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REVIEW

Experimental Glucocorticoid Receptor Agonists for the Treatment of Asthma: A Systematic Review

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Abstract: Inhaled corticosteroids (ICSs) are considered the cornerstone of asthma treatment. Despite the solid evidence documenting the efficacy and safety of ICSs at the level of the airways, their use can be affected by pulmonary and systemic adverse events (AEs) when administered chronically and/or at high doses. Thus, there is a pharmacological and medical need for new glucocorticoid (GC) receptor (GR) ligands with a more favorable therapeutic index, in order to overcome the shortcomings of currently available ICSs. The therapeutic profile of GCs can be improved by enhancing genomic mechanisms mediated by transrepression, which is assumed to be responsible for several anti-inflammatory and immunomodulatory actions, rather than transactivation, which causes most of the GC-associated AEs. It was assumed that an independent modulation of the molecular mechanisms underlying transactivation and transrepression could translate into the dissociation of beneficial effects from AEs. Therefore, current research is looking for GCs that are able to elicit prevalently transrepression with negligible transactivating activity. These compounds are known as selective glucocorticoid receptor agonists (SEGRAs). In this review, experimental GR agonists currently in pre-clinical and clinical development for the treatment of asthma have been systematically assessed. Several compounds are currently under pre-clinical development, but only three novel experimental GR agonists (GW870086X, AZD5423, AZD7594) seem to have some potential therapeutic relevance and have entered clinical trials for the treatment of asthma. Since data from pre-clinical studies have not always been confirmed in clinical investigations, well-designed randomized controlled trials are needed in asthmatic patients to confirm the potentially positive benefit/risk ratio of each specific SEGRA and to optimize the development strategy of these agents in respiratory medicine.

Keywords: asthma, glucocorticoid agonists, SEGRA, efficacy, safety

Introduction

Asthma is a chronic inflammatory disorder of the airways affecting more than 300 million people worldwide, and is associated with a huge social and economic burden, estimated to rank as one of the highest among chronic illnesses.[1] According to the World Health Organization, asthma causes 250,000 deaths annually worldwide, and it is responsible for more than 500,000 hospitalizations every year in the USA.[2]

Inhaled corticosteroids (ICSs) are considered the cornerstone of asthma treatment, and are administered alone or in combination with long-acting β_2-adrenoceptor agonists (LABAs) as first-line therapy for persistent asthma.[3] Despite the solid

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evidence documenting the efficacy and safety of ICSs at the level of the airways, their use can be affected by pulmonary and systemic adverse events (AEs) when administered chronically and/or at high doses, along with potential steroid resistance.[4] Therefore, researchers are currently looking for new glucocorticoid (GC) receptor (GR) ligands with a more favorable therapeutic index, in order to overcome the shortcomings of currently available ICSs.[5]

The therapeutic profile of GCs can be improved by enhancing genomic mechanisms mediated by transrepression, which is assumed to be responsible for several anti-inflammatory and immunomodulatory actions by inhibiting the expression of cytokines and other pro-inflammatory molecules, rather than transactivation, which causes most of the GC-associated AEs.[6] However, transactivation may also modulate some therapeutic effects, leading to the expression of anti-inflammatory and regulator proteins.[7] It was assumed that an independent modulation of the molecular mechanisms underlying transactivation and transrepression could translate into the dissociation of beneficial effects from AEs. Therefore, the main goal of research is to identify GCs that are able to elicit prevalently transrepression with negligible transactivating activity.[8] These compounds are known as selective glucocorticoid receptor agonists (SEGRAs), selective glucocorticoid receptor modulators (SEGRMs), or dissociated GR ligands, and they are able to activate specific GR mechanisms and alter GR-mediated gene expression (Figure 1).[9]

At the beginning, these ligands were called SEGRAs, since they were developed from a steroidal scaffold and often displayed a partial agonistic activity on transactivation.[9] The term SEGRM is more recent, and used in order to differentiate the more recent non-steroidal compounds from the older agents with an

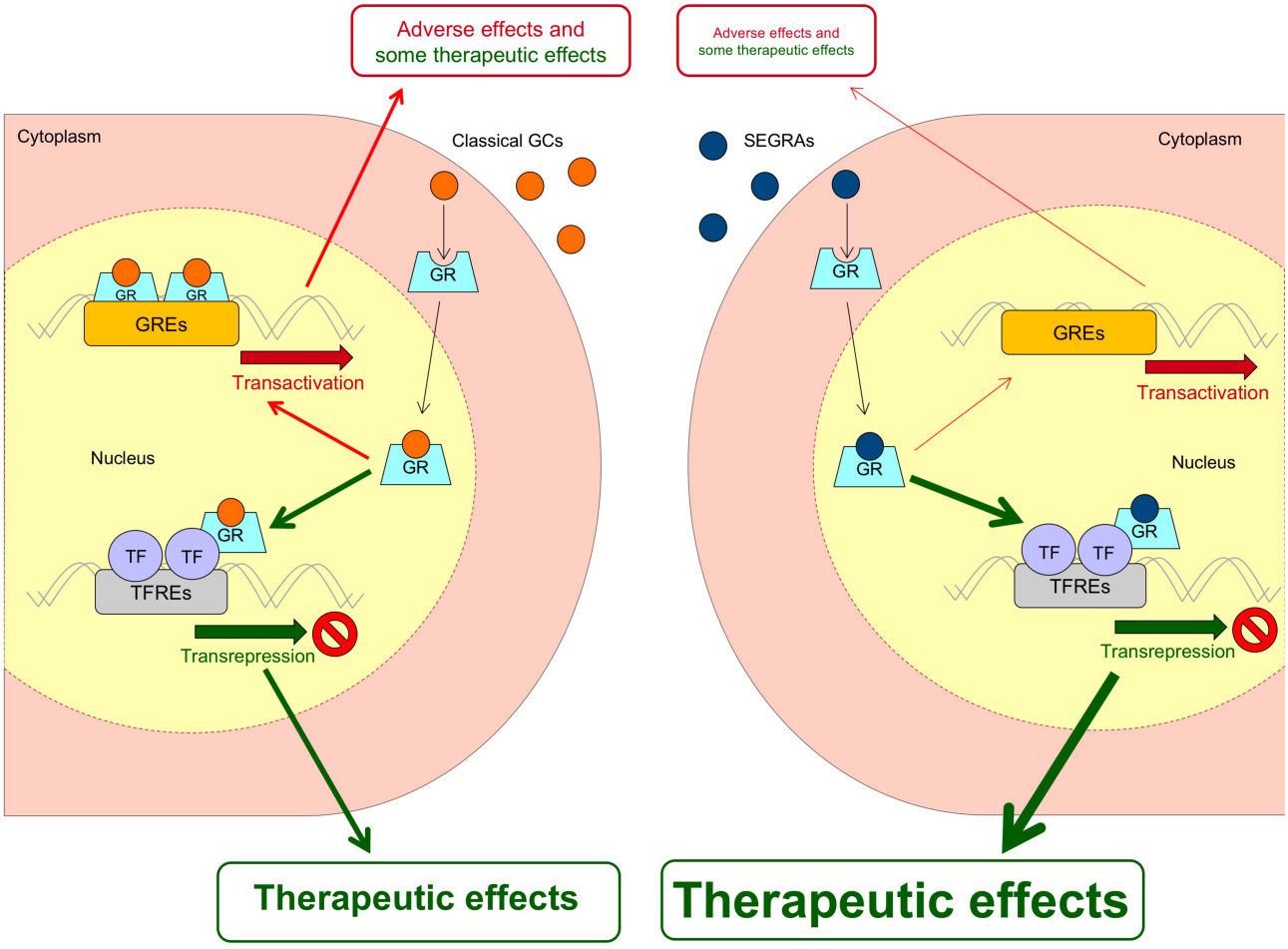

Figure 1 Model of GR transactivation and transrepression of genes, when induced by classical GCs and SEGRAs. SEGRAs have been designed to improve the therapeutic index compared to classical GCs, by preferentially inducing transrepression with negligible transactivating activity.
Abbreviations: GC, glucocorticoid; GR, glucocorticoid receptor; GRE, glucocorticoid response element; SEGRA, selective glucocorticoid receptor agonist; TF, transcription factor; TFRE, transcription factor responsive element.

improved therapeutic ratio, and/or to identify GR ligands able to modulate the activity of a GR agonist and that may not classically bind to the receptor pocket.[9,10]

The aim of this review was to systematically assess the experimental GR agonists currently in pre-clinical and clinical development for the treatment of asthma.

Materials and Methods

Review Question

The question investigated by this systematic review was whether the current experimental GR agonists might be suitable for an effective and safe treatment of patients with asthma.

Search Strategy

The protocol of this qualitative synthesis of the current literature has been submitted to the international prospective register of systematic reviews (PROSPERO, submission ID: 171,465), and performed in agreement with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P),[11] with the relative flow diagram reported in Figure 2. This study satisfied all the recommended items reported by the PRISMA-P checklist.[11]

The PICO (Patient problem, Intervention, Comparison, and Outcome) framework was applied to develop the literature search strategy and question, as previously reported.[12] Namely, the "Patient problem" included patients suffering from asthma; the "Intervention" regarded experimental GR agonists; the "Comparison" was performed with active comparators and/or placebo; and the assessed "Outcomes" were the activity in vitro, lung function, use of rescue medications, asthma symptom control, pharmacokinetic (PK) and pharmacodynamic (PD) characteristics, and safety profile.

In this study, experimental GR agonists are considered investigational medications, which in turn are defined as drugs that have received approval by either the US Food and Drug Administration or the European Medicines Agency for human testing but that are not approved for marketing.[13,14]

A comprehensive literature search was performed for in vitro studies, in vivo studies performed on laboratory animals, and clinical trials, written in English and investigating the impact of experimental GR agonists for the

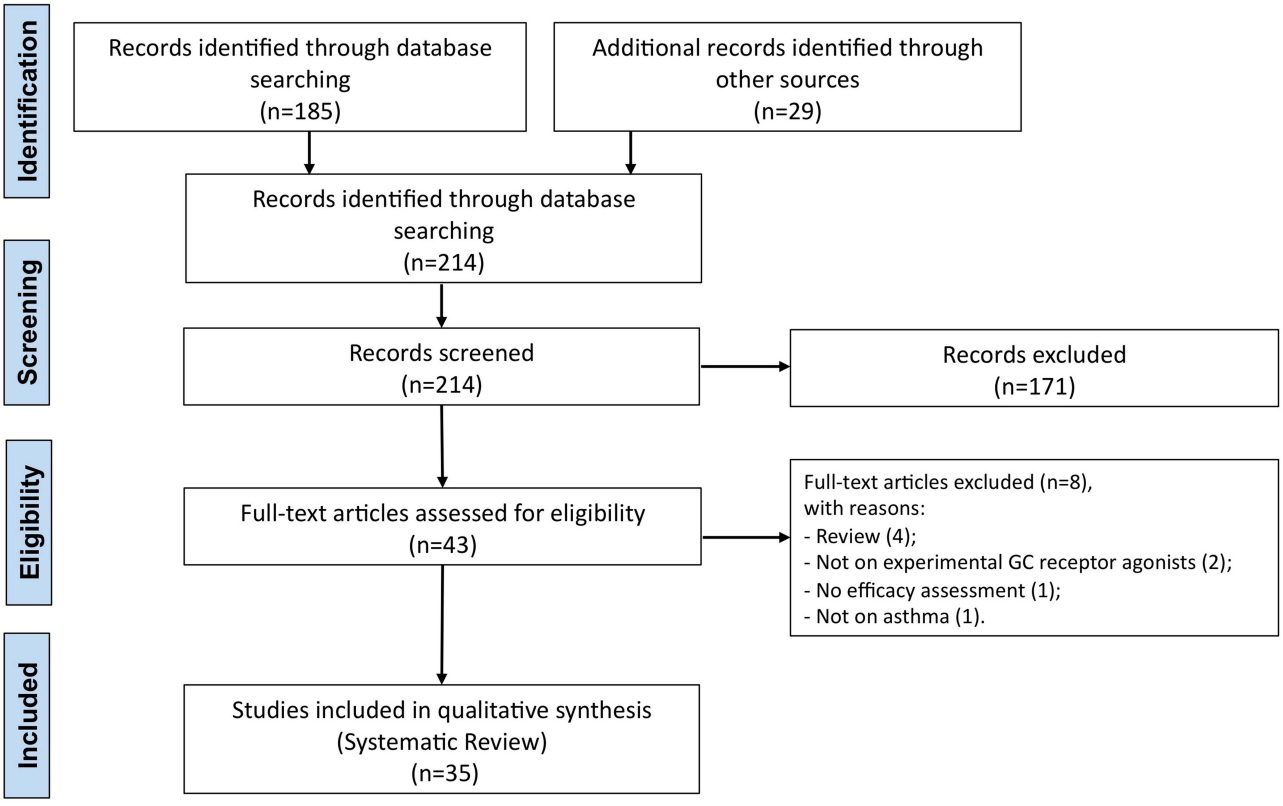

Figure 2 PRISMA flow diagram for the identification of the studies included in the systematic review concerning the impact of experimental GR agonists for the treatment of asthma.

Abbreviations: GC, glucocorticoid; GR, glucocorticoid receptor; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

treatment of asthma. The search was performed in ClinicalTrials.gov, Cochrane Central Register of Controlled Trials, Embase, EU Clinical Trials Register, MEDLINE, Scopus, and Web of Science in order to provide for relevant studies available with no time limit up to April 30th, 2020. The searched terms were "glucocorticoid receptor agonists AND asthma", and the research string was as follows: (("receptors, glucocorticoid"[MeSH Terms] OR ("receptors"[All Fields] AND "glucocorticoid"[All Fields]) OR "glucocorticoid receptors"[All Fields] OR ("glucocorticoid"[All Fields] AND "receptor"[All Fields]) OR ("glucocorticoid receptor"[All Fields]) AND ("agonists"[Subheading] OR "agonists"[All Fields]) AND ("asthma"[MeSH Terms] OR "asthma"[All Fields]). Studies reporting the in vitro profile and the impact of investigational GR agonists on lung function, the use of rescue medications, asthma symptom control, PK and PD characteristics, and safety were included in this systematic review.

Citations in previous published reviews were checked to select further pertinent studies, if any.[5,15–18]

Two reviewers independently checked the relevant studies identified from literature searches obtained from the above-mentioned databases. The studies were selected in agreement with previously mentioned criteria, and any difference in opinion about eligibility was resolved by consensus.

Data Extraction

Data from the included studies were extracted and checked for study references, NCT number identifier, study characteristics, treatments and comparators with doses and regimen of administration, patient characteristics and number of analyzed patients, age, gender, body mass index, serious adverse events (SAEs), forced expiratory volume in 1 second (FEV_1), PK and PD characteristics, use of rescue medication, asthma symptom control, and Jadad score.

Endpoints

The co-primary endpoints of this systematic review were the in vitro activity of experimental GR agonists and their impact on FEV_1, peak expiratory flow (PEF), fraction exhaled of nitric oxide (F_ENO), use of rescue medication, PK characteristics, and safety profile.

Strategy for Data Synthesis

Data from original papers were extracted and reported via qualitative synthesis.

Quality of Studies and Risk Bias

The summary of the risk of bias for each selected randomized controlled trial (RCT) was analyzed via the Cochrane Risk of Bias 2 (RoB 2) and Jadad score.[19,20]

The weighted assessment of the overall risk of bias was analyzed via the Cochrane RoB 2.[20]

The Jadad score, with a scale of 1–5 (score of 5 being the best quality), was used to assess the quality of the clinical trials concerning the likelihood of bias related to randomization, double blinding, withdrawals, and dropouts.[19] The quality of studies was assessed as follows: total score ≤2, low quality; total score =3, medium quality; total score ≥4, high quality.

Two reviewers independently assessed the quality of individual studies, and any difference in opinion about the quality score was resolved by consensus.

Results

Obtained data were extracted from 35 studies, among which 12 were in vitro studies,[21–33] five were performed in vivo,[34–39] three were both in vitro and in vivo,[40–42] and 15 were RCTs,[43–64] the characteristics of which are reported in Table 1.

Most RCTs included in this systematic review had a low risk of bias for the missing outcome data and selection of the reported results (100.0%) and deviation from intended interventions (53.3%). The risk of bias for the randomization process was low in 40% of the RCTs. Some concerns on the risk of bias were detected for the measurement of the outcome (80.0%), deviation from intended interventions (46.7%), and randomization process (40.0%). A high risk of bias due to randomization process was detected in 13.3% of the RCTs. The weighted plot for the assessment of the overall risk of bias and the traffic light plot for the assessment of each RCT are reported in Figures 3 and 4, respectively.

Most of the RCTs (60.0%) included in this systematic review were ranked as being of medium to high quality in agreement with Jadad score, whereas 40.0% of them were characterized by low quality level (Table 1).

Experimental GR Agonists

Detailed information on the PK of experimental GR agonists is reported in Table 2.

A222977

The SEGRA A222977 (also called compound 13), a 5-aryl-2,5-dihydro-10-methoxy-2,2,4-trimethyl-1H-[1]

benzopyrano-[3,4-f]quinolone, is derived from a modified structure of A276575.[42,65] A222977 exhibited high affinity for GR and low affinity and efficacy for progesterone receptors (PRs), and in a cross-linked Sephadex® dextran gel rat model of asthma with induced eosinophil influx in lung, A222977 per os (PO) was as effective as prednisolone against inflammation.[42] Despite the promising in vitro profile, no further documented research was performed, perhaps owing to the inability of A222977 and similar molecules to separate the transcriptional repression from the glucocorticoid response element (GRE) transactivator activity.[15]

A276575

The SEGRA A276575 (2,5-dihydro-9-hydroxy-10-methoxy-2,2,4-trimethyl-5-(1-methylcyclohexen-3-y1)-1H-[1]benzopyrano[3,4-f]quinoline) has a high transrepression activity and a low GRE transactivation activity and, unlike traditional GCs, it does not contain the terpenoid structure.[22] A276575 is a 7:1 mixture of syn- and anti-diastereomers. The (–)-enantiomers showed 10–30-fold greater affinity for GRs than the respective (+)-enantiomers.[22] Both the (–)-syn and (-–)-anti enantiomers were potent inhibitors of prostaglandin E_2 release in A549 lung epithelial cells challenged by interleukin-1β (IL-1β); on the other hand, only the (–)-anti-enantiomer inhibited the production of the chemokine C-C motif ligand 5 (CCL5)/regulated on T-cell activation, normal T-cell expressed and secreted (RANTES).[22]

Further clinical development in vivo was precluded, perhaps owing to some properties of A276575 such as a high affinity for PRs and a super-agonistic activity in mouse mammary tumor virus (MMTV) PR-B (MMTV-PR-B) transfection assays, which are undesirable effects not induced by dexamethasone (DEX).[22]

AZD5423

The SEGRA AZD5423 (2,2,2-trifluoro-N-[(1R,2S)-1-[1-(4-fluorophenyl)indazol-5-yl]oxy-1-(3-methoxyphenyl)propan-2-yl]acetamide) is under development for the treatment of asthma.[66]

In transfected pulmonary A549 cells, AZD5423 activated the 2XGRE reporter by inducing a super-agonistic effect on the maximal response (E_{max}) relative to DEX and budesonide (BUD).[30] The effect of AZD5423 was not affected by IL-1β, whereas both DEX and BUD reduced E_{max} in the presence of IL-1β.[30] AZD5423 was as effective as DEX and BUD in repressing the release of IL-1β-induced granulocyte–macrophage colony-stimulating factor (GM-CSF), IL-6, and IL-8, and in inducing TSC22 domain family member 3 (TSC22D3, also known as glucocorticoid-induced leucine zipper), dual-specificity phosphatase-1 (DUSP1, also known as mitogen-activated protein kinase phosphatase 1 [MKP1]), and regulator of G-protein signaling 2 (RGS2) gene expression.[30]

In a Phase I RCT (NCT01225549), nebulized AZD5423 75–300 µg, but not BUD, reduced the fall in FEV_1 during the late asthmatic response (LAR) compared to placebo (8.7–14.0%) in mild allergic asthma. No effect was detected on early asthmatic response (EAR).[54,55] AZD5423 reduced the allergen-induced sputum eosinophilia and airway hyperresponsiveness (AHR) to methacholine compared to placebo.[54,55]

A further three Phase I RCTs evaluated the tolerability of inhaled AZD5423 in healthy volunteers: a single-ascending dose study performed mainly on Caucasians, a multiple-ascending dose study, and a single- and multiple-ascending dose trial conducted in Japanese volunteers.[50] The Caucasian-dominant single-ascending dose RCT documented that AZD5423 8.4–2400 µg via the Spira Electra 2® jet nebulizer caused no clinically significant abnormalities in laboratory variables.[50] AZD5423 was rapidly absorbed in the lung, with a fast initial concentration decrease and slow plasma elimination in the terminal phase.[50] PK data from single-ascending dose studies indicated dose-proportional plasma exposure of AZD5423, with no difference between the Caucasian-dominant and Japanese data sets.[50] The repeated-dose plasma exposure investigated in the multiple-ascending dose study confirmed the dose-proportional PK,[50] with the steady state reached after 7 days.[50] AZD5423 50–300 µg via a hand-held vibrating mesh nebulizer did not alter laboratory variables, electrocardiogram, vital signs, or spirometry measurements.[50] According to the two single-ascending dose Caucasian-dominant and Japanese studies, accumulation ratio of AZD5423 was low, with no evidence of time-dependent PK.[50] AZD5423 100–300 µg produced a maximum drug concentration (C_{max}) of 4.96–11.1 nmol/L and a time to reach C_{max} (t_{max}) of 0.08–0.1 h.[50] In the single-ascending dose study performed mainly on Caucasians, AZD5423 500–1248 µg suppressed plasma cortisol compared to placebo.[50] The maximum reduction in plasma cortisol was detected after a single dose of AZD5423 1248 µg.[50] In the single- and multiple-ascending dose study conducted in Japanese volunteers, AZD5423 300 µg reduced urinary excretion cortisol. In the multiple-ascending dose study,

Table 1 Characteristics of the Clinical Studies Included in the Systematic Review

Study and Year	ClinicalTrials.gov Identifier and/or Company ID	Study Characteristics	Treatment Duration (Days)	Number of Analyzed Patients	Drugs, Doses, and Regimen of Administration	Comparator	Route of Administration
Brown et al, 2019[43,44]	NCT02479412	Phase IIa, multicenter, randomized, double-blind, 3-period, placebo-controlled, incomplete-block, crossover	15	54	AZD7594 58 μg (q.d.), 250 μg (q.d.), 800 μg (q.d.)	Placebo (q.d.)	Oral inhalation
Prothon et al, 2019[45,46]	NCT02645253	Phase I, single-center, randomized, single-blind, placebo-controlled, sequential-group	20	27	AZD7594 200 μg (q.d.), 400 μg (q.d.), 1600 μg (q.d.)	Placebo (q.d.)	Oral inhalation
Melin et al, 2017[47,48]	NCT01310322, Study A	Phase I, single-center, partly randomized, open-label, 4-way, crossover	1	13	AZD5423 250 μg, 420 μg, 450 μg, 1200 μg (single dose)	NA	AZD5423 420 μg, 450 μg: oral inhalation, AZD5423 250 μg: IV, AZD5423 1200 μg: PO
Melin et al, 2017[48,49]	NCT01635985, Study B	Phase I, single-center, partly randomized, open-label, 6-way, crossover	1	18	AZD5423 250 μg, 332 μg, 405 μg, 456 μg, 523 μg, 1200 μg (single dose)	NA	AZD5423 332 μg, 405 μg, 456 μg, 523 μg: oral inhalation, AZD5423 250 μg: IV, AZD5423 1200 μg: PO
Chen et al, 2017[51,52]	NCT02648438	Phase I, single-center, partiy randomized, open-label, 4-period, parallel	1	30	AZD7594 150 μg, 400 μg, 1200 μg	NA	AZD7594 400 μg: oral inhalation, AZD7594 150 μg: IV, AZD7594 1200 μg: PO
Werkström et al, 2016[50]	NA, Study A	Single-dose Phase I, single-center, randomized, double-blind, placebo-controlled, escalated-dose	1	59	AZD5423 8.4–2400 μg	Placebo	Oral inhalation
Werkström et al, 2016[50]	NA, Study B	Multiple-ascending dose Phase I, randomized, double-blind, placebo-controlled, parallel	14	27	AZD5423 125 μg (q.d.), 375 μg (q.d.), 499 μg (q.d.)	Placebo	Oral inhalation
Werkström et al, 2016[50]	NA, Study C	Single- and multiple-ascending dose Phase I, single-center, randomized, double-blind, placebo-controlled, parallel	14	30	AZD5423 50 μg (single-dose), 100 μg (q.d.), 300 μg (q.d.)	Placebo	Oral inhalation

Inhaler Device	Patient Characteristics	Age (Years)	Male (%)	Current Smokers (%)	Smoking History (Pack-Years)	BMI (kg/m^2)	Pre-Bronchodilator FEV_1 Predicted (%)	Investigated Outcomes	Jadad Score
DPI	Mild to moderate asthmatic (pre-bronchodilator FEV_1 ≥40% and ≤90% of predicted, F_ENO ≥25 ppb)	50.8	82.9	0.0	NA	27.3	≥40.0 and ≤90.0	Lung function, symptom control, PK, PD, and safety	5
DPI	Healthy Japanese subjects (NA)	34.0	100.0	NA	NA	23.1	NA	PK, PD, and safety	3
Jet nebulizer, hand-held vibrating mesh nebulizer	Healthy subjects (NA) and mild allergic asthmatic (pre-bronchodilator FEV_1 ≥70%)	18.0–42.0	100.0	0.0	NA	20.5–28.4	≥70.0	PK and safety	1
Jet nebulizer, hand-held vibrating mesh nebulizer, approved DPI, new DPI	Healthy subjects (NA)	21.0–40.0	100.0	0.0	NA	19.2–30.0	NA	PK and safety	1
Mono-dose DPI, MDI	Healthy subjects (NA)	32.9	100.0	0.0	NA	18.0–30.0	NA	PK and safety	1
Jet nebulizer	Healthy subjects (NA)	26.0	100.0	NA	NA	24.0	NA	PK, PD, and safety	2
Jet nebulizer	Healthy subjects (NA)	28.0	100.0	NA	NA	25.0	NA	PK, PD, and safety	2
Hand-held vibrating mesh nebulizer	Healthy Japanese subjects (NA)	29.6	100.0	NA	NA	22.2	NA	PK, PD, and safety	2

(*Continued*)

Table 1 (Continued).

Study and Year	ClinicalTrials.gov Identifier and/or Company ID	Study Characteristics	Treatment Duration (Days)	Number of Analyzed Patients	Drugs, Doses, and Regimen of Administration	Comparator	Route of Administration
Leaker et al, 2015[53]	NCT00483899, Part B	Phase II, multicenter, randomized, double-blind, placebo-controlled, 3-way, crossover	21	21	GW870086X 1 mg (q.d.), 3 mg (q.d.)	Placebo	Oral inhalation
Gauvreau et al, 2015[54,55]	NCT01225549	Phase II, multicenter, randomized, double-blind, double-dummy, placebo- and active-controlled, 4-way, crossover	7	20	AZD5423 75 μg (q.d.), 300 μg (q.d.), and BUD 200 μg (b.i.d.)	Placebo	Oral inhalation
Bareille et al, 2013[56,57]	NCT00945932	Phase II, multicenter, randomized, double-blind, placebo-controlled, 2-way crossover	28	36	GW870086X 1 mg (q.d.)	Placebo	Oral inhalation
Allen et al, 2013[58,59]	NCT01160003, SIG113209	Dose-ascending, Phase I, single-center, randomized, double-blind, placebo-controlled, 3-way crossover	14	12	GW870086X 5 mg (q.d.), 8.75 mg (q.d.)	Placebo	Oral inhalation
Bareille et al, 2013[60,63]	NCT01245426, SIG114749	Phase II, multicenter, randomized, double-blind, placebo-controlled, parallel	27	135	GW870086X 2 mg (q.d.), 4 mg (q.d.), 3 mg (q.d. added at interim)	Placebo	Oral inhalation
Bareille et al, 2013[61,64]	NCT00857857, SIG110762	Phase IIa, multicenter, randomized, double-blind, placebo- and active-controlled, incomplete block, 3-way crossover	13	24	GW870086X 0.25 mg (q.d.), 1 mg (q.d.), 3 mg (q.d.), and FP 0.25 mg (b.i.d.)	Placebo	Oral inhalation
Boulet et al, 2009[62]	NA	Dose-ascending, Phase I, multicenter, randomized, double-blind, escalated-dose	21	26	TPI 1020 600 μg (b.i.d. for 2 weeks), 1200 μg (b.i.d. for 1 week), BUD 400 μg (b.i.d. for 2 weeks), 800 μg (b.i.d. for 1 week)	NA	Oral inhalation

Abbreviations: b.i.d., twice daily; BMI, body mass index; BUD, budesonide; DPI, dry powder inhaler; F_ENO, fraction exhaled of nitric oxide; FEV_1, forced expiratory volume in 1 second; FP, fluticasone propionate; IV, intravenous administration; MDI, metered-dose inhaler; NA, not available; PD, pharmacodynamics; pMDI, pressurized metered-dose inhaler; PO, oral administration; PK, pharmacokinetics; ppb, parts per billion; q.d., once daily.

Inhaler Device	Patient Characteristics	Age (Years)	Male (%)	Current Smokers (%)	Smoking History (Pack-Years)	BMI (kg/m^2)	Pre-Bronchodilator FEV_1 Predicted (%)	Investigated Outcomes	Jadad Score
DPI	Mild asthmatic (pre-bronchodilator FEV_1 ≥60% of predicted, F_ENO ≥25 ppb)	28.0	100.0	NA	NA	24.0	87.0	Lung function, PK, PD, and safety	3
AZD5423: vibrating mesh nebulizer I-neb®, BUD: DPI (Turbuhaler®)	Mild atopic asthmatic (pre-bronchodilator FEV_1 ≥70% of predicted, NA)	29.6	55.0	0.0	NA	NA	92.1	Lung function, PD, and safety	4
DPI (Diskhaler®)	Mild to moderate asthmatic (pre-bronchodilator FEV_1 ≥40% and ≤85% of predicted)	49.0	56.0	0.0	≤10.0	26.0	73.7	Lung function, and safety	4
Nebulizer (NA)	Healthy subjects (NA)	54.0	100.0	0.0	>5.0	24.5	NA	PK, PD, and safety	3
NA	Persistent asthmatic (pre-bronchodilator FEV_1 ≥60% and <85% of predicted)	43.5	80.7	0.0	≤10.0	25.4	NA	Lung function, and safety	5
DPI	Mild asthmatic (pre-bronchodilator FEV_1 >65% of predicted)	39.4	100.0	0.0	≤10.0	NA	>65.0	Lung function, PD, and safety	5
DPI	Mild asthmatic (pre-bronchodilator FEV_1 ≥75% of predicted)	34.4	51.9	100.0	10.8	NA	85.3	PK, PD, and safety	3

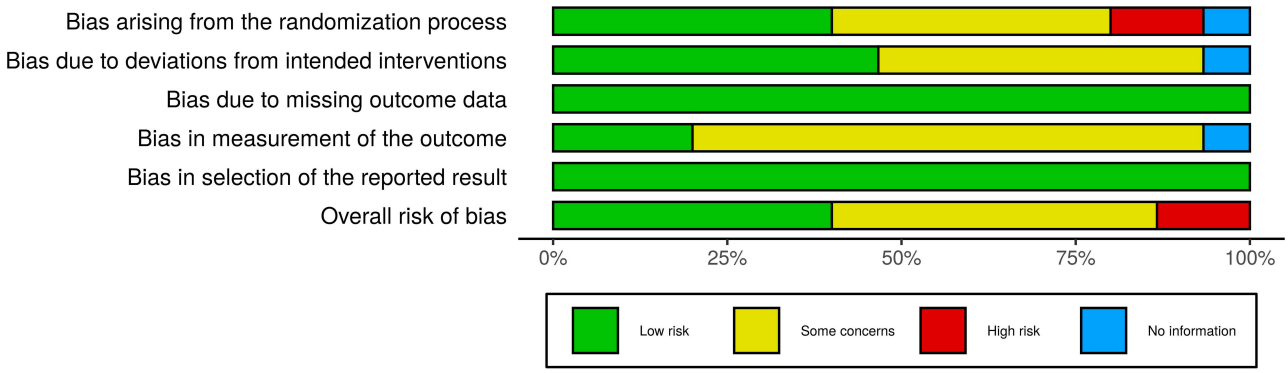

Figure 3 Weighted plot for the assessment of the overall risk of bias via the Cochrane RoB 2 tool (n=15 RCTs).
Abbreviation: RCT, randomized controlled trial.

values of 3.7–14.4 nmol/L.[50] The t_{max} values were similar across the investigated doses.[50] In the multiple-ascending dose study, AZD5423 499 µg induced a partial suppression of plasma cortisol and a marked reduction in urinary excreted cortisol level.[50]

In an open-label partly randomized Phase I study (NCT01310322) performed in healthy subjects and mildly asthmatic patients, AZD5423 420–450 µg administered via a hand-held vibrating mesh nebulizer and a jet nebulizer achieved a pulmonary bioavailability of 27.0–49.0%, an oral bioavailability of 1.3–2.1%, a C_{max} of 3.29–7.90 nmol/L, a t_{max} of 0.17 h, and a half-life ($t_{1/2}$) of 11.5–21.4 h. Intravenous (IV) AZD5423 250 µg produced a C_{max} of 0.6 nmol/L, a t_{max} of 0.42 h, and a $t_{1/2}$ of 25.0 h.[47,48] Oral AZD5423 1200 µg elicited a C_{max} of 0.841 nmol/L, a t_{max} of 0.84 h, and a $t_{1/2}$ of 4.0 h.[47,48] Drug disposition showed a multi-phasic profile characterized by a fast process of absorption from the alveolar space into the systemic circulation due to the small particle size of the nebulized formulations.[47,48]

In an open-label partly randomized Phase I study (NCT01635985) performed in healthy subjects, the pulmonary bioavailability of AZD5423 405–420 µg via a hand-held vibrating mesh nebulizer was 27.0%, while it was 37.0–49.0% for AZD5423 450–523 µg via a jet nebulizer, 31.0% for AZD5423 456 µg via the approved dry powder inhaler (DPI) Turbuhaler®, and 46.0% for AZD5423 332 µg via a new DPI.[48,49] The oral bioavailability of AZD5423 1200 µg was low (2.3–3.4%).[48,49] The C_{max} of AZD5423 administered via inhalation was 2.36–4.04 nmol/L, t_{max} was 0.17–0.33 h, and $t_{1/2}$ 17.9–26.6 h.[48,49] AZD5423 via DPIs was absorbed more slowly than AZD5423 administered via nebulized formulations due to the different particle size.[48,49] The slow absorption of AZD5423 via the approved DPI and the new DPI was permeation rate limited, and related to a relatively short retention time in the lung.[48,49]

AZD5423 was generally well tolerated and neither SAEs nor clinically relevant alterations were reported in the studies. AZD5423 is not currently under investigation for asthma; the last update was posted in 2015 and the status of the clinical trials remains to be completed.

Overall, AZD5423 exerted a superior efficacy compared to DEX and BUD in vitro.[39] AZD5423 showed a dose-proportional plasma exposure, limited accumulation, and a dose-related effect on plasma and urine cortisol in healthy subjects,[50] whereas it effectively reduced the allergen-induced response in mild allergic asthma.[54,55] The pulmonary bioavailability was related to the device and considerably lower than that predicted in vitro.[47,48] AZD5423 is retained in the lung for a short time and its oral bioavailability is low.[48,49] AZD5423 was generally well tolerated.[48,49,54,55]

AZD7594

The SEGRA AZD7594 (3-[5-[(1R,2S)-2-(2,2-difluoropropanoylamino)-1-(2,3-dihydro-1,4-benzodioxin-6-yl)propoxy]indazol-1-yl]-N-[(3R)-oxolan-3-yl]benzamide) has recently entered clinical development for the treatment of asthma.

AZD7594 is a potent and selective agonist of the progesterone, androgen, mineralocorticoid, and estrogen-α and β receptors. In human alveolar macrophages stimulated by lipopolysaccharide (LPS), AZD7594 potently reduced the release of tumor necrosis factor-alpha (TNF-α).[39] AZD7594 via DPI inhibited in a dose-dependent manner the lung edema induced in a cross-linked dextran gel rat model of asthma, showing an improved therapeutic ratio and prolonged anti-

Table 2 Main PK Characteristics of Investigational GR Agonists for the Treatment of Asthma

Medication	Dose	Route of Administration and Inhaler Device	C_{max} (pg/mL)	t_{max} (h)	$t_{1/2}$ (h)	AUC (nmol*h/L)	AUC_{0-t} (nmol*h/L)	AUC_{0-24} (nmol*h/L)	$AUC_{0-\infty}$ (nmol*h/L)	*CL*/*F* (L/h)	V_d (L)
GW870086X	1 mg (repeat dose)	Via inhalation, DPI	198.0	0.08	NA	NA	NA	2.4	NA	NA	NA
	3 mg (repeat dose)	Via inhalation, DPI	440.0	2.5	18.6	NA	NA	NA	NA	NA	NA
	3 mg (single and repeat dose)	Via inhalation, DPI	207.0	4.5	NA	NA	NA	6.9	NA	NA	NA
	5 mg	Via inhalation, jet nebulizer	1212.0	0.4	25.0	NA	NA	10.7	NA	NA	NA
	6 mg (repeat dose)	Via inhalation, DPI	NA	0.8–3.5	22.7	47.71	NA	NA	NA	NA	NA
	8.75 mg	Via inhalation, jet nebulizer	2073.0	0.3	29.6	NA	NA	24.2	NA	NA	NA
	12 mg (single and repeat dose)	Via inhalation, DPI	NA	0.8–3.5	22.7	47.71	NA	NA	NA	NA	NA
	15 mg (single and repeat dose)		NA	0.8–3.5	22.7	47.71	NA	NA	NA	NA	NA
AZD5423	100 μg	Via inhalation, hand-held vibrating mesh nebulizer	2417.7	0.1	62.5*	NA	NA	4.3**	NA	67.5	NA
	125 μg	Via inhalation, jet nebulizer	1803.6	0.08	51.3*	NA	NA	4.3**	NA	91.6	NA
	250 μg	IV	5166.9	0.4	25.0	10.9	10.4	NA	NA	47.2	1700.0*
			6531.8	0.4	30.7	13.5	12.8	NA	NA	NA	NA
	300 μg	Via inhalation, hand-held vibrating mesh nebulizer	5410.7	0.08	65.0*	NA	NA	10.1**	NA	85.1	NA
	332 μg	Via inhalation, DPI	1798.7	0.2	25.5	8.5	8.0	NA	NA	NA	NA
	375 μg	Via inhalation, jet nebulizer	8091.6	0.1	95.1*	NA	NA	15.6**	NA	75.8	NA
	405 μg	Via inhalation, hand-held vibrating	1150.4	0.3	17.9	6.2	5.9	NA	NA	NA	NA
	420 μg	mesh nebulizer	1603.7	0.2	21.4	4.5	4.3	NA	NA	NA	NA
	450 μg	Via inhalation, jet nebulizer	3850.8	0.2	11.5	9.0	8.9	NA	NA	NA	NA
	456 μg	Via inhalation, DPI	1438.0	0.2	21.5	8.1	7.7	NA	NA	NA	NA
	499 μg	Via inhalation, jet nebulizer	7019.2	0.1	58.2*	NA	NA	17.9**	NA	88.1	NA
	523 μg		1969.3	0.3	26.6	10.9	10.4	NA	NA	NA	NA
	1200 μg	PO	409.9	0.8	4.00	1.6	1.7	NA	NA	NA	NA
			293.9	1.5	13.0	2.9	2.5	NA	NA	NA	NA
TPI 1020	600 μg	Via inhalation, DPI	95.2	3.0	NA	342.6	NA	NA	NA	NA	NA

(*Continued*)

Table 2 (Continued).

Medication	Dose	Route of Administration and Inhaler Device	C_{max} (pg/mL)	t_{max} (h)	$t_{1/2}$ (h)	AUC (nmol*h/L)	AUC_{0-t} (nmol*h/L)	AUC_{0-24} (nmol*h/L)	$AUC_{0-\infty}$ (nmol*h/L)	*CL/F* (L/h)	V_d (L)
AZD7594	58 μg	Via inhalation, DPI	36.4	0.25	NA	NA	0.467	0.467	NA	NA	NA
	150 μg	IV	6598.0	NA	1.8–9.2	NA	3.34	NA	6.19	NA	NA
	200 μg (single dose)	Via inhalation, DPI	56.1	0.25	39.9*	NA	1.314	2.426	NA	NA	NA
	250 μg	Via inhalation, DPI	92.0	0.25	NA	NA	1.728	1.725	NA	NA	NA
	400 μg (single dose)	Via inhalation, DPI	76.9	0.52	NA	NA	2.736	4.409	NA	NA	NA
	400 μg (repeat dose)	Via inhalation, DPI	NA	NA	NA	NA	NA	2.426	NA	NA	NA
	400 μg (single dose)	Via inhalation, DPI	112.6	NA	NA	NA	2.524	NA	NA	NA	NA
		Via inhalation, DPI	68.9	NA	NA	NA	2.648	NA	NA	NA	NA
		Via inhalation, pMDI	13.9	NA	NA	NA	0.04293	NA	NA	NA	NA
	800 μg	Via inhalation, DPI	169.7	0.25	NA	NA	4.897	4.894	NA	NA	NA
	1200 μg	PO	19.3	NA	NA	NA	0.110	NA	NA	NA	NA
	1600 μg (single dose)	Via inhalation, DPI	430.8	0.50	43.6*	NA	13.96	NA	32.63	144.5	NA
	1600 μg (repeat dose)	Via inhalation, DPI	NA	NA	NA	NA	NA	20.830	NA	NA	NA

Notes: *PK parameter associated with the terminal slope of a semi-logarithmic concentration–time curve; **PK parameter evaluated at steady state.

Abbreviations: AUC, area under the curve; AUC_{0-t}, area under the plasma concentration–time curve up to the last measurable concentration; AUC_{0-24}, area under the plasma concentration–time curve extrapolated from 0 to 24 hours; $AUC_{0-\infty}$, area under the plasma concentration–time curve extrapolated to infinity; C_{max}, peak plasma concentration; *CL/F*, apparent total body clearance; DPI, dry powder inhaler; GR, glucocorticoid receptor; IV, intravenous; NA, not available; PK, pharmacokinetics; pMDI, pressurized metered-dose inhaler; PO, oral administration; t_{max}, time to peak concentration; $t_{1/2}$, half-life; V_d, volume of distribution.

Figure 4 Traffic light plot for assessing the specific risk of bias of each RCT via the Cochrane RoB 2 tool. D1: bias arising from the randomization process; D2: bias due to deviations from intended intervention; D3: bias due to missing outcome data; D4: bias in measurement of the outcome; D5: bias in selection of the reported result. Red circle indicates high risk of bias, yellow circle indicates some concerns on the risk of bias, green circle represents low risk of bias, and blue circle refers to lack of information due to limited data results available on Clinicaltrials.gov database.

Abbreviations: RCT, randomized controlled trial; RoB, Risk of Bias.

inflammatory activity compared to fluticasone propionate (FP).[39] In a murine model of LPS- or tobacco smoke-induced pulmonary inflammation, the intra-tracheal administration of AZD7594 dose-dependently reduced lung neutrophilia.[39]

A Phase I RCT (NCT02645253) investigated the PK and PD of single and repeat doses of AZD7594 200–1600 µg delivered via a DPI in healthy Japanese male subjects.[45,46] Plasma exposure indicated dose-proportional PK.[45,46] The C_{max} of single doses of AZD7594 200–1600 µg was 56.05–430.8 pmol/L and t_{max} was 0.25–0.50 h.[45,46] Only in a few subjects, the terminal $t_{1/2}$ was reliably estimated to be 40.0–44.0 h since the investigated drug showed a slow terminal phase and achieved low sustained concentrations over the sampling period.[45,46] Urinary excretion of AZD7594 was considered a negligible elimination pathway since less than 0.02% of unchanged drug was excreted in the urine.[45,46] Only multiple doses of AZD7594 1600 µg elicited a partial cortisol suppression compared to placebo, although no reduction in osteocalcin level occurred at any dose.[45,46]

AZD7594 58–800 µg induced a rapid increase in plasma concentrations with a mean C_{max} of 36.4–169.7 pmol/L, followed by a rapid decline in plasma concentration and a slow elimination phase.[43,44] The t_{max} was 0.25 h at all doses.[43,44]

A Phase I device bridging trial (NCT02648438) assessed that when administered to healthy male subjects, AZD7594 400 µg via mono- and multi-dose DPIs produced a systemic bioavailability of 28.2–30.9%. A single dose of AZD7594 400 µg via a pressurized metered-dose inhaler (pMDI) induced a low systemic exposure.[51,52] AZD7594 400 µg via a mono-dose DPI induced a slow absorption with a C_{max} of 112.6 pmol/L, compared to multi-dose DPI and pMDI, which achieved C_{max} values of 68.88 pmol/L and 13.93 pmol/L, respectively.[51,52] AZD7594 IV and PO produced C_{max} values of 6598 pmol/L and 19.31 pmol/L, respectively.[51,52] Following an IV single dose of AZD7594 150 µg, the elimination $t_{½}$ was 1.8–9.2 h, while after inhalation this value was considerably longer.[51,52]

In a Phase IIa RCT (NCT02479412) performed in patients with mild to moderate asthma, once-daily AZD7594 800 µg via a DPI, but not 58–250 µg, improved trough FEV_1 compared to placebo (mean difference [MD] 148 mL).[43,44] While evening PEF improved at all the investigated doses compared to placebo, morning PEF improved only at the highest dose.[43,44] At all doses, AZD7594 induced a reduction in F_ENO, and when administered at 250–800 µg, it decreased the daily use of rescue medication, compared to placebo (MD −0.49 to −0.80 inhalations/day).[43,44] Asthma control markedly improved with AZD7594 58–800 µg, but only AZD7594 800 µg increased the number of symptom-free days and asthma control days and reduced night-time awakenings, compared to placebo.[43,44] No difference in plasma cortisol level was observed between AZD7594 and placebo.[43,44]

AZD7594 was safe and well tolerated, and no SAEs were reported in the studies.[43–46,51,52] AZD7594 is still under investigation for asthma in an ongoing Phase I study.[67]

In general, inhaled AZD7594 exerted potent anti-inflammatory effects in animal models of pulmonary inflammation.[39] AZD7594 improved lung function, asthma control, and symptoms, and reduced airway inflammation in mild to moderate asthma.[43,44] AZD7594 showed a dose-proportional plasma exposure and moderate accumulation, with a marginal impact on systemic markers of GC activity in healthy subjects.[45,46] The PK characteristics AZD7594 support the once-daily dosing.[51,52] AZD7594 was characterized by a favorable safety profile.[43,44]

Compound 7

Compound 7 (N-ethylcarbamic acid 9alpha-fluoro -11beta,21-dihydroxy-16betamethyl-3,20-dioxopregna -1,4-dien-17-yl ester) is a betamethasone-derived 17alpha-carbamate with selective activity on GRs.[15] In A549 cells stimulated with phorbol 12-myristate 13-acetate, compound 7 showed a full transrepressor activity leading to potent reduction of matrix metalloprotease-1 levels.[23] Compound 7 has never been under clinical investigation for asthma; the only in vivo results come from a study performed on rats where the administration of the molecule caused a significant anti-inflammatory effect with low impact on glucose, insulin, and triglyceride levels.[23]

Compound A

Compound A or CpdA (2-(4-acetoxyphenyl)-2-chloro-N-methylethylammonium chloride) is a stable analogue of the hydroxyphenylaziridine precursor present in the Namibian shrub *Salsola tuberculatiformis* Botschantzev.[68] Although CpdA is not characterized by a classical steroidal chemical structure, it interacts with the GR and interferes with nuclear factor-kappa B (NF-κB)-driven gene expression.[68] However, a recent study reported that CpdA modulated its anti-inflammatory action in macrophages via the autophagy receptor SQSTM1 and not by the GR, although the research was not specifically related

to asthma. CpdA is as effective as DEX on inflammation, and it does not stimulate GRE-driven transactivation, with a potential lack of the typical AEs of ICSs.[68,69]

CpdA reduced, in a concentration–response manner, the gene and protein expression of fluticasone-resistant chemokines CCL5/RANTES and C-X3-C motif ligand-1 in airway smooth muscle (ASM) cells from healthy subjects and asthmatic patients. It also decreased the overexpression of the chemokine C-X-C motif ligand 10 (CXCL10).[25–27] CpdA also suppressed the production of GC-resistant chemokines via GRα-independent mechanisms through the inhibition of interferon regulatory factor-1 (IRF-1) and the gene upregulation of DUSP1.[25,26] CpdA had no effect on the kinetic activation of the signal transducer and activator of transcription 5 and p38 induced by TNF-α/interferon-gamma (IFN-γ) combination in ASM cells, but it inhibited the cytokine-induced activation of IRF-1.[24] In human respiratory epithelial A549 cells, combining CpdA 10 μM with DEX 10 nM inhibited the expression of chemokine C-C motif ligand 2 (CCL2), CCL5/RANTES, TNF-α, and intracellular adhesion molecule compared to monocomponents.[29]

In a predominantly Th2-driven murine model of asthma, CpdA 100–300 μg was as effective as DEX 5 μg in abolishing ovalbumin-induced AHR.[37] CpdA also counteracted mucus production, collagen deposition, goblet cell metaplasia, recruitment of eosinophils, neutrophils, dendritic cells, B cells, T cells, macrophages, and mast cells in bronchoalveolar lavage fluid (BALf).[37] Furthermore, both CpdA and DEX inhibited the infiltration of Th2, Tc2, Th17, and Tc17 cells, suppressed cytokine production in BALf, and prevented the nuclear translocation of NF-κB to the IκBα promoter in the lung.[37] Unlike DEX, CpdA confirmed the "dissociating" GR modulator profile as it failed to upregulate DUSP1 gene expression.[37]

No clinical trials on CpdA have been performed in asthmatic patients.[9]

Overall, CpdA differentially suppressed the expression of steroid-resistant inflammatory genes in ASM cells[25,26] and modulated the mechanisms leading to the pathogenesis of asthma.[24–27] CpdA is characterized by a favorable GR profile, by cooperatively suppressing inflammation while increasing the expression of specific anti-inflammatory genes.[29] In a murine asthma model, CpdA inhibited airway inflammation and AHR without inducing transactivation, and the overall anti-inflammatory effect was mainly GR dependent via inhibiting NF-κB activity.[37]

GSK9027

The SEGRA GSK9027 (N-[4-[1-(4-fluorophenyl)-1H-indazol-5-yl-3-(trifluoromethyl)phenyl]benzenesulfonamide) is a reverse sulfonamide benzyl analogue, with limited information concerning in vitro and in vivo studies. MMTV transactivation assays in human A549 epithelial cells demonstrated that GSK9027 was characterized by a high plasma protein binding compared to DEX, with a <100-fold reduction in potency.[41]

An in vitro study investigated the activity of GSK9027 in human bronchial epithelial BEAS-2B cells transfected with 2XGRE-driven luciferase reporter plasmid either not treated or pre-treated with TNF-α.[32] Relative to the maximally effective concentration of DEX, GSK9027 produced lower 2XGRE reporter activation compared to fluticasone furoate (FF), FP, and BUD; therefore, it can be considered a partial agonist.[32] Unlike full agonists, GSK9027 induced weak gene expression of TSC22D3 and RGS2.[32]

In mice challenged with IL-1, GSK9027 0.1–100 mg/kg PO dose-dependently reduced circulating IL-6 levels.[41] In mice and rats, GSK9027 PO produced a t_{max} >6.0 h, and showed low clearance and a moderate volume of distribution, with an elimination $t_{1/2}$ of 3.0–4.0 h.[41] Evaluation of systemic exposure of GSK9027 documented a low level of unbound drug fraction in plasma, compared to DEX.[41] The compound is not currently under investigation for asthma, and therefore no clinical data regarding the safety and efficacy of GSK9027 are available.

GW870086X

The SEGRA GW870086X (also called GW870086), currently under development for the treatment of asthma, is characterized by a classical steroidal structure similar to that of FF, but with a modification at position 17-α.[70] This confers enhanced affinity for the GR, leading to potent anti-inflammatory activity mediated by the ability to regulate only a subset of those genes that are normally affected by classical ICSs.[40]

In BEAS-2B cells transfected with 2XGRE-driven luciferase reporter plasmid, either pre-treated or not with TNF-α,[32] GW870086X induced lower E_{max} and 2XGRE reporter activation compared to FF, FP, and BUD, and can thus be considered a partial agonist.[32] Unlike full agonists, GW870086X only weakly induced the gene expression of TSC22D3 and regulator of RGS2.[32]

In A549 lung epithelial cells, the anti-inflammatory profile of GW870086X was similar to that of FP and antagonized the activity of DEX on MMTV-driven reporter gene transactivation.[40] GW870086X induced the expression of specific genes that were also activated by other GCs, without compromising the repression of known pro-inflammatory target genes.[40] In human normal 16HBE bronchial epithelial cells, GW870086X was able to strengthen tight junctions similarly to FP, although no protective effect against elastase-mediated damage was reported.[40]

In a Phase I RCT (NCT00483899) performed in steroid-naïve mildly asthmatic patients, GW870086X 1–3 mg via the DPI Diskhaler® produced a C_{max} of 198–207 pg/mL and a t_{max} of 0.08–4.50 h.[53,71] There was no reduction in total urinary free cortisol and osteocalcin after repeat dosing with GW870086X, indicating a lower potential for metabolic and bone AEs.[53,71] GW870086X protected against adenosine-induced bronchoconstriction,[53,71] leading to estimated mean doubling dose differences of 1.12–1.18.[53,71] GW870086X 1 mg, but not 3 mg, reduced F_ENO concentrations 2–26 h post-dose compared to placebo.[53,71]

A Phase I RCT (NCT00549497) conducted in healthy subjects assessed that inhalation of GW870086X via DPI at 15 mg, but not at 6–12 mg, reduced the 24-hour serum cortisol level, although this reduction was not considerably different from placebo.[59,72] The t_{max} of GW870086X was 0.8–3.5 h and $t_{1/2}$ was 22.7 h.[59,72]

According to a Phase I RCT (NCT01160003), GW870086X 5–8.75 mg was absorbed 20–25 min after administration. The C_{max} was 1212–2073 pg/mL, t_{max} was 0.33–0.43 h, and $t_{1/2}$ was 25.0–29.59 h.[58,59] GW870086X 5 mg produced a partial reduction in total 24-hour serum cortisol.[58,59]

In a Phase II RCT (NCT00945932), GW870086X 1 mg administered in patients with mild to moderate asthma did not improve FEV_1 or the use of rescue medication compared to placebo.[56,57]

A Phase II RCT (NCT01245426) investigated the treatment efficacy of GW870086X in adults with mild to moderate asthma.[60] Inhaled GW870086X 2 mg and 4 mg, but not GW870086X 3 mg, consistently improved FEV_1 compared to placebo (MD 159–172 mL).[60,63]

In a Phase IIa RCT (NCT00857857), repeat inhalation of GW870086X 0.25–3 mg considerably improved LAR, but not allergen-induced EAR, in steroid-naïve atopic mildly asthmatic patients. GW870086X 3 mg was as effective as FP 0.25 mg in enhancing FEV_1 (MD 229–256 mL vs placebo).[61,64]

In another Phase II RCT (NCT01245426), GW870086X 2–4 mg produced C_{max} values of 216–419 pg/mL.[60,63]

No safety issues were identified in patients treated with GW870086X 0.25–15 mg.[56,59-61,63,64] GW870086X is not currently under investigation for asthma; the last update was posted in February 2018 and the status of the clinical trials is yet to be completed.

GW870086X is a partial agonist with weak anti-inflammatory activity,[32] although it protects epithelial cells from elastase-induced damage.[40] In mild to moderate asthma, GW870086X reduced airway inflammation,[53,71] improved lung function,[56,57,60,63] and protected against allergen-induced LAR.[61,64] GW870086X was rapidly absorbed,[59,72] and did not produce a clinically relevant reduction in cortisol or osteocalcin.[53,59,71,72] GW870086X was generally well tolerated.[59,72]

JTP117968

The SEGRA JTP117968 ((4b′S,7′R,8a′S)-4b′-benzyl-7′-hydroxy-N-(2-methylpyridin-3-yl)-7′-(trifluoromethyl)-4b′,6′,7′,8′,8a′,10′-hexahydro-5′H-spiro[cyclopropane-1,9′-phenanthrene]-2′-carboxamide) was found to have the same affinity to GRs as prednisolone, and a moderate affinity for PRs.[21] JTP117968 did not bind to androgen and estrogen receptors, and, differently from prednisolone, it showed no mineralocorticoid receptor activity.[21] In human A549 lung epithelial cells pre-treated with TNF-α, JTP117968 1 μM exerted a partial transrepressor activity and reduced approximately by half the production of IL-6, compared to the efficacy of prednisolone 1 μM.[21] In the MMTV/A549 reporter gene assay, JTP117968 demonstrated an extremely low transactivator activity compared to prednisolone.[21] No further data regarding the efficacy and safety of JT117968 are currently available and the compound is not under investigation for asthma.

PF802

PF802 ((4bS,7R,8aR)-4b-benzyl-7-hydroxy-N-(2-methylpyridin-3-yl)-7(trifluoromethyl)−4-b,5,6,7,8,8a,9,10-octahydrophenanthrene-2-carboxamide) is an active form of the SEGRA fosdagrocorat.[21] PF802 was as potent as JTP117968 in binding GRs, with a moderate binding affinity for PRs, and no binding to androgen and estrogen receptors.[21] Similarly to JTP117968, PF802 had no mineralocorticoid receptor activity.[21] In human A549 lung epithelial cells pre-treated with TNF-α, PF802 demonstrated a more potent

transrepressor activity in respect to JTP117968, leading to a greater inhibition of IL-6 production.[21] In the MMTV/A549 reporter gene assay, PF802 showed a greater transactivator activity than that elicited by JTP117968, although previous data did not confirm this finding.[21] No further data regarding the efficacy and safety of PF802 in asthma are currently available and the compound is not under investigation for asthma, although there are data concerning the parent drug fosdagrocorat, which was shown to be well tolerated with an acceptable safety profile, as observed in two RCTs on rheumatoid arthritis (NCT01393639 and NCT00938587).[73,74]

RU24858

RU24858 (9α-fluoro-11β-hydroxy-16α-methylpregna-21-cyanide-1,4-diene-3,20-dione) is the first SEGRA to demonstrate dissociation between transactivation and transrepression.[70] RU24858 elicits strong transrepressor activity by inhibiting activator protein-1, with no relevant transactivator activity compared to DEX.[70]

RU24858 and DEX both repressed IL-1β-induced expression of cyclooxygenase-2 and IL-8 in A549 pulmonary cells.[31] RU24858 is nearly as effective as DEX at inducing transrepression of NF-κB-dependent transcription by eliciting a lower GRE-dependent transactivator activity than DEX.[31] Two further in vitro studies failed to demonstrate the full "dissociative" profile of RU24858 in human peripheral blood eosinophils and neutrophils.[28,33]

RU24858 1 μM induced transactivation in eosinophils by increasing the expression of chemokine receptor-4 and annexin-I, and elicited transrepression by suppressing the production of IL-8 and monocyte chemoattractant protein-1, similarly to mometasone (MOM) 1 μM and DEX 1 μM.[28]

RU24858 increased spontaneous eosinophil apoptosis as well as DEX and MOM, but unlike the classical GCs, RU24858 was unable to reverse IL-5- or GM-CSF-induced eosinophil survival, indicating a less effective anti-inflammatory activity.[28] In human neutrophils, RU24858 increased the gene expression of growth factor receptor bound protein-2, leukotriene B_4 receptor-1 and annexin-1, suppressed the production of C-X-C motif ligand 8 (CXCL8, also known as IL-8) and macrophage inflammatory protein-1 alpha, and enhanced GM-CSF-induced neutrophil survival to a similar extent to DEX.[33]

In human BEAS-2B cells transfected with 2XGRE-driven luciferase reporter plasmid either pre-treated or not with TNF-α, RU24858 was less effective than DEX, FF, FP, and BUD on 2XGRE reporter activation, indicating that RU24858 should be considered as a partial agonist. The effect of RU24858 on the gene expression of TSC22D3 and RGS2 was weak compared to DEX.[32]

In a rat cross-linked dextran gel model of lung edema, RU24858 was as effective as BUD on inflammation, although it induced systemic effects similar to classical GCs, namely a reduction in osteocalcin levels and body weight, and changes in quantitative osteopenia of the femur.[38] These data indicate that although RU24858 may have some separation between transactivation and repression in vitro, these effects are diminished in vivo and do not translate into an improved safety profile.[38]

No safety data are available since no clinical trials are currently ongoing.

Overall, RU24858 is effective in inducing GC-inducible genes and repressing expression of inflammatory markers,[31] but it did not demonstrate a fully dissociative potential between GRE-dependent transactivation and transrepression.[28] In fact, RU24858 can be considered a partial GR agonist.[32] RU24858 induced the expression of specific anti-inflammatory genes and inhibited the production of pro-inflammatory mediators,[33] although it was less potent than other GCs.[28] The benefit/risk ratio profile of RU24858 was not superior to that of classical GCs.[38]

TPI1020

TPI1020 (NCX 1020, NO-budesonide) is a novel anti-inflammatory compound consisting of a BUD molecule linked to a nitric oxide (NO) donor.[5] When topically administered in the airways, TPI1020 undergoes enzymatic cleavage to yield BUD and gaseous NO at the target site, thus inducing an ASM relaxant effect.[5]

In guinea pigs challenged with LPS, pre-treatment with inhaled TPI1020 inhibited histamine-induced AHR reduced neutrophil and myeloperoxidase levels compared to BUD.[36] TPI1020 also induced concentration-dependent bronchodilation in conscious guinea pigs.[34] When combined with salbutamol (SAL) 80 μM, TPI1020 0.11–0.33 mM elicited a greater inhibition of histamine-induced bronchoconstriction compared to either drug administered individually.[34] TPI1020 0.33 mM plus SAL 80 μM prolonged the bronchodilatory effect (45–75 min) compared to monocomponents.[34] In another pre-clinical study on conscious guinea-pigs, only high doses of TPI1020 (0.33–0.7 mM) induced short-term inhibition of histamine-induced bronchoconstriction.[35] Combining TPI1020 0.11 mM with either formoterol 2.5 μM or tiotropium 2 μM increased the bronchoprotection against provocation with histamine and methacholine compared to monocomponents.[35]

According to a randomized escalated-dose study performed on smokers with mild asthma, TPI1020 had similar effects to equivalent doses of BUD on FEV_1, PEF, rescue-medication use, response to methacholine, asthma control scoring system, F_ENO, and sputum and blood eosinophils.[62] TPI1020 was more effective than BUD on sputum neutrophils in patients with neutrophilia at baseline.[62] Unlike BUD, TPI1020 showed no modulatory effect on 24 h urinary free cortisol, owing to a lower systemic corticosteroid exposure of the investigated drug.[62] TPI1020 600 µg produced a C_{max} of 95.2 pg/mL and a t_{max} of 3.0 h, whereas BUD 400 µg elicited a C_{max} of 490.1 pg/mL and a t_{max} of 0.5 h.[62]

TPI1020 was safe in mild asthmatic smoking patients, and no SAEs were recorded.[62] Compared to BUD, TPI1020 caused three-fold fewer treatment-emergent AEs.[62] The compound is not currently under investigation for asthma; the only study performed in asthmatic patients was a Phase II trial, with the last update posted in December 2012.

In general, TPI1020 is effective against airway inflammation and AHR,[36] and when combined with a LABA, it elicited a greater bronchodilation compared to monocomponents.[34,35] TPI1020 was as effective as BUD, generally safe, and characterized by a favorable PK profile with no effects on cortisol level.[62]

Discussion

For more than half a century, classical GCs have been considered the most important and most frequently used anti-inflammatory and immunosuppressive drugs, and they are still considered the mainstay for the treatment of asthma. Despite the efforts to improve the benefit/risk ratio of GCs, their use may be problematic owing to their safety profile, especially when administered as lifetime therapy and at high dose. Novel selective GR agonists capable of maintaining a beneficial anti-inflammatory action while reducing the risk of AEs are highly anticipated for the treatment of inflammatory disorders such as asthma.

Several compounds are currently under pre-clinical development, but only three novel experimental GR agonists (GW870086X, AZD5423, and AZD7594) seem to have some potential therapeutic relevance and have entered clinical trials for the treatment of asthma.

So far, limited success has been obtained in the development of novel GR agonists, perhaps because the hypothesis that AEs result only from transactivation and the beneficial anti-inflammatory effects from transrepression seems to be oversimplified. Indeed, identifying a fully dissociated GR agonist showing exclusively transrepressive activity without transactivation turned out to be challenging. It was documented that transactivation activities rely strongly on GR levels, co-repressors, and co-activators, and are cell type and tissue dependent.[75] For example, the activity of RU24858 was found to be highly dependent on the level of GR expression and any increase in the co-activators could stabilize the RU24858/GR complex, changing RU24858 into a potent agonist.[75] Conversely, the over-expression of the co-repressor silencing mediator of retinoid and thyroid receptor led to a reduction in the transcriptional potency of RU24858.[75]

Another critical point regards the real binding selectivity of SEGRAs for the GR, which has a common protein structure with other steroidal receptors such as mineralocorticoid, estrogen, and androgen receptors. Although A276575 had high repressive and very low transactivator activities, it failed to show an effective anti-inflammatory action owing to the high affinity for PRs, which translated into undesirable AEs.[22] This evidence highlights the relevance of thorough drug design in order to minimize off-target AEs due to scarce selectivity, while increasing GR therapeutic effects.[76]

On the other hand, GW870086X, RU24858, and GSK9027 exhibited a partial agonistic activity on GRE reporters and a weak gene expression of TSC22D3 and RGS2, which is required for the beneficial therapeutic activities of GCs.[32] Therefore, it has been hypothesized that, on the one hand, partial agonists may exert suboptimal biological effects compared to those exerted by classical GCs owing to their reduced gene expression profile, while on the other hand, this feature may have conferred SEGRAs with the ability to induce fewer AEs, given that genes responsible for AEs are induced in a ligand efficacy-dependent manner.[32] This could translate into an optimized strategy of drug delivery, with full agonists such as classical GCs being used as topical drugs via inhalation, and partial agonists administered systemically, where AEs represent a major concern.[40,56]

In any case, it seems very difficult to really uncouple the therapeutic and harmful effects mediated by GRs. AZD7594 is the most recent non-steroidal GR agonist known to have progressed to Phase II studies for the treatment of asthma. Considering that the last Phase II trial on GW870086X terminated in 2011, AZD7594 and AZD5423 could be considered the only two experimental selective GR agonists in active clinical development for asthmatic patients. Among the newly discovered

compounds, JTP117968 exhibited improved transrepressor versus transactivator activity with no mineralocorticoid effects. Thus, it is expected that JTP117968 could be a suitable compound for developing ideal SEGRAs in the future. Also, GSK9027 demonstrated a potent transrepressor action, with a pharmacological profile similar to DEX, despite a low potency due to the high protein binding. Further larger clinical trials are needed to confirm the dissociated nature of currently developed SEGRAs and their potential superiority over traditional GCs.

Conclusion

SEGRAs capable of optimizing genomic GC effects by preferentially inducing transrepression over transactivation remain a challenging matter to be further investigated for the treatment of asthma. Since data from pre-clinical studies have been not always been confirmed in clinical investigations, well-designed RCTs are needed in asthmatic patients to confirm the potentially positive benefit/risk ratio of each specific SEGRA and to optimize the development strategy of these agents in respiratory medicine.

Abbreviations

AE, adverse event; AHR, airway hyperresponsiveness; ASM, airway smooth muscle; BALf, bronchoalveolar lavage fluid; BUD, budesonide; CCL2, C-C motif ligand 2; CCL5, C-C motif ligand 5 (also known as RANTES); C_{max}, maximum drug concentration; CXCL8, C-X-C motif ligand 8 (also known as IL-8); CXCL10, C-X-C motif ligand 10; DEX, dexamethasone; DPI, dry powder inhaler; DUSP1, dual-specificity phosphatase-1 (also known as mitogen-activated protein kinase phosphatase-1 [MKP1]); EAR, early asthmatic response; E_{max}, maximal response of efficacy; F_ENO, fraction exhaled of nitric oxide; FEV_1, forced expiratory volume in 1 second; FF, fluticasone furoate; FP, fluticasone propionate; GC, glucocorticoid; GM-CSF, granulocyte–macrophage colony-stimulating factor; GR, glucocorticoid receptor; GRE, glucocorticoid response element; ICS, inhaled corticosteroid; IFN-γ, interferon gamma; IL, interleukin; IRF-1, interferon regulatory factor-1; IV, intravenous administration; LABA, long-acting β_2-adrenoceptor agonist; LAR, late asthmatic response; LPS, lipopolysaccharide; MD, mean difference; MMTV, mouse mammary tumor virus; MOM, mometasone; NF-κB, nuclear factor-kappa B; NO, nitric oxide; PD, pharmacodynamics; PEF, peak expiratory flow; PICO, patient problem, intervention, comparison, and outcome; PK, pharmacokinetics; pMDI, pressurized metered-dose inhaler; PO, per os; PR, progesterone receptor; PRISMA-P, preferred reporting items for systematic reviews and meta-analyses protocols; RANTES, regulated on T-cell activation, normal T-cell expressed and secreted; RCT, randomized controlled trial; RGS2, regulator of G protein signaling 2; RoB2, Risk of Bias 2; SAE, serious adverse event; SAL, salbutamol; SEGRA, selective glucocorticoid receptor agonist; SEGRM, selective glucocorticoid receptor modulator; $t_{1/2}$, half-life; t_{max}, time to reach C_{max}; TNF-α, tumor necrosis factor-alpha; TSC22D3, TSC22 domain family member 3 (also known as glucocorticoid-induced leucine zipper).

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