ensuring the knowledge gained from scientific learning and research available or useful for economic or societal utilisation, or translating it to competing products, services, processes, and new business.[1] In this section, the societal relevance of this work will be discussed, alongside how this dissertation is currently impacting society.

Health Problem

Chronic obstructive pulmonary disease (COPD) is a common, preventable and treatable disease characterised by relentless respiratory symptoms and airflow limitation that is due to airway and/or alveolar aberrations usually triggered by significant exposure to noxious gases.[2] COPD is a leading cause of morbidity and mortality worldwide. Within non-communicable diseases, it was the third leading cause of disability-adjusted life years according to the Global Burden of Disease Study 2017,[3] and it is projected to hold an equal position among the leading causes of death worldwide in 2030.[4,5] Additionally, the disease is associated with tremendous social and economic impact.[6] In the European Union, COPD accounts for 38.9 billion euros and 52.4 billion dollars in direct and indirect cost in the United States (U.S),[7,8] and places a very high burden on health systems.[2]

The natural course of COPD is characterised by acute events, referred to as exacerbations, defined as the acute worsening of a patient's condition beyond normal day-to-day variation in symptoms that requires additional pharmacotherapy.[2] Exacerbations of COPD have considerable impact on health status[9], lung function.[10] and exercise capacity.[11] Furthermore, exacerbations are associated with substantial mortality and economic impact. Nearly 60% of all cost of COPD is associated with severe acute exacerbations requiring hospital admission.[12]

A biomarker is defined as a measure of any molecule or material, which could be either cells or tissues that reflect a disease process.[13] The essential roles of biomarkers in health includes; enhancing disease diagnosis, monitoring of disease prognosis, and guiding therapy, with the aim of improving patient outcomes and reducing potential side effects of treatments.[13] Over the past decade, there has been an increased interest in biomarkers such as C-reactive protein (CRP) and blood eosinophil counts in COPD.[14–16]

Research Investigations

In this dissertation, we investigated the long-term stability of blood eosinophils as a biomarker among patients with COPD using real-life data from general practice. In a detailed analysis, we assessed the stability of this biomarker by age, sex, smoking status, and baseline blood eosinophil counts among patients with COPD. In addition, we explored the role of blood eosinophil counts as a biomarker for guiding inhaled corticosteroids (ICS) therapy in COPD management. Furthermore, we studied the

trends of moderate-to-severe and severe exacerbations by age and sex. We also determined the potential of creatine reactive protein (CRP) as a biomarker to help guide ICS use in COPD management. We employed data from the UK general practice setting for most of the research presented in this thesis. We also evaluated the management of exacerbations with high-dose intermittent glucocorticoids (GCs) and the risk of fractures among COPD patients using data from the Danish population.

Main findings

In contrast to short-term studies, which tried to evaluate the stability of blood eosinophil counts among patients with COPD by assessing counts over short hospital visits spanning few weeks. In this thesis, we evaluated the long-term stability of blood eosinophil counts and the impact of age, sex, smoking status, and baseline eosinophil counts. Our study was the first and largest observational study to explore the long-term stability of blood eosinophil counts among COPD patients. We found that blood eosinophil counts stability though lower in COPD patients compared to controls was relatively stable in COPD patients. We also showed that age and sex had a significant impact on the stability of blood eosinophil counts. Furthermore, we found that blood eosinophil counts did not serve as a clinically relevant guide for the initiation or withdrawal of ICS among newly diagnosed COPD patients. We also showed that CRP was not a reliable biomarker for targeting ICS therapy among COPD patients. However, we found an increased risk of all-cause mortality among patients with elevated CRP levels regardless of ICS exposure. Furthermore, in this thesis, we showed an increased incidence of moderate-to-severe exacerbations among COPD patients, especially among women, and this trend is increasing. Lastly, intermittent use of high-dose glucocorticoids was not associated with increased risk of fractures among COPD patients.

Target population and perspective for future research

This dissertation is of importance to general practitioners, especially those managing newly diagnosed COPD patients, pulmonologists, rheumatologists, respiratory researchers, policymakers, and other stakeholders. Short-term studies have tried to assess the stability of blood eosinophils as a biomarker in COPD management. However, for blood eosinophil counts to play a vital role in COPD management the long-term stability of this biomarker among large populations of COPD patients was needed to establish its potential. Our findings on the stability of blood eosinophil counts provided useful insight into the potential of this biomarker to help guide COPD treatment. The study was published in the American Journal of Respiratory and Critical care Medicine, and was incorporated into the 2019 Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommendations from the management of COPD, and played a pivotal role in the recommendations of blood eosinophils as a biomarkers in COPD management.[2] This work has been of relevance to various

researchers investigating the role of blood eosinophil counts in COPD management in real-world settings and has been cited by numerous sources.

Post-hoc analyses of data from randomised controlled trials (RCTs) reported reduced risk of exacerbations among COPD patients, with elevated blood eosinophil counts treated with ICS. While this might be true among patients with advanced disease and history of prior exacerbations as reported by post-hoc analyses of RCTs, we found no reduced risk of moderate-to-severe or severe exacerbations among newly diagnosed COPD patients exposed to ICS. Additionally, we did not observe an increased risk of moderate-to-severe exacerbations or severe exacerbations following the withdrawal of ICS among newly diagnosed COPD patients with elevated blood eosinophil counts. This finding is beneficial to clinicians managing newly diagnosed COPD patients in general practice. Future research should, therefore, focus on the potential of blood eosinophil as a guide to ICS therapy among newly diagnosed COPD patients.

Only a few studies have assessed the long-term trends of moderate or severe exacerbations in general populations, but none has explored this trend among COPD patients in the United Kingdom (UK) general practice. Our findings on the trends of exacerbations are of importance as it could help target essential interventions and policies aimed at reducing the incidence of moderate or severe exacerbations especially, among female patients. Furthermore, oral glucocorticoids are additionally used in the management of exacerbations among COPD patients. We found no increased risk of fractures with exposure to high-dose intermittent GCs. Our findings are supported by a previous study, which employed similar definitions for intermittent GCs exposure in evaluating fractures risk among COPD patients in the general practice.[17] Therefore, emphasis on prophylactic treatment of fractures by clinicians may not be essential in patients with COPD exposed to intermittent dose of GCs, whereas this should be considered for high-dose long-term users with advanced COPD disease, postmenopausal women, and men over 40 years.

Furthermore, observational research focused on the potential of biomarkers in the personalised management of various diseases can benefit from the pharmacoepidemiological approaches employed in this dissertation. Particularly the novel approach used in the evaluation of the stability of blood eosinophil counts, adopting composite definitions for outcomes, the use of validated definitions for exposures and outcomes, time-dependent assessment of biomarkers and medication exposures.

In conclusion, this thesis provides essential real-life evidence on the stability of blood eosinophil counts in large populations of COPD patients, and this finding has been incorporated into the 2019 GOLD recommendations. Additionally, it provides insights into blood eosinophil counts as a guide to ICS management of COPD exacerbations among newly diagnosed patients without prior history of exacerbations, ICS use or asthma, which serves as useful information for practitioners charged with the management of this group of COPD patients. We hope that the results from this

dissertation will help stimulate interventions and policies aimed at addressing the rising trend of exacerbations among COPD patients in the UK, especially among women. Lastly, clinicians can be confident in the use of high-dose intermittent GCs in the management of COPD patients with fewer concerns of any potential risk of fractures.

References

1. Buzink R, Cauffman C, Cruijssen M, Massar K. *Valorization of Knowledge: The Desirability and Financing of Spin-Offs at Maastricht University*.; 2015. https://www.maastrichtuniversity.nl/sites/default/files/downloadables/steep_face_alp-valorisation_of_knowledge.pdf.
2. GOLD. Global strategy for the prevention, diagnosis and treatment of chronic obstructive pulmonary disease (2019 Report). 2018. https://goldcopd.org/wp-content/uploads/2018/11/GOLD-2019-v1.7-FINAL-14Nov2018-WMS.pdf. Accessed November 15, 2018.
3. Roth GA, Abate D, Abate KH, et al. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. 2018;392(10159):1736-1788.
4. GBD 2010 Mortality and Causes of Death Collaborators. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: A systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012;380(9859):2095-2128.
5. Vos T, Flaxman AD, Naghavi M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: A systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012;380(9859):2163-2196.
6. Jinjuvadia C, Jinjuvadia R, Mandapakala C, Durairajan N, Liangpunsakul S, Soubani AO. Trends in Outcomes, Financial Burden, and Mortality for Acute Exacerbation of Chronic Obstructive Pulmonary Disease (COPD) in the United States from 2002 to 2010. *COPD*. 2016; 14(1):72-79.
7. Lõpez-Campos JL, Tan W, Soriano JB. Global burden of COPD. *Respirology*. 2016;21(1):14-23.
8. Guarascio AJ, Ray S, Finch CK, Self T. The clinical and economic burden of Chronic Obstructive Pulmonary Disease in the USA. *Clin Outcomes Res*. 2013;5:235-245.
9. Spencer S, Jones PW. Time course of recovery of health status following an infective exacerbation of chronic bronchitis. *Thorax*. 2003;58(7):589-593.
10. Celli BR, Thomas NE, Anderson J a, et al. Effect of pharmacotherapy on rate of decline of lung function in chronic obstructive pulmonary disease: results from the TORCH study. *Am J Respir Crit Care Med*. 2008;178(4):332-338.
11. Cote CG, Dordelly LJ, Celli BR. Impact of COPD exacerbations on patient-centered outcomes. *Chest*. 2007;131(3):696-704.
12. Hilleman DE, Dewan N, Malesker M, Friedman M. Pharmacoeconomic evaluation of COPD. *Chest*. 2000.
13. Cazzola M, MacNee W, Martinez FJ, et al. Outcomes for COPD pharmacological trials: from lung function to biomarkers. *Eur Respir J*. 2008;31(2):416 LP - 469.
14. Sin DD, Man SFP, Marciniuk DD, et al. The effects of fluticasone with or without salmeterol on systemic biomarkers of inflammation in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2008;177(11):1207-1214.
15. Pascoe S, Locantore N, Dransfield MT, Barnes NC, Pavord I. Blood eosinophil counts as markers of response to inhaled corticosteroids in COPD? - Authors' reply. *Lancet Respir Med*. 2015;3(8):e27.
16. Watz H, Tetzlaff K, Wouters EFM, et al. Blood eosinophil count and exacerbations in severe chronic obstructive pulmonary disease after withdrawal of inhaled corticosteroids: A post-hoc analysis of the WISDOM trial. *Lancet Respir Med*. 2016;4(5):390-398.
17. De Vries F, Bracke M, Leufkens HGM, Lammers JWJ, Cooper C, Van Staa TP. Fracture risk with intermittent high-dose oral glucocorticoid therapy. *Arthritis Rheum*. 2007;56(1):208-214.