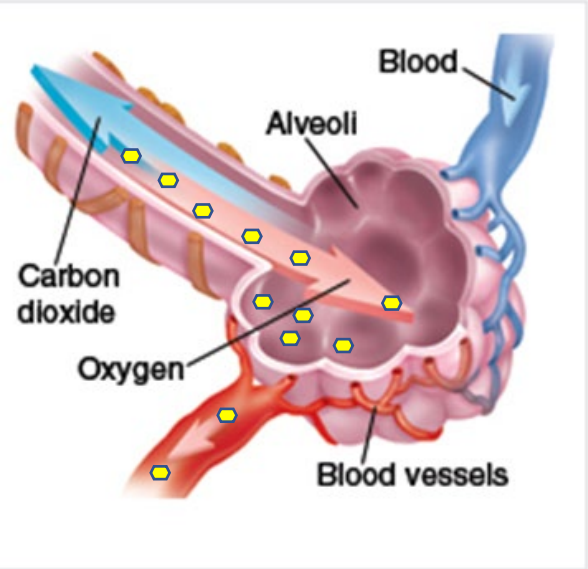
WHICH IS THE PREFERRED APPROACH FOR IMATINIB AS A TREATMENT OF PAH, ORAL OR INHALED?

While oral delivery of tablets and capsules remains the preferred treatment modality for most patients, inhaled therapeutics have dominated the landscape for managing many common lung diseases, particularly asthma and chronic obstructive pulmonary disease, where the target is the bronchial tree.[1] In these diseases, the inhalation route allows drugs to be delivered directly to the site of disease leading to improved efficacy while reducing the potential for side effects due to lower systemic exposure. These inhaled treatments are available in a variety of formats, including nebulizers, metered dose inhalers (MDIs), and dry powder inhalers (DPIs). [2] The potential to use the inhalation route to treat systemic disease has long been debated, since its initial appeal was to **reduce** the systemic absorption of the drugs.

Pulmonary drug delivery is relatively complex because the respiratory tract has evolved defense mechanisms to keep inhaled drug particles out of the lungs and to remove or inactivate them once deposited. [3] In addition to these mechanical, chemical, and immunological barriers pulmonary drug delivery is adversely affected by the behavioral barriers of poor adherence and poor inhaler technique. Poor inhaler technique has long been recognized as a limitation of inhaled drug delivery, and worryingly a recent review concluded that the ability of patients to use inhalers correctly has not really improved over the last 40 years.[4] Thus, while the concept of an inhaled route for drug administration was considered for many products more than two decades ago, few have reached the market, and none has achieved commercial success.

Pulmonary drug delivery is a form of drug targeting, whether to the site of action in the lungs for topically acting drugs, or the site of absorption for systemically acting drugs. For the former, the advantages of pulmonary delivery include the possibility to use a relatively low dose, a low incidence of systemic side effects and for some drugs a rapid onset of action. For systemically acting drugs, pulmonary delivery offers an opportunity to avoid injections for drugs that are not well absorbed via the GI tract, and the possibility for more advantageous pharmacokinetic profiles. [5]

The lungs consist of a complex network of branching airways, termed the ‘bronchial tree’. If a particle is to penetrate to the alveolar region and gain access to the large vascular target site, it must pass numerous airway bifurcations. Deposition also depends critically on inhalation parameters, most notably inhaled flow rate, inhaled volume and breath-hold pause. Most inhalers deposit less than 20% of the dose in lungs, with the majority usually being deposited in the oropharynx. [6]



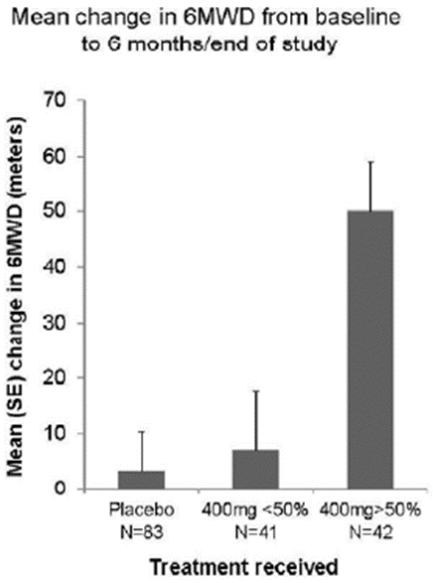
For systemic absorption of inhaled therapies to be effective, the drug (⬣) needs to reach the alveoli where it will be absorbed into the capillaries of the lung. The drug will enter the pulmonary venules (red) where it will drain into the left heart and then the systemic circulation.

The delivery of drugs by inhalation to achieve a systemic effect has yet to fulfill its promise. The best example of the challenges using an **inhaled formulation for PAH** has been treprostinil, the prostacyclin analogue. It was initially approved for subcutaneous administration, but it turned out, unexpectedly, that severe and often intolerable site pain from the injection site occurred in over 80% of patients. That led to the development of an inhaled formulation as an alternative route of administration to achieve adequate systemic exposure. A Phase 3 clinical trial (TRIUMPH) was conducted in the United States and Europe which reported an improvement in 6-minute walk of only 12 meters, with no improvements in the key secondary endpoints.[7] While this was sufficient for approval by the FDA, the application was denied by the EMA. They noted that the treatment effects were non-significant in the patients studied in the U.S. In addition, while the effect was better in the patients studied in Europe, after a closer inspection they rejected the findings due to *"several critical and major findings in the two investigator sites inspected, pertaining to trial management, and quality of the data."* Removing those 2 sites eliminated a favorable treatment effect.[8]

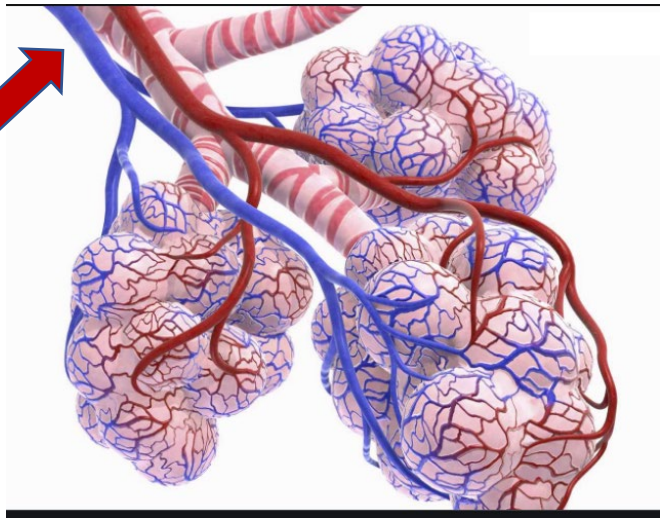
The **Phase 3 IMPRES** trial of imatinib for PAH was very informative. It established the efficacy (based on the improvement in 6-minute walk distance) of imatinib as a treatment for PAH. It also identified gastrointestinal side effects as being problematic for patient acceptance. While that observation provided consideration for an alternative route of delivery, the trial also clearly showed that the dose of imatinib necessary to achieve the level of systemic exposure to the drug ***was critical*** for efficacy.

Data from the IMPRES trial is shown. The change in 6-minute walk is displayed, comparing the placebo group to the patients receiving imatinib divided into those whose dose was 400 mg less than 50% of the time with those whose dose was 400 mg greater than 50% of the time.

Patients who were administered imatinib 400 mg more than 50% of the time had markedly better responses in terms of 6MWT (59.2 ± 13.8 m) compared to those who whose dose was 200 mg most of the (17.7 ± 11.7 m), showing that the dose of imatinib was an essential feature of efficacy. [9]



It is important to note that the gastrointestinal side effects of imatinib in IMPRES were similar to what has been encountered in the oncology trials with imatinib, but in none of those did it result in an excessively high dropout rate. Oncologists have successfully used simple mitigation strategies such as taking imatinib with meals and fluids. Our development of a delayed release formulation, which prevents the drug from being released in the stomach, should reduce or eliminate the gastric irritation associated with the immediate release formulation used in IMPRES. At the same time, we can assure that the established effective dose of drug administered will be sufficient for a robust drug response. While an inhaled route for imatinib should eliminate gastric irritation, questions about bronchial irritation and whether an adequate systemic exposure of a lower dose of imatinib via inhalation will be effective in PAH remain unanswered.



The predominant area of the pulmonary vasculature that shows the proliferative vascular changes of PAH are the pulmonary arterioles which are 100-200 microns in diameter (arrow).[10] They are upstream of the capillary bed where inhaled drugs are absorbed. For any concentration of inhaled drug to reach that site it must either migrate upstream against blood flow or be deposited downstream after it enters the systemic circulation.

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