REPURPOSING BETA-LACTAMS FOR BURULI ULCER TREATMENT

Santiago Ramón-García[1, 2, 3] and Alfonso Mendoza-Losana [4]

[1]Research & Development Agency of Aragon (ARAID) Foundation, 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, Life Sciences Centre, University of British Columbia, Canada; [4]GlaxoSmithKline-Diseases of the Developing World, Spain.
Email: *santiramon@unizar.es* and alfonso.x.mendoza@gsk.com

Introduction. Before 2004, the only treatment option for Buruli ulcer (BU) was surgery. A recent clinical trial (ClinicalTrials.gov Identifier: NCT01659437) compared the efficacy of replacing streptomycin by clarithromycin. Since clarithromycin is orally available and with fewer side effects compared to the injectable streptomycin, BU treatment is now moving toward adoption of a full oral treatment of 8 week daily combination therapy of rifampicin-clarithromycin.

Although a major step toward the management of this infectious disease, recent reports describe the emergence of *M. ulcerans* strains resistant to rifampicin and streptomycin (PMID: 28070190). No alternatives for rifampin are currently available, thus making it the cornerstone drug for BU therapy; the emergency of rifampicin resistance in *M. ulcerans* would virtually bring BU treatment to the pre-antibiotic era. In addition, new treatment regimens that could reduce the long median time to healing (up to 20 weeks) would allow for better BU control and management.

Beta-lactams are one of the largest groups of antibiotics available today with a long track record of safe clinical use. Thought to be ineffective to treat mycobacterial infections due to intrinsic beta-lactam resistance, a recent clinical trial convincingly demonstrated for the first time the clinical efficacy of meropenem combined with amoxicillin/clavulanate for tuberculosis (TB) treatment (PMID: 27433841). The repurposing TB potential of the cephalosporins alone and in combination with rifampicin was also demonstrated (PMID: 27678056). Both studies provided evidence of the clinical potential of beta-lactams alone and in synergistic combinations with rifampicin, opening a new avenue to identify new drugs and optimize current BU therapy.

Objectives. To evaluate the potential of repurposing clinically approved beta-lactams for BU therapy.

Methods. We are applying knowledge gathered in TB R&D programs (PMIDs: 27678056, 21576426, 27433841), using two innovative approaches: drug repurposing and synergy.

Results. While there were no interactions among rifampicin and streptomycin or clarithromycin, *in vitro* synergy studies demonstrated strong synergism between rifampicin and beta-lactams. What is more, triple combinations of rifampicin-clarithromycin-beta lactams also displayed synergistic patterns, and this was further enhanced in the presence of the beta-lactamase inhibitor clavulanate.

Conclusions. Beta-lactams have the potential to replace or complement current rifampicin-clarithromycin combination. Co-administration in a triple combination could increase efficacy by reducing time to heal or reduce toxicity. In addition, they could act as a second-line therapy in the eventual situation of treatment failure and drug resistance development.

We thus propose to repurpose clinically approved beta-lactams for BU therapy because: (i) they are readily available in developing countries and; (ii) they are active and safe with good soft tissue penetration and can be administered orally, especially important for paediatric indications.

Drug development for neglected diseases such as BU is especially complicated due to lack of interest from the main scientific community and, as a consequence, lack of investment. Among all the beta-lactams tested, amoxicillin is commercialized in combination with clavulanate as Augmentin; it is oral and widely distributed and accessible in low-income countries.

For these reasons, we propose to prioritize Augmentin as a new BU treatment in combination with rifampicin and clarithromycin.