

# From the TORCH trial to the UPLIFT trial

## Parallel or different routes?

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Chronic obstructive pulmonary disease (COPD) is a world epidemic. It is currently the fourth leading cause of death in the USA, with its prevalence increasing worldwide. It has been estimated that it will become the third most common cause of death in both the USA and the rest of the world by the year 2020<sup>1</sup>. In 1976, Fletcher and coworkers showed that a subgroup of active smokers had an accelerated decline in lung function, as assessed by the FEV<sub>1</sub> % predicted. This rapid decline would gradually lead to respiratory insufficiency and eventually result in death at a younger age<sup>2</sup>. This concept led to the consideration that disease modification could have as the primary and even the sole target the effect on FEV<sub>1</sub> decline. Accordingly, many studies focused on this parameter and simultaneously ignored the “many faces of the disease”. However, COPD is more than solely a pulmonary disorder, and has well recognized effects on cardiovascular morbidity, the risk of lung cancer development, osteoporosis and depression. The disease mortality is considered a complicated issue, and it is usually underestimated in terms of the contribution of both co-morbidities and various different aspects of disease severity<sup>3</sup>. The FEV<sub>1</sub> % cannot identify the rate of exacerbations, the exacerbation-related hospitalizations or the overall quality of life (QoL). In the current approach to COPD, we need studies which will identify the many faces of the disease or, more precisely, the different clinical and therapeutic phenotypes. In the last two years two pharmacological studies, TORCH<sup>4</sup> and UPLIFT<sup>5</sup>, attempted to explore the phenotypes theory, in order to prove that aiming at only one parameter of the disease belongs to the past and has no place in the future.

TORCH was a randomized double blind trial, comparing combination therapy with inhaled steroids (ICS) and long acting  $\beta_2$  agonists (LABA) with placebo (short acting bronchodilators on demand), LABA alone or ICS alone for a time period of three years. The primary outcome was all cause mortality, and the frequency of exacerbations, QoL and rate of decline in FEV<sub>1</sub> were assessed. UPLIFT was a randomized double blind trial comparing tiotropium with placebo for four years. Patients were allowed to use all available relevant medications. The primary outcome was the rate of decline in mean FEV<sub>1</sub>, and as secondary outcomes, the frequency of exacerbations, QoL and mortality were also assessed. The two studies had a different design regarding the placebo component. Realistically, the placebo component in UPLIFT could be combination therapy, while in TORCH it was short acting bronchodilators on demand. We strongly believe that the design of UPLIFT was closer

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to the real world of COPD. Anybody reading the editorial for TORCH would realize that the option of a real placebo component has ended<sup>6</sup>. Another important issue is that in UPLIFT, stage II COPD patients were also recruited. This could provide some definite answers about the direction of early intervention. The third important issue in UPLIFT is the percentage of active smokers, which was much lower compared to previous studies. The main differences in the study design may be explained by the fact that the TORCH study was designed in the late 90s, when the many faces of the disease were not so evident.

Despite the non statistically significant result for the primary outcome, the TORCH trial showed that combination therapy (ICS + LABA) positively influenced the rate of decline of lung function, as assessed by FEV<sub>1</sub>, the exacerbation rate and the overall QoL. The UPLIFT trial did not reach statistical significance in its primary outcome, but demonstrated that tiotropium decreased exacerbations, related hospitalizations and the occurrence of respiratory failure, and it also improved QoL. What was really important was its positive effect on mortality and cardiovascular morbidity. Did we get a clear message from these two trials? They confirmed that both the management of the disease and its natural history remain two parameters with many hidden secrets.

From our point of view, the TORCH trial yielded an important observation with two components; mortality in COPD is not influenced either by the decline in lung function or by the decrease in the exacerbation rate. Was this a real effect or was it just a sub-phenotype of patients whose mortality is not influenced by exacerbation rate and decline in lung function? This is a complicated question with no clear answer at present. On the other hand the UPLIFT trial showed that the addition of a long acting anticholinergic to the current treatment of COPD reduces the rate of exacerbations, related hospitalizations and respiratory failure. Through this effect, both mortality and cardiovascular morbidity were positively affected. Are the results of the two studies completely different? Definitely no. They overlapped each other in the finding that the rate of decline in FEV<sub>1</sub> alone does not solely define overall mortality either for COPD or for the related co-morbidities. The question arising, then, is which is the stronger parameter determining the natural history of the disease? Is it just the decrease in the rate of exacerbations? Possibly yes, and especially those exacerbations that require hospitalization and lead to life-threatening respiratory failure. The phenotype of frequent exacerbations is mainly

related to increased cardiovascular morbidity, irrespective of preexisting disease. The TORCH trial did not reach this target, because of its inadequate primary design, while the UPLIFT trial reached the target, due to its more realistic design in relation to everyday COPD.

Where did these trials meet? Probably in a third study, the INSPIRE study<sup>7</sup>. This study compared combination therapy (ICS + LABA) with tiotropium, setting as its primary outcome the number of exacerbations. No winner was found, probably due to the different mechanisms acting to decrease the rate of exacerbations. Where else did they meet? On their positive effects in severe to very severe COPD, where they act synergistically and effectively. Where did they not meet? Possibly in phenotype differences which will emerge from future analysis, mainly for the UPLIFT trial, which has the potential to examine the mild to moderate disease phenotype, the ex-smoker phenotype and the non-steroid treated phenotype.

Both studies, even though unintentionally, have managed to convince every clinician and researcher to view COPD as a syndrome that encompasses a variety of obstructive diseases, but differs in terms of the mechanism of disease and the response to therapy, as it is supported in the editorial for UPLIFT<sup>8</sup>: A heterogeneous syndrome with a mathematical notation as follows: COPD= $\sum_{n=1}^{\infty}$ ·COPD<sub>n</sub>, where n represents the many faces of disease.

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