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Toward managing chronic rejection after lung transplant: The fate and effects of inhaled cyclosporine in a complex environment

Ralph W. Niven *

APT Pharmaceuticals, Burlingame, CA 94010, USA

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ABSTRACT

The fate and effects of inhaled cyclosporine A (CsA) are considered after deposition on the lung surface. Special emphasis is given to a post-lung transplant environment and to the potential effects of the drug on the various cell types it is expected to encounter. The known stability, metabolism, pharmacokinetics and pharmacodynamics of the drug have been reviewed and discussed in the context of the lung microenvironment. Arguments support the contention that the immuno-inhibitory and anti-inflammatory effects of CsA are not restricted to T-cells. It is likely that pharmacologically effective concentrations of CsA can be sustained in the lungs but due to the complexity of uptake and action, the elucidation of effective posology must ultimately rely on clinical evidence.

Contents

Abbreviations: AP-1, activator protein-1 transcription factor; API, active pharmaceutical ingredient; BM, basement membrane; BALF, bronchoalveolar lavage fluid; BALT, broncho-associated lymphoid tissue; BCS, biopharmaceutical classification system; BOS, bronchiolitis obliterans syndrome; CLAD, chronic lung allograft dysfunction; CsA, cyclosporine A; DC, dendritic cell; ECM, extracellular matrix; ELT, effector lymphoid tissue; EMT, epithelial to mesenchymal cell transition; LEC, lymphatic endothelial capillary; MAPK, mitogen activated protein kinase; MeBmt, methylated butenyl-methyl-L-threonine; MMAD, mass median aerodynamic diameter; MMF, mycophenolate mofetil; NF-AT, nuclear factor of activated T-cells; NO, nitric oxide; SP, surfactant protein (A through D); OB, obliterative bronchiolitis; PG, propylene glycol; pMDI, propellant metered dose inhaler; RAS, restrictive airway syndrome; RBC, red blood corpuscle.

* Tel.: +1 650 931 1666x114; fax: +1 650 931 1638.
E-mail address: rniven@aptbio.com.

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1. Introduction

Cyclosporine A (CsA) is an immunosuppressive agent that has been in widespread use for over 25 years and is predominantly administered by oral administration to prevent or treat rejection of solid-organ transplants. In recent years concerted efforts have been made to develop an aerosol dosage form for the prevention and treatment of chronic rejection [1–7] post-lung transplant and several mid-stage and late stage clinical trials are ongoing.

An underlying hypothesis is that long-term systemic immunosuppression provides insufficient protection to the transplanted lung: not because a drug like CsA is ineffective but because the drug concentration levels are neither high nor sustained enough within the lungs to be efficacious when administered orally or by injection.

This review discusses the fate and effects of CsA after inhalation. It does not compare and contrast the many formulation and delivery approaches that have been taken to administer CsA by aerosol but assumes that a specific dose of drug has been deposited on the lung surface (the "initial condition"). The review then begins with a discussion on the pharmacokinetics and clearance of the drug from the lungs, taking into consideration the barriers that face CsA as well as the potential for its metabolism and degradation within the lung microenvironment. This is followed by a summary of the known effects of the drug on various cell types within the lungs that have been implicated in rejection and then finally by a commentary on calcineurin and other targets of CsA. The implicit argument being made throughout is that the potential benefits of regional targeting outweigh the potential pitfalls.

Wherever possible points are reinforced by employing source documentation as references but it will soon be recognized that little is known about the disposition of CsA from the time of deposition to the point of sub-cellular action. Consequently much of what is discussed is speculative and extrapolated. Clearly, the promise of an inhaled therapy does not replace the clinical evidence of benefit that will emerge within the next few years. Nevertheless, this exercise is instructive and highlights many gaps in our understanding. Hopefully new opportunities for further research will emerge.

2. CsA in an aerosol 'particle'

CsA has been administered as an aerosol in the form of a powder [8] and as a liquid formulation. As a liquid, the drug has been administered via nebulizer in aqueous liposome dispersions [9–11] and as a solution in ethanol [12,13] or propylene glycol (PG) [14–16]. A phase II clinical trial is being conducted in lung-transplant patients using a lyophilized and reconstituted liposomal dispersion in conjunction with the eFlow device (Pari GmbH, Germany) and a phase III trial is well underway evaluating a PG solution formulation delivered by a classical nebulizer system to prevent chronic rejection post-transplantation (APT Pharmaceuticals, USA). Details of the delivery methodology and earlier preclinical and clinical studies can be found in a review by Corcoran [17].

The emphasis of the discussion herein will be on the use of CsA in a PG vehicle at a concentration of 62.5 mg/ml. This is a low concentration relative to the solubility limit of the drug which approaches 400 mg/ml at room temperature and it is unlikely that significant evaporation of the PG will occur prior to droplets depositing in the lungs as PG has a low vapor pressure at room temperature compared with that of water (0.129 mmHg vs. 289.1 mmHg at 25 °C) [18]. Some moisture uptake may take place during transit within the humidified airways as PG is a humectant but irreversible precipitation of the drug is unlikely to take place unless this exceeds ~20% of the droplet volume (data not shown). However, even small amounts of water can cause transient precipitation and it is feasible that precipitation may occur on the surface of the droplets if there is not significant mixing as they traverse the airways (see Section 6.1).

3. The initial condition

When a patient inhales aerosolized CsA the droplets will deposit and accumulate within the extracellular airway and alveolar fluids during the dosing period [17].

The distribution of drug that deposits within the lungs will vary depending on a number of factors including the nature of the allograft (single vs. double), the positioning of and state of the anastomoses [19], the droplet size and the breathing pattern of the patient during dosing [13]. The state of the lungs at the time of dosing will also be critical [20] and in the case of lung-transplant patients lung deposition patterns may well change throughout the course of therapy depending upon whether they have ongoing episodes of acute rejection [21], periodic or persistent lung infection [22] or whether they are experiencing declining lung function due to progressive bronchiolitis obliterans syndrome (BOS) [1,2]. We can also expect that patients who start therapy within days of transplant will still be adjusting to