MESA: Proyectos internacionales

Moderadores: **Vicente Martín.** *Medicina Preventiva y Salud Pública. Universidad de León. León. Sociedad Española de Médicos de Atención Primaria (SEMERGEN). Madrid..*

Josep Franch. *Médico de Atención Primaria. CAP Raval Sud. IDIAP Jordi Gol. Barcelona.*

SMA-TB project: A novel Stratified Medicine Algorithm to predict treatment responses to host-directed therapy in TB patients

Lilibeth Arias de la Cruz[1,2], Kaori Levy Da Fonseca[1], Iwona Maryla Maciejewska[3], Cristina Vilaplana[1,2*]

[1]Experimental Tuberculosis Unit (UTE). Fundació Institut Germans Trias i Pujol (IGTP). Universitat Autònoma de Barcelona (UAB). Edifici Mar. Can Ruti Campus. Badalona, Catalonia. [2]Centro de Investigación Biomédica en Red de Enfermedades Respiratorias (CIBERES). Madrid. [3]TES2A SL. Sant Quirze del Vallès, Catalonia.

Correspondencia:
Cristina Vilaplana
E-mail: cvilaplana@gmail.com

Tuberculosis (TB) is a chronic, life-threatening infectious disease that poses a tremendous challenge for physicians, researchers and Health Systems, which treatment is long, based only on the drug susceptibility of the responsible infective strain and very costly in drug-resistant cases (MDR-TB)[1]. Host-Directed Therapies (HDT) have been recently proposed to shorten treatment length and to improve the patients' outcomes while not increasing the risk of generating drug resistance. As hyperinflammation is responsible for the lung damage associated with patients' worse outcomes and sequelae, one of the approaches is to add an anti-inflammatory to the current drug regimen to cure the patients faster while having less permanent lung damage[2].

Taking into account this background, a 9 partner consortium from 6 different countries set up 3 objectives: 1) To evaluate in a CT the potential impact of two repurposed drugs (anti-inflammatories HDT) as adjunct to standard therapy for drug sensitive (DS-) and MDR-TB. This potentially will reduce tissue damage, decrease the length of the treatment and the risk of bad outcomes; 2) To identify and clinically validate host and pathogen biomarkers for further selection according to their relevance in terms of their ability to predict TB course and outcomes and response to treatment thanks to data science protocol; and 3) To generate a medical algorithm to stratify patients using network-based mathematical modelling for predicting the course of the disease and its response to the intervention, to be applied during clinical management to improve and personalize TB.

The SMA-TB Project received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 847762[3], and started on January 2020. The project has already involved up to 74 people of 6 different countries. The COVID pandemic has had a negative impact on the project, as has meant a delay on deliverables submission and milestones achivement. And yet, SMA-TB partners have intensively worked to start the clinical trial (CT) before the end of 2020. The trial (ClinicalTrials.gov Identifier: NCT04575519) will be a multicenter, phase IIB, placebo controlled, randomized trial which expects to recruit 354 participants with TB in South Africa and Georgia to evaluate the the potential efficacy and safety of Acetylsalicylic Acid and Ibuprofen, for Use as Adjunct Therapy Added to the Standard WHO-recommended TB Regimen[4]. Approvals have been submitted to the correspondent Regulatory and Ethics authorities in South Africa (approved) and Georgia (under review).

During this first year, the consortium has successfully developed several tools, including the project's website[5], but most of them related to the clinical trial: 8 Standard Operation Procedures, 8 work-flow infographics, 1 e-consent and 1 training videos. Most of these tools will be available at the end of the project to be used by others under an open-access Creative Commons license.

The consortia has also trained 34 people and conducted several joint activities with other EC-funded consortia so far, and we are open to establish collaborations with stakeholders.

Next steps include to use the samples obtained within the CT to identify and validate host and pathogen biomarkers according to their capacity to predict TB outcomes and response to treatment thanks to a data science protocol. The result expected is the generation of a medical algorithm to stratify patients for predicting TB course and its response to intervention, to be applied during clinical management.

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Trying to improve the prognosis of tuberculous meningitis: the INTENSE-TBM Project

Juan Ambrosioni

Enfermedades Infecciosas. Hospital Clinic-IDIBAPS. Universidad de Barcelona.

Correspondencia:
Juan Ambrosioni
E-mail: ambrosioni@clinic.cat

In this clinical session of International Projects, Dr. Juan Ambrosioni (PI for Hospital Clinic-IDIBAPS and Spain of WP2) will present the ongoing EDCTP-funded project INTENSE-TBM. The project started in January 2019 and the first 15 months were dedicated to Capacity Building of Clinical Center, Laboratories and personnel training in the 13 clinical centers of 4 African Countries. Following the delays imposed by the COVID-19 pandemics, the RCT is now ready for initiation in most of the countries.

Overview of the project

Mortality due to Tuberculous meningitis (TBM) reaches 30% in HIV-negative and up to 70% in HIV-positive individuals with drug resistant TB strains, with death occurring most frequently in the first 2 weeks after diagnosis. Amongst TBM survivors, 50% are disabled due to neurological sequelae. Treatment of TBM has remained unchanged for decades despite this high level of mortality. INTENSE-TBM aims to improve the prognosis of TBM in patients with or without HIV co-infection in sub- Saharan Africa by reducing TBM mortality and neurological sequelae as well as improving the clinical management of TBM-HIV co-infection. For this purpose, INTENSE-TBM will carry out a multicentre randomised controlled trial in 4 Sub-Saharan African countries (Madagascar, Ivory Coast, Uganda and South Africa). Patients with suspected TBM will be randomised 1:1:1:1 to standard WHO TBM therapy, versus an intensified treatment (INTENSE-TBM programme), and into aspirin versus placebo therapy in a factorial design. The intensified TBM programme will consist of:

- First 5-7 days (in patients unable to swallow): high dose intravenous (IV) rifampicin 20 mg/kg/d, IV linezolid 1200 mg/d, IV isoniazid 5 mg/kg/d, pyrazinamide 30 mg/kg/d and corticosteroids.
- Up until 2 month (oral): rifampicin 35 mg/kg/d, linezolid 1200 mg/d, isoniazid, pyrazinamide, and corticosteroids.
- Seven months: isoniazid 5 mg/kg/d and rifampicin 10 mg/kg/d

Patients will also be randomized to receive either aspirin 300 mg per day or placebo for the first two months of treatment.

If superiority of this experimental arm is demonstrated in terms of reduced mortality, INTENSE-TBM will become the first Phase III study to demonstrate survival benefit from intensified TBM treatment.

HIV co-infected patients will start a generic formulation of tenofovir, lamivudine, and dolutegravir four weeks after TBM treatment initiation, and continue with dexamethasone for at least the first four weeks of antiretroviral treatment. Incidence and risk-factors for severe immune reconstitution inflammatory syndrome will be determined and the pharmacokinetics of the drug-drug interactions between standard and high dose rifampicin with dolutegravir analyzed.

INTENSE-TBM responds directly to the a clinical unanswered need by evaluating (i) the impact of an optimized drug regimen for TBM on mortality including high dose rifampicin and linezolid, a repurposed drug for the treatment of TBM, (ii) the impact of the addition of aspirin on TBM mortality, a drug that has not previously been authorised for use against any infectious disease (iii) an antiretroviral therapy strategy in TBM patient co-infected with HIV to specifically assess the risk of severe IRIS, and to study drug-drug interactions.

Effectiveness of 3HP annually vs once for HIV-positive people: the WHIP3TB trial

Alberto García-Basteiro[1,2], Gavin Churchyard[2], Vicky Cardenas[2], Violet Chihota[2], Kathryn Mngadi[2], Modulakgota Sebe[2], William Brumskine[2], Salome Charalambous[2], Neil A. Martinson[2], Getnet Yimer[2], LeeAnne Masilela[2], Susan Van Den Hof[2], Richard E. Chaisson[2], Alison Grant[2], Katherine Fielding[2]

[1]Medicina Preventiva y Salud Pública. Centro de Investigação em Saúde de Manhiça e Instituto de Salud Global de Barcelona. [2]The WHIP3TB Team

Correspondencia:
Alberto García Basteiro
E-mail: alberto.garcia-basteiro@isglobal.org

Introduction

The use of TB preventive therapy (TPT) plays a crucial role in efforts to reduce tuberculosis transmission in high burden settings and to eliminate tuberculosis in low burden settings. People living with HIV is one of the risk groups in whom TPT is highly recommended due to the higher risk of progressing to active disease and the increased mortality associated with TB[1]. There are several potential regimens that are recommended by the World Health Organization for this purpose. The 2020 update of WHO guidelines on TPT makes 9 or 6 months of daily isoniazid (6H or 9H respectively), 4 months of daily Rifampicin (4R), 3 months of weekly isoniazid and rifapentine (3HP), 3 months of daily rifampicin and isoniazid (3HR) or 1 month of daily isoniazid and rifapentine (1HP) as alternative options for use across all disease burden settings and target populations including the PLHIV[2]. The choice will depend on availability of appropriate formulations and considerations for age, safety, drug–drug interactions and adherence. Nonetheless, the most frequently used TPT among PLHIV in high burden settings continues to be 6H.

Weekly isoniazid (900 mg) and rifapentine (900 mg) for 12 weeks (3HP) has similar efficacy to 6 months of daily isoniazid (6H) as TB preventive therapy[3,4]. In this clinical trial, we compared treatment completion rates and effectiveness of 3HP *vs*. 6H and the effectiveness of 3HP given annually *vs.* once among HIV-positive people. This trial has been registered in www.clinicaltrials.gov (NCT02980016).

Methods

We recruited HIV-positive people in South Africa, Ethiopia and Mozambique aged ≥2 years, without active TB and on antiretroviral therapy (ART) for ≥3 months or ineligible were randomized 9:9:2 to periodic (annual) 3HP (p3HP), 3HP, or 6H. Participants in

the 3HP/p3HP and 6H arms were followed for 24 and 12months, respectively; all were seen monthly for the first three months of each participation year. Medication doses were directly observed at dispensing visits and otherwise self-administered. Participants in the 6H arm were dispensed 3 months treatment at month 3. Participants were screened for TB with symptoms, chest X-ray and sputum culture after 12 and 24 months. Completion of the initial treatment course in the combined 3HP/p3HP arms *vs*. 6H was compared using pill counts. TB incidence and all-cause mortality over 12 months was compared in the 3HP and 6H arms, and TB incidence, all-cause mortality, and permanent discontinuation of 3HP for adverse events over 24 months was compared in the p3HP and 3HP arms.

Results

Between November 2016 and November 2017, 4593 participants were screened, 4027 enrolled and 4014 analysed. The median age was 41 years (19 (0.5%) <18 years), all were on ART, 70% were female, 38% were QuantiFERON-TB GOLD Plus positive; 63%, 22% and 15% were from South Africa, Ethiopia and Mozambique, respectively. Treatment completion in the combined 3HP (n=3610) and 6H (n=404) arms was 90.4% versus 50.5% (risk ratio: 1.79; 95%CI:1.62-1.79). TB incidence and mortality by study arm are shown in the table. TB incidence and mortality from month 0 to month 12 was similar in the 3HP and 6H arms. TB incidence over 24 months and from month 12 to month 24 was similar in the p3HP (n=1808) and 3HP (n=1802) arms. Over 24 months, TB incidence among QuantiFERON Plus positive participants, incidence of rifampicin resistant TB, and mortality were similar in the p3HP and 3HP arms. Treatment discontinuation in the p3HP and 3HP arms was 1.2% *vs*. 0.6% (OR2.11, 95%CI:0.95-5.02).

Conclusions

Treatment completion was higher in the 3HP arms *vs*. 6H. In high TB transmission settings, annual 3HP did not provide additional benefit to people receiving ART.

Preliminary results of this study have been presented at CROI conference 2020[5]. The study was led by the Aurum Institute and sponsored by the KNCV Tuberculosis Foundation and funded by USAID through the Challenge TB project. The WHIP3TB trial was implemented by the Aurum Institute and Perinatal HIV Research Unit (PHRU) in South Africa, The Ohio State University Global One Health initiative in Ethiopia and by Centro de Investigação de Saúde de Manhiça (CISM) in Mozambique. Other senior investigators were from the London School of Hygiene and Tropical Medicine and Johns Hopkins University Center for TB Research.

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El papel de la diabetes en la incidencia de nuevos casos de tuberculosis en Ciutat Vella

Violeta Antonio[1], Joan A. Caylà[2], Josep Franch[3] y grupo de trabajo de DMTB (Àngels Orcau, Antonio Moreno, Jordi Real, José Luis del Val, Elena Navas, Ray Puig y Susana García Pleyán)

[1]Medicina Familiar y Comunitaria. EAP Bordeta Magòria. Gerencia Territorial de Barcelona Ciudad. ICS. Barcelona. [2]Epidemiólogo. Fundación de la Unidad de Investigación en Tuberculosis de Barcelona. Barcelona. [3]Médico de Atención Primaria. CAP Raval Sud. IDIAP Jordi Gol. Barcelona.

Correspondencia:
Violeta Antonio
E-mail: violeta.antonio@gmail.com

Introducción

La tuberculosis (TB) es una de las primeras causas de mortalidad por enfermedad infecciosa en el mundo, y afecta a unos 10 millones de personas cada año[1]. Uno de los principales factores de riesgo para el desarrollo de esta infección, según la OMS, es la diabetes (DM). Se trata de una de las enfermedades crónicas más prevalentes en nuestro entorno, afecta a unos 436 millones de personas en todo el mundo y su incremento se está objetivando especialmente en países de medios y bajos ingresos. Debido al infradiagnóstico, menor acceso a tratamiento y mayores complicaciones, estos países son los que ya concentran la mayor carga de enfermedad diabética[2].

Es en dichas regiones con medios y bajos ingresos donde encontramos mayores incidencias de TB. Este hecho convierte el abordaje conjunto de ambas enfermedades en una prioridad.

La relación entre DM y TB ha dado lugar a múltiples estudios y sigue despertando interés. A pesar de que los mecanismos inmunológicos no están todavía esclarecidos, parece que este aumento de susceptibilidad de los pacientes diabéticos a la infección tuberculosa se debería sobre todo a los efectos directos de la hiperglicemia, inicialmente comportando un defecto en la inmunidad innata, con alteración de la activación celular y la función fagocítica de macrófagos y neutrófilos, lo que implicaría una menor producción de quimiocinas y citoquinas. En concreto, la secreción de interferón γ, una de las moléculas clave en el desarrollo de la función microbicida de los macrófagos, se vería también reducida por un retraso en la activación de las células productoras. Posteriormente, se objetivaría también un retraso en la presentación antigénica y en la diferenciación de las células T, por lo tanto, un defecto en la inmunidad adaptativa. Todos los mecanismos se desarrollarían en un ambiente mucho más proinflamatorio y con mayor carga bacteriana[3].

Los pacientes diabéticos tendrían hasta 3 veces más riesgo de desarrollar una TB respecto de los no diabéticos[4], y parece presentarían con más probabilidad una evolución más tórpida, más formas cavitadas en las radiografías de tórax, más efectos adversos a los fármacos antituberculosos y mayor necesidad de ingreso al momento del diagnóstico[5], mayor probabilidad de recaída y mayores tasas de resistencias a los tratamientos[6].

Ante esta evidencia, se nos planteó la necesidad de estudiar, en nuestro ámbito de trabajo (un distrito de Barcelona con alta prevalencia de TB: Ciutat Vella), la relación epidemiológica entre ambas enfermedades y conocer el riesgo de TB entre la población diabética en un distrito de alta incidencia de TB.

Según datos del Ayuntamiento de Barcelona del 2018, en Ciutat Vella -el distrito de la ciudad socio-económicamente más deprimido- viven unas 100.714 personas, de los cuales un 55,2% son nacidos fuera de España, principalmente Asia y Oceanía (36,1%) y Centro y Sur América (25,6%). La media de edad de 39.8 años. Presenta una esperanza de vida al nacer de 78.1 años, la más baja de toda Barcelona, con una tasa de mortalidad anual de 7 por cada 1.000 habitantes. La tasa de mortalidad por causa infecciosa estandarizada por edad en el período de 2012 a 2016 fue de 2.4 por 10.000. En el caso de la TB, los datos de 2016 muestran una incidencia de 43,8 casos por cada 100.000 habitantes/año, frente a los 16,2 casos por cada 100.000 habitantes/año en el global de Barcelona.

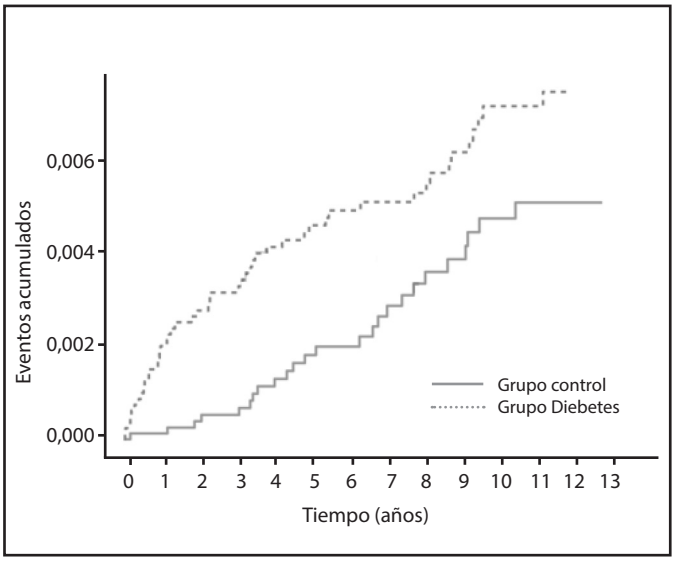
Estudio sobre la relación epidemiológica entre DM y TB en Ciutat Vella

Se diseñó un estudio longitudinal y retrospectivo de cohortes apareadas, formadas por pacientes diabéticos y no diabéticos apareados por edad y sexo en relación 1:1. Se incluyeron en la cohorte de "expuestos" los diabéticos prevalentes a 1 de enero de 2007 y diabéticos incidentes durante el periodo de estudio, un total de 11 años. Se trata de un estudio multicéntrico, que incluye la población del distrito de Ciutat Vella, atendida en 5 equipos de Atención Primaria (Raval Nord, Raval Sud, Gòtic, Casc Antic y Barceloneta). Se obtuvo información tanto de la base de datos del registro informático de Atención Primaria como del registro de TB de la Agència de Salut Pública de Barcelona: datos demográficos, problemas de salud, visitas realizadas en Atención Primaria, variables clínicas y de laboratorio, inmunizaciones, medicación dispensada en las oficinas de farmacia, datos específicos sobre el diagnóstico y tratamiento tanto de la DM como de la TB.

Resultados

En cuanto a las características de la población estudiada, al comparar el grupo de diabéticos con el de no diabéticos, la media de edad era de 57,5 años con un 61,1% de hombres en ambos grupos. En la cohorte de diabéticos, objetivamos el doble de pacientes de origen indostaní (13,6% frente a 6,42% en no diabéticos). En relación a las variables clínicas, entre los pacientes diabéticos encontramos valores de IMC más altos, y mayores niveles de colesterol y triglicéridos, además de más prevalencia de enfermedades cardiovasculares (ictus, insuficiencia renal crónica, arteriopatía periférica y cardiopatía isquémica). No encontramos diferencias significativas en cuanto a presentación de enfermedades autoinmunes, pero si más tratamientos con corticoesteroides en pacientes con diabetes. Encontramos también más casos de SIDA en pacientes diabéticos, pero no de otras enfermedades de transmisión sexual. Los pacientes diabéticos se visitaban en Atención Primaria más frecuentemente que los no diabéticos.

Detección de pacientes con y sin DM.



Como principales resultados a destacar, encontramos que los pacientes diabéticos tenían un riesgo de 1,77 (IC 1,092-2,863) veces mayor de presentar una TB respecto los no diabéticos. Además, ajustando los datos por el origen de los pacientes, objetivamos que los pacientes diabéticos procedentes de Indostán presentan un riesgo 3 veces mayor (IC 1,507-6,019) respecto a los pacientes de otros orígenes.

Conclusiones

La relación entre DM y TB está poco estudiada hasta el momento en nuestro medio, pero este estudio refuerza el hecho que la TB afecta principalmente a los sectores más desfavorecidos de la población, se relaciona frecuentemente con malas condiciones de vida y hacinamiento, pobreza e inmigración. Por otra parte, dichas condiciones suelen propiciar estados de obesidad, mala alimentación y mal control metabólico en casos de DM. Esta situación se da en zonas urbanas socioeconómicamente más perjudicadas, como es nuestra población de estudio.

Se objetiva un riesgo claramente superior de presentar una TB en pacientes diabéticos (HR 1,77) en nuestro entorno, y especialmente en pacientes de origen indostaní, una población mayoritaria en Ciutat Vella, por lo que es necesario impulsar campañas de búsqueda activa de infección tuberculosa en las personas con diabetes, que nos permitirían diagnósticos y tratamientos más precoces y, por lo tanto, evitarían el desarrollo de TB más graves. Estos cribados reducirían el impacto de la TB en los pacientes con DM y comportarían también un beneficio a nivel poblacional.

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