International Journal of Mycobacteriology xxx (2016) xxx–xxx

Available at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/IJMYCO

Development of the food supplement Nyaditum resae as a new tool to reduce the risk of tuberculosis development

Nestani Tukvadze[a], *Paula Cardona*[b], *Sergo Vashakidze*[a], *Natalia Shubladze*[a], *Zaza Avaliani*[a], *Cris Vilaplana*[b], *Pere-Joan Cardona*[b,*]

[a] *National Center of Tuberculosis and Lung Diseases (NCTLD), Tbilissi, Georgia*

[b] *Unitat de Tuberculosi Experimental, Institut Germans Trias i Pujol (IGTP), CIBERES, Universitat Autònoma de Barcelona (UAB), Badalona, Catalonia, Spain*

ARTICLE INFO

Article history:
Received 19 September 2016
Accepted 20 September 2016
Available online xxxx

Keywords:
Mycobacterium manresensis
Nyaditum resae
Low dose Tolerance
Supplement food
Tregs
Tuberculosis
Close contacts

ABSTRACT

Nyaditum resae (NR) is a galenic preparation of heat-killed *Mycobacterium manresensis* (hkMn). This is a new species that belongs to the *Mycobacterium fortuitum* complex, and it is present in drinking water—thus, regulatorily speaking, it is considered a food supplement.

Preclinical studies in the murine model of active tuberculosis (TB) in the C3HeB/FeJ strain have demonstrated that daily administration of NR containing 10^3–10^6 hkMn for 14 days was able to stop the progression toward active TB [1]. The mechanism of action was linked to the induction of low dose tolerance and was related to the increase of Tuberculin Purified Protein Derivative (PPD) memory-specific Tregs ($CD4^+CD25^+CD39^+$ cells) after ex vivo incubation of splenocytes for 7 days. This increase of Tregs was related to the increase of interleukin (IL)-10 in the spleen and in the reduction of IL-17 in the lungs, where there was also a reduction in bacillary load and the pathology caused by a reduction of neutrophiles' infiltration [2].

Two randomized, double-blind placebo-controlled clinical trials (CTs) have been conducted in humans. The NYADATREG study (Clinicaltrials.gov identifier NCT02076139; 2013–2014) was aimed to evaluate the safety and the immunogenicity of two concentrations of NR (containing 10^4 hkMn and 10^5 hkMn) versus placebo (all administered orally everyday for 14 days) in tuberculin-positive and tuberculin-negative volunteers (total $n = 51$). The results demonstrated an excellent safety record, with no differences between groups in terms of adverse effects. A significant increase in PPD-specific memory regulatory T cells was also detected in both NR groups [3]. The NYADAPETRICS study (Clinicaltrials.gov identifier NCT02581579) is evaluating the safety and immunogenicity of NR 10^5 hkMn (capsule format, orally) in the pediatric population. Currently, an efficacy study (randomized, double-blinded, placebo-controlled CT) is being conducted in Georgia. This NYADAGEORG trial includes close contacts of active TB cases with positive sputum not tributaries of chemoprophylaxis (<5-year-old children and HIV-positive individuals), which will receive NR (containing 10^5 hkMn) or placebo (orally, every day for 14 days). A total of 3300 partici-

* Corresponding author at: Unitat de Tuberculosi Experimental, Crta de can Ruti, camí de les Escoles, 08916 Badalona, Catalonia, Spain.
E-mail address: pjcardona@igtp.cat (P.-J. Cardona).

Peer review under responsibility of Asian African Society for Mycobacteriology.
http://dx.doi.org/10.1016/j.ijmyco.2016.09.073

pants will be recruited in four medical centers around Tbilissi. The participants are monitored by telephone for up to 2 years to evaluate the incidence of active TB. The hypothesis is that the NR group will exhibit a 40% reduction in expected TB incidence. Thus, the anticipated TB incidence will be 3% in the NR group versus 5% in the placebo group. The CT is projected to end by 2021 (Clinicaltrials.gov identifier NCT02897180).

The administration of the food supplement NR appears to be a new, easy, safe, and reliable method for reducing the risk of developing active TB, and new CTs must be encouraged to discern the particular efficacy power according to different population characteristics.

Conflicts of interest

P.J.C. and C.V. are founders of Manremyc, the "Spin-off" of the Institut Germans Trias i Pujol (IGTP) that is developing the use of *M. manresensis* as a food supplement to reduce the risk of TB development. P.J.C. is also the CEO/CSO of the company. P.J.C. and C.V. are the inventors of this food supplement.

Acknowledgments

This study is funded by the Health Department of the Catalan Government; the Spanish Government through the CIBER CRP-TB project; Plan Nacional I+D+I cofinanced by ISCIII-Subdirección General de Evaluación and Fondo-EU de Desarrollo Regional (FEDER) and cofinanced through Projects PI11/01702 and PI14/01038.

REFERENCES

[1] E. Marzo, C. Vilaplana, G. Tapia, et al, Damaging role of neutrophilic infiltration in a mouse model of progressive tuberculosis, Tuberculosis (Edinb) 94 (2014) 55–64.

[2] P. Cardona, E. Marzo-Escartín, G. Tapia, et al, Oral administration of heat-killed *Mycobacterium manresensis* delays progression toward active tuberculosis in C3HeB/FeJ mice, Front. Microbiol. 6 (2016) 1482.

[3] E. Montane, A.M. Barriocanal, A.L. Arellano, et al, PD-1027-01 clinical trial with the food supplement Nyaditum resae: a new tool to reduce the risk of developing active tuberculosis, Int. J. Tuberc. Lung. Dis. 11 (2014) S427.

Please cite this article in press as: N Tukvadze et al. Development of the food supplement Nyaditum resae as a new tool to reduce the risk of tuberculosis development. Int. J. Mycobacteriol. (2016), http://dx.doi.org/10.1016/j.ijmyco.2016.09.073