Revisiting the copd mega-trials in the new decade:

The end of the road or just a new beginning?

Stelios Loukides,
Petros Bakakos,
Konstantinos Kostikas

Editorial Board Pneumon

Chronic obstructive pulmonary disease (COPD) is a worldwide epidemic. It is currently the fourth leading cause of death in the USA, with its prevalence increasing throughout the world. It has been estimated that it will become the third leading cause of death in both the USA and the rest of the world by the year 2020[1]. From the late 1990s a significant change has been observed in relation to the pharmaceutical approach to this disorder. The positive results of pharmacological trials have brought about changes in our views on the management of COPD. TORCH[2] and UPLIFT[3] were the largest and most ambitious COPD trials ever conducted, each involving approximately 6,000 patients with COPD patients. We strongly believe that the publications derived from these trials closed the first cycle of big pharmacological trials in COPD. In terms of their primary outcomes, both trials were negative, but various secondary outcomes and results derived from further post-hoc sub-analyses showed positive effects for both tiotropium and/or the combination of inhaled steroids (ICS) and long acting beta two agonists (LABA)[2-7].

Regarding the UPLIFT trial, the addition of tiotropium to any current treatment was associated with improvement in lung function, quality of life, rate of exacerbations and mortality, particularly that of cardiovascular origin. In a further analysis of a cohort that included patients with less severe COPD, the addition of tiotropium reduced the decline of lung function. This effect was not evident, however, in the whole study population and this was the negative primary outcome of the UPLIFT trial as a whole. Further analysis showed that tiotropium can, in addition, maintain adequate control on long term basis, irrespective of concomitant treatment, and any positive effect was further up-regulated in younger patients, irrespective of the underlying severity[5,8].

On a parallel course, the TORCH study, which compared the combination of salmeterol-fluticasone with its individual components given separately and placebo, demonstrated significant reduction in exacerbation rate and improvement in quality of life, but failed – marginally – to show improvement in survival[3]. In a post-hoc analysis, however, the LABA/ICS combination showed a significant reduction in lung function decline compared to placebo[6]. Moreover, in a sub-analysis of less severe patients, the combination resulted

Correspondence to:
Stelios Loukides
Smolika 2 16673 Athens
Tel.: +302105831136
Fax: +302105326414
E-mail: ssat@hol.gr

in a reduction of mortality[7], which may be of particular importance since current guidelines do not support the use of ICS in the early stages of the disease, something that does not represent current clinical practice.

Both trials are important for practising clinicians, since they provide considerable contributions to the understanding of how the disease progression might be influenced. At the same time, the results of both these trials raised important questions: Should we attempt early intervention with tiotropium and/or LABA/ICS combinations? What is the threshold for "early intervention"? Is 60% predicted FEV_1 a reasonable cut-off point for the initiation of early intervention or should lower spirometry limits be implemented? It is quite difficult to provide a definite answer to these questions, since the currently available study results do not support any relative efficacy of multiple treatments. Smaller trials have provided some evidence of superiority of the combination of tiotropium plus LABA/ICS combos compared to their components in terms of reduction of exacerbations[9,10], but further large long-term randomized trials are now needed, which should include adequately long-term follow up, implementing procedures similar to those undertaken in TORCH and UPLIFT.

At the same time, two other pharmacological options have become available for COPD: indacaterol, an ultra LABA, and roflumilast, a phosphodiesterase 4 inhibitor. Clinical trials of indacaterol provide support for its 24-hour bronchodilating effect and its positive effect on quality of life and exacerbation rate, and provide evidence that indacaterol is superior to the existing LABAs and not inferior to tioropium[11,12]. Does the addition of indacaterol to our treatment options influence current guidelines? From a practical point of view, indacaterol is recommended for all patients in GOLD stages II-IV, but with one possible dilemma: should the clinician interrupt a fixed LABA/ICS combination in order to administer indacaterol? This could be done in order to improve adherence in some patients, although there is no real evidence for this. Finally, there may be strong physiological evidence for an additive bronchodilative effect of the addition of indacaterol to tiotropium, but this remains to be proved in long-term trials.

On the other hand, the position of roflumilast in current treatment guidelines is more strictly specified, since it is recommended as additive treatment to bronchodilators for patients with severe and very severe COPD, and in patients with a clinical phenotype of chronic bronchitis and repeated exacerbations. In such patients, however, the recently published trial findings demonstrate evidence that roflumilast provides a significant improvement in both lung function and quality of life and – most importantly – leads to a significant reduction in exacerbations[13]. Roflumilast represents the only novel systemic treatment for COPD that can be combined with all the currently used inhaled drugs[14]. A recent revision of the GOLD guidelines has included roflumilast in the treatment options of COPD[15].

Have we reached the end of the road represented by the major efforts of the past decade? Possibly yes. We have had large industry-sponsored pharmacological trials providing strong evidence that our current treatment options significantly affect disease progression in COPD, by influencing various different outcomes including mortality, exacerbation rate, quality of life and lung function decline. These COPD mega-trials have shown in addition that these therapeutic interventions may be effective even in patients with less severe disease. Only a few years ago all these positive targets of disease modification were considered unrealistic, representing a nihilistic attitude towards COPD. In the meantime we have sought the Holy Grail of disease modification and we have become a lot more optimistic, but what is the next step? Many questions arise: Which combinations of the current treatment regimens are more effective? Do we need all those combinations and for all patients, especially in a forthcoming era where medication costs will become a major issue?[16] Finally, can we modify the disease at even earlier stages? For the first question, the answer is quite simple since the triple combination of LAMA plus LABA/ICS seems to be more beneficial than its individual components. The replacement of a LABA with an ultra-LABA, from a practical point of view may improve adherence, but long-term trials are needed to support this option. Regarding the second question, it is quite difficult to give a definite answer since the published data are not sufficient. Experienced respiratory physicians definitely have the critical ability to select the appropriate treatment regimens for each patient, but when it comes to guidelines for primary care the data are still contradictory and cost is a major issue in such settings. The final question is even more difficult, since the majority of the big trials did not involve patients with mild or even mild-to-moderate COPD. The crucial issues in these stages are to fight underdiagnosis and to implement effective strategies for the identification of new cases of COPD, providing access to specialized respiratory evaluation and good quality spirometry at reasonable cost. Current guidelines are often criticized for being somewhat conservative in the management of early COPD, but published evidence does not so far

support the use of more medication in those early stages. New large trials, particularly designed to investigate the detrimental effects of delaying treatment until later in the course of the disease, are urgently required to render the evidence for early intensive intervention[17].

The most important message from the past decade in COPD management is now clearer than ever: our patients are being treated better and are already experiencing the benefits of our multidimensional management. There is now evidence that COPD patients in the past decade had better prognosis compared to those of the 1990s and earlier, and this improvement is likely to be associated with better management and treatment of the disease and its co-morbidities. Perhaps we will never know which of all is the single most important intervention, since it is now accepted as unethical to deprive patients of effective treatments in clinical trials. If we look, however, for the most important message coming from the COPD mega-trials, it will definitely be the timeless quote by the former US Surgeon General C. Everett Koop that "Drugs don't work in patients who don't take them"! Indeed, adherence to inhaled medication had the most impressive effect on the survival of COPD patients in the TORCH trial cohort[18]. We are, therefore, definitely more optimistic and more confident than ever that we can make a difference to the lives of our COPD patients, but we still have to improve our skills in identifying and treating them early in the course of the disease, as well as in convincing them to be adherent to their medication for life, just like all the rest of the patients with chronic diseases[19]. Given the fact that we are not expecting any novel therapeutic agents to be introduced in the near future, this target, along with the appropriate management of comorbidities, may represent the landmark of a new beginning for COPD in the next decade.

REFERENCES

1. Rabe KF, Hurd S, Anzueto A, et al. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med 2007;176:532-55.
2. Tashkin DP, Celli B, Senn S, et al; UPLIFT Study Investigators. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. N Engl J Med 2008;359:1543-54.
3. Calverley PM, Anderson JA, Celli B, et al. TORCH investigators. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. N Engl J Med 2007;356:775-89.
4. Decramer M, Celli B, Kesten S, Lystig T, Mehra S, Tashkin DP. UPLIFT investigators. Effect of tiotropium on outcomes in patients with moderate chronic obstructive pulmonary disease (UPLIFT): a prespecified subgroup analysis of a randomised controlled trial. Lancet 2009;374:1171-8.
5. Troosters T, Celli B, Lystig T, et al. Uplift Investigators. Tiotropium as a first maintenance drug in COPD: secondary analysis of the UPLIFT trial. Eur Respir J 2010;36:65-73.
6. Celli BR, Thomas NE, Anderson JA, 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;178:332-8.
7. Jenkins CR, Jones PW, Calverley PM, et al. Efficacy of salmeterol/fluticasone propionate by GOLD stage of chronic obstructive pulmonary disease: analysis from the randomised, placebo-controlled TORCH study. Respir Res 2009;10:59.
8. Morice AH, Celli B, Kesten S, Lystig T, Tashkin D, Decramer M. COPD in young patients: a pre-specified analysis of the four-year trial of tiotropium (UPLIFT). Respir Med 2010;104:1659-67.
9. Welte T, Miravitlles M, Hernandez P, et al. Efficacy and Tolerability of Budesonide/Formoterol Added to Tiotropium in Patients with Chronic Obstructive Pulmonary Disease. Am J Respir Crit Care Med 2009;180:741-50.
10. Aaron SD, Vandemheen KL, Fergusson D, et al; Canadian Thoracic Society/Canadian Respiratory Clinical Research Consortium. Tiotropium in combination with placebo, salmeterol, or fluticasone-salmeterol for treatment of chronic obstructive pulmonary disease: a randomized trial. Ann Intern Med 2007;146:545-55.
11. Dahl R, Chung KF, Buhl R, et al; INVOLVE (INdacaterol: Value in COPD: Longer Term Validation of Efficacy and Safety) Study Investigators. Efficacy of a new once-daily long-acting inhaled beta2-agonist indacaterol versus twice-daily formoterol in COPD. Thorax 2010;65:473-9.
12. Donohue JF, Fogarty C, Lötvall J, et al; INHANCE Study Investigators. Once-daily bronchodilators for chronic obstructive pulmonary disease: indacaterol versus tiotropium. Am J Respir Crit Care Med 2010;182:155-62.
13. Rabe KF. Roflumilast for the treatment of chronic obstructive pulmonary disease. Expert Rev Respir Med 2010;4:543-55.
14. Kostikas K, Bakakos P, Loukides S. Phosphodiesterase 4 inhibitors: A new treatment option for copd. Are we there yet? Pneumon 2009;4:290-5.
15. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2010. Available from: http://www.goldcopd.com
16. Kostikas K, Bouros D. "Show me the money": a fair criticism of economic studies on inhaled bronchodilators in COPD. BMC Pulm Med 2010;10:48.
17. Decramer M, Cooper CB. Treatment of COPD: the sooner the better? Thorax 2010;65:837-41.
18. Vestbo J, Anderson JA, Calverley PM, et al. Adherence to inhaled therapy, mortality and hospital admission in COPD. Thorax 2009;64:939-43.
19. Bakakos P, Kostikas K, Loukides S. COPD and co-morbidities. Pneumon 2010;1:21-7.