Medications for chronic obstructive pulmonary disease: a historical non-interventional cohort study with validation against RCT results

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Scientific summary

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Scientific summary

Background

Chronic obstructive pulmonary disease affects 3 million people in the UK. The most common cause is smoking, and patients exhibit airflow obstruction that is not fully reversible. The disease is progressive, with declining lung function and worsening symptoms. Most troublesome are acute exacerbations manifested as a sudden worsening of symptoms (e.g. severe coughing, shortness of breath and chest congestion) that require urgent treatment and possibly hospitalisation. Although smoking cessation remains the most effective intervention, the rate of exacerbation can be reduced by regular medication, such as combination long-acting beta agonists and inhaled corticosteroids or long-acting muscarinic antagonists.

Chronic obstructive pulmonary disease treatment guidelines are largely informed by randomised controlled trial results, but it is not clear if these findings apply to large patient populations that are not studied in these trials. Fluticasone propionate plus salmeterol (FP-SAL) [Seretide (GlaxoSmithKline plc)] is a long-acting beta agonist/inhaled corticosteroid combination and is one of the most widely used chronic obstructive pulmonary disease treatments. It has been studied in large randomised trials [e.g. the TORCH (TOwards a Revolution in COPD Health) trial], but the effects of treatment in important patient groups who were not studied are unknown. Some patient groups were excluded from trials (e.g. those aged > 80 years, those with concomitant asthma or those with substantial comorbidity), whereas others are under-represented (e.g. people with mild chronic obstructive pulmonary disease), meaning that conclusions about these groups are difficult to make.

Although the conduct of non-interventional studies (sometimes also referred to as 'observational studies') to investigate possible drug harms is well established, the use of these studies to estimate treatment effectiveness is in its infancy. Issues of treatment channelling and indication bias mean that measuring the intended benefit of a treatment is beset with difficulties. Over the next few years, we believe that we will see more non-interventional studies of drug effectiveness emerging because of recent legislation that requires pharmaceutical companies to study the real-world effects of medications; however, rigorous, validated methodology is needed to translate these complex data into reliable evidence. For example, the availability of anonymised individual patient data from randomised controlled trials provides the potential for 'randomised controlled trial-analogous' cohorts to be selected from non-interventional data sources (by matching patient records from non-interventional data to the randomised controlled trial patient records on key characteristics). If subsequent analysis of a non-interventional randomised controlled trial-analogous cohort generates results that are similar to those generated by the reference randomised controlled trial, one could be confident in the validity of the results and in the non-interventional methods used to obtain these results in this setting.

In this study we used TORCH individual trial data to validate non-interventional methods for assessing chronic obstructive pulmonary disease treatment effectiveness, before going on to apply these methods to the analysis of treatment effectiveness within people excluded from, or under-represented in,

the TORCH trial. Non-interventional data were obtained from the UK Clinical Practice Research Datalink (linked to the Hospital Episodes Statistics database). The results generated could aid patients, prescribers and policy-makers in deciding the most appropriate treatment for chronic obstructive pulmonary disease for all types of patients. The approach used can also provide a template for treatment effectiveness research using non-interventional data with inbuilt validation against a randomised trial.

Aims and objectives

The aims of our study were as follows:

- to measure the association between treatments for chronic obstructive pulmonary disease and a number of chronic obstructive pulmonary disease outcomes, including exacerbation rate, mortality, pneumonia and time to treatment change, among patients not included in randomised clinical trials for chronic obstructive pulmonary disease treatments
- to develop a methodological framework with inbuilt validation against randomised controlled trial data for using non-interventional electronic health records to answer questions about drug treatment effects (i.e. both benefits and risks).

Specific objectives were to:

- validate methods for measuring chronic obstructive pulmonary disease medication effectiveness in electronic health record data by comparing with trial results
- use electronic health record data to measure chronic obstructive pulmonary disease medication effectiveness in patients excluded from trials (most importantly, those aged > 80 years or those with comorbidities)
- determine chronic obstructive pulmonary disease treatment effectiveness in an understudied disease stage (i.e. mild chronic obstructive pulmonary disease).

Methods

We performed a historical cohort study (2000–17) of chronic obstructive pulmonary disease drug treatment effects in the UK Clinical Practice Research Datalink. For objective 1 (i.e. validation of methods against the TORCH trial), two control groups were selected from the Clinical Practice Research Datalink by applying TORCH trial inclusion/exclusion criteria and 1 : 1 matching to individual TORCH trial participants. Control group 1 included people with chronic obstructive pulmonary disease not prescribed FP-SAL and control group 2 included people with chronic obstructive pulmonary disease who were prescribed salmeterol only. FP-SAL-exposed groups were then selected from Clinical Practice Research Datalink by propensity score matching to each control group. Outcomes studied were chronic obstructive pulmonary disease exacerbations, death from any cause and pneumonia. For objectives 2 and 3 (i.e. analyses of chronic obstructive pulmonary disease medication effectiveness in patients excluded from trials or with an understudied disease stage), the validated methods for patient selection and propensity score development from objective 1 were used to select and analyse the same outcomes in cohorts of people with chronic obstructive pulmonary disease in the Clinical Practice Research Datalink who would have been excluded from the TORCH trial because of age, comorbidities or having mild chronic obstructive pulmonary disease (but who would have otherwise met the TORCH trial criteria). For objectives 2 and 3, the control group was people with chronic obstructive pulmonary disease who were prescribed salmeterol.

Results

For the validation stage (i.e. objective 1), 2652 FP-SAL-exposed people were propensity score matched to 2652 unexposed people, and 991 FP-SAL-exposed people were propensity score matched to 991 salmeterol-exposed people. Exacerbation rate ratio was comparable to the TORCH trial for FP-SAL compared with salmeterol (0.85, 95% confidence interval 0.74 to 0.97, vs. TORCH trial 0.88, 95% confidence interval 0.81 to 0.95), but not for FP-SAL compared with no FP-SAL (1.30, 95% confidence interval 1.19 to 1.42, vs. TORCH trial 0.75, 95% confidence interval 0.69 to 0.81). Active comparator results were also consistent with the TORCH trial for mortality (hazard ratio 0.93, 95% confidence interval 0.65 to 1.32, vs. TORCH trial hazard ratio 0.93, 95% confidence interval 0.77 to 1.13) and pneumonia (risk ratio 1.39, 95% confidence interval 1.04 to 1.87, vs. TORCH trial risk ratio 1.47, 95% confidence interval 1.25 to 1.73). However, different result were obtained from the TORCH trial for the FP-SAL-exposed compared with FP-SAL-unexposed analysis of mortality and pneumonia (mortality hazard ratio 1.11, 95% confidence interval 0.95 to 1.26, vs. TORCH trial mortality hazard ratio 0.83, 95% confidence interval 0.68 to 1.00; pneumonia risk ratio 1.14, 95% confidence interval 0.96 to 1.34, vs. TORCH trial pneumonia risk ratio 1.59, 95% confidence interval 1.35 to 1.88). Time to treatment continuation differed from the TORCH trial for both the FP-SAL compared with salmeterol and FP-SAL compared with no FP-SAL analyses (e.g. FP-SAL vs. SAL hazard ratio 0.23, 95% confidence interval 0.20 to 0.27, vs. TORCH trial hazard ratio 0.89, 95% confidence interval 0.79 to 0.99).

For the over-80s cohort exacerbations analysis, we obtained a propensity score-matched rate ratio of 0.59 (95% confidence interval 0.36 to 0.95) and a propensity score-adjusted rate ratio of 0.83 (95% confidence interval 0.60 to 1.14), which is consistent with the association measured in the TORCH trial-analogous Clinical Practice Research Datalink population (0.85, 95% confidence interval 0.74 to 0.97). For the mortality outcome, we obtained a propensity score-matched hazard ratio of 0.99 (95% confidence interval 0.56 to 1.74) and a propensity score-adjusted hazards ratio of 1.29 (95% confidence interval 0.84 to 2.00). Again, this is consistent with the TORCH trial-analogous Clinical Practice Research Datalink result (0.93, 95% confidence interval 0.65 to 1.32). For the pneumonia analysis, we found no evidence for an increased risk associated with FP-SAL, with a propensity score-matched rate ratio of 0.82 (95% confidence interval 0.44 to 1.53) and a propensity score-adjusted rate ratio of 0.88 (95% confidence interval 0.54 to 1.42).

For the analysis of exacerbations in the cohort of people with concomitant asthma, we found a propensity score-matched rate ratio of 0.74 (95% confidence interval 0.62 to 0.89) and a propensity score-adjusted rate ratio of 0.67 (95% confidence interval 0.59 to 0.78), which is consistent with the association measured in the TORCH trial-analogous Clinical Practice Research Datalink population (0.85, 95% confidence interval 0.74 to 0.97). For the mortality outcome, we obtained a propensity score-matched hazard ratio of 1.49 (95% confidence interval 1.21 to 1.85) and propensity score-adjusted hazards ratio of 1.20 (95% confidence interval 1.04 to 1.40), contrary to the null findings with the TORCH trial-analogous Clinical Practice Research Datalink result (0.93, 95% confidence interval 0.65 to 1.32). For the pneumonia analysis, we found no evidence for an increased risk associated with FP-SAL, with a propensity score-matched rate ratio of 1.09 (95% confidence interval 0.74 to 1.63) and a propensity score-adjusted rate ratio of 1.04 (95% confidence interval 0.79 to 1.37).

For the people with mild chronic obstructive pulmonary disease, we found a propensity score-matched rate ratio for exacerbations of 0.56 (95% confidence interval 0.46 to 0.70) and a propensity score-adjusted rate ratio of 0.52 (95% confidence interval 0.45 to 0.61), which suggests a stronger protective association than that measured in the TORCH trial-analogous Clinical Practice Research Datalink population (0.85, 95% confidence interval 0.74 to 0.97). Notably, however, the crude association in those with mild chronic obstructive pulmonary disease was also strongly protective, unlike in the TORCH trial-analogous population. For the mortality outcome, we obtained a propensity score-matched hazard ratio of 0.98 (95% confidence interval 0.67 to 1.45) and a propensity score-adjusted hazards ratio of 0.84 (95% confidence interval 0.66 to 1.08). Again, this is consistent with the TORCH trial-analogous Clinical

Practice Research Datalink result (0.93, 95% confidence interval 0.65 to 1.32). For the pneumonia analysis, we found no evidence for an increased risk associated with FP-SAL, with a propensity score-matched rate ratio of 0.78 (95% confidence interval 0.45 to 1.35) and a propensity score-adjusted rate ratio of 1.08 (95% confidence interval 0.74 to 1.57).

Conclusions

Our results suggest that routinely collected electronic health record data can be used to successfully identify the expected beneficial and harmful effects of treatments for chronic obstructive pulmonary disease when validating against results obtained from randomised trials. Importantly, successful replication was possible only when comparing between two active treatments, and could not be achieved for comparisons between active treatment and no treatment. These conclusions are specific to investigations of the effects of chronic obstructive pulmonary disease medication and cannot be assumed to replicate in other disease areas. In validating against the results of a large international multicentre randomised trial, it was also clear that, in some instances, some patient characteristics observed in a trial are not always observed in a single-country electronic health record setting. This raises questions of possible trial result heterogeneity by geographic region, which should be considered in future attempts to replicate trial findings in non-interventional data.

The step of directly comparing findings from non-interventional data with those from the trial provided a methodological validation and template, allowing further work to focus on the types of patients excluded from the original trials.

Analyses involving patients who would have been excluded from, or were under-represented in, chronic obstructive pulmonary disease treatment trials mostly suggest that treatment effects for FP-SAL are similar in patients aged > 80 years, those with mild chronic obstructive pulmonary disease and those with both asthma and chronic obstructive pulmonary disease. However, some potential differences were also suggested. For people with mild chronic obstructive pulmonary disease, the use of FP-SAL appears to be more beneficial with respect to exacerbations than was seen in the TORCH trial-analogous population. By contrast, we observed a small increased risk of mortality when comparing FP-SAL with salmeterol in the group with both chronic obstructive pulmonary disease and asthma. These associations should be interpreted with caution, and we recommend future studies to focus on further characterising these associations.

Overall, we have demonstrated the utility of non-interventional data to investigate the expected treatment effects of chronic obstructive pulmonary disease medications, in both trial-included and trial-excluded patient groups. Analyses largely suggest that chronic obstructive pulmonary disease treatment effects are consistent across different patient groups, but highlighted a small number of possible differences that should be investigated further in other data sets. Unanswered questions about the effectiveness of currently recommended chronic obstructive pulmonary disease inhaled combination therapy (other than FP-SAL) in patients excluded from trials should also be investigated using these methods, and further work on advanced technique (e.g. high-dimensional propensity scores) could be performed to investigate whether or not placebo-controlled randomised controlled trials can ever be replicated in this therapeutic area.

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