An approach to studying clinical efficacy and immunological parameters in crenotherapy for respiratory disease in Portugal

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Chronic rhinitis / rhinosinusitis (CRS) and bronchial asthma are two significantly prevalent respiratory diseases worldwide, namely in Portugal. Both are associated with inflammation of the respiratory mucosa, with subsequent clinical symptoms. Sulfurous (natural mineral) thermal waters (STW) have been used as complementary therapeutic approach to these diseases, with studies demonstrating clinical efficacy, particularly in CRS. However, few prospective, randomised, double-blind, placebo-controlled studies have been developed in order to assess clinical efficacy and none has been implemented in Portugal. Furthermore, worldwide, there is scant information of the modulatory effects STW crenotherapy may have on immuneinflammatory aspects underlying CRS and asthma.

It is, therefore, very important to carry out the first prospective, randomised, placebocontrolled, double-blind study of the clinical efficacy of crenotherapy with STW in patients with CRS or asthma, in Portugal. In addition, it is also crucial to assess the relationship between clinical efficacy and underlying changes in immunological parameters.

Our study group has thus designed a two arm, parallel design study, in which 200 adult patients with confirmed CRS and 200 adult patients with bronchial asthma will be recruited and randomised to an active (STW crenotherapy) or a control (saline crenotherapy) arm. This study was approved by the Ethics Committee of UBI, and the National Agency for Data Protection. All patients will sign a written, informed consent. Recruitment will take place at three natural mineral water Spas in Central Portugal, with predominantly STW (São Pedro do Sul, Caldas da Felgueira, and Unhais da Serra). At these places specifically designed equipment was set up in order to allow application of crenotherapy treatments with saline, in a fashion that is

similar to that involving active STW. Patient inclusion criteria include moderate CRS or asthma, with frequent exacerbations, insufficiently controlled with pharmacological treatment. Primary clinical outcomes have been defined for CRS (changes in the 22-item Sino-Nasal Outcomes Test - SNOT-22) and asthma (). Secondary outcomes will be both clinical (symptom score, medication score, number of medical visits due to exacerbations, nasal and bronchial symptom control (CARAT and ACT), quality of life (Rhino-AQLQ and AQLQ), medication costs, inspiratory nasal peak flow (CRS), peak expiratory flow (asthma), and Lund-Kennedy anterior rhinoscopy score (CRS). Secondary laboratory outcomes will be studied in CRS and asthma patients: changes in cytokine levels (IL-2, IL-4, IL-5, IL-6, IL-10, TNF, IFN-gamma, IL-17), in cisteinyl-leucotriene levels, and in differential cell counts, both in nasal fluid (CRS) and in peripheral blood (CRS and asthma). Levels of exhaled nitric oxide (FeNO) will also be studied in asthmatic patients. Statistical analysis will involve Mann-Whitney U test, ANCOVA and Spearman rank correlation test. Clinical data analysis will follow an Intention-to-Treat model.

We expect that these prospective, randomised, double-blind, placebo-controlled studis will allow, for the first time, an adequate analysis of the clinical efficacy of STW crenotherapy in CRS and in asthma in Portugal, as well as the study of its effects on underlying pathophysiological aspects.