ANTHELMINTIC AVERMECTINS FOR THE TREATMENT OF NON-TUBERCULOSIS MYCOBACTERIA INFECTIONS IN CYSTIC FIBROSIS

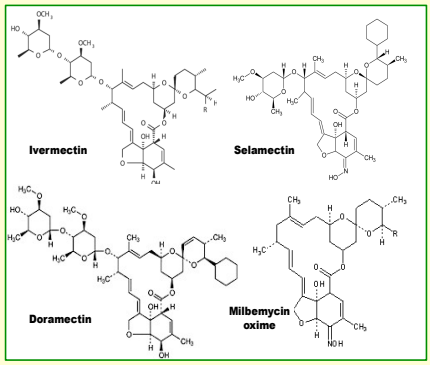
Lara Muñoz Muñoz[1,2,*], Charles J. Thompson[3], and Santiago Ramón-García[2,3,4,*]

[1] Clinical University Hospital Lozano Blesa, Zaragoza, Spain [2] Department of Microbiology, Preventive Medicine and Public Health, Faculty of Medicine, University of Zaragoza, Spain; [3] Department of Microbiology and Immunology, Centre for Tuberculosis Research, University of British Columbia, Canada;
[4] Research & Development Agency of Aragon (ARAID) Foundation, Spain.
*Email: laramm01@gmail.com and santiramon@unizar.es

INTRODUCTION

Pulmonary disease caused by non-tuberculosis mycobacteria (NTM) has emerged as a major threat to the health of individuals with cystic fibrosis (CF). The NTM most commonly identified are *Mycobacterium abscessus* (MABSC) and *Mycobacterium avium* (MAC) complexes. MABSC includes 3 species *M. abscessus sb. abscessus*, *M. abscessus sb. bolletii* and *M. abscessus sb. masiliense*.

Avermectins are a family of macrocyclic lactone compounds used as anthelmintics. Although inactive against Gram-positive and Gram-negative bacteria, they have demonstrated *in vitro* activity against mycobacterial species, including *Mycobacterium tuberculosis*, *Mycobacterium ulcerans* and *Mycobacteriym marinum* (PMID: 26270480 & 23165468).



OBJECTIVE

To evaluate the *in vitro* activity of the avermectins against MABSC and MAC.

CONCLUSIONS

The avermectins comprise clinically approved drugs (i.e. ivermectin) and are extensively used in veterinary medicine (i.e. milbemycin oxime). Since large packages of pharmacological and toxicity data are readily available, they could form the basis of new therapeutic approaches (alone or in combination) against NTM infections. However, further studies are needed to assess their clinical potential for this indication.

RESULTS

(i) Milbemycin oxime (MBO) was the most active avermectin against MABSC and MAC strains, and displayed bactericidal activity; (ii) MBO was superior to ivermectin, and; (iii) In contrast to clarithromycin, the MIC of MBO did not increase with extended periods of incubation (3 *vs.* 14 days).

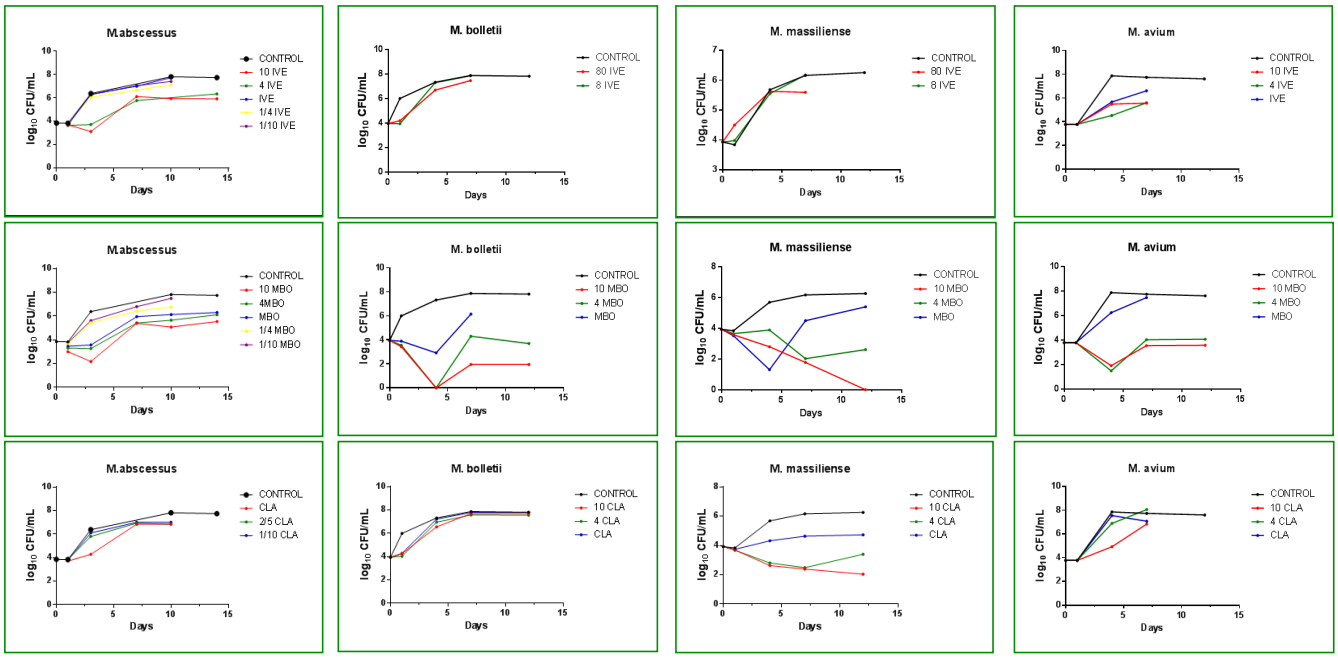
MIC (µg/mL)	DOR	IVM	EPR	ABA	SEL	EMA	MXD	MBO	CLA
AVIUM	>64	4-16	>64	>64	2	16	>64	4-8	1-8
ABSCESSUS	1-2	2-4	>64	>64	32-64	8-16	>64	8	0.12-0.06
BOLLETII	>64	>64	>64	>64	>64	32	>64	8-16	1-8
MASSILIENSE	>64	>64	>64	>64	>64	32	>64	8	0.25-0.5

Table 1. Antimicrobial activity against MAC and MABSC.
Milbemycin oxime was active against all strains tested.
DOR: Doramectin, IVM: Ivermectin, EPR: Eprinomectin, ABA: Abamectin, SEL: Selamectin, EMA: emamectin, MXD: moxidectin, MBO: milbemycin oxime and CLA: Clarithromycin.

3 days	IVM	SEL	MBO	CLA	14 days	IVM	SEL	MBO	CLA
AVIUM	4-16	2	4-8	1-8	AVIUM	>64	16	4	>8
ABSCESSUS	2-4	64	8	0.12-0.06	ABSCESSUS	4	>64	4	0.5-8
BOLLETII	>64	>64	8-16	1-8	BOLLETII	>64	>64	8	8->32
MASSILIENSE	>64	>64	8	0.25-0.5	MASSILIENSE	>64	>64	4-8	4

Table 2. MIC (µg/mL) determination after 3 and 14 days of incubation.
Treatment with milbemycin oxime prevented an increase in the MIC values. This could be an improvement over the first-line drug clarithromycin that also contains a macrocyclic ring, for which induction of resistance through the *erm* gene compromised its clinical effectiveness.

Figure 1. Kill kinetic assays against MAC and MASBC.
Ivermectin and milbemycin oxime were tested at different concentrations based on their MIC values. Clarithromycin was also included as internal comparator.



ACKNOWLEDGEMENTS & FUNDING