Challenges of Systemic Glucocorticoids Taper in the Treatment of Severe Asthma

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Abstract

Asthma is a chronic airway inflammatory disease, characterized by reversible airway obstruction and airway hyperresponsiveness. It affects 1-18% of population in different countries and approximately 5–10% of the overall asthma population has severe asthma. Systemic glucocorticoids still represent a significant burden due to treatment of asthma exacerbations and severe forms of asthma. Monoclonal antibodies are powerful anti-inflammatory agents with glucocorticoid-sparing properties. With the increasing use of biologics, tapering and cessation of maintenance systemic glucocorticoids have become much more common. Personalized approach to tapering and careful assessment for adrenal insufficiency in all patients are recommended by the experts.

Keywords: severe asthma, glucocorticoids, side effects, adrenal insufficiency

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Introduction

Asthma is a chronic airway inflammatory disease, characterized by reversible airway obstruction and airway hyperresponsiveness[1]. It affects 1-18% of population in different countries[2]. Approximately 5–10% of the patients have severe asthma[3], which remains uncontrolled despite adherence to maximal optimized therapy and treatment of contributory factors and comorbidities[2].

Systemic glucocorticoids (GC) became available in 1956 and they have provided effective treatment of asthma ever since[4]. Their widespread use led to the recognition that long-term systemic GC use is associated with significant adverse events[5] and to introduction of inhaled GC in 1972 as maintenance treatment for asthma[4]. However, there is still a significant burden of systemic GC due to treatment of asthma exacerbations and of severe asthma[4,6].

The many systemic effects associated with long-term systemic GC use have been well studied and described[7]. The most common serious systemic GC-associated comorbidities include osteoporotic fractures, diabetes, obesity, cardiovascular disorders, and hypothalamic-pituitary-adrenal (HPA) axis suppression. In addition, use of systemic GC has been associated with psychiatric symptoms such as insomnia, mania, depression, anxiety, or aggressive behavior. Dyspepsia, hypertension, dyslipidemia, opportunistic infections, muscle atrophy, cataracts, glaucoma, bruising, cushingoid appearance, skin striae and change in appetite can also occur[5,8,9]. Moreover, there is published evidence suggesting that even brief (3–7 days), but repetitive courses of systemic GC can provoke

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significant negative outcomes for patients, such as bone density loss, hypertension, gastrointestinal bleeding, and have negative impact on mental health[7].

Evidence from European Registries

The European Respiratory Society (ERS) Severe Heterogeneous Asthma Research collaboration (SHARP) was set up in 2018 to harmonize severe asthma management across Europe and to unravel underlying heterogeneity in a patient-centered way[10]. The current project involves the first structured assessment and comparison of national severe asthma registries that are part of SHARP to discover strengths/weaknesses in those registries and to evaluate severe asthma and its treatment across Europe.

Across-sectional retrospective analysis of aggregated patients' characteristics and their treatments before starting biologicals from 11 national SHARP affiliated severe asthma registries showed that patients were treated differently between countries. Their mean inhaled GC daily dose (fluticasone equivalent) ranged from 700 µg in Slovenia to 1335 µg in Poland when starting anti-interleukin (IL)-5 antibody and from 772 µg in Slovenia to 1344 µg in Spain in those starting anti-IgE, respectively. Maintenance oral GC use ranged from 21.0% (Belgium) to 63.0% (Sweden) and from 9.1% (Denmark) to 56.1% (the UK) in patients starting anti-IL-5 and anti-IgE, respectively[11]. The reasons for these differences are not entirely clear. Potential explanations, which would require a focused study by the SHARP clinical research collaboration, might include the cost of treatment and the fear of high-dose treatment-related side-effects[11].

Indeed, a recent systematic review and meta-analysis has suggested that the majority of oral GC-sparing effect of high-dose inhaled GC was likely to be due to their systemic effects[12]. Regarding the effects on HPA axis, 1000 µg of fluticasone propionate might have similar systemic effects to 5 mg of prednisone[13], which might be also true for 2500 µg of budesonide[14]. Therefore, high doses of inhaled GC should potentially be considered as harmful as low doses of systemic GC[15] and their effects are accumulative on top of systemic GC[7].

Approaches to Systemic GC Taper After Introduction of Monoclonal Antibodies

Monoclonal antibodies are powerful anti-inflammatory agents with GC-sparing properties[16-19]. Their availability represents a cornerstone for systemic GC taper and withdrawal in severe asthma, which is becoming a common scenario in clinical practice with the increasing use of biologics. However, a specific guidance on how to proceed is lacking[20].

Accordingly, over 130 international experts employed a modified Delphi method to develop a consensus statement on appropriate systemic GC use and tapering in patients with asthma, adverse effects, patient–physician shared decision-making, and future research domains[21]. The paper provided a broader guidance on when and how to taper systemic GC in patients with asthma, regardless of whether biological therapy has been initiated. According to consensus, tapering should be individualized and attempted in all patients with asthma receiving maintenance systemic GC therapy, regardless of comorbidities. The recommendations generated support for minimizing systemic GC use as much as possible. Global Initiative for Asthma (GINA) recommendations restrict systemic GC use to those patients who are ineligible for biologic treatment and define the lowest acceptable systemic GC maintenance daily dose at less than 7.5 mg of prednisolone[2]. On the other hand, the Delphi expert consensus considered a daily dose of less than 5 mg of prednisolone as acceptable, if no alternative treatment is available[21]. However, even merely 5 mg of prednisolone a day contributes to a cumulative dose of more than 1.8 g per year. Additional

awareness is therefore needed, if we consider the evidence that a lifetime cumulative systemic GC load of 0.5-1 g was associated with diabetes, while most other adverse effects emerged at 1 to less than 2.5 g[5].

Therefore, a routine screening using a minimal checklist for adverse effects and comorbidities is recommended in all patients with asthma on systemic GC treatment (Table 1).

Table 1. Minimal checklist for glucocorticoid adverse effects screening[21]

Glycemic control
Bone mineral density
Blood pressure
Cataracts and glaucoma
Weight change
Fracture risk assessment (e.g., FRAX)

Definition of abbreviation: FRAX=Fracture Risk Assessment Tool.

According to the expert consensus systemic GC tapering should be initiated only when it is considered appropriate for the clinical situation and asthma phenotype.

Three common baseline clinical scenarios were provided[21]:

1. *Do not attempt tapering* in EGPA (eosinophilic granulomatosis with polyangiitis) and ABPA (allergic bronchopulmonary aspergillosis) that relapses during tapering and no other changes can be proposed.
2. *Tapering with caution* in cases with:
   - history of life-threatening attacks,
   - systemic GC dependence for extended period (e.g., more than 6 months),
   - in patients with comorbidities that respond to systemic GC.
3. *Tapering should be done if:*
   - systemic GC result in no asthma improvement and/or side effects,
   - dose or duration of systemic GC treatment is cause for concern,
   - asthma control is achieved (especially with biologics),
   - there is a reasonable likelihood of HPA axis recovery.

Table 2. Consensus information on systemic GC tapering and suggested tapering speeds according to current systemic GC (methylprednisolone) dose[21]

Daily dose ≥ 16 mg	Daily dose 8-16 mg	Daily dose 4-8 mg
Faster pace	Medium pace	Slower pace
Reduce by 8 mg/ week or 30-50 % every 2-4-weeks	Reduce 2-4 mg every 1-2 weeks	Reduce by 1-2 mg every 1-2 weeks

During systemic GC tapering patients should be continuously evaluated for adrenal insufficiency (AI), comorbidities, and asthma symptoms. If GC taper is intolerable, tapering attempts should be stopped and postponed to a later date. Return to previous efficacious dose is also recommended. When symptoms are mild, current GC dose should be maintained and tapering speed should be reduced.

Proceeding toward GC cessation is suggested when:

- daily systemic GC dose is ≤ 4 mg of methylprednisolone,
- a sparing strategy has been initiated,
- the patient has agreed to cessation,
- there is no evidence of EGPA/ABPA,
- there is no evidence of adrenal insufficiency.

AI is very common among users of systemic GC after tapering[22] and experts[21] agreed that this condition is insufficiently assessed or underrecognized. Risk factors for development of GC-induced AI include the duration of GC therapy, mode of administration (e.g., oral vs. inhaled), GC dose and potency, concomitant drugs that interfere with GC metabolism, and individual susceptibility. Importantly, the risk of developing GC-induced AI is difficult to predict on an individual basis

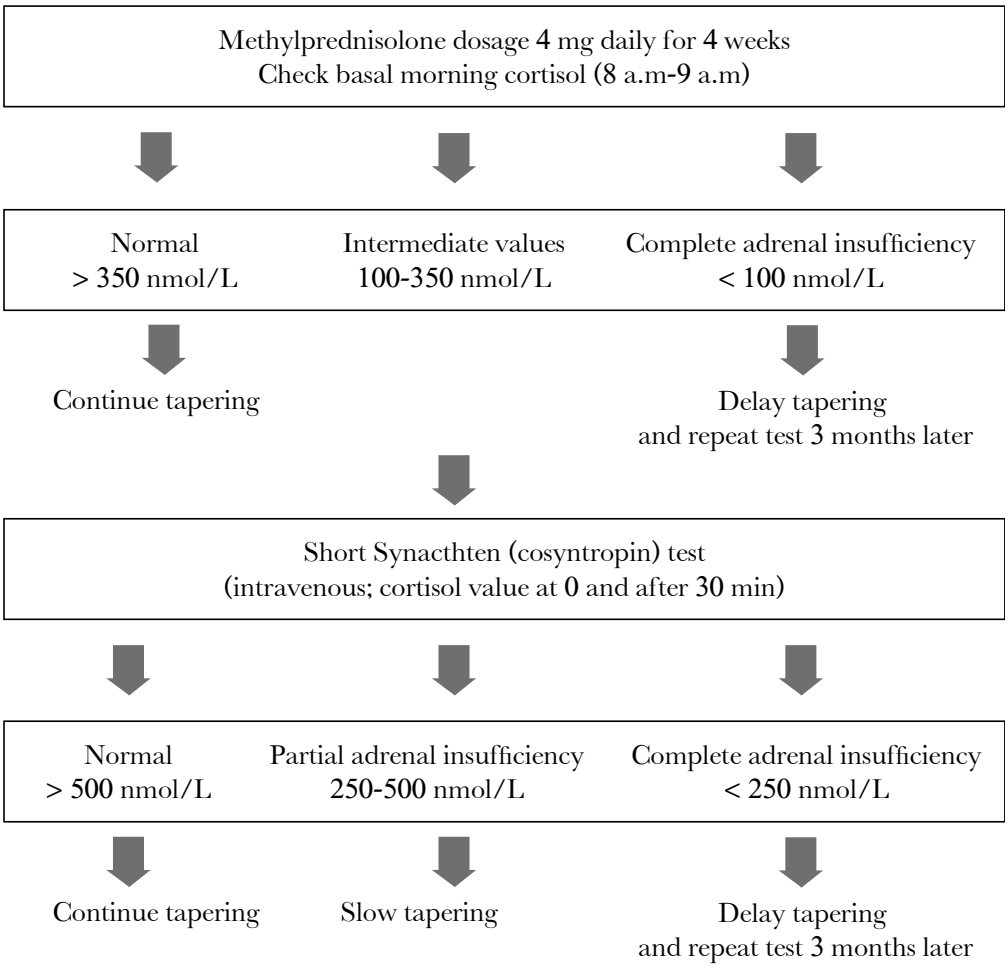

Figure 1. Recommended evaluation for adrenal insufficiency in severe asthma patients, previously treated with systemic GC (adapted from Menzies-Gow et al., 2021)

and low threshold for HPA axis evaluation is advised if clinical suspicion of AI exists. Use of basal morning cortisol is generally recommended for this purpose with short Synacthen (cosyntropin) testing to follow in the case of intermediate results[23].

Successful systemic GC dose reduction in patients with severe asthma after initiation of biological therapies, using preset tapering protocols, has been recently demonstrated. Specifically, the PONENTE study[24] has successfully authenticated a personalized systemic GC reduction algorithm with incorporated HPA axis integrity assessment . The investigators recommended evaluation for AI after patients had been receiving 5 mg of prednisolone (equivalent to 4 mg of methylprednisolone) daily for 4 weeks, as shown in Figure 1.

Clinicians should be aware that such protocols can serve as a guide only and that real-life management should be tailored on an individual basis. Moreover, cut-offs vary

according to the cortisol assay used and local practices. For example, basal morning cortisol that excluded AI varied between 336 and 506 nmol/L when measured by three different immunoassays. Therefore, the cut-offs proposed here should be seen as a direction only. Additionally, patients should be tested at least 24 h after the last dose of exogenous GC, because (methyl) prednisolone can interfere with immunoassays and cause falsely elevated cortisol values. To completely exclude this possibility, patients could be also switched to a replacement dose of hydrocortisone, a short-acting GC, before testing serum cortisol[23].

In the case of AI, the switch to hydrocortisone replacement therapy was generally preferred by the experts to continued prednisolone, but the consensus was not reached[25,21]. Theoretically, its shorter half-life might accelerate the recovery of HPA axis by negative feedback, especially when avoiding late afternoon exposure to hydrocortisone[23]. Switch to hydrocortisone is also recommended from practical reasons, for instance when low-strength GC tablets, such as (methyl) prednisolone 1 mg tablet, are not available.

Conclusions

Modern anti-inflammatory treatment with biologics is changing lives of many patients with severe asthma who had to rely on systemic GC and cope with their potentially serious side effects in the past. However, clinicians should be aware that life-threatening AI is common among systemic GC users and should familiarize themselves with correct GC tapering and cessation.

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