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Commentary

Commentary on the effect of an aerosol of Treignac mineral water concentrated by inverse osmosis *in vitro* on normal bronchial cells and *in vivo* on normal rabbit lungs

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Introduction

Our previous publication [1] highlighted a novel biological property of Treignac thermal water concentrated by reverse osmosis: its suppressive effect on cytokine release (IL-6, IL-8, TNF-α) by activated normal bronchial cells. This anti-inflammatory activity complements other biological properties previously demonstrated *in vitro* and *in vivo.*

The main aim of the present paper is to provide more details about our objectives and the clinical trial we intend to set up in order to test the effect of an aerosol of this concentrated mineral water *in vivo,* in humans, on nasal and bronchi mucosa.

Current Therapeutic Arsenal in Otorhinolaryngology and Pulmonology

The nasal and bronchial mucosa consist mainly of ciliated epithelial cells and mucus-secreting goblet cells [2], supported by basal stem cells in both upper and lower airways [3]. In COPD, subsets of basal cells secrete IL-13 and IL-33 [4].

The epithelium acts as a first line of defense, clearing inhaled particles, regulating ionic and water exchanges, and secreting antimicrobial molecules [5].

The periciliary fluid and mucus layer forms a continuous protective interface at the airway surface [6].

A pro-regenerative strategy of the surface epithelium seeks not only to repair damage but also to reconstitute a functional epithelial structure through coordinated processes of cell migration, proliferation, and differentiation. These are regulated by growth factors, cytokines, extracellular matrix proteins, and proteolytic enzymes.

According to international reports, inhaled short-acting inhaled B2 agonists with or without short-acting anticholinergics are recommended to treat chronic obstructive pulmonary disease (COPD) exacerbations [7–19] complemented more recently by biotherapies. In acute and chronic rhinosinusitis, the medical management is mainly based on the use of antibiotics, local corticoids and even general corticoids as adjunctive therapy. Saline nasal irrigation may be also helpful as a post-operative treatment.

The treatment of these inflammatory diseases is therefore essentially based on chemotherapy and biotherapy, and a natural long-term therapy would certainly have its place.

Why Mineral Waters and Interest of Aerosol Therapy?

The main therapeutic objectives of thermal spa centers are the regeneration and healing of the respiratory mucosa, the reduction of inflammation, the improvement of nasal permeability and sustained airway ventilation while limiting infections and relapses.

An extensive review of papers dealing with *in vitro* and *in vivo* biological effects of thermal waters suggest that inhalation of thermal waters may have some beneficial effect, and particularly significant improvements were observed for nasal mucociliary transport time, in chronic and acute rhinitis [20–22] and in asthma and COPD [23–25]. In bronchiectasis, as in cystic fibrosis, efficacy of hypertonic saline aerosol has been demonstrated to enhance mucociliary clearance. An *in vitro* study [26] showed that mineral waters from Ledesma, Paracuellos and Archena spas, three Spanish health resorts, induced a significant increase on human lung fibroblasts, a significant increase of cell proliferation and an increase of the release of mediators (MIF, IL-6, CL-1, CCL-5 and ICAM-) involved in proliferation, wound healing, and cell migration.

In thermal spas, hydrotherapy is based on the use of aerosols, nasal baths, nasal irrigation, inhalation techniques, spraying, sniffing, nebulization, pharyngeal showers, gargling, and exposure to a thermal water mist in a vaporarium.

These different arguments underline the potential interest of hydrotherapy by mineral waters.

What is Known about Concentrated Treignac Water®

Mineral waters are classified as weakly mineralized (<500 mg/L), moderately mineralized (between 500 and 1500 mg/L) and highly mineralized (>1500 mg/L). Treignac natural mineral water is the less mineralized mineral water in France (22 mg/L of dry residue at 180°C), hydroxysilicic acid representing about 32% of total residue (**Table 1**).

Several arguments [1] were in favor of the involvement of hydroxysilicic acid in the biological properties of Treignac mineral water leading us to prepare a concentrated form with a concentration factor of around height. This process has been patented (European patent [27]) in 2024. Concentrated Treignac mineral water (CTMW) is a weakly mineralized solution with an increase hydroxysilicic acid concentration (6.9 mg/L in the natural water to 53.8 mg/L in the concentrated form). We have chosen a factor of height (**Table 1**) due to the risk of spontaneous silica condensation for higher concentrations [27]. Even concentrated, Treignac water remains slightly mineralized and so is hypo-osmolar as compared to saline (9 g/L) but keeps its salt equilibrium as in the natural water.

After production, CTMW is quickly sterilized by gamma ray irradiation and is stable (composition and bacteriology) at least for seven years.

The production of a concentrated mineral water by reverse osmosis containing a high concentration of soluble hydroxysilicic acid and maintaining its original ionic balance, while remaining very weakly mineralized due to the risk of ionic interference which could affect the activity of this active molecule, requires starting with a very low-mineralized mineral water such as Treignac mineral water.

Mechanistic Hypothesis

The main potential active molecule contained in CTMW is soluble hydroxysilicic acid whose condensation, leading to its film-forming property, has been extensively confirmed. This property seems to be original as not observed in a lot of other mineral waters [28] even having a similar chemical composition (drinking waters or mineral waters used as a cosmetic base).

We have previously shown that an aerosol of concentrated Treignac water was markedly active on sensitive skin together with a protective action, a soothing effect, and prolonged moisturization.

Moreover, these biological activities do not allow us to prejudge of its mechanism of action on mucosa or on a cellular layer as in the study of cytokine synthesis (IL-6, IL-8, TNF-α) inhibition by bronchial cells [1].

Soluble silica can associate with macromolecules, affecting their tertiary or quaternary structures—notably with collagen, elastin, glycoproteins, and membrane phospholipids [29].

A biosilicification (condensation of soluble silica) in the presence of biological polymers has been described [30] and has to be considered as an interesting hypothesis.

As, on the basis of these biological effects, we plan to test the activity of an aerosol of CTMW on inflammatory pathologies of the respiratory tract, we have now to complete the next two steps on human mucosal explants in order to confirm *in vitro* the absence of potential toxicity due to its hypo-osmolarity (180 mg/L of dry residue) although we have previously demonstrated the absence of toxicity *in vivo* on rabbit lung, and also to test its efficacy (antibacterial and/or cytokine release inhibition).

Moreover, on intestinal mucosa, low-salt waters have been shown to reduce intestinal permeability in atopic patients [31].

Aerosol Standardization

Thermal waters aerosols are applied in spas either individually (using a personal aerosol generator with a mask) or collectively in a closed room, where compressed air-powered misters create a thick fog.

Table 1. Mean main characteristics of eight times concentrated Treignac mineral water®.

Calcium	8.33 mg/L	Chloride	27 mg/L
Magnesium	3.52 mg/L	Sulfates	5.05 mg/L
Sodium	20.40 mg/L	Nitrates	26.8 mg/L
Potassium	2.34 mg/L	Dry residue at 180°C	182 mg/L
Silica	53.8 mg/L	pH	6.9
Hydrogenocarbonates	26.2 mg/L	Resistivity (ρ)	47 Ω.m

Generally, protocols used in spas are based on aerosol generators delivering particles of 2 to 20 µm, thus ensuring good coverage of the upper and middle respiratory tract. Treatment lasts 10 to 20 minutes and the course of treatment is around 18 days. The particle size is essential for reaching deep airways (particles <5 µ) or to limit the treatment to sinus mucosa (particles >10–15 µ) [32]. For clinical studies we will use standardized aerosol generators. Clinical trials protocols will include different doses of CTMW aerosol taking account of the differences of surfaces between nasal (120 cm^2 et bronchi (300 m^2) mucosa but they have not yet been determined.

At least in France, in spite of the use in routine of mineral waters aerosols in spas, the only authorized solution for aerosol treatment is saline [32] which is widely used either as a vehicle for certain drugs or on its own for nasal irrigation and bronchial clearance. Treignac concentrated water differs mainly by its biological properties, which may be based on dissolved hydroxysilicic acid as an active molecule.

Future Clinical Perspectives and Scientific Program

Whereas numerous therapeutic approaches aim to restore the mucosal barrier through pharmacological means, our purpose is to advocate for future clinical trials in order to evaluate a natural potentially safe background treatment mainly in chronic and acute rhinitis and COBP (Chronic Obstructive Broncho Pneumopathy). In parallel, we intend to start a scientific program in order to elucidate the original condensation properties of hydroxysilicic acid contained in Treignac water and its role in Treignac water's cellular reactivity modulation

Conclusion

The treatment protocol proposed here mirrors current spa practices but introduces a standardized mineral water aerosol with proven biological properties.

Such a protocol—defined by controlled particle size and dosage—may represent a safe, natural, and complementary therapy in both otorhinolaryngology and pulmonology, paving the way for a new thermal water treatment potentially devoid of adverse effects in line with the already described beneficial effects of hydrotherapy [33].

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