Rifapentine's long and winding road to European patients

El largo y sinuoso camino de la rifapentina hasta llegar a los pacientes europeos

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The story of rifapentine begins in 1957, when a new class of agents produced by *Nocardia mediterranei* was isolated during a screening program for new antimicrobials[1].The raw material extracted by fermentation contained antimicrobial agents called rifamycins. Rifampicin was developed at Dow-Lepetit Research Laboratories (Milan, Italy) as part of an extensive chemical modification program for rifamycins. Rifampicin was finally introduced for therapeutic use in 1968, after a large number of clinical and biological studies confirmed the important role of this drug in the treatment of tuberculosis (TB) and some other infectious diseases[2].

Rifapentine is a semi-synthetic cyclopentyl-substituted rifamycin that was first synthesized in 1965 by the Italian company that developed rifampicin. Despite its approval by the U.S. Food and Drug Administration (FDA) in 1998 for the treatment of people with pulmonary TB, rifapentine had a slow uptake by physicians – probably due to rifapentine's higher cost in these years and the high efficacy demonstrated for rifampicin[3,4].

Rifapentine has a longer half-life in the blood, which suggested that it could be effective for the treatment of both people with active TB and those with latent tuberculosis infection (LTBI). Slowly, yet steadily, clinical trials were designed and implemented – mostly promulgated by investigators forming part of the Tuberculosis Trials Consortium (TBTC) sponsored by the U.S. Centers for Disease Control and Prevention (CDC). In a clinical trial (Study-26) this consortium recruited during a 7-year interval (between 2001 and 2008) a total of 7731 people at high risk of progression from latent *M. tuberculosis* infection to active TB disease. These study participants were randomized to treatment with isoniazid and rifapentine administered once weekly for 3 months under directly observed therapy (DOT) or isoniazid administered daily for 9 months, and followed for 33 months. This clinical trial demonstrated that the use of rifapentine with isoniazid for 3 months had similar efficacy to 9 months of isoniazid in preventing progression to active TB, in addition to achieving a higher rate of treatment completion with the shortened regimen[5]. It is remarkable to observe that the day after the publication of this study, CDC was already recommending this new regimen for preventive treatment against TB in the U.S[6].

In another study by TBTC (study 33), it was found that this treatment regimen via self-administered route had acceptable adherence when compared to reminders using SMS text messages or DOT as in study 26, which facilitates the administration of the treatment[7] Subsequently, it was found that this regimen was also effective for persons coinfected with *M. tuberculosis* and HIV, and that in this group a one-month daily regimen with rifapentine and isoniazid was also effective[8,9]. In 2017, a systematic review and network meta-analysis assessed data from randomized controlled trials (RCTs) in patients with confirmed LTBI that used treatment regimens with isoniazid and rifapentine administered once weekly for 12 weeks, 6 and 9 months of daily isoniazid, 3–4 months of daily isoniazid plus rifampicin, and 4 months of daily

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rifampicin alone – and reported on efficacy or completion. Studies included in this review were published between 1968 and 2015. The authors found no significant differences in the efficacy of "active regimens" evaluated in these studies and concluded that shorter rifamycin-based regimens of 3–4 months duration offer comparable benefits and "are more likely to be completed than longer regimens[10]."

In the treatment of people with active TB, another clinical trial sponsored by the TBTC compared (Study 31) the efficacy of a 4-month regimen with rifapentine, isoniazid, pyrazinamide, and moxifloxacin against two other regimens: a 4-month regimen with rifapentine, isoniazid, pyrazinamide, and ethambutol, and the other for 6 months with rifampicin, isoniazid, pyrazinamide, and ethambutol (standardized treatment regimen for people with active TB)[11]. This study concluded that, in the treatment of people with active TB and strains susceptible to these drugs, the 4-month regimen based on rifapentine and moxifloxacin was non-inferior to the standardized 6-month regimen, and better than the 4-month regimen based on rifapentine, moxifloxacin, and ethambutol[12]. This study represented a great innovation in the treatment of people with TB disease because it allowed treatment duration to be shortened from 6 to 4 months. Now that rifapentine is approved for the treatment of TB worldwide, including some European countries, the challenge is to promote the optimal use of rifapentine-based treatment regimens.

Considering the clinical trial published in 2011 that demonstrated both the efficacy and safety of 3 months of rifapentine with isoniazid in the treatment of people with LTBI, and subsequent studies that have shown the benefit of this regimen in people with HIV infection and children, the guidelines recommending its use were updated by CDC in 2018 and by WHO in 2018 to enable the use of treatment regimens containing rifapentine in all countries of the world[13,14]. More recently, WHO consolidated guidelines for the treatment of people with LTBI reinforce the use of 3-month schedules with rifapentine and isoniazid administered weekly, as well as the 1-month schedule with rifapentine and isoniazid administered daily[15]. As a complement to these guidelines, WHO also updated its Model Essential Medicines Lists (EMLs) to include rifapentine to encourage countries to have this drug on their national EMLs, in order to optimize its procurement and ultimately facilitate access[16]. In addition, rifapentine products have been included in the expression of interest (EOI) of the Global Fund's Expert Review Panel, a list that includes a subgroup of medicines included in the WHO Medicines Prequalification Program (PQM) and that functions as an interim mechanism to allow access to quality-assured priority medicines prior to WHO prequalification.

Despite all the scientific advances and guidelines promulgated by WHO, incomprehensibly, rifapentine is not approved in most of Europe for the treatment of people with LTBI. These European countries are still waiting for the pharmaceutical company Sanofi-Pasteur to definitively submit its request for approval and marketing, and the formulation of fixed-dose drug combinations which would reduce the pill burden and number of daily tablets taken by the patient, thus favorably influencing adherence to these treatment regimens[17]. The consortium "Tuberculosis Network European Trials Group (TBNET)," made up of European healthcare providers and researchers, carried out a survey during the months of June to December 2020, and updated in October 2021, to investigate access to TB drugs in countries in the WHO European Region. Of 53 countries in the region, TBNET contacted 46 and 43 responded to the survey. Rifapentine is available in only 9 of these. In 2010, the European Commission granted orphan drug designation for rifapentine. Twelve years later, Sanofi-Pasteur, one of the largest pharmaceutical companies worldwide, has not yet submitted the application for registration of rifapentine in the European Medicines Agency (EMA)[18].

Ironically, rifapentine is already available in low- and middle-income countries through the catalog of products offered by the Global Drug Facility of the Stop TB Partnership[19]. In August 2022, UNITAID, in collaboration with the Clinton Health Access Initiative (CHAI) and MedAccess, announced agreements to reduce the cost of rifapentine-based TB treatment regimens for these countries[20].

In this global context, Europe is in a situation of comparative grievance regarding the non-availability of rifapentine. This is a frustrating situation for European physicians who treat TB patients, and this perception is more pronounced among the many researchers in the Barcelona area who participated for years in clinical trials of TBTC[21].

Given all the scientific achievements to date and considering that shorter treatment regimens have been consistently associated with improved treatment completion, we anticipate that fewer human resources will be needed to monitor shorter effective treatment. In this context, it is indefensible to continue denying access to optimal medical care to health providers and their patients with TB or LTBI in European countries.

Research investments and advances are useless if they fail to benefit those in need. We must endeavor to close the gap in the long and winding road to have rifapentine reach patients with TB in Europe and elsewhere. Faced with this predicament, it is crucial for all healthcare providers to instill a sense of urgency on behalf of those in need, and join forces with affected communities to make rifapentine access a political priority throughout the

world. Access to effective drugs for optimal treatment outcomes is crucial if we are to realistically achieve the TB elimination goals promoted by WHO, Heads of State at the 2018 United Nations High Level Meeting on TB, and the Global Stop TB Partnership[22,23].

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