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CONTROVERSY ABOUT THE USE OF INHALED CORTICOSTEROIDS IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE(COPD): THE ESSENTIAL TO KNOW

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GOLD Definition of COPD 2018

- common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases.

- **In 2016 and before inflammation was included**

COPD, a common preventable and treatable disease, is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and Comorbidities contribute to the overall severity in individual patients.

As you see above, the word inflammation has been deleted from the definition in 2017, the aim was to reduce the use of ICS even in combination with long acting bronchodilators (LABA and/ or LAMA) as preventive daily treatment. That was because, follow up studies evidenced pneumonia caused by ICS in COPD patients, and withdrawal syndrome.

This was more pronounced when ICS was prescribed alone, and in this case mortality rate is higher.[1]

Burden and risk factors

COPD is one of the most common chronic lung diseases, 210 millions in the world suffer of COPD[2], and it is projected to be the 3rd cause of mortality in the world by 2020 if risk factors are not avoided.[3]

Environmental Risk factors are mainly active and passive smoking of cigarette or waterpipe, air-pollution, cooking or heating indoor with biomass fuel, workplace exposure. Small particles 2.5 micrometer play an oxidative role in terminal bronchi(small airways), small vessels and lung parenchyma, leading to pathogenetic changes and physiopathological features consistent with chronic airflow limitation: especially, chronic inflammation is mainly marked by the presence of macrophage and neutophils but unlike atopic asthma, rarely eosinophils. This chronic inflammation provoke an irreversible changes in small airways, which are progressively_narrowed, leading to air-trapping and dyspnea. Together with parenchymal destruction due to unbalance in protease-antiprotease. And to small vessels remodeling.[1]

Diagnosis of COPD

-Early diagnosis is the unique opportunity to limit progression of the disease, in case this leads to successful intervention for smoking cessation. For early diagnosis, and to improve COPD diagnosis ratio and overcome under-diagnosis, we should do spirometry when in exposed to risk factors there is chronic cough, sputum and dyspnea on exersion. If spirometry shows FEV1/FVC<70% after bronchodilators (BD), and far from exacerbation, it is COPD.

FEV1 % predicted define the severity of COPD, it could be normal in mild and less than 50% in moderate to severe.[1]

-COPD alter quality of life, causing daily symptoms especially progressive dyspnea, and exacerbations which could lead to hospitalization. life expectancy_decreases, and annual decline in FEV1 is higher compared to non smokers.[1,5]

Treatment

When we treat COPD patients, our aim ideally is to improve their quality of life, avoid exacerbations, reduce mortality rate and slow FEV1regression. Accordingly we should emphasize on that, the only treatment which could stop the progression of COPD is quitting smoking, while available pharmacologic therapies help to relieve symptoms and reduce exacerbations. But non benefit in mortality or very limited benefit on FEV1decline.[1,4,5]

If we consider pathogenetic features of COPD inflammation, we will see that ICS have not a key role in treatment because inflammatory cells are macrophage and neutrophils. While

eosinophils in asthma. Accordingly, BD will reduce symptoms and are the main treatment for COPD.[1]

When COPD is initiated, inflammation will persist even after stopping exposure to risk factor especially tobacco smoking, this is recently revealed to be attributed to lung microbiome alteration and the consequent immunologic modification.[6]

In order to initiate and evaluate COPD treatment, a stepwise approach is required by international guidelines, four groups were identified: According to severity of dyspnea as by the modified Medical Research Council Scale (mMRC) and number /severity of exacerbations the last year. A,B,C,D.[1]

Our Editorial will focus on why ICS are never used alone for COPD.[1,4,5] And why ICS combined to LABD are not routinely recommended or prescribed, but reserved to special phenotypes with eosinophyls and if Asthma COPD overlap, while adding ICS to Long Acting Broncho-Dilators (LABD) in severe and repeated exacerbation could be evaluated at individual level.[1,5]

As we said above A,B,C,D groups are based on symptoms and exacerbation risk. FEV1 is considered only when <50% in group D for.[1]

Treatment of stable COPD 2017-2018 is based on these 4 groups:

- **Group A:** When dyspnea is very mild, stage 1 mMRCS (dyspnea only when hurrying on the level, or walking up a slight hill), and non exacerbation, we utilize only Short Acting Bronchodilators (SABD) or Short Acting Muscarinic Antagonists (SAMA).
- **Group B,** Walks slower than people of the same age because of breathlessness or has to stop for breath when walking at own pace on the level (Step2 in mMRCs) or dyspnea for less than 100 meters walk (step3 mMRC), or At rest (step4mMMRC), but non history of exacerbation, in this step LA BD (LABA or LAMA or combination) is prescribed.
- **Group C:** Mild dyspnea like group A, but exhibit exacerbation history last year, in this group we can initiate therapy by LABA or LAMA, and escalate to LABA+LAMA if not improved, escalation to LABA+ICS is another but less efficient choice.

While ICS as add on therapy to BD has its place in the guidelines of GOLD[1], Use of ICS for COPD treatment in the medical literature is disputed

- Pierre Ernst et al.[4] In a state of the art article, reviewed Randomized clinical trials favoring the use of ICS or adding ICS to Long Acting $Beta_2$ Agonists (LABA) in COPD. From the data reviewed, they noticed that there is methodological limitation. They conclude that, in fact there is no survival benefit independent of the effect of LABA, or Long Acting Muscarinic antagonists(LAMA) and no effect on FEV1 decline, and that the possible benefit on reducing severe exacerbations is unclear. And they conclude that there are substantial adverse effects from the use of ICS in patients with COPD, most notably severe pneumonia resulting in hiking death rate. They recommend the use of LABA for COPD, and ICS avoidance?

- Davide Price et al in the IPCRG Recommend that LABA plus LAMA is more efficient on end points: Mortality, and exacerbations number or severity of symptoms Than LABA combined to ICS. Even adding ICS to LABA or LAMA in group B or C prove non additional benefit, Second we want to avoid pneumonia and other side effects like cataract or osteoporosis, Physicians should carefully weigh the likely benefits of ICS use against the potential risk of side-effects and costs in individual patients with COPD. ICS is never used alone in COPD.[5]

- In a recent survey, it was proved in persons with COPD that, ICS use is associated with an increased risk of Non Tuberculosis Mycobacteria-Pulmonary Diseases, but not tuberculosis. Accordingly, clinicians should consider this risk when prescribing ICSs to patients with COPD. and if they are needed like in asthma –COPD overlap, strive to use the lowest effective dose.[7]

However, the list of essential medications of WHO 2017(20th WHO Model List of Essential Medicines) includes for asthma and COPD: ICS, Combined Unisonide-Fromoterol, SABA & and SAMA, but non lABA and LAMA alone are included. This leads chest physicians and general practionners in health centers led by MOH-WHO to overprescribe Inhaled corticosteroids combined to formoterol or salmeterol in COPD groups B,C,D aiming at prescribing formoterol or salmeterol, which is the case in Syria. Even further general or internal physicians in the private give the cheaper ICS alone.

But If we consider the WHO 2012 recommendations, they stated that it is preferable, even in severe COPD (C,D for GOLD) to give repeated daily short acting BD when LABA and

LAMA are not available, rather than combined therapy of ICS+LABA, in order to avoid side effects of ICS.[8,9]

It is critical to underline that, highly priced LAMA and LABA are available for the private in many LMIC, and could be prescribed only for the middle and low income persons who benefit from health insurance.

More surprising is in USA, - In a national cross sectional observational surver 2013; In a cohort of COPD patients, Prescription of short-acting bronchodilators was most common (in 42.5%). A long-acting bronchodilator or inhaled corticosteroid was prescribed to 32.3% of included patients, ICS was prescribed alone in many cases.[10]

- In Latin America a national survey on Pulmonary specialized clinics, showed an overuse of ICSs in patients with COPD from this region: 65% in combination, and 4.3% only ICS. Guidelines exist but are neglected.[11]

In this regard, we should emphasize on the urgent need of not only producing guidelines for COPD management, which are available in USA, Latin America and many LMIC[2,6,7,11,12], but also emphasize on strengthening health system, multisectorial and before all academic involvement on updating MOH-WHO health programs. Academicians can also help for auditing and evaluation of the practice for COPD.[12]

CONCLUSION

210 million patients worldwide suffer from COPD. COPD is expected to be the third cause of mortality in 2020. Early diagnosis by spirometry(FEV1/FVC<70%) in symptomatic patients exposed to risk factor_could improve prognosis, especially if the patient quit smoking. Pharmaceutical therapy is aiming to reduce symptoms and exacerbations. All patients presenting with dyspnea stage 2 or more (mMRC), could benefit from treatment with LABD(LAMAand/or LABA). While prescribing ICS is not recommended, because it adds non extrabenefits on symptoms, FEV1 decline or mortality. For instance, it causes pneumonia and withdrawal symptoms.

Certain phenotypes could benefit from adding ICS to LABD: Patients with eosinophilia, Asthma –COPD overlap, and it is controversial for COPD patients with severe repeated exacerbations.

It should never be used alone for COPD patients.

WHO programs prefer short acting BD to combined therapy with ICS if LABD alone are not available. Academicians should be deeply involved in programming, as well as auditing and evaluation of COPD care at country level. Especially in developing countries.

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