Asthma – Inhaled Corticosteroids (ICS): different molecules - different devices – different treatment concepts: what really makes a difference?

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ABSTRACT

Bronchial asthma is a chronic, heterogeneous disease with different clinical phenotypes and inflammatory endotypes. Anti-inflammatory treatment with inhaled corticosteroids (ICS) has revolutionized the therapy of asthma and is indicated in almost all patients across all degrees of severity and therapy stages. Nevertheless, there is a broad spectrum of ICS molecules, dosages, combination partners, application concepts (maintenance therapy and/or as-needed therapy), and devices. Thus, there is a large number of variables, whose clinical significance is often unclear. This overview will therefore present clinically relevant aspects in the use of ICS and their combination partners.

Keywords: Bronchial asthma, inhaled corticosteroids, MART-treatment, AIR-treatment

INTRODUCTION

Over the last decades, the understanding of the pathomechanisms of bronchial asthma, as well as the treatment options have improved substantially. Nevertheless, there is still no cure, and a tremendous burden of the disease for the individual patients and for the society remains. Therefore, novel therapeutic approaches and optimization of existing treatments are urgently needed. GINA (Global Initiative for Asthma; www.ginasthma.org) defines asthma as a heterogeneous disease, usually characterized by chronic airway inflammation and by a history of respiratory symptoms, such as wheeze, shortness of breath, chest tightness and cough, that vary over time and in intensity, together with variable airflow limitation.

Development of the treatment of bronchial asthma

Formerly, the concepts of asthma focused on bronchoconstriction, and this disease was considered as purely psychosomatic. In the middle of the former century, the concept of chronic inflammation prevailed. Accordingly, around this time, systemic corticosteroids (SCS) were introduced in the treatment of asthma, but at the same time, inhaled beta-2 agonists (BA) were widely used for symptomatic relief of the disease. Soon, it was recognized, that the use of SCS was accompanied by relevant side effects. On the other hand, overuse and monotherapy with BA were associated with increased mortality[1]. Furthermore, at that time, systemically acting sympathomimetics such as oral ephedrine or intravenous adrenaline, anticholinergics such as inhaled scopolamine and methylxanthines such as caffeine or theophylline were used to treat bronchial asthma[2-7]. These therapies mainly focused on symptom relief and not yet on a suppression of the pathomechanisms of asthma, which were largely unknown at the time. Therefore, these medications had no long-term therapeutic benefit. This situation changed when, around 1970, the first inhaled corticosteroid (ICS), beclomethasone, was developed, initially applied alone and later in combination with inhaled beta-2 agonists[8].

With a better understanding of chronic inflammation in asthma pathogenesis, anti-inflammatory treatment with ICS became the cornerstone in asthma therapy. Therefore, anti-asthmatic drugs have been divided into controllers and relievers, conceptualized on control of the underlying inflammation and symptomatic relief of bronchial obstruction[7]. Controllers include different ICS, which have revolutionized asthma therapy and still display the basis of anti-inflammatory treatment. They are used either alone or preferably in combination with long-acting beta-2 agonists (LABA). The controllers also include the leukotriene receptor antagonists (LTRA), which, however, are less effective as compared to ICS in the vast majority of patients. Therefore, because of relevant side effects, they fade into the background of asthma therapy[9,10].

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With a better understanding of the inflammatory mechanisms of asthma, and especially the relevance of type 2 inflammation, monoclonal antibodies against IgE or relevant type-2-cytokines have been developed in the last two decades for patients with severe asthma[11]. These so-called biologicals target specific inflammatory pathways and are used in patients who are still uncontrolled despite treatment with high-dose ICS and a second controller medication. Current guidelines strongly recommend the use of biologics before the repeated or continuous application of SCS. With the development of biologicals, complete disease remission has become a realistic therapeutic goal in many patients with severe asthma[12]. Asthma remission is accomplished when, in a one year, there is a permanent absence of asthma symptoms and exacerbations as well as stable lung function without necessitating therapy with systemic corticosteroids[7]. Biologicals proved very effective in common comorbidities associated with asthma, such as chronic rhinosinusitis with nasal polyps or atopic dermatitis[13]. Furthermore, in patients with a relevant IgE-mediated allergy, allergen immunotherapy (AIT) provides an additional therapeutic option in suitable patients, which is recommended in current guidelines[7,14].

These recent developments open up the possibility of an individually tailored treatment. Nevertheless, ICS in varying doses remains the basis of asthma therapy in almost all patients with varying degrees of severity and for different therapy stages[15]. Given the extensive diversity of ICS molecules, encompassing varying dosages, distinct combination partners, divergent therapeutic regimens (including maintenance and/or as-needed therapy), and a multitude of delivery devices, there exists a substantial array of variables. The clinical implications of these variables, however, remain frequently indeterminate. This overview attempts to present clinically relevant aspects in the use of ICS and their combination partners.

ICS and beta-2 sympathomimetics

Already in the early 2000s, it was shown, that even low doses of ICS significantly reduce mortality in bronchial asthma[16]. In contrast, it has been observed that monotherapy and/or overdosage of inhaled short-acting beta-2-agonists (SABA) are associated with an increased risk of exacerbations and increased mortality[17,18]. Later on, this was also found for monotherapy with long-acting beta-2 agonists (LABA)[19].

After the launch of the first LABA/ICS combinations in the mid-1980s, many studies compared the efficacy and safety of these combinations with ICS or LABA-monotherapies. One landmark study, the FACET study, demonstrated that a combination of low-dose budesonide with formoterol (LABA/ICS) was superior to a higher ICS dose in terms of lung function, but a higher dose of ICS was more effective in the prevention of exacerbations[20]. Later on, the GOAL study showed in more than 3400 patients with mild to moderate asthma, that a relevant proportion of patients did not achieve complete disease control despite combination therapy with salmeterol (LABA) and fluticasone (ICS) in maximal dosage[21]. This affirmed the need for additional effective treatment options and/or concepts and led, among others, to the development of the "single inhaler maintenance and reliever therapy ([S]MART)" concept[22]. This concept refers also as (S)MART ("maintenance and reliever therapy"), as the "S" in SMART originally stood for the trade name of the first formoterol/budesonide fixed combination, which was used in the initial large studies. After these results were confirmed with another ICS, the "S" now stood for "single inhaler". In everyday practice, SMART and MART are used synonymously.

The "single inhaler maintenance and reliever therapy" ([S]MART)

This treatment concept involves continuous therapy ("maintenance") with regular, twice daily application of a fixed ICS/formoterol combination in one device and an additional as-needed inhalation ("reliever") of the same ICS/formoterol fixed combination[23]. Of the LABAs, only formoterol is suitable for this application, as it has both a long duration and a rapid onset of action - a so-called rapid and long-acting beta-2 agonist (RABA)[24]. The efficacy of (S)MART therapy is based on the fact that bronchial inflammation increases a few days before a clinical worsening and an early increase in anti-inflammatory ICS therapy can prevent or at least mitigate this worsening[25]. (S) MART thus adapts the anti-inflammatory effects of ICS therapy to the course of the disease and the intensity of bronchial inflammation. The superiority of (S)MART over conventional rigid treatment regimens has been demonstrated in several large studies. A relevant reduction in both the total number and severity of exacerbations was demonstrated[26].

(S)MART, originally developed for patients with moderate to severe asthma in GINA treatment steps 3-5,[27] is further recommended in patients with asthma in national and international guidelines, as there is overwhelming evidence of the benefits[28].

Anti-inflammatory reliever therapy (AIR)

For many years, as-needed SABA inhalation, e.g., albuterol, was standard of care in mild asthmatics (GINA Step I) and continuous treatment with low-dose ICS plus SABA as needed in GINA Step II[29]. This harbours the risk of SABA overuse with consecutively increased mortality. Therefore, the use of fixed ICS/formoterol and ICS/albuterol combinations on an as-needed basis without continuous background therapy has been investigated in patients with mild asthma. This conceptualized the development of AIR ("anti-inflammatory reliever") therapy[30]. Again, it is necessary to use formoterol as a LABA because of its rapid and long action. Alternatively, a fixed SABA/ICS-combination (albuterol/beclomethasone) in a single inhaler showed beneficial results, though this combination is not approved in many countries[31].

Several large studies demonstrated the superiority of AIR therapy in all relevant endpoints over both as-needed SABA

monotherapy in GINA-step I and regular low-dose ICS plus as-needed SABA in GINA-step II[32-34]. Therefore, AIR therapy is strongly recommended in national and international guidelines for these patients[35-37].

The positioning of the two concepts (AIR and (S)MART) in the current stepwise regimen of asthma therapy for adults according to GINA is shown in Fig. 1. Depending on the severity and the course of the disease, switching between the two modalities, in terms of an escalation or de-escalation of treatment intensity may be indicated (Fig. 2).

Although the ICS/LABA combination therapy is now established as the standard for the overwhelming majority of patients, further questions arise:

Is (S)MART appropriate for every asthma patient?

After adequate information about the advantages of this treatment concept, it will be possible to treat the majority of patients accordingly. However, it remains an individual decision which must be discussed with patients in the sense of "shared decision making". If patients have attained optimal disease control with an alternative treatment regimen that aligns with established clinical guidelines, there is no imperative to modify their therapeutic approach. Conversely, some patients exhibit a preference for a stringent treatment protocol, while others possess a subjective inclination to rely on an additional inhaler, typically a SABA, for emergent use. This reliance often provides a supplementary sense of security.

Is every ICS/LABA combination suitable for (S)MART?

As already mentioned, (S)MART requires a beta agonist with a rapid onset of action and long-lasting efficacy, which until now has been demonstrated only with formoterol[24]. Thus, formoterol is explicitly mentioned in the GINA treatment algorithm as the LABA for as-needed application in fixed combination with an ICS (Fig. 1). In regard to the ICS combination partner, most (S)MART studies used budesonide, although beclomethasone exhibited similar effectiveness.[38]

Is it possible to combine ICS/formoterol a reliever with an alternative ICS/LABA as maintenance therapy in (S)MART?

For patients who use a maintenance therapy with another ICS/LABA combination other than ICS/formoterol, the use of ICS/formoterol as a reliever is not recommended, as there is no evidence of effectiveness and safety of such a mixture, and a risk of confusion and treatment errors by the patients cannot be ruled out. Therefore, we recommend using the same fixed ICS/formoterol combination in the same device for the (S)MART treatment.

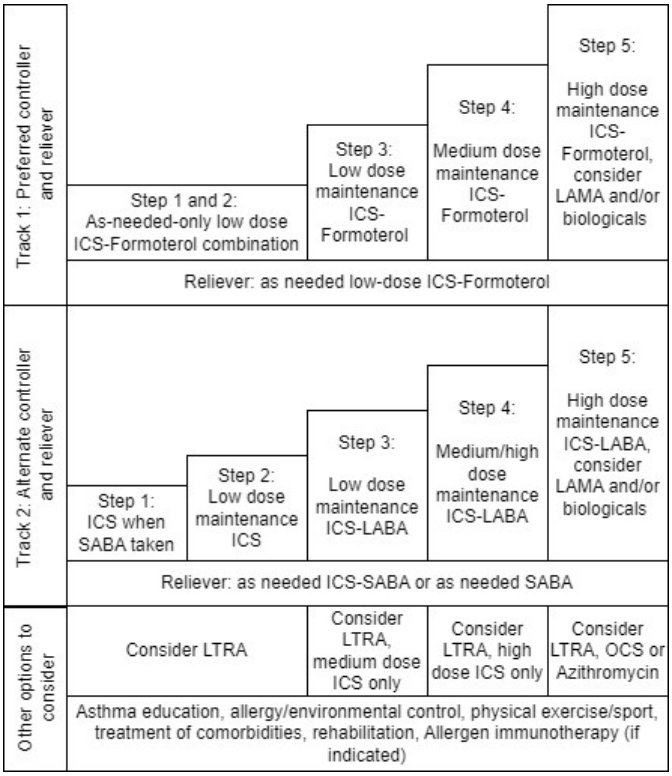

Figure. 1: Asthma therapy step-by-step scheme for adults (modified after GINA 2024; ICS: inhaled corticosteroids, SABA: short-acting-beta-agonists, LABA: long-acting-beta-agonists, LAMA: long-acting-muscarinic-antagonists, OCS: oral corticosteroids, Biologicals include anti-IgE, anti-IL-5(R), anti-IL-4/13, anti-TSLP)

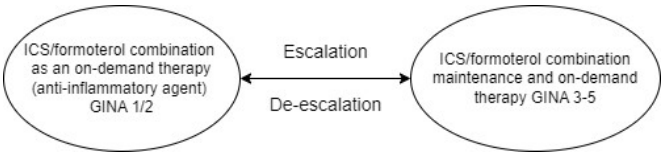

Figure. 2: Escalation (AIR→(S)MART) and de-escalation ((S) MART→AIR) of the combination of ICS/formoterol depending on the course of the disease (modified after Lipworth B et al. 2020; ICS: inhaled corticosteroids)[30]

Can (S)MART therapy be de-escalated?

Upon achieving sustained disease control, usually after six to twelve months, a stepwise de-escalation of therapy is necessary[39], concerning the ICS dosage[40]. Evidence suggests that this approach is safe, nevertheless every dose reduction carries the risk of loss of asthma control, which is also applicable when (S)MART is de-escalated to AIR treatment in some patients with mild asthma[41]. In patients with a high seasonal variability of the disease, these variable therapy regimens offer the possibility of adapting the intensity of therapy to the course of the disease.

Is (S)MART therapy suitable for patients with severe asthma and biologic therapy?

The relevant studies on (S)MART therapy were conducted before the introduction of biologicals. However, there is no plausible reason to withhold the benefits of this treatment, which is adapted to the course of the disease, from these patients. Furthermore, clinical experience supports that patients on biological therapy also benefit from (S)MART. Accordingly, it is also recommended in the current guidelines.

Should ICS or (S)MART therapy be de-escalated after the initiation of biologic therapy?

One question that often arises in the clinic is whether ICS or (S)MART therapy can be reduced after the initiation of biologicals. Most national and international guidelines recommend the use of biologicals when there is insufficient asthma control in patients treated with high (or maximum) ICS dose plus LABA. The recently published SHAMAL study showed that ICS can be reduced without increased risk for exacerbations in patients, who are well controlled with the anti-interleukin-5-receptor (IL-5R) antibody Benralizumab[42]. However, there is no general recommendation yet to reduce ICS under biologicals.

Are AIR and (S)MART suitable for children and adolescents?

According to the evidence and the approvals, children and adolescents from 12 years of age and from GINA treatment step 3 can be treated with a fixed combination of ICS + formoterol as (S)MART treatment. Also, mild asthmatics (GINA steps 1 and 2) from this age can use a fixed combination of low-dose ICS + formoterol on an as-needed basis (AIR concept) in accordance with current guidelines[43].

Different ICS - are they all the same?

There are several different ICS molecules available, such as budesonide, beclomethasone, ciclesonide, flunisolide, fluticasone, mometasone, and triamcinolone. They differ in terms of pharmacokinetics, e. g. receptor affinity and protein binding, which constitutes for different potencies. Physical differences, such as particle size influencing bronchial deposition, also play a role in the efficacy of ICS. Thus, there is a close correlation between receptor affinity and therapeutic efficacy[44,45]. Table 1 shows the differences in protein binding. With regard to pharmacodynamics, the intracellular signalling pathways and ultimately the mechanisms of anti-inflammatory efficacy, all ICS are comparable.

Table 1: Protein binding of inhaled corticosteroids[44]

Corticosteroid	Protein binding (%)
Beclomethasone	87
Budesonide	88
Ciclesonide	99
Flunisolide	80
Fluticasone	90
Mometasone	98
Triamcinolone	71

ICS: dose dependence of effects and side effects

Regarding the therapeutically desirable positive effects, such as improvement in asthma control, improvement in lung function, reduction of the number of exacerbations, and reduction in bronchial hyperreactivity, the dose-response relationships are not linear. High efficacy is often achieved at very low doses, with incremental benefits diminishing as dosage increases, eventually reaching a plateau at higher dosages. For example, a study by Beasley et al. showed that 80 % of the benefit achieved at 1000 µg/d was already achieved at a dose of 70-180 µg/d and 90 % at a dose of 100-250 µg/d, so that a further increase of the ICS dosage did not have any relevant advantages[46].

On the other hand, even inhaled and therefore local ICS therapy has systemic effects and therefore can cause side effects. It has been shown that, measured in terms of the incidence of adrenal insufficiency, a daily dose of 1000 µg ICS corresponds to a dose of 2-5 mg oral prednisone. Side effects include diabetes mellitus, the development of cataracts, an increase in osteoporosis and fractures, as well as a slight reduction in the growth of children[47]. For these adverse systemic ICS effects, the dose-response relationships are characterized by a higher degree of linearity, than the local bronchial effects. It is therefore important to determine the lowest effective ICS dose for each patient. It has proven useful to consider the low, medium, high, and maximum doses for the different ICS (Table 2).

In addition to the undesirable systemic effects, ICS can also cause local side effects - above all hoarseness due to a reversible myopathy of the vocal cords and oropharyngeal candidiasis[48]. If dose reduction and mouthwashes are not sufficiently effective in this situation, it may be useful to choose a medication such as Ciclesonide, which is a prodrug and is activated by esterase's directly on the bronchial mucosa.

Table 2: ICS dose ranges in adults[36].

ICS	Low dose (µg)	Middle dose (µg)	High dose (µg)	Maximum dose (µg)
Beclometasone dipropionate: standard particle size	200-500	> 500-1000	> 1000	2000
Beclometasone dipropionate: Fine particle size	100-200	> 200-400	> 400	800
Budesonid	200-400	> 400-800	> 800	1600
Ciclesonid	80	160	320	640
Fluticasonfuroat	100	100	200	200
Fluticasonpropionat	100-250	> 250-500	> 500	1000
Mometasonfuroat (Twisthaler)	200	400	> 400	800
Mometasonfuroat (Breezhaler)	80	160	320	320

Methods of inhaled application of ICS

Furthermore, the type of administration and the correctness of the application by the patients are relevant, sometimes crucial, as critical errors of inhalation technique are quite frequent. Currently, there are three methods for the topical bronchopulmonary administration of ICS: Metered-dose inhalers (MDI), dry powder inhalers (DPI) and nebulizers.[49]

In MDIs, the medication is either dissolved or suspended in a liquefied, pressurized propellant. When the MDI is triggered, a defined quantity of the propellant is converted into an aerosol that exits the opening at high speed[50]. With MDIs, the patient must coordinate a deep inspiration with the triggering of the MDI, which is difficult for some patients. Errors during application can significantly affect the applied ICS dose. In the case of MDI the use of spacers is recommended, especially in children or elderly patients, which can both improve the effective inhaled ICS dose and minimize local side effects[51]. With dry powder inhalators (DPI) the release and distribution of the drug are triggered by the patient's inhalation and the medication is transported by the inhaled air deeply into the lungs. In DPI no synchronization is required between inhalation and actuation of the[52]. Nevertheless, inhalation errors may occur with all devices.

For the vast majority of patient's sufficient therapy is possible with MDI or DPI. When used correctly, the effectiveness is similar. However, a combination of MDI and DPI in the same patient should be avoided, as they require different breathing manoeuvres, which can cause difficulties for some patients.

Nebulizers convert a liquid solution or suspension into an aerosol by using either a jet of compressed air or ultrasonic energy[53]. The aerosol is then delivered to the patient via a mouthpiece. Face masks should be avoided because of the high nasal and cutaneous and comparatively low bronchial deposition. They are only of some value in younger children. Nebulizers need low requirements on the inhalation technique of the patients. Therefore, they are preferably prescribed to patients who can use neither a MDI nor a DPI, e.g. geriatric patients.

SUMMARY:

Asthma management has undergone significant advancements over the years. ICS therapy has fundamentally revolutionized the management of asthma, particularly in patients with moderate to severe forms of the disease. The integration of ICS with LABA in Maintenance and Reliever Therapy ((S)MART) has become a standard approach. Emerging evidence suggests that this combination may offer therapeutic advantages even in the early stages of asthma as part of an anti-inflammatory reliever strategy. Specifically, the combination of ICS and formoterol is gaining increasing recognition globally as an effective treatment option for mild asthma.

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