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Innovations in asthma therapy: is there a role for inhaled statins?

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Abstract

Introduction—Asthma manifests as chronic airflow obstruction with persistent inflammation and airway hyperresponsiveness. The immunomodulatory and anti-inflammatory properties of the HMG-CoA reductase (HMGCR) inhibitors (a.k.a. statins), suggest a therapeutic role in chronic inflammatory lung diseases. However, despite positive laboratory investigations and promising epidemiological data, clinical trials using statins for the treatment of asthma have yielded conflicting results. Inadequate statin levels in the airway compartment could explain these findings.

Areas covered—HMGCR is in the mevalonate (MA) pathway and MA signaling is fundamental to lung biology and asthma. This article will discuss clinical trials of oral statins in asthma, review lab investigations relevant to the systemic versus inhaled administration of statins, address the advantages and disadvantages of inhaled statins, and answer the question: is there a role for inhaled statins in the treatment of asthma?

Expert commentary—If ongoing investigations show that oral administration of statins has no clear clinical benefits, then repurposing statins for delivery via inhalation is a logical next step. Inhalation of statins bypasses first-pass metabolism by the liver, and therefore, allows for delivery of significantly lower doses to the airways at greater potency. Statins could become the next major class of novel inhalers for the treatment of asthma.

Keywords

Asthma; drug repositioning; drug repurposing; inflammatory lung disease; inhalation; inhaled; inhaler; pravastatin; rosuvastatin; simvastatin; atorvastatin; statins

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Declaration of interest

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1. Introduction

1.1. The impact of asthma

Asthma is a complex disease of airway hyperresponsiveness, chronic airway inflammation, and reversible airflow obstruction leading to symptoms of breathlessness, wheezing, and cough. Between 40 and 60% of asthmatics fail to obtain symptom control [1–3], and up to ~60% are nonresponders to inhaled corticosteroids (ICS) [4]. Given that 1 in 12 Americans (27 million people) [5,6] and approximately 300 million people worldwide have asthma [7], the high percentage of failed therapy has a major impact and burden on society. Asthma prevalence in adults and children has increased over the past few decades, with 250,000 annual deaths worldwide attributed to the disease [7]. In the USA alone, 9–10 patients with asthma die each day due to lack of effective treatment for this disease [5,6,8]. The total cost of asthma in the USA exceeded $81 billion in 2013 [9], up from $56 billion in 2007.

Severe asthma comprises 10–15% of all asthmatics, yet it constitutes the majority (80%) of asthma-related healthcare costs [2,10–13]. Unfortunately, inhaler therapies are ineffective at controlling symptoms and reducing exacerbations for many of these patients [14]. Suboptimal responses to current standard therapies lead to acute exacerbations, emergency department visits, hospital admissions, and respiratory failure requiring intensive care, all of which contribute to the high and increasing cost of asthma. In addition, the refractory nature of severe asthma calls for the development of more effective therapies [14,15].

There have been advances in the realm of injectable biologics for treatment of asthma. For example, anti-IgE (e.g. omalizumab) is US FDA approved for the treatment of moderate-to-severe asthma in the USA, while anti-IL-5 biologics (e.g. mepolizumab, reslizumab, benralizumab) are FDA approved for the treatment of severe asthma with eosinophilia [16,17]. These medications, however, are relatively new (omalizumab was FDA approved in 2014, while mepolizumab, reslizumab, and benralizumab were FDA approved in 2015, 2016, and 2017, respectively), not yet widely available, and are expensive as compared to corticosteroids. Similarly, potentially repurpose-able drugs like statins [18] are widely used, extensively studied for long-term effects, and are currently generic and off-patent, which decreases their overall cost [19]. Additionally, the absence of noninvasive delivery options for biologics by the inhaled or oral routes may discourage some patients from using these injectable medications which are typically administered on a monthly or more frequent basis.

Novel but affordable systemic and/or inhaled therapies are urgently needed in asthma, in particular for those with severe asthma, which has a disproportionate burden on healthcare costs [9,20–23]. Although strides have expanded the current armamentarium of asthma therapy, pharmacologic therapies for the different phenotypes of asthma remain limited and inadequate, in particular for non-eosinophilic asthma [24–26]. Moreover, we currently have only three classes of inhaled medications for the treatment of asthma: glucocorticoids, β-agonists, and muscarinic antagonists.

1.2. Challenges and opportunities in novel asthma therapeutics: the statins

The statin drugs have been in clinical use for at least three decades for the treatment of hyperlipidemia and cardiovascular disease, including ischemic heart disease and stroke. Statins inhibit 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase (HMGCR), the rate-limiting step in cholesterol biosynthesis, known as the mevalonate (MA) pathway (Figure 1). Mevalonate is the immediate product of HMGCR, and MA is further metabolized into several molecules important in diverse cellular functions relevant to lung biology (discussed in detail below in Section 3) [27–29].

Over the past 17 years, the discovery of statins' pleiotropic immunomodulatory properties led to numerous studies evaluating their impact on key disease outcomes, particularly via their anti-inflammatory, anti-proliferative, anti-fibrotic, and antioxidant effects (Figure 2) [29–33]. For example, preclinical animal studies using systemic (i.e. intraperitoneal (i.p.)) administration of statins for the treatment of allergic asthma demonstrated reduced eosinophilic inflammation, airway mucus production, and airway hyperresponsiveness [31,32,34–38]. The repurposing of statins for the treatment of lung diseases is, therefore, a worthwhile opportunity since there is a growing need to find alternative therapies for the treatment of severe asthma refractory to standard controller therapy, i.e. inhaled and/or systemic corticosteroids and inhaled β-agonists.

In epidemiological and observational studies, statins are associated with therapeutic benefits in asthma and chronic obstructive pulmonary disease (COPD) [18,39–41]. In addition, statins have biological plausibility in various lung disease models based on positive animal and cell culture data [31,32,35,36,42–50]. However, several small randomized clinical trials (RCT) using oral statins for the treatment of asthma have yielded conflicting results [51,52]. While results from these RCTs show a consistent anti-inflammatory effect by reducing sputum inflammatory cell counts and cytokine levels [53–56], they do not demonstrate improved clinical outcomes in terms of symptoms or lung function [41,57–60]. The reasons for this disconnect between basic and clinical studies are unclear, but for clinical trials choosing the right disease phenotype and treating for years rather than weeks or months may be necessary to see clinical benefits [41].

Statin dosing, treatment duration, statin tissue levels in the airway compartment/wall, statin class and physicochemical properties (e.g. lipophilic versus hydrophilic), asthma clinical severity, and disease phenotype are just some of the important variables that could explain the equivocal clinical trial data. This controversy and lack of clarity regarding statin efficacy in treating asthma demands additional research, especially given statins' pulmonary-relevant biological effects (Figure 2), relative drug safety file, wide availability, and low cost (of the off-patent statins).

We hypothesize that a key determinant in the conflicting RCT results to date is the inconsistency of statin airway distribution (D_{airway}). The concept of *distribution* in pharmacology is the amount of drug that reaches a particular tissue compartment after administration regardless of the delivery route [61,62]. Therefore, we define D_{airway} as the fraction of a drug dose that reaches the airway compartment or wall (which includes the

mesenchymal and/or epithelial cell layers) whether administered intravenously (IV), orally, or inhaled.

In pharmacology, *bioavailability* is one of the principal pharmacokinetic (PK) properties of drugs and represents the fraction of an administered dose that enters systemic circulation. For instance, a medication administered IV has a bioavailability of 100%. The bioavailability of a drug administered orally will typically be less as compared to IV administration, and this is particularly true for orally ingested statins. Simvastatin ingested orally, for example, has a bioavailability of less than 5%, and thus the amount of simvastatin that reaches the lung or airways after oral administration may very well be too low to be clinically effective; this concept is further explored in Section 3.0 below [63,64]. Consequences of low bioavailability include the requirement for higher administered doses in order to achieve required drug levels at the target site, i.e. airways. Such a dose of orally administered statin may prove to be quite high for treatment of pulmonary disorders, raising concerns about the safety of alternative higher oral dosing.

Statin class based on drug lipophilicity may be a major determinant of D_{airway}, where the most lipophilic statin is predicted to have the greatest extrahepatic tissue distribution [65]. Therefore, large, prospective, and well-designed clinical trials in severe asthma using oral statins as adjunctive therapy to corticosteroids should include a careful assessment of statin D_{airway}. In other words, if we aim to target the airways using oral statins, then it is critically important that we directly measure statins and their active acid metabolites both in the systemic circulation and airway epithelium (or other parts of the airways compartment via endobronchial biopsies). This will allow us to determine which class or type of statin has the highest D_{airway} at a given dose, will inform how we design future clinical trials, and eventually provide further insight into whether statins should alternatively be developed for inhalation rather than oral administration in the treatment of asthma. Therefore, in this review we propose the following central question: **should statins be repurposed as inhalational therapy for the treatment of asthma?**

2. The mevalonate pathway, statins, and relevance to asthma

2.1. The mevalonate pathway and asthma

The mevalonate (MA) pathway is an essential metabolic pathway that includes cholesterol and isoprenoid biosynthesis. The rate-limiting enzyme, HMGCR, is ubiquitously expressed in all cells and converts HMG-CoA into MA (Figure 1). The isoprenoids known as isopentenyl-5-pyrophosphate (IPP), farnesyl-pyrophosphate (FPP), and geranylgeranyl-pyrophosphate (GGPP) are downstream metabolites synthesized from MA. These isoprenoids post-translationally modify various groups of proteins, a process called ‘isoprenylation’ [66]. For example, the monomeric small guanosine triphosphatases (GTPases) are prenylated via farnesyltransferase (FTase) and geranylgeranyltransferases (GGTases I and II), allowing GTPases to anchor in cell membranes to facilitate cell signaling [67]. GTPases function as ‘molecular switches’ that are critical in cell signaling, cellular inflammation, transmigration and cell motility, proliferation, immune responses, barrier integrity, and cytoskeletal dynamics [29,66,68].

Metabolites of the MA pathway, particularly the isoprenoids, have been associated with processes linked to asthma and respiratory ailments, including allergic eosinophilic inflammation [31,36,69], Rho GTPase signaling in airway smooth muscle cells and airway hyperreactivity (AHR) [48,70,71], adaptive immunity and type 2 inflammation [72,73], airway smooth muscle cell proliferation [43], and mucus production [74] (Figure 2). Since these pathogenic mechanisms occur in asthma, perturbation of the MA pathway likely affects disease pathogenesis [29,70]. Metabolites of the MA cascade play a critical role in cell physiology, and therefore, play a fundamental role in disease [29,72,75]; and statins have the capacity to rectify this imbalance in cells and tissues.

2.2. The HMG-CoA reductase inhibitors (Statins)

The statin drugs (“statins”, a.k.a. HMGCR inhibitors) are FDA approved, orally administered medications used for the treatment of cardiovascular diseases. They are classified based on their (1) origin/source (fungal metabolites vs. chemical synthesis), (2) hepatic metabolism, and (3) physiochemical properties such as lipophilicity [65,76–79]. All statins share an ‘HMG-like’ moiety and competitively inhibit HMGCR by this shared mechanism [80] (Figures 1 and 3). It is this moiety that binds the enzymatic site in HMGCR to inhibit the biosynthesis of MA.

However, each statin has distinct pharmacologic properties related to its respective chemical structure, and this is an important variable to consider when selecting statins for studies involving animal models or human clinical trials. The basic biochemical effect of statins is known classically via its inhibition of the MA pathway; by depleting the pool of isoprenoid intermediates IPP, FPP, and GGPP, and downstream squalene and cholesterol. Statins also possess diverse pleiotropic and immunomodulatory properties beyond lipid-lowering, including various anti-inflammatory, antioxidant, anti-fibrotic, and anti-proliferative effects [31,81–84] (Figure 2).

In addition, statins can directly bind to proteins other than HMGCR [84] such as PPARα [83], LFA-1 [85], and histone deacetylase [86]. This suggests that statins have unexpected off-target effects that should be considered when planning and executing experiments to address mechanism(s) of action.

2.3. Statin treatment of asthma: response, outcomes, and next steps

The effectiveness of statins in asthma is biologically plausible and the inhibition of the MA pathway by statins offers a unique treatment opportunity in severe asthmatics, as this pathway is not affected by corticosteroids, β-agonist therapies, or any other current therapies [87–89].

Multiple large observational studies in asthma have shown a positive correlation between 12 months of statin use and improved clinical outcomes, such as a decrease in age-related lung function decline [39], reduced oral corticosteroid use, and reduced emergency department (ED) visits [18,39,40]. Based on the literature and our own studies, steroid-insensitive asthmatics with type 2 inflammation and persistent airway eosinophilia should respond positively to added statin therapy [31,54]. It is important to note that this does not necessarily preclude asthmatics with non-Th2/non-type 2 (or type 2-low) inflammation, non-

eosinophilic asthma, or neutrophilic predominant asthma where we still know very little [24]. For example, smoking asthmatics may also benefit from statins, but the specific sputum inflammatory cell subtypes relevant to severe asthma have not been fully characterized [53,57]. Overall, both animal and human data suggest that combined statin and corticosteroid therapy has additive and possibly synergistic anti-inflammatory effects in the lungs, something that would be very beneficial in severe asthma [54,90,91].

A University single-center observational study in a dedicated severe asthma clinic showed that statin use in addition to standard-of-care ICS/long-acting β-agonist (LABA) therapy was associated with a clinical benefit [92]. In this population, 100% of patients were on ICS, 80% on LABA, and nearly 23% on oral corticosteroids, and all met the American Thoracic Society (ATS) definition of severe asthma [93,94]. Statin use for a median of at least 1 year was associated with improved asthma symptom control as measured by the asthma control test (ACT), with adjusted mean ACT score of 2.2 ± 0.94, $p < 0.02$ [92]. The results from this study indicate that oral statin+ICS/LABA combination therapy is associated with better symptom control than standard-of-care inhaler therapy alone, thus substantiating the rationale for investigating statins in severe asthma. RCTs in this cohort are now needed to determine if a statin intervention added to standard controller inhaler therapy could benefit those with severe asthma.

Seven well-executed RCTs using statins in mild or moderate asthmatics have been published using relevant clinical endpoints, including lung function (e.g. peak expiratory flow rate, forced expiratory volume in the first second (FEV1), forced vital capacity (FVC)), airway inflammation (sputum cell counts and cytokine levels), symptom surveys, and quality-of-life score(s) [53,55–60,87]. However, results from these RCTs have produced equivocal and at times conflicting results. While asthmatics may benefit from added statin therapy by reducing airway inflammation, consistent improvement in lung function or symptoms has not been definitively established in these RCTs [51,52,55]. Although these results can be characterized as equivocal at best [57–60], statins did reduce sputum eosinophils [54,55], macrophages [56], leukotriene B_4, sputum proinflammatory cytokines and growth factors [53]. Statins also improved asthma quality-of-life scores [57]. Moreover, co-treatment with simvastatin and inhaled budesonide caused a greater reduction in sputum eosinophils than treatment with budesonide alone [54]. This suggests that oral statins enhance the anti-inflammatory effects of corticosteroids in the airways of human asthmatics [31,84]. Although not powered to detect differences in lung function, the budesonide+simvastatin combination group also had a greater improvement in lung function, as measured by FEV1, when compared to budesonide alone. Perhaps treating with a statin for a longer duration, and powering studies to detect changes in lung function and exacerbation rates could yield positive results.

These interesting yet incomplete results may be due to several important factors. The RCTs conducted so far have been short-induration (≤8 weeks) using subjects with mild or moderate rather than severe asthma. Indeed, no RCTs have investigated patients with severe asthma or determined the most effective statin or statin class to use. These RCTs also utilized relatively small sample sizes (<75 participants), had varied study designs, used different corticosteroid treatment regimens, and administered oral statin doses typically used

to treat hyperlipidemia [95]. Importantly, these clinical trials did not assess primary end-points such as acute exacerbation requiring systemic corticosteroid treatment, ED visits, hospitalizations, and/or respiratory failure [87]. Finally, to our knowledge, no study has ever determined statin D_{airway} leaving us with no direct knowledge of drug penetration into the airway compartment, and more specifically, the bronchial epithelium.

It is important to emphasize that statins were not developed *a priori* to target asthma pathophysiology. The varied oral statin doses used in these asthma studies reflect knowledge and standards established in patients with cardiovascular diseases, i.e. hyperlipidemia and ischemic heart disease. Therefore, our current statin types and classification, and their dosing regimens were originally optimized for lowering cholesterol in basic and clinical studies of cardiovascular disease, rather than for statins' immunomodulating or anti-inflammatory effects relevant to asthma [46]. One cannot simply extrapolate such dosing practices without first understanding their effects on asthma-relevant pathophysiological mechanisms. This is a limitation of repurposing drugs that have initially been studied and approved for different disease pathophysiologies and clinical outcomes.

In nearly all animal studies, the statin doses used (via intraperitoneal (i.p.) injection) are much higher (> three orders of magnitude based on weight) than that used in humans (oral route), likely to account for the differences in drug metabolism between typical rodent models and humans. For example, the half-life of statins in rodents is minutes (e.g. 4 min) [96] rather than hours as seen in humans (e.g. 1–14 h) [64,97]. Such a wide range exits due to drug–drug interactions that can affect statin metabolism in humans [98]. This difference in dosing and pharmacokinetics could also explain the disparate findings between rodent disease models and human RCTs.

Key questions that must be taken into consideration when designing future human clinical trials include: (1) which asthma phenotype, (2) what stage of disease severity, (3) what statin treatment duration, and (4) which statin with the highest D_{airway} will yield significant clinical benefits (e.g. reduce acute exacerbations, improve symptom control, enhance lung function, steroid-sparing, etc.)? These important questions should be addressed or taken into consideration before conducting large, multicenter RCTs investigating the therapeutic benefits of statins in asthma.

While not a necessary prerequisite to conducting clinical trials, having a better understanding of statin mechanism(s) of action relevant to airway inflammation, fibrosis, remodeling, and resolution/healing [99], particularly whether this occurs via HMGCR inhibition and/or other non-canonical targets, will complement drug development and innovations in drug delivery that may follow.

Moving forward, any planned clinical trials that administer oral statins should also simultaneously measure statin drug concentrations in the blood and airway compartment to determine bioavailability and statin D_{airway}. Since the lung is the target organ of interest, it is vital to know if statins are reaching the lungs and airways. Mass spectrometry can be utilized to quantify statin levels and statin metabolites in plasma, and in the airway epithelium and bronchoalveolar lavage fluid [100–102]. Having this information combined with outcome-

driven clinical data in asthma will help investigators determine the most effective route of administration: oral versus inhaled.

3. Statin pharmacological properties and drug metabolism: oral versus inhaled statins

The chemical structure of statins determines drug activity by inhibiting HMGCR. Statins exist in equilibrium between the lactone (closed ring) inactive form and the acid (open ring) active form (Figure 3). This acid configuration resembles the precursor metabolite HMG-CoA, and this 'HMG-like' structure is preserved in all statins, and directly binds the HMGCR active site [80]. For the oral statins developed as a lactone prodrug, like simvastatin, conversion to the active acid form occurs naturally in the host body by several different enzyme families including lactonases, paraoxonases, alkaline hydrolases, and carboxylesterases. Whether this conversion into the active form also happens when statins are delivered via inhalation still requires further study. This conversion likely occurs in the lungs and airways because many of the metabolizing enzymes present in the liver and gut are also present in the lungs, but at much lower concentration. Based on the anti-inflammatory and bronchodilatory effects of intra-tracheally delivered or inhaled statins in animal models, as well as on *in vitro* tracheal epithelial cells, we speculate that lung airway cells contain the enzymes necessary to activate statins [34,100,103,104]. This hypothesis is further corroborated by our recent PK and pharmacodynamic (PD) study of inhaled simvastatin in a nonhuman primate model. In this study, we successfully measured the active drug metabolite simvastatin acid in the bronchoepithelial cells of rhesus macaques following nebulization of the prodrug simvastatin directly into the lungs [102,105].

As mentioned earlier, a major reason for the conflicting data from RCTs in asthma using a statin intervention may relate to inadequate target-tissue drug levels in the lungs and airways. Therefore, it is important to know if orally administered statins are detected in the airway compartment, and specifically, the airway epithelial layer, a central player in the development of asthma and other airway disorders [106,107]. Because statins vary in their lipophilicity and in their systemic and peripheral tissue distribution [65,108] and because they are *orally* administered, their extrahepatic effects must first be understood, specifically within the context of human lungs and airways.

There are many variables that can affect bioavailability and the tissue distribution of statins outside the liver. The volume of distribution of drugs depends on protein binding, tissue binding, and membrane permeability [64,108]. In the aforementioned asthma RCTs, statins were administered orally, which is the only FDA-approved route of administration. Hydrophilic statins like pravastatin or rosuvastatin typically require selective membrane transporters, i.e. the organic anion transporting polypeptide (OATP), to reach extrahepatic tissues [65,100]. However, lipophilic statins like simvastatin, readily diffuse across cell plasma membranes and do not require active transporters. Thus, it is thought that lipophilic statins like simvastatin or atorvastatin have greater extrahepatic distribution [65,78,109], and therefore, are more likely to reach the lungs after oral delivery.

Despite this understanding, orally administered lipophilic statins have not demonstrated significant effects in the lungs [110]. This is partially due to extensive clearance by first-pass metabolism in the liver, leaving only <5–20% systemic bioavailability, depending on the statin (<5% for simvastatin and 14–20% for atorvastatin and pravastatin) [63,111]. Also, nearly all statins are highly protein bound in the plasma [33]. Therefore, in the aforementioned RCTs it is possible that D_{airway} was low and the local concentrations achieved were insufficient to exert physiologic and clinical benefits (i.e. inhibit inflammation, reduce mucus production, cause smooth muscle cell relaxation, thereby, improving airflow and alleviating asthma symptoms). This could also explain the lack of consistent and/or robust clinical benefits that would have been expected from the numerous positive observational human and preclinical experimental studies. In addition, the concentrations of the active statin metabolite (i.e. the hydroxyl acid) that reached the airway compartment may not have been high enough to render any significant therapeutic benefits.

This implies the need for PK and PD studies (relevant to both orally administered and inhaled statins) that further establishes the relevance of repurposing of statins as an inhaled therapy. Statin drug metabolism also likely occurs locally in the lung, as well as drug–drug interactions, given that the major metabolizing enzymes are present in lung cells including cytochrome P450 (CYP450), monoamine oxidases, aldehyde dehydrogenases, esterases, NADPH-CYP450 reductases, and various proteases. This also adds to the complexity when considering the fate of statins in the lungs and airways.

Statins' HMGCR inhibitory potency based on the known half maximal inhibitory concentration (IC_{50}) measures also vary. Based on these IC_{50} values, the statins with the highest potency are rosuvastatin > atorvastatin > simvastatin, and the lowest are fluvastatin > pravastatin [33,77,112]. Drug tissue distribution must be balanced against enzyme inhibitory potency, i.e. first, the statin must enter cells (or be actively transported in), before inhibitory potency has any immediate relevance. Therefore, the selection of a statin for clinical studies should be informed by these pharmacological and host organism considerations, as these factors can also affect drug formulation and route of administration choice.

3.1 Using mass spectrometry to measure statins in the lungs: a critical step in the innovation of inhaled statins

Given the complexities described so far, the discrepancies between rodent and human data, and the need to better characterize statin pharmacokinetics and pharmacodynamics, the ability to quantify statins and their active metabolites in plasma and airway/lung tissues using metabolomics is crucial.

When delivering statins by inhalation, sampling of both the airways/lung and the plasma should be performed to assess pulmonary and systemic drug distribution. Nonterminal animal studies can assess lung deposition via sampling of tracheobronchial epithelial cells and bronchoalveolar lavage fluid (BALF). Terminal animal studies can include harvesting the entire lung for comprehensive evaluation, in addition to tissues and bodily fluids, such as skeletal muscle, heart, liver, kidneys, bile fluid, fecal matter, and urine. For example, statins can cause myopathy as a side effect in some individuals; thus, the muscle of the experimental animal could be evaluated for myositis (or more subtle changes following

simvastatin inhalation). This can then be compared to the frequency of side effects that may result from oral administration of the same statin. Corollary blood tests including liver function, skeletal muscle enzymes (e.g. creatine phosphokinase), kidney function and electrolytes, complete blood counts, lipids, and inflammatory biomarkers are also important to include.

Quantitative analysis of statins and their metabolites is well documented and several groups have reported the pharmacokinetic profile of orally administered statins in plasma [113–120]. Effective methods employ liquid chromatography-tandem mass spectrometry (LC-MS/MS) for accurate quantification and high sensitivity detection [100–102,113,121]. The handling of samples for targeted analyses requires proper care to avoid drug metabolism post-harvest and to minimize conversion between the lactone (inactive pro-drug) and acid (active) forms of the statins, which is sensitive to temperature and pH. We predict that the proper quantitation of statins in the airways to determine D_{airway} is one of the keys to elucidating whether statins are beneficial in asthma, and to determine the optimal route of administration.

4. Rationale for developing inhaled statins

The reevaluation and repurposing of existing and approved drugs for the treatment of chronic conditions remains a relatively under-explored area in biomedical research, including in asthma. Drug repurposing refers to the application of known drugs to treat new disease indications, thereby building upon previous research efforts and significantly reducing risks associated with toxicity. The potential for drug repurposing has never been better, especially in the current age of ‘-omics’ and personalized medicine, where we can investigate which asthma phenotypes show a positive clinical response to statin treatment [122–125]. Ideally, future research will also identify specific biomarkers or genotypes to guide statin responsiveness in asthma [126].

The challenges associated with developing inhaled pharmaceuticals (and their delivery devices), coupled with the challenges of novel drug discovery, and pharmaceutical company perceived risks associated with developing inhaled formulations, may contribute to the lack of diversity in current classes of inhalers. Thus, identifying FDA-approved drugs that can be efficiently repurposed for inhalation may present a viable, shorter path toward answering an unmet medical need in severe asthma.

Despite the plethora of molecular targets and pathways discovered in recent decades, we still have only three major classes of inhalers: ICS, short- and long-acting β-agonists (SABA and LABA), and short- and long-acting muscarinic antagonists (SAMA and LAMA). This limited selection and lack of innovation is in part due to the technical challenges inherent to the development of inhaler medications that are not typically associated with development of orally administered medications [127]. Some of these potential obstacles include drug solubility and formulation, aerosolized particle size distribution and lung deposition, and particle-lung interactions (e.g. airway geometry, mucociliary clearance) [127]. In addition, there may be unique regulatory hurdles worth considering when developing inhaled formulations.

However, overcoming these hurdles is worthwhile because direct pulmonary delivery of medications for the treatment of airway diseases may have some merit over oral delivery. For example, inhaled drugs are delivered directly to the site of disease activity in asthma, i.e. the airway, specifically the bronchial epithelium. In doing so, first-pass metabolism by the liver is bypassed and the drug dose required is therefore significantly lower (i.e. microgram instead of milligram doses), thereby potentially decreasing the risks of medication adverse effects, off-target effects, and other unwanted or unanticipated drug–drug interactions. Additionally, dosing studies could reveal effectiveness at doses low enough to minimize systemic absorption and systemic adverse effects, which also reduce undesired off-target effects.

Could delivering statins by inhalation achieve better results in terms of asthma therapy? Direct airway administration of statins has several potential advantages and some attendant caveats and perceived disadvantages (Table 1). However, given the conflicting data from published RCTs and the opportunity costs of waiting for a definitive answer from RCTs using oral statins, we believe the time is ripe to also investigate the potential therapeutic benefits of inhaled statins.

Given the present uncertainty regarding the use of statins in asthma, we and others began investigating the safety and efficacy of delivering statins via inhalation in animal models, as an alternative approach to orally administered statins [100–102,104,105,128–130]. We are currently designing studies using mass spectrometry to measure concentrations of statins and their active metabolites in the plasma, airways, and lungs of patients ingesting oral statins. Preliminary unpublished data from our lab suggest that the D_{airway} and concentration of various statins in tracheobronchial epithelial cells following oral administration is several orders of magnitude lower than the oral dose. Such low statin levels may not have the beneficial biological effects demonstrated in cell culture and animal studies at the low micromolar doses tested experimentally [131]. This relatively poor epithelial D_{airway} may be one explanation for the lack of consistent clinical benefits of statins. Yet, it is premature to draw final conclusions and additional research is required to fully address this important question.

In asthma, the airway epithelium is the central mediator of airway inflammation and remodeling [107,132]. Inhalation directly delivers the drug to the airway without extensive clearance by the liver via first-pass metabolism, thus maximizing target site distribution. Further, by circumventing the systemic route and giving statins directly into the lungs, delivery by inhalation theoretically allows for lower doses with greater effect in the airways. Lower doses may avert off-target and adverse effects associated with the oral ingestion of statins such as myopathy, the most common adverse effect [133]. It is possible that, with the properly adjusted dose, inhaled statins could result in reduced systemic absorption, and therefore, reduced toxicity.

Conversely, we also recognize that inhaled statins could also result in equivalent or higher bioavailability compared to oral statins. If so, this could increase the risk for toxicity and adverse reactions. However, if lower bioavailability is achieved, then lower drug doses given via inhalation may be of greatest benefit for patients intolerant to statin systemic treatment

and the pediatric asthma population where statins are generally not used. Of note, the *pulmonary bioavailability* of statins, defined as the amount of drug that reaches the systemic circulation following inhalation, has not been studied and indeed will depend on each statin's unique physiochemical properties, patient-specific metabolism, drug–drug interactions, and any technical barriers to pulmonary drug delivery. Off-target effects of inhaled statins also need further investigation, with results heavily dependent on drug pharmacokinetic profile, dose, total effect in the lungs, and disease model (i.e. rodent vs. nonhuman primate).

At this juncture, there is a clear rationale to innovate the statins for inhaled delivery. These investigations are urgently needed given the possibility of developing novel adjunctive therapy for the treatment of severe asthma. Given the complexities and unresolved issues concerning treatment of asthma with orally administered statins, coupled with the need to target airways in the treatment of asthma, we speculate that delivery of statins directly to the lung via inhalation could be a better option.

4.1. Inhaled statins for the treatment of asthma: what's the evidence?

There are only a handful of rodent studies that have investigated the effects and mechanisms of inhaled statins; and initial results are promising. Xu et al. [104] showed that treatment with simvastatin via inhalation (1, 5, 20 mg/mL) or intratracheal (i.t.) instillation (2 mg/kg) in an ovalbumin (OVA) mouse model of allergic asthma caused a marked inhibition of airway inflammation, lung eosinophilia, airway mucus production, and airway hyperresponsiveness. Interestingly, the statin anti-inflammatory effect was comparable to dexamethasone (1 mg/kg) administered by the intraperitoneal (i.p.) route.

Conversely, Tschernig et al. [134] showed that i.t. simvastatin did not have significant anti-inflammatory effects in an asthmatic rat model, except for a reduction of BALF eosinophils at a lower dose (0.1 vs. 10 mg i.t.). However, very low doses of simvastatin in the 0.06–6 μg/kg range administered by intranasal (i.n.) inhalation inhibits murine house dust mite allergen-induced airway inflammation and airway resistance [135].

Jha et al. [91] evaluated the effects of simvastatin combined with glucocorticoid therapy. Treating allergic Balb/c mice with subcutaneous (s.c.) simvastatin, i.n. fluticasone, or their combination showed that the coadministration of simvastatin and fluticasone significantly enhances the suppressive effects of either drug alone on airway inflammation and AHR. This further adds to the aforementioned evidence in humans that adding statins to corticosteroids reduces not only eosinophilic inflammation, but also may enhance the beneficial effects of corticosteroids on lung function [54].

Our group showed that treatment of OVA-exposed mice with i.t. pravastatin (30 mg/kg) improved asthma pathology [100]. Unlike Xu et al.'s study of simvastatin, the much more hydrophilic pravastatin had a rather modest anti-inflammatory effect if any; however, it caused significant inhibition of airway goblet cell metaplasia/hyperplasia, and reduced bronchoalveolar lavage fluid (BALF) levels of proinflammatory cytokines including TNFα and KC [100]. Pravastatin also blunted methacholine-induced airway hypersensitivity, but

not AHR, suggesting that pravastatin has basal effects on increasing the threshold to trigger bronchospasm, thereby reducing the likelihood of significant bronchoconstriction.

We do not know if this intriguing discrepancy in results between the different inhaled statin studies is largely due to experimental design or the different types of statins used. In the Zeki et al. and Xu et al. studies, drug levels in the plasma, lung lavage, and whole lung tissue were directly measured. Of note, the pravastatin dose given was 15-fold higher [100] as compared to simvastatin [104], 30 vs. 2 mg/kg i.t., respectively. By this simple comparison in the OVA mouse model of the same strain mice (Balb/c), simvastatin i.t. appears to have greater anti-inflammatory potency and greater improvement in lung function as compared to pravastatin i.t. This suggests that statins' physiochemical properties such as lipophilicity and local lung tissue drug metabolism, may be directly related to its biological and physiological effects *in vivo*. Effects due to low level systemic absorption are also possible. Further research is needed to determine if these observations in mice are applicable in human asthma.

Going a step further, in a series of publications by Tulbah et al. [103,136,137], investigators developed a novel simvastatin formulation for inhalation via a pressurized metered-dose inhaler (pMDI) for human use. A dry powder inhaler (DPI) formulation was also developed and found to be nontoxic to bronchial epithelial cells (Calu-3 cell line) and able to reduce mucus production *in vitro*. The pMDI formulation of simvastatin was subsequently shown to also reduce mucus production, proinflammatory cytokine levels (IL6, IL8, TNFα), and oxidative stress in Calu-3 epithelial cells [103].

Although the above-mentioned studies provide important preliminary data and are crucial in the early development of inhaled statins, assessment in models with a respiratory system that more closely resembles humans is needed (i.e. nonhuman primates), including the use of asthma disease models. We have begun to test the feasibility of inhaled statins, delivered both by masked exposure and via endotracheal intubation, in nonhuman primates (rhesus macaque). We are investigating the pulmonary and systemic bioavailability of statins, more specifically, the pharmacokinetics and pharmacodynamics of simvastatin and pravastatin [101,102,105], and their active metabolites. This research will help advance innovations in the repurposing of statins for the treatment of asthma.

5. Summary

Statins for the treatment of asthma remains an unresolved clinical question. While investigators debate whether oral statins will be effective in the treatment of asthma, especially in severe asthma where the need is greatest, the opportunity to innovate statins for delivery by inhalation is supported by promising *in vitro* and *in vivo* data. We therefore argue that additional research is now warranted to determine if inhaled statins can be used to treat asthma (i.e. phase I/II clinical trials).

We predict that inhaled statins' optimal role will be as an add-on therapy to ICS/LABA, rather than using statins as a single agent. This can be accomplished in a step-wise escalation of therapy to provide enhanced symptom control. Such benefits could potentially

extend to the broader spectrum of airway disease patients including those with COPD or asthma-COPD overlap syndrome (ACOS), and/or the pediatric asthma population. If successful, statins could be the next class of inhaled medications for the treatment of asthma.

6. Expert commentary

Given the biological plausibility of statins, their beneficial action in lungs, promising preclinical data, and conflicting results from asthma RCTs that used oral statins, phase I and II clinical trials in patients with asthma are now needed to assess the safety and efficacy of inhaled statins. If inhaled statins are proven to be safe, then phase II/III RCTs will determine clinical efficacy in asthma. Inhaled statins could be especially useful in severe asthmatics refractory to standard inhaler controller therapy (i.e. high-dose ICS/LABA or ICS/LABA/LAMA), and in those who are corticosteroid-insensitive (including to oral corticosteroids).

7. Five-year view

In the next few years, properly designed RCTs using *oral* and *inhaled* statins for the treatment of asthma will address statins' clinical efficacy. Investigations will also help identify a statin-responsive asthma phenotype or subgroup using biomarkers, metabolomics, or genomics approaches. Depending on the strength of the results and magnitude of the effect(s), these studies will reveal if statins are a viable therapeutic option in asthma and by what route. For patients with severe asthma refractory to corticosteroid treatment, being the 10–15% of asthmatics who incur the greatest healthcare costs [2,12,13], answering this question is especially worthwhile.

Since asthma pathophysiology has a systemic immune component, some systemic absorption of statins could be beneficial whether this is achieved via the oral, inhaled, or combined routes. Delivering the drug directly to airways and bypassing first-pass metabolism will likely permit administration of a much lower dose with equivalent (or greater) effect than if delivered orally, thereby reducing the risk of adverse effects. Inhaled statins at comparatively low doses could potentially benefit the pediatric asthma population, where current therapies are also limited. Similarly, if large multicenter RCTs using oral statins to treat asthma ultimately prove to be negative, then innovating statins for inhaled delivery would be the next logical step.

Key elements in the engineering of inhaled statins include parallel codevelopment of inhaler device technologies and the attendant drug propellant, drug vehicle or solvent, and optimal delivery method and regimen. This can be incorporated into the safety/toxicity (phase I) and preliminary efficacy (phase II) studies necessary before larger, multicenter clinical trials (phase III) can commence.

The design of clinical trials should include an assessment of statin drug levels in the lungs, airways, and systemic circulation, as well as effects on the key endpoints of asthma exacerbation, lung function, symptom control, oral corticosteroid use, and validated biomarkers such as eosinophilia (blood and/or sputum) and fraction of exhaled nitric oxide (FeNO).

Despite the plethora of work still to be done, because statins are FDA approved, repurposing them for the treatment of asthma may be more efficient and less expensive than developing a new drug compound not previously vetted and approved by the FDA. Therefore, the next 5 years affords us a good opportunity to incorporate well-designed clinical trials to answer the central question: is there a role for inhaled statins in the treatment of asthma?

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Key issues

- Current therapies for the treatment of asthma, especially severe asthma, are still lacking. Notably, ICS is the only class of currently available inhalers that is broadly anti-inflammatory. But treating inflammation alone may be insufficient in asthma. Statins have broad therapeutic effects beyond just reducing inflammation, fibrosis, and mucus production that may be beneficial in asthma (Figure 2).
- The use of statins remains an open question in asthma, however, the ideal delivery route is unknown: oral versus inhaled.
- Several small randomized clinical trials (RCTs) using oral statins have yielded equivocal, negative, or conflicting results in the treatment of mild or moderate asthma. However, no RCTs have been conducted in patients with severe asthma.
- Recent pre-clinical data (*in vitro* and *in vivo*) support the use of airway-targeted/inhaled statins for the treatment of experimental asthma.
- The use of targeted and untargeted metabolomics is a powerful tool to assess both statin metabolites and systemic versus airway and lung bioavailability, D_{airway}, and to investigate changes in the human asthma metabolome.
- Given the conflicting results so far from several statin clinical trials in asthma, Phase I and II clinical trials using statins delivered by inhalation are now warranted.
- Patients with severe asthma should be the focus of forthcoming inhaled statin studies where statins are added to standard-of-care ICS/LABA or ICS.

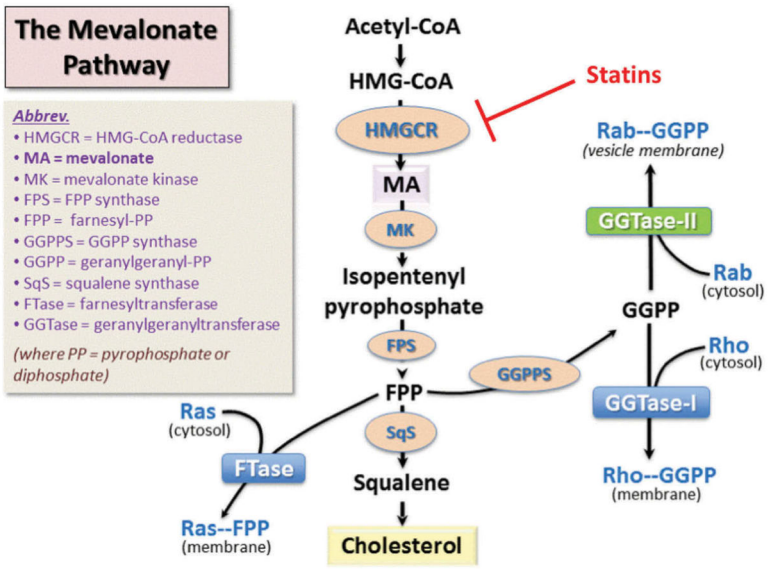

Figure 1. The mevalonate pathway and statin mechanism

The mevalonate (MA) pathway is a ubiquitous biochemical pathway present in all cells. It is essential for many diverse and basic cellular functions, and is necessary for cell survival. The downstream metabolites of MA include the sterol (e.g. squalene, cholesterol) and isoprenoid (IPP, FPP, GGPP) metabolites. The isoprenoids are essential for the function of the small GTPases Rho, Rab, and Ras families. The statins directly inhibit HMG-CoA reductase which depletes intracellular pools of MA and downstream metabolites important in cell cycle, survival, proliferation, regeneration, signaling, and homeostasis.

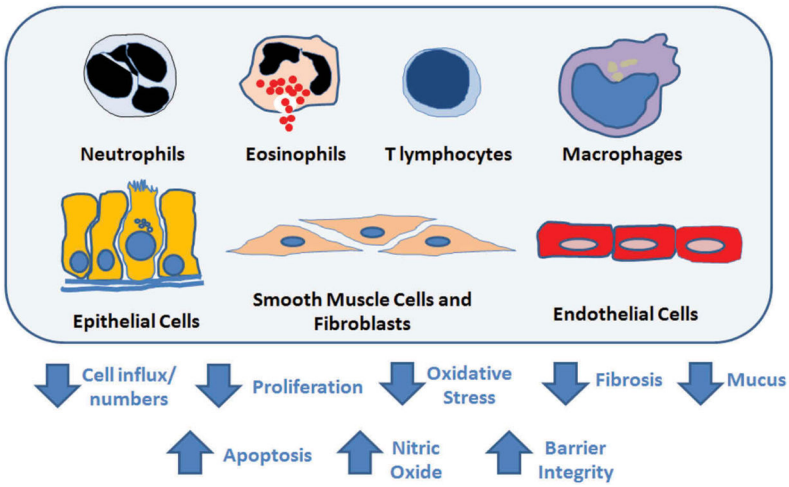

Figure 2. Cell types and pathways affected by statins in the lung

The statins have been studied in various cell culture and animal models. They affect diverse mechanisms and cellular processes in both lung immune cells and resident cells [29]. The statins inhibit the influx of inflammatory cells into airway and lung tissues (e.g. neutrophils, eosinophils, lymphocytes, macrophages) [31,36,138], and reduce airway smooth muscle cell proliferation [43], oxidative stress [129], fibrosis [44], cytokine production [34,139], and mucus production [140]. The statins also induce apoptosis in cancerous or proliferative cells and airway mesenchymal cells [141], enhance macrophage efferocytosis [142], increase endothelial cell nitric oxide production [37], and improve cell barrier integrity [143].

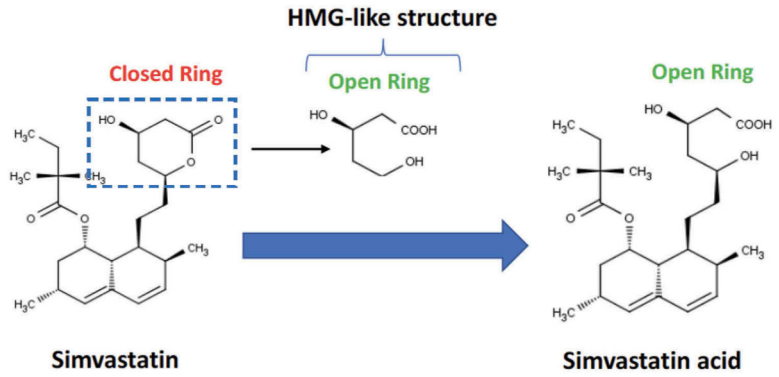

Figure 3. The chemical structure of simvastatin

Statins exist in equilibrium between the lactone inactive form (‘closed ring’) and acid active form (‘open ring’). The acid form of statins is the ‘HMG-like’ structure that binds the HMGCR enzyme active site. This HMG-like structure is present in all statins. *In vivo*, these two chemical forms are in equilibrium. The conversion from lactone to acid depends on the activity of several different classes of enzymes including lactonases, paraoxonases, alkaline hydrolases, and carboxylesterases.

Table 1

Comparing Oral vs. Inhaled Statins.

Advantages	Disadvantages
Oral statins	
• Known oral formulation. • FDA approved. • Systemic levels, side effects, and clinical effects well documented in cardiovascular disease. • Repurposing for other diseases is straightforward (i.e. administration via the oral route). • Rapid transition to the clinical arena if found to be effective in asthma or other airway disorders.	• Airway distribution (D_{airway}) unknown. • Airway drug metabolism unknown (i.e. PK and PD). • RCTs in mild-to-moderate asthma have yielded negative and conflicting data. • Systemic side effects or safety concerns may preclude use in some patients, the elderly, and children. • Oral dosing is optimized for cholesterol-lowering effect, not anti-inflammatory or immune-modulating effects.
Inhaled Statins	
• Direct application into the airway lumen at the disease site of action avoiding liver first-pass metabolism. • Known airway drug levels based on chosen dose of administration. • Initial studies in animals do not show systemic or airway/lung toxicity. • Novel mechanism of action for the treatment of asthma (i.e. inhibition of the MA pathway). • Enhancement of ICS anti-inflammatory effects. • Potential anti-remodeling effects (i.e. reduction of collagen production and fibrosis, mucus production, proliferation, smooth muscle cell hypertrophy/proliferation). • Lower dose as compared to the oral route with equal or potentially greater response.	• Not FDA approved. • Requires development and testing of inhaler drug vehicle and drug propellant. • May require the development of a new inhaler medical device. • Unknown side effects in human airways/lungs. • Degree of systemic absorption unknown and may vary significantly by statin type and physiochemical properties (i.e. lipophilicity vs. hydrophilicity). • Dosing regimen unknown (i.e. frequency, dose, interactions, etc.). • Metabolism in the lung unknown. • Requires time to develop and test before it can be brought to the clinical arena, including IND FDA approval.

PK: pharmacokinetics, PD: pharmacodynamics, ICS: inhaled corticosteroid, MA: mevalonate, IND: investigational new drug, FDA: Federal Drug Administration, RCT: randomized clinical trial.