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EDITORIAL



# Do the current guidelines for asthma pharmacotherapy encourage over-treatment?

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## 1. Introduction

Asthma is a common airway disease, affecting worldwide a percentage of people between 1% and 18%. Although the proper management of asthmatic patients should be ensured by following international documents or guidelines (GL), e.g. GINA (Global Initiative for Asthma), several evidences in literature show that they're not always fully applied in daily clinical practice, leading to a poor control of the disease. Furthermore, one of the first causes of poor symptoms control is adherence to therapy, drastically low in asthmatic patients than in other diseases. Secondarily, the choice of therapeutic scheme could be crucial for the control of the disease. With the evidence that patients in GINA steps 1 and 2 may be at risk of serious exacerbations, following the suggestion that an as need treatment with SABA alone could increase the risk of serious exacerbations, and that ICS use reduces that risk, in novel GINA guidelines the use of as-needed therapy with ICS+formoterol has been added to treatment suggestions.

## 2. The burden of adherence

One of the main problems in the management of asthmatic patients, regardless of the severity, type and therapeutic strategy chosen, is adherence to treatment. In fact, it is well known that adherence to prescribed therapies, in subjects suffering from asthma, is very low, resulting in one of the principal causes of poor control of the disease [1]. In order to overcome this problem, in addition to an essential health education aimed to raise awareness of the importance of therapy, some add-on devices have been studied and tested to monitor the frequency and the correct way in which patients take their drugs.

## 3. Mild-moderate asthma

Mild asthma is a well-controlled asthma with step 1 or step 2 treatment, including as-needed therapy, usually SABA, low-dose ICS, or antileukotrienes (LTRA) [1]. Some evidence assumed that the poor control of symptoms in mild asthma could be principally due to an inadequate treatment or a low compliance. Another healthy burden in patients with mild asthma is the frequency of exacerbations, reported as any change in lung function test or in symptoms from the patient's usual status [1].

### 3.1. Therapy in mild-moderate asthma

The first crucial step in the management of asthmatic patients is the choice of the better therapy or therapeutic plan. The most recent drafting of the GINA document, in the case of mild-moderate patients at steps 1 and 2, offers to the clinician the possibility to use different schemes, ranging from the use of an as-needed therapy to a fixed therapy [1]. One of the most significant changes, made in GINA 2019, is just in STEP 1 and 2, with the possibility to choose between the novel therapeutic strategy with a combination of inhaled corticosteroids/formoterol (ICS/Formoterol) or the already existing as-needed short-acting beta 2 agonist (SABA) or low ICS dose therapy according to patient's step. The need for change stems from the fact that patients of the first two GINA steps, despite the therapy, have frequent exacerbations and 30-40% of them requiring emergency management [2]. Despite this, until the last version, GINA suggested only SABA as an as-needed therapy with or without the additional chronic use of low-dose ICS controllers for these patients. As previously mentioned, in this group of patients, generally poorly symptomatic or asymptomatic, adherence to treatment, particularly ICS, is generally rather poor [1,3], resulting in an overuse of SABA, usually easily accessible in pharmacies also without a medical prescription (i.e. Italy, Spain, and UK for emergency access only) [3]. In addition, the subjective perception of a rapid improvement in symptoms, after SABA inhalation, can contribute to greater confidence in bronchodilator drugs [4]. Notwithstanding an unquestionable efficacy of SABA, the overuse has been associated to an increased risk of poor asthma control, exacerbations and in several cases also death [5], principally because patients usually can preferentially use the as need therapy rather than regular ICS or ICS/LABA, masking worsening symptoms [6]. Therefore, preferred controller treatment in GINA 2019, suggested at STEP 1, is the combination ICS/formoterol, prescribed also for as need strategy rather than SABA [1,4].

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The first study able to corroborate this choice was SYGMA 1, where 3836 Step 2 GINA patients have been enrolled [7]. The investigators found that the as-needed budesonide/formoterol (BUD/FM) combination was able to provide no less protection than the maintenance regimen with BUD, and both therapeutic approaches resulted to be better than the only as-needed terbutaline strategy [7]. The subsequent study called SYGMA 2, where 4176 asthmatic patients, once again belonging to the GINA Step 2, were treated with placebo twice daily plus BUD/FM (200/6 μg) on demand or with BUD twice daily plus SABA as needed for 52 weeks [3] demonstrated a non-inferiority of on-demand treatment compared to continuous BUD, in asthma exacerbations rate, although the on-demand formulation resulted worst in symptom control [3] (Table 1). In the most recent Novel START study, 668 patients with mild asthma were recruited in three different treatment arms: 1. SABA when needed; 2. BUD twice daily (BID) plus SABA when needed; or 3. BUD/FM, as needed, treating them for 52 weeks. The rate of disease relapse was found to be lower in patients treated with BUD/FM as needed, compared to those treated with SABA and were no different from patients treated with BUD BID. Despite this, maintenance treatment with BUD was found to be superior to BUD/FM on demand in terms of asthma symptoms [8] (Table 2). Finally, the variation in exacerbations frequency has been sought also in a PRACTICAL trial, where 885 mild asthmatic patients received BUD/FM as needed or BUD maintenance therapy, resulting in a higher reduction in exacerbations rate in BUD/FM arm (0.119 vs 0.172; relative rate 0.69, 95% CI 0.48–1.00; p = 0.049) [9]. In addition, a recent study analyzing the preferences of a cohort of patients enrolled in the Practical study showed that they preferred as-needed combination therapy to the maintenance BUD one, if they had experienced it [10]. Finally, new observations lead to the question of how much the steroid therapy can be modulated in patients depending on the degree of eosinophilic inflammation. A recent study published in NEJM, where 295 patients were treated with tiotropium, mometasone, or placebo, concludes that there was no substantial difference in response to the two drugs in subjects with low eosinophilia in sputum, laying the foundation for further studies to compare the effect of ICS with other treatments in subjects with low eosinophilia [11].

### 3.1.1. Long-term therapy with ICS, benefits

The steroids act by binding to a specific site at the intracytoplasmic receptor, which migrates to the nucleus and modulates specific targeted gene transcription. As these drugs directly affect the bronchial wall, several factors condition the severity of side-effects. These factors include the condition of the bronchial wall, the properties of the drug, the dosage regimen, and the acceptability of the drug by the patient. Various studies have been conducted to explore the risk–benefit ratio of ICS in asthma. The inhaled corticosteroids have been known to be effective in the control of the symptoms of asthma, bronchial inflammation, relapse of the disease and occurrence of the inflammation of the bronchus after discontinuation of the treatment. Furthermore, a report on asthma deaths published by the College of Physicians of the United Kingdom highlighted that among the most important risk factors which can lead to asthma death, is the abuse of β 2-agonists and the nonuse of ICS maintenance therapy [12].

### 3.1.2. Long-term therapy with ICS, side effects

As previously described, ICS are considered to be the most effective treatment for the management of persistent asthma due to their anti-inflammatory effect. Although administered by inhalation, several side effects have been reported in the chronic use of ICS, with a direct relationship between systemic exposure, and therefore dosage, and severity of effects. Controversial data exist on the possibility that ICS affect growth in children with mild-to-moderate asthma. Leonibus et al. [13] showed that ICS can act on pubertal growth by determining a reduced final height in children with asthma, with an effect proportional to the dosage taken by the patient. A further meta-analysis, about data of 16 trials, demonstrates that in ICS treated children there is a reduction of growth of 0.7% compared with not treated one [14]. The effect of ICS in adults is less evident, some cases of variation in urinary cortisol secretion are reported, while other articles do not report the same effect.

Table 1. Principal observations in SYGMA 1 and 2 study.

**SYGMA 1 [7]**

| | Group 1. Terbutaline as needed | Group 2. BUD/FM as needed | Group 3. BUD maintenance |
|---|---|---|---|
| Exacerbations rate | 0.20 | 0.07- | 0.09 |
| Comparison with Gr.2, ratio (95% CI) | 0.36 (0.27–0.49) | | 0.83 (0.59–1.16) |
| Symptoms control | − 0.17 | − 0.33 | − 0.48 |
| (ACQ-5) change from baseline (95% CI) | (- 0.21/-0.14) | (−0.36 to −0.29) | (−0.51 to −0.44) |
| CS need | 27.0% | 12.8% | 14.6% |
| Adherence | 79.0 ± 23.3% | 79.0 ± 23.3% | 78.9 ± 22.4% |
| Lung function test | 11.2 | 65.0 | 119.3 |
| (Change in FEV1 L vs baseline) | (−6.4 to 28.9) | (47.6 to 82.4) | (101.9 to 136.7) |

**SYGMA 2 [3]**

| | Group 1. BUD/FM as needed | Group 2. BUD maintenance |
|---|---|---|
| Exacerbations rate | 0.11 | 0.11 |
| Time to first exacerbation hazard ratio | 0.96; 95% CI, 0.78 to 1.17 | |
| Symptoms control (ACQ-5) change from baseline | − 0.35 | − 0.46 |
| difference | 0.11 (95% CI, 0.07 to 0.15) p < 0.001 | |
| CS need (mean/SD) (daily inhaled glucocorticoid metered dose [μg]) | 103.9 (109.6) | 251.1 (117.7) |
| Lung function (FEV1 change from baseline) | 104 ml | 136.6 ml |
| difference | −32.6 ml (95% CI, −53.7 to −11.4) p = 0.003 | |
| Adherence | 64.0 ± 30.0% | 62.8 ± 29.4% |

Table 2. Principal observation in Novel START and practical study.

| **NOVEL START Study [8]** | | | |
|---|---|---|---|
| | Group 1. Albuterol as needed | Group 2. BUD maintenance + SABA as needed | Group 3. BUD/FM as needed |
| Annualized Exacerbation Rate absolute rate, per patient, per year Comparison with Gr.3, relative rate, (95% CI) | 0.4000.49 (0.33–0.72) p < 0.001 | 0.1751.12 (0.70–1.79) p = 0.65 | 0.195- |
| Number of severe exacerbations Comparison with Gr.3, relative risk, (95% CI) | 230.40 (0.18–0.86) | 210.44 (0.20–0.96) | 9- |
| Number of patients withdrawn because of treatment failure Comparison with Gr.3, mean difference, (95% CI) | 370.33 (0.17–0.63) | 220.56 (0.28–1.13) | 12- |
| (ACQ-5) score difference across timepoints Comparison with Gr.3, mean difference, (95% CI) | − 0.15 (−0.24 to −0.06) | -+ 0.14 (0.05 to 0.23) | – |
| FEV1% (L) difference across timepoints Comparison with Gr.3, mean difference, (95% CI) | -0.03 L (−0.006 to 0.07) | -0.004 L (−0.03 to 0.04) | - |
| Geometric mean FeNO difference across time points Comparison with Gr.3, mean difference, (95% CI) | -0.83 (0.75–0.91) | -1.13 (1.02–1.25) | – |
| BUD mean dose (±SD),- µg, per day | NA | 222 ± 113 | 107 ± 109 |
| Overall mean adherence to twice-daily dose of BUD maintenance therapy | NA | 56% | NA |
| **PRACTICAL Study [9]** | | | |
| | Group 1. BUD/FM as needed | Group 2. BUD maintenance + terbutaline as needed | |
| Severe asthma exacerbations (absolute rate per patient per year) | 0.119 | 0.172 | |
| Gr.1 vs Gr.2, relative rate, (95% CI) | 0.69 (0.48–1.00) p = 0.049 | | |
| Time to 1st severe exacerbation Gr.1 vs Gr.2, hazard ratio, (95% CI) | 0.60; (0.40–0.91) p = 0.015 | | |
| Time to 1st severe or moderate exacerbation Gr.1 vs Gr.2, hazard ratio, (95% CI) | 0.59; (0.41–0.84) p = 0.004 | | |
| Severe/Moderate asthma exacerbations (absolute rate per patient per year) Gr.1 vs Gr.2, relative rate, (95% CI) | 0.165<br>0.70 (0.51–0.95) p = 0.024 | 0.237 | |
| Number of patients withdrawn because of treatment failure Gr.1 vs Gr.2, relative risk, (95% CI) | 9<br>0.84; (0.35–2.00) p = 0.69 | 11 | |
| ACQ-5 score difference across timepoints Gr.1 vs Gr.2, mean difference, (95% CI) | 0.06; (−0.005 to 0.12) p = 0.69 | | |
| FEV1% (L) difference across timepoints Gr.1 vs Gr.2, mean difference, (95% CI) | 0.006 L (−0.026 to 0.04) p = 0.69 | | |
| FeNO geometric mean difference across timepoints Gr.1 vs Gr.2, mean difference, (95% CI) | 1.13; (1.07–1.21) p < 0.001 | | |
| BUD mean dose Gr.1 vs Gr.2, daily inhaled budesonide metered mean dose [µg], (95% CI) | −126.5 µg per day, (- 171.0 to − 81.9) | | |
| Overall mean adherence to twice-daily dose of BUD maintenance therapy | NA | 76% | |

Other rare effects reported effects are impoverishment of bone density, skin thinning, and bruising [15].

## 4. Therapy in severe asthma

Severe asthma deserves a separate mention and, also in this case, the therapeutic approach is substantially changed. In GINA 2019 biological drugs are moved to first place in the case of a therapeutic add-on need, downgrading OCS to a second choice.

In this case, GINA 2019 looks at the side effects of medium-long term therapy with OCS, of which it is well known that chronic use can lead to serious comorbidities (i.e. diabetes, hypertension, osteoporosis) [16].

Biological drugs have also proven to be widely effective in symptom control both in trials and in real life, in most patients, and have a good safety profile, proving to be a valid substitute for OCS in most cases.

## 5. Conclusion

In conclusion, the GINA 2019 document opens up to a greater therapeutic choice in the first two steps, with the indication of ICS/formoterol as the first choice therapy and as-needed therapy in the first two Steps. In addition, in patients with severe asthma, biological drugs have been indicated as the first therapeutic choice, proving to be effective in many forms of this disease, in order to reduce the use of systemic corticosteroids and their side effects.

## 6. Expert opinion

The therapeutic approach suggested by GINA 2019 provides clinicians with an important opportunity in patient management. By using the ICS/formoterol combination on demand, compared to SABA alone, the intake of ICS is inevitably increased, but with a limited risk of side effects, as described in the dedicated paragraph, in favor of greater symptom control, as demonstrated by the studies described in the text, therefore, this approach seems to be more effective than SABA.

In GINA recommendation one of the crucial points is the problem of the adherence, which is dramatically low in asthma patients. Regardless of the type of therapeutic approach and the molecules chosen by the clinicians, in the management of asthmatic patients, the problem linked to the fact that very often therapies are not taken, thus greatly increasing the risk of exacerbations, must also be taken into

account. It is, therefore, necessary, during periodic visits, to check the patient's ability to take the drug and the real adherence to the prescribed therapy. To overcome this problem, improve and monitor adherence to the therapy, the use of devices to be connected to the devices should be implemented, able to monitor the doses taken by the patients and the quality of inhalation maneuvers, already in study and in use in some protocols.

Another time, with the goal to reduce the burden of the poor adherence of patients to a low ICS dose therapy, GINA 2019 purpose the possibility of replacing low dosage ICS with ICS/FM as needed. In this case, in the trials mentioned in the text, we have seen how sometimes a similar effectiveness and sometimes a better result is demonstrated in the use of the ICS/FM combination rather than BUD maintenance alone. Despite this, we believe that the choice of one therapy rather than another should be carefully evaluated on a case-by-case basis and choosing the most appropriate molecules also based on the clinical-biological characteristics of the patients (i.e. eosinophilia). In any case, further studies would be necessary.

The last important changes, dedicated to step 5, respond to the need to reduce the use of OCS in asthmatic subjects. The important well-known side effects related to the chronic use of corticosteroids (i.e. cataract, osteoporosis, diabetes, hypertension, increased susceptibility to infections) are a serious burden both from a clinical and economic point of view and therefore must be reduced. The data, coming from both clinical trials and real life, regarding the effects of monoclonal antibodies are extremely positive and consequently, we believe it's important, in these patients, to research biological and clinical parameters in order to use more and more biological drugs instead of OCS.

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