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Commentary

A Breathe in Cystic Fibrosis Therapy: A New Therapeutic Endeavor for Cysteamine

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Cystic fibrosis (CF) is a lethal monogenic disease with mortality and morbidity mostly associated to lung destruction (O'Sullivan and Freedman, 2009). This, in turn, is strictly dependent on recurrent pulmonary infections, with bacteria growing also in biofilms, leading to an unsatisfactory effect of antibiotics (Ratjen and Döring, 2003). The CF registry of patients reports an improvement of both patient survival and quality of life, due to a global care of several aspects of the disease. Yet, it is an unmet need, hence, the urgency of new antibiotics. Recently, Vertex Ph. has introduced in therapy a new potentiator (a channel gating activator), namely ivacaftor (Kalydeco), whose effects, are beneficial, to date, for patients exhibiting the G551D mutation (Ramsey et al., 2011). Furthermore, the same company has introduced a combination of lumacaftor (a corrector of defective CFTR folding/cellular processing, Orkambi) and ivacaftor (Kalydeco) for patients exhibiting F508del-CFTR, the most common mutation (Wainwright et al., 2015). The effects of this approach have been discussed in several papers (see an extensive comment in (Maiuri et al. (2015)). Interestingly, a recent paper reported the effects of Cysteamine in combination with epigallocatechin gallate, in restoring CFTR function and expression at plasma membrane in nasal brushing from CF patients, via rescue of defective autophagy (De Stefano et al., 2014). Noteworthy, cysteamine has received an Orphan Drug Designation in CF also for its mucolytic properties. Such an effect is extremely attractive, being thick mucus an important issue for CF patients. Charrier et al. described the antimicrobial, antibiofilm and mucoactive properties of cysteamine, either alone or in combination with recommended antibiotics, a novel mucoactive antimicrobial and antibiofilm agent for the treatment of CF (Charrier et al., 2014). The authors subsequently reported in the study recently published and herein discussed, that patients were invited to provide their sputum, the most being infected with P. aeruginosa (Devereux et al., 2015). The results of the study prove that daily incubation of sputum with cysteamine significantly decreased the sputum bacterial load and decreased mucus viscosity. The major limitation regarding this study is that no patient has been directly administered. Although cysteamine exhibits also a mucolytic activity that might help in reaching the infected pulmonary site, such an issue must be addressed. Moreover, no characterization of the bacterial type has been provided, meaning that it is also difficult to establish a proper mechanism of action. Finally, the patient mutation type should be taken into account. The study, however, has a great appeal. In fact, cysteamine is an already FDA approved drug for another rare disease, cystinosis, and, thus, in therapy in children. Moreover, side effects have been extensively documented and cysteamine is a safe drug for cystinosis patients although it is well known that pharmacokinetic profile and, thus, tolerability, might be different in CF patients. Moreover, cysteamine is endogenously present, although at very low levels, as a consequence of coenzyme A metabolism (Besouw et al., 2013). The herein cited study, per se, offers the opportunity to address a new mechanism of action for cysteamine and to have a novel drug exhibiting multiple mechanisms of action, being cysteamine an antibiotic, mucolytic and capable of functionally rescuing misfolded CFTR at plasma membrane. These results have been developed from independent research groups and allow to prospectively be positive on the opportunity that cysteamine will be also authorized for CF therapy. In conclusion, there is a strong hope that future studies, carried on with CF patients, will clarify the antibiotic effects of cysteamine, possibly identifying also a dose regimen and, if the case, the bacterial strains that can be treated. Cysteamine, therefore, represents an old drug with several new targets for CF therapy.

Conflict of Interest

The authors declare no conflicts of interest.

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