TITLE: Tackling 'people remodelling' in corticosteroid-dependent asthma with type-2 targeting biologics and a formal corticosteroid weaning protocol

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ABSTRACT

People with severe corticosteroid-dependent asthma have greater comorbidity, mortality, and corticosteroid side effects than any other asthmatics. Just as type-2 inflammation and recurrent asthma attacks remodel airways, we propose the concept of 'people remodelling' to represent the utter disruption of people's lives by the consequences of severe asthma and its associated corticosteroid treatments. To tackle this important problem, three biologics targeting type-2 inflammation – mepolizumab, benralizumab, and dupilumab – have shown efficacy in dedicated phase 3 trials to taper corticosteroids. We herein review the literature and propose an evidence-based, dose- and agent-specific corticosteroid weaning protocol for busy clinicians looking to get the best outcomes possible for their patients: independence from corticosteroids and reversal of people remodelling.

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ABBREVIATIONS

IL: interleukin

OCS: Oral corticosteroids

TSLP: thymic stromal lymphopoietin

Asthma is a common and heterogeneous disease affecting approximately 5-10% of the population. Severe asthma – a subset of the disease which affects a fraction of asthmatics but comprises more than half of the morbidity, mortality and costs – is predominantly caused by smouldering type-2 eosinophilic airway inflammation. Strategies to tackle this incendiary process and ensuing bronchial remodelling, asthma attacks and premature deaths has been, and often still is, to douse the fire with oral corticosteroids (OCS) [1] . The persistence of eosinophilic airway inflammation in some patients with severe asthma indicates that the airway mucosal mechanisms driving recruitment of eosinophils towards the airway epithelium are, or have become resistant to the effects of inhaled corticosteroids. In this situation OCS are helpful because they deplete the reservoir of circulating eosinophils thus preventing eosinophil recruitment even in the presence of a strong chemotactic pull towards the airway epithelium [2].

While they may prevent the inflammation from remodelling airways, OCS have been shown to reshape the appearance, health status and life of patients [3–6]. In consequence, traditional treatment with OCS makes an important contribution to what could be called ‘people remodelling’.

Short and infrequent OCS burst therapies are generally considered safe by physicians; they are not [3, 5]. Both in inpatients and outpatients, mood changes and insomnia can lead to disturbing situations for their neighbours, families, physicians, and especially for the person living with asthma. Dyspepsia and gastrointestinal ulcers lead to increased healthcare utilisation, while fluid retention is uncomfortable for many patients [7]. A significant increase in the frequency and severity of both short term and long-term OCS related complication have been observed with a lifetime cumulative dose as low as 500 to 1000 mg of prednisolone equivalent. Although the treatment is most often necessary, this does imply that we inadvertently start harming patients after two-to-four bursts of OCS in a lifetime [8, 9].

Long terms impacts of corticosteroid-dependence are better recognised. The consequences of even a small daily dose of OCS comprise at worst premature mortality and at best the likely possibility of experiencing weight gain and a cushingoid appearance, an increased risk of osteoporosis and fracture, hypertension, diabetes mellitus, and cardiovascular disorders [3–5]. Evidence also suggests that adrenal insufficiency, a potentially life-threatening condition, might affect 60% of OCS-treated asthmatics[10]. Compared to non-corticosteroid-dependant asthma patients, those treated with OCS have an excess incident morbidity of 12 comorbidities per 1000 patient-years and have been estimated to require up to three time more healthcare resources [4, 5].

The scope, rigour and reproducibility of these toxicological data highlight the importance of making OCS-avoidance a shared treatment goal in severe asthma [1]. The need for incisive action is especially dire in corticosteroid-dependent asthma. Fortunately, dedicated phase 3 trials have demonstrated the steroid-sparing effect of three of the six biologics approved for use in asthma [11]. They also provide a framework to develop formal weaning protocols.

The first marketed steroid sparing biologic drugs was mepolizumab, an anti-interleukin (IL)-5 monoclonal antibody. In the 2014 SIRIUS trial [12] , when compared to placebo, mepolizumab demonstrated a 50% versus 0% reduction of the median dose of OCS at 24 weeks, while also reducing the exacerbation rate, improving quality of life, and improving lung function. The four-weekly weaning protocol was initiated 4 weeks after the first injection on the basis of asthma and adrenal insufficiency symptoms.

The 2017 ZONDA trial [13] demonstrated significant results with benralizumab, an anti-IL-5 alpha-receptor monoclonal antibody. In this study which employed a similar weaning protocol to SIRIUS, the OCS median dose reduction at 28 weeks was 75% with benralizumab versus 25% with placebo. The exacerbation rate was also significantly lower in the treatment group, and, whilst

not statistically significant, symptoms and lung function showed a tendency toward improvement. More recently, the PONENTE study [14]holds special interest. The focus of this single-arm study was on rapid OCS tapering benralizumab-treated patients. The weaning strategy was nearly four times quicker than in ZONDA/SIRUS, insofar as reductions occurred every 1, 2, or 4 weeks depending on asthma symptoms and programmed adrenal testing. During the 24 weeks observation period, the median OCS reduction was 100% and 91% of patients achieved a dose of ≤ 5 mg prednisone. The exacerbation rate was again lower and asthma control was better in the study population than in the year preceding the study. The positive effect of this large reduction in OCS exposure on people remodelling and other aspects of benralizumab treatment was reflected by a large 1.0-point improvement in the Asthma Control Questionnaire score (minimally important difference: 0.5 points).

Dupilumab, an anti-IL-4 alpha-receptor monoclonal antibody, was also shown to be effective in corticosteroid sparing in the 2018 VENTURE study [15]. Corticosteroid-weaning occurred between weeks 4 and 20 of treatment. Dupilumab treated patients had a median OCS dose reduction of 100% at 24 weeks compared with a 50% in the placebo group. The exacerbation rate was lower and lung function was improved in the biologic group. The quality-of-life evaluation, although showing a tendency toward improvement with treatment, did not meet the clinical endpoint.

Of these trials, VENTURE alone did not require raised type 2 biomarkers for enrolment of patients. However, most patients had raised biomarkers (Appendix 1). Therefore, none of the biologic drugs can be assumed to be cortico-sparing with certainty in type-2 low asthma.

The ambitious 2022 SOURCE trial [16] evaluated tezepelumab, an anti-thymic stromal lymphopoietin (TSLP) monoclonal antibody. The alarmin TSLP plays a role upstream where it

sets off type-2 and non-type-2 inflammatory pathways. However, blocking this protein did not translate into a statistically significant OCS-sparing effect in SOURCE. Noteworthy methodological differences were the longer weaning period (44 weeks in total) and the possibility of continuing weaning after an asthma attack occurred. These differences might have accounted for the differences in outcome of SOURCE *vs* the studies outlined above although it is also possible that Tezepelumab, which acts primarily on the abnormally activated airway epithelium, does not have a sufficiently large suppressive effect on the reservoir of circulating eosinophils to be OCS sparing. Nevertheless, it is noteworthy that significant differences in OCS sparing effect of Tezepelumab were observed in people with greater baseline blood eosinophil counts. Lastly, Omalizumab and reslizumab underwent no dedicated corticosteroid-sparing trial.

Across the corticosteroid-weaning trials, adverse events were reported equally between the biologic and placebo groups. Anti-drug antibodies were identified in less than 10% of both biologic and placebo-treated patients. These antibodies did not seem to have any impact on the treatment's efficacy during the observation period. Despite the impressive evidence supporting OCS dose reduction in patients treated with mepolizumab, benralizumab, or dupilumab, many challenges still prevent effective dose lowering, even when safe and clinically appropriate. The most important obstacle to OCS reduction is patient adherence to dose modification advice. According to Busby *et al.*[17], up to 30% of patients did not reduce their OCS doses when advised to do so, even though they voluntarily and knowingly enrolled in an algorithm-driven reduction trial. Strikingly, the adherence levels were largely dependent on the recruiting centre, suggesting that the local culture and the manner physicians and nurses present the advice are important factors. This may translate into an even lower adherence to advice in a real-world clinical setting.

In practice, it is difficult for clinicians to taper by themselves the OCS treatments of their steroid-dependant asthma patients without prespecified trajectories. Few institutions use a standardised protocol which would systematically enact these changes in OCS-dependant patients or provide resources for patients who are understandably worried about stepping down from what had been a life-saving salvage treatment. Inspired by the SIRIUS, ZONDA, VENTURE and PONENTE trial protocols [12–15] as well as pharmacodynamic data indicating that Benralizumab acts immediately [18], we herein propose an agent-and-patient-dependent protocol for corticosteroid weaning when initiating a biologic (Figure).

We acknowledge that asthma represents the clinical expression of a spectrum of inflammatory pathways rather than a simple one-size-fits-all pathology [1]. This progress has meant interesting treatment opportunities, and important ensuing clinical challenges.

In conclusion, although lifesaving, corticosteroids induce a debilitating process of 'people remodelling'. OCS reduction while maintaining asthma control has been shown to be possible with mepolizumab, benralizumab and dupilumab. However, many challenges still stand in the way of steroids reduction by clinicians. The proposed personalised corticosteroid weaning protocol (Figure) is intended to alleviate some of these obstacles.

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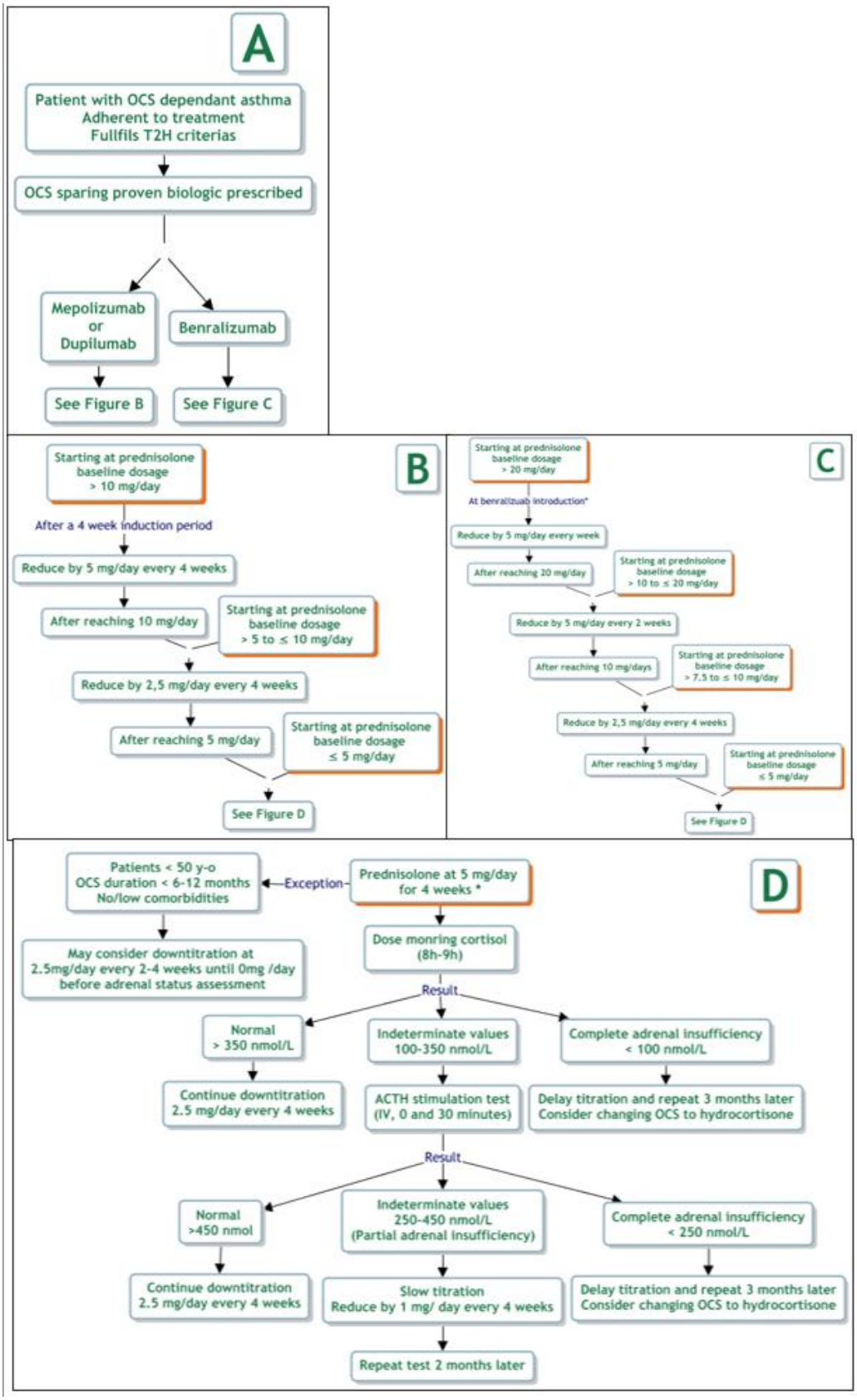
FIGURE LEGEND

Choice of OCS reduction protocol according to the initiated biologic treatment and starting dose. Based on phase 3 studies, a recent CHEST expert review, and pharmacodynamic data showing that *benralizumab acts immediately[12]. **Note 1:** Reducing OCS daily doses is only recommended if a) 4 weeks induction period completed b) no exacerbation seen last reduction in OCS or sine last seen c) no worsening of asthma symptom score or reduction in lung function. **Note 2:** We suggest clinical visits A) after the 4 weeks induction period, before reducing OCS dosage for the first time B) every 2 months during OCS reduction, with phone appointments with physician or respiratory therapist every other month C) when reaching a 5mg/day dose and when reaching 0mg/day dose D) in case of failure to wean according to the protocol may require medical evaluation.


A
Patient with OCS dependant asthma
Adherent to treatment
Fullfils T2H criterias
OCS sparing proven biologic prescribed
Mepolizumab
or
Dupilumab
Benralizumab
See Figure B
See Figure C
B
Starting at prednisolone baseline dosage > 10 mg/day
After a 4 week induction period
Reduce by 5 mg/day every 4 weeks
After reaching 10 mg/day
Starting at prednisolone baseline dosage > 5 to ≤ 10 mg/day
Reduce by 2,5 mg/day every 4 weeks
After reaching 5 mg/day
Starting at prednisolone baseline dosage ≤ 5 mg/day
See Figure D
C
Starting at prednisolone baseline dosage > 20 mg/day
At benralizuab introduction*
Reduce by 5 mg/day every week
After reaching 20 mg/day
Starting at prednisolone baseline dosage > 10 to ≤ 20 mg/day
Reduce by 5 mg/day every 2 weeks
After reaching 10 mg/days
Starting at prednisolone baseline dosage > 7.5 to ≤ 10 mg/day
Reduce by 2,5 mg/day every 4 weeks
After reaching 5 mg/day
Starting at prednisolone baseline dosage ≤ 5 mg/day
See Figure D
D
Patients < 50 y-o
OCS duration < 6-12 months
No/low comorbidities
Exception
Prednisolone at 5 mg/day for 4 weeks *
May consider downtitration at 2.5mg/day every 2-4 weeks until 0mg /day before adrenal status assessment
Dose monring cortisol (8h-9h)
Result
Normal > 350 nmol/L
Indeterminate values 100-350 nmol/L
Complete adrenal insufficiency < 100 nmol/L
Continue downtitration 2.5 mg/day every 4 weeks
ACTH stimulation test (IV, 0 and 30 minutes)
Delay titration and repeat 3 months later
Consider changing OCS to hydrocortisone
Result
Normal >450 nmol
Indeterminate values 250-450 nmol/L (Partial adrenal insufficiency)
Complete adrenal insufficiency < 250 nmol/L
Continue downtitration 2.5 mg/day every 4 weeks
Slow titration
Reduce by 1 mg/ day every 4 weeks
Delay titration and repeat 3 months later
Consider changing OCS to hydrocortisone
Repeat test 2 months later

APPENDIX 1 – Summary of corticosteroid-sparing trials

Trial	*Biologic*	*Duration of follow-up* (*weeks*)	*Initial blood eosinophil level* *(Cells per microliter)*	*Patients mean age* *Years* *(Active vs placebo)*	*OCS weaning rate* *(mg in prednisolone equivalent)* *(Dd = daily dose in mg)*	*Comorbidities* *(Active vs placebo)*	*Median % dose reduction in OCS dose with active and placebo*	*Change in FEV1, active - placebo (mL)*	*% Reduction in exacerbations*
SIRIUS (1)	Mepolizumab (Anti-IL-5)	24	≥300 in last year Or ≥ 150 in optimisation phase	50 vs 50	Reduction every 4 weeks: Steps of -10mg if Dd ≥ 20 Steps of -5mg if Dd <20 but >5 Step of -2.5when dose is 5mg Wait 3 steps (12 weeks) at a Dd of 2.5 mg Then discontinue	% Former smokers 28 vs 25 BMI 27,8 vs 29,5	50 vs 0	114	32
ZONDA (2) (2 benralizumab arms administered q4 weeks and q8 weeks vs placebo)	Benralizumab (Anti-IL-5Ra)	28	≥ 150 in last year	50.2 & 52.9 vs 49,9	Reduction every 4 weeks: Steps of 5mg if Dd >10 Steps of 2.5mg if Dd ≤10 but >2.5 Steps of 1.25mg when Dd is ≤2.5	Median smoking history 5.2 & 5.0 vs 6.0 BMI 29.8 & 30.2 vs 28.7	75 vs 25	113	55
PONENTE (3) (No placebo arm, compared to patients the year before)	Benralizumab (Anti-IL-5Ra)	36	≥150 at enrollment Or ≥300 in last year	53.3	See figure C Initially reduction every week, then every other week	Non-smoker 75% BMI 29 Allergy 64% Allergic rhinitis 48% Chronic rhinosinusitis with nasal polyposis 30% Past polypectomy 21%	100 (No placebo arm) 91% of patients reached a daily dosage of OCS of ≤ 5mg (No placebo arm)	Not measured	Results expressed differently: 75% of patients exacerbation free compared to 16% the year before
VENTURE (4)	Dupilumab (Anti-IL-4Ra)	24	No requirement regarding blood eosinophils or type 2 inflammation markers	51.1 vs 50.7	Reduction every 4 weeks: Steps of 5 mg if Dd ≥ 20 Steps of 2.5 if Dd ≤ 15 mg	% Former smoker 24 vs 17 % Nasal polyposis 33 vs 38 % Food allergy 10 vs 10	100 vs 50	220	50
SOURCE (5)	Tezepelumab (Anti-TSLP)	48	No requirement regarding blood eosinophils or type 2 inflammation markers	53.5 vs 53.4	Reduction every 4 weeks: Steps of 5 mg if Dd > 10 mg Steps of 2.5mg if Dd ≤ 10 May ad steps of 1 to 1.25mg if Dd ≤2.5	BMI 29.3 vs 29.4 % Chronic sinusitis 32 vs 32 % Nasal polyposis 23 vs 24 % Rhinitis 57 vs 58	Not significant (100 vs 75)	260	Not significant (31)

BMI, body mass index; Dd, daily dose; FEV1, forced expiratory volume in 1 second; IL, interleukin; OCS, oral corticosteroid; Ra, receptor-alpha; TSLP, thymic stromal lymphopoietin.