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EDITORIAL

And Then There Were Three: Time to Move Onward in COPD Drug Development Beyond LAMA/LABA/ICS at Last?

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The year 1978 witnessed the release of Genesis' ninth studio album with the self-referential title "and then there were three", after founding members Peter Gabriel and Steve Hackett had left the band. As the musical style of the three remaining members changed into lighter, more chart-oriented pop-rock songs, this album inevitably marked the great divide between traditionalist early stage supporters of 10-minute-plus progrock hymns like the "*Return of the Giant Hogweed*" and the ever-growing fanbase of 80s charttoppers like "*Invisible Touch*" or "*In too deep*". For either party, only black and white existed with nothing in between: you loved the 70s progrock hymns and despised the 80s repertoire or vice versa. It seemed as if there were two entirely different bands linked only by the common name "Genesis". However, many heretics (like myself), if secretly, dared to enjoy listening to both chapters of the Genesis storybook, recognizing the gems and pearls among the later song repertoire as well as admitting that some of the bombastic, pompous, or sentimental pieces from the earlier years were impossible to listen to, at least under a sober state-of-mind. Why Gabriel versus Collins and not have both worlds? Here, COPD comes in. Similar to the split in the Genesis supporters, two partially conflicting universes of COPD treatment paradigms exist, albeit in parallel: the "pure" bronchodilation approach versus "anti-inflammatory" therapy containing regimes, the former underscoring the limited benefit of inhaled corticosteroids (ICS) in this indication, owing to an inflammatory process largely unresponsive to steroids, the latter emphasizing the inflammatory nature of COPD and, in particular, exacerbations of the disease. Nearly 20 years ago, the first once-daily long-acting antimuscarinic (LAMA) bronchodilator, tiotropium, as well as two different twice-daily fixed combinations of an inhaled corticosteroid (ICS) with a long-acting beta-agonist (LABA), were approved for COPD. Here, the conflict in clinical research started. Manufactures of either therapy considered their respective product a "first-line" approach for this devastating disease, trying to support their claim by clinical trial data. The bronchodilator fraction argued that concepts from asthma about the importance of ICS could not be translated into COPD management: already the earliest studies with ICS in

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COPD indicated, that the efficacy was confined to a single outcome in a subset of patients at risk for the respective outcome: exacerbations [1]. However, clinical reality revealed that many physicians struggled to distinguish COPD from asthma, as there were cases with overlapping features of both diseases, and no gold standard definition existed. As there were concerns about the safety of bronchodilator monotherapy in asthma [2], many doctors decided to err on what they considered to be the "safe side", i.e., choosing a strategy that contained an ICS, thus covering also possible asthma "overlap" subjects. Nonetheless, already the first edition of the GOLD strategy paper of 2001 stated that ICS in COPD should only be used together with regular bronchodilators, and be restricted to patients with poor lung function and a history of repeated exacerbations [3]. Contrary to this recommendation, ICS/LABA products have since then been massively (over-) prescribed for COPD subjects with low or absent risk of exacerbations [4], overestimating the clinical benefits of ICS in this population, and, importantly, underestimating risk associated with long-term use of higher ICS doses in COPD, in particular increased pneumonia rates [5]. Although ever since there have been countless review papers, workshops and conferences about "who needs ICS in COPD", it appeared that the overuse of ICS in COPD was indeed a hard habit to break. Even when well-designed clinical trials confirmed the effectiveness of non-ICS containing combinations for COPD exacerbation prevention [6], and the feasibility of weaning off ICS in subjects with a questionable indication for this type of drug [7, 8], change was reluctant and slow. Why were doctors so persistent with their prescription habits? One potential answer to this question lies within the progressive nature of COPD: "cure" or even normalization of the physiological changes does not happen, and many patients get worse over time, hence treatment intensity gradually increases until the maximum possible inhaler regime (ICS/LABA plus LAMA) is reached. Recent data from registries confirm that this usually takes only 5–-10 years in the career of a COPD subject [9]. Taking the time axis into account, it is not surprising that for many doctors the prevailing discussion of ICS yes/no in COPD is simply not that relevant. Eventually, there are few things left to offer. Physicians simply made use of both parts of the COPD treatment universe, similar to the ecumenical listeners of Genesis before/after. If the starting point was a LAMA, escalation included add-on of an ICS/LABA combination, and vice versa. Full stop. End of story. Unfortunately, this will probably continue to be the case for another decade at least. We have simply forgotten to move on. Imagine a patient with severe COPD, to whom in the year 2001 I would have prescribed an open combination of—let's say—tiotropium (LAMA) and budesonide/formoterol (ICS/LABA) fixed combination. Had this patient asked me, what would happen if these inhalers were not working anymore because his disease got worse, what might I have answered? *There is hope on the horizon, don't worry, other, better, drugs will be available in a few years from now. You'll be fine*. Indeed, I got it wrong: the drug industry (as well as clinical researchers and expert committees) has spent (wasted?) over 20 years with the question of searching for often marginal differences in outcomes with "optimal" treatment regimes comparing one, two or three single or combined (pharmacologically old) components, often following their canonical imperatives of "maximized" bronchodilation versus ICS-containing combos: LAMA versus ICS/LABA [10], ICS/LABA versus LABA [11], LABA/LAMA versus LAMA [12, 13], LABA/LAMA versus ICS/LABA [6], plus a number of studies circling around the question if it was possible to withdraw ICS safely or not [7, 8, 14]. Tellingly, the only study that ignored the "one-or-another" agenda and looked at the effects of combining all three (ICS/LABA plus LAMA) compounds together (the Canadian OPTIMA trial) [15], mimicking usual practice of clinicians, particular in more severe forms of COPD, was non-industry sponsored. Years later, counting one and one together, two manufactures of inhaler drugs have finally completed their mathematics to conclude that the result of the addition is three: fixed triple combinations of LAMA/LABA/ICS have recently been approved for COPD in the EU. The publications of two recent large-scale studies [16, 17] now mark the apogee—for the

time being—of this endless exercise in combinatorics: the TRIBUTE and IMPACT trials compared the effects of fixed "triple" ICS/LABA/LAMA combinations against dual LABA/LAMA bronchodilation (and ICS/LABA, in IMPACT). The bottom line of the results from theses studies reported in high-ranked clinical journals was that "triple" provided a small, statistically significant benefit in the prevention of moderate to severe exacerbations in COPD subjects "at risk". In other words: it took 20 years of clinical research to re-confirm that GOLD 2001 already had it correct: ICS added to bronchodilators may improve exacerbation prevention in some patients. So what? Will these studies finally put an end to the discussion of inhaled combination strategies in COPD? When in fact the maths behind it haven't been rocket science from the start—step one a bronchodilator, two add another one, three add an ICS if exacerbations still occur? And the principal components of theses inhalers have been available for a quarter of a century? Will we finally move on from here? Doubts remain. In IMPACT, an approximate 50% increased pneumonia rate was confirmed with ICS containing treatment arms versus "pure" dual bronchodilation, casting additional doubt upon the safety of ICS in COPD. No comparable signal was observed in TRIBUTE. In TRIBUTE, however, the additional effect of triple was small versus dual LABA/LAMA, and effects were driven by subjects with higher blood eosinophil levels only, reinforcing the ongoing discussion about the usefulness of a simple blood eosinophil count to predict response to ICS in COPD. Surprisingly, IMPACT results were less indicative of an eosinophil effect, so no final conclusion may be reached at this time. But should these residual uncertainties occupy our minds for another 15 years to dwell on the question of "who needs ICS in COPD"? It may be. Meanwhile, severe COPD patients as mine of 2001 treated with "open" triple therapy for nearly 20 years are still waiting for therapeutic progress. When will we finally get over the arithmetics of ICS, LABA, LAMA and strive for real progress for those patients in desperate need? After all, COPD is a deadly disease in many. Once more, COPD may need to take a lesson from asthma research—there, identification of biological mechanisms has led to significant improvement of outcomes beyond inhaler combination therapy, at least in certain subgroups of subjects. Undoubtedly, the odds of success for targeted therapies in COPD are lower than in asthma. But the impact of any beneficial novel therapy beyond LABA/LAMA/ICS for patients will be even greater. The advent of fixed triple inhaler combinations must be the starting gun. Let's get moving, even if the task seems difficult. Speaking with Tennyson's words: for any achievement in COPD treatment beyond "triple", researchers, clinicians and industry need *to strive, to seek, to find—and not to yield!*

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