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REVIEW ARTICLE

Understanding the Tuberculosis Disease Progression and Future Directions of Research in Tuberculosis: A Mini Review

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ABSTRAK

Pembasmian tuberkulosis adalah semakin sukar dengan peningkatan tuberkulosis dan HIV jangkitan-bersama tuberkulosis yang mempunyai ketahanan terhadap dadah. Pengetahuan yang kurang beserta biomarker sensitif dan spesifik yang terhad terutamanya bagi jangkitan tuberkulosis tersembunyi menjadikan ianya bertahan sehingga kini. Nasib rawatan tuberkulosis adalah pelbagai, dari sembuh kepada kegagalan dan terdapat banyak faktor risiko yang terlibat selain daripada keadaan imun dan usia. Oleh itu, tujuan ulasan ini adalah memberi tumpuan kepada pemahaman perkembangan penyakit tuberkulosis dan faktor risiko yang berkaitan dengan kejadian dalam perkembangan penyakit. Artikel ini juga menekankan penanda diagnostik dan ramalan yang digunakan untuk meramal perkembangan penyakit. Di samping itu, artikel ini menyoroti potensi penggunaan rifabutin dalam rejimen rawatan tuberkulosis. Diharapkan manuskrip ini dapat memberikan gambaran mengenai arah tuju penyelidikan masa depan bagi tuberkulosis.

Kata kunci: faktor risiko, penanda-biologi, perkembangan penyakit, rifabutin, tuberkulosis

ABSTRACT

Eradication of tuberculosis seems to be a long way off especially with the growing of drug resistance tuberculosis and HIV co-infection tuberculosis. The gaps in our knowledge and the limited sensitive and specific biomarkers especially for latent tuberculosis infection make it defensive. The fate of tuberculosis treatment

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ranged from cured to failure and there are many risk factors involved apart from the immune state and age. Therefore, this review focuses on the understanding of tuberculosis disease progression and the associated risk factors of the events in the disease progression. This article also highlights the diagnostic and predictive marker that may predict the disease progression. In addition, this review highlights the potential use of rifabutin in tuberculosis treatment regimen. It is hoped that this review could give an overview on future directions of research in tuberculosis.

Keywords: biomarkers, disease progression, risk factors, rifabutin, tuberculosis

INTRODUCTION

Despite continuous bench-to-bedside research, there are still a lot of uncertainties regarding tuberculosis. Gaps in our understanding and limitations in predictive biomarkers are a serious handicap. Furthermore, the emergence of multidrug resistance tuberculosis and the extensively drug resistance tuberculosis as well as HIV co-infection make the eradication of tuberculosis as not yet possible. Understanding the clinical spectrum, the fate upon treatment and the risk factors of disease progression of tubersulosis is the prerequsite knowledge for us to find the keys for both preventive and curative interventions. Therefore, the first part of this review aims to give an overview on the tuberculosis disease progression and the clinical spectrum of tuberculosis. The second part of this article highlights the risk factors of the events in the tuberculosis disease progression. The later part of this review will link the diagnostic and predictive biomarkers used to predict the tuberculosis disease progression. Furthermore, this review does not aim to discuss on the treatment regimen of tuberculosis as it is available in various international guidelines. Rather, we would focus on the role of rifabutin in substitutions for rifampicin in tuberculosis treatment. Thus far, no regimen has been able to replace the standard 6-month regimen for drug sensitive tuberculosis. This fact is partly due to the excellent sterilizing capacity of the rifampicin. However, rifampicin-related adverse drug reactions and resistance cause unfavourable disease progressions. If rifampicin is to be discontinued due to rifampicin-related adverse drug reactions, patients will require a longer regimen which is associated with higher probability of poor adherence and therefore may lead to drug-resistance tuberculosis (Chien et al. 2013).

METHODOLOGY

EBSCOhost medline (published between 1990 and 2017) and Springerlink (published between 1990 and 2017) databases were used for literature search. The search strategy involved a combination of the following sets of keywords: tuberculosis AND disease progression AND risk factors. Articles from previous ten years up to

2017 were mostly used. This narrative review selects only the relevant articles.

DISEASE PROGRESSION AND CLINICAL SPECTRUM OF TUBERCULOSIS

The pathology of tuberculosis follows a two-stage process. The first stage is infection of *Mycobacterium tuberculosis* via air droplets therefore requires contact with someone who has active pulmonary tuberculosis (PTB). In this stage, *Mycobacterium tuberculosis* infection may not be eliminated by the innate immune response and become dormant within granuloma, without causing obvious symptoms and signs, called as latent TB infection (LTBI). The second stage consists of progression from LTBI to active disease, and presents with signs and symptoms caused by endogenous reactivation or via exogenous reinfection (Moreno et al. 2017). This active tuberculosis whether limited to the lung parenchyma, known as pulmonary TB (PTB) or lymphohematogenously disseminated to other extra-pulmonary sites forming extra-pulmonary tuberculosis (EPTB) (Kiran et al. 2016). Common forms of EPTB include TB lymphadenitis, military TB or disseminated TB, TB meningitis, Pleural TB, abdominal TB, osteoarticular, pericardial and ocular TB (Kok et al. 2006; Umi Kalthum et al. 2012; World Health Organization 2014). LTBI are not infectious, but at risk of developing active disease and becoming infectious (Kizza et al. 2015). Therefore, identifying and treating individuals with LTBI before it progress to active TB is extremely crucial in tuberculosis prevention. The recently revised guideline defined active TB as either presumptive TB, which refers to a patient who presents with symptoms and signs suggestive of TB or TB case, which further subdivided as bacteriologically confirmed TB case or a clinically diagnosed TB case (World Health Organization 2014).

The fate of tuberculosis upon treatment could be either success, failed or died. Treatment success may further defined as *cured* (negative smear/culture at the last month of treatment) and *treatment completed* (finished treatment, but without bacteriology result at the end of treatment for instant in smear negative cases). Even after patient had declared cured or completed treatment, he or she can develop recurrent episode of TB (either a true relapse or a new episode of TB caused by reinfection) (World Health Organization 2014).

Treatment failure is when the patient remains smear positive at 5 months or later despite adherence to medication while mortality from any cause during the course of treatment is classified as *died* (World Health Organization 2014). *Mycobacterium tuberculosis* strain could become resistance to anti tuberculosis drugs. Multidrug resistance TB (MDR-TB) are strains of TB that are resistant to at least two main first-line anti-tuberculosis drugs specifically both isoniazid and rifampicin while extensively drug-resistant TB (XDR-TB) is resistance to any fluoroquinolone and to at least one of three second-line injectable drugs (capreomycin, kanamycin and amikacin) in addition

to multidrug resistance (World Health Organization 2014).

RISK FACTORS OF DISEASE PROGRESSION

Understanding the risk factors of events in the disease progression is the key for both preventive and curative intervention. Reducing risk factors may results in favourable outcome or prevent the progression of the disease. Moreover, separating patients into different groups based on the risk factors they possess may enable decisions and interventions being tailored to the individual patient based on their predicted response or disease progression.

The risk of progression to active TB disease in LTBI child is influenced by the virulence of the mycobacteria, bacillary load, age and patient's immune response (Seddon et al. 2013; Ma et al. 2014). HIV co-infection is the strongest known risk factor for progression of LTBI to active TB disease (Lai et al. 2016). Although HIV co-infection does not affect the success or failure rate of TB treatment (Tessema et al. 2009), infection of TB in HIV co-infected patients may accelerate the progression of HIV disease. Previously, a MDR-TB contact study has demonstrated children less than 3 years old, HIV positive, exposed to MDR-TB source and poor socioeconomic factor had higher risk for TB infection (Seddon et al. 2013). In addition, homeless people who are smoking for more than 5 years and underweight have higher risk of progress to active TB (Semunigus et al. 2016).

Although it was believed that the mycobacterial load increase risk of progression to active TB (Seddon et al. 2013), Phillips et al. (2016) found that bacillary load was an independent predictor for relapse rate. Rather, patient's geographical region and presence of cavitation is more important risk factor for relapse. For instance, in Brazil rates of relapse are more dominant compared to rate of reinfection (Moreno et al 2017).

HIV co-infection has undoubtedly increased the chances to get tuberculosis. TB-HIV co-infection is a lethal combinations, with challenges in diagnosis and treatment monitoring in adults and even more in children. Children with HIV-positive are 20 times higher risk to develop TB and 6 times more likely to die from TB, compared to HIV-negative children (Evangelopoulos et al. 2017). The development of multidrug resistance TB (MDR-TB) with co-existing HIV is even more difficult especially in low-resource countries which are usually TB-endemic, due to lack of rapid and reliable second-line susceptibility testing, more frequent extrapulmonary dissemination, higher risk of drug toxicity and incidence of immune reconstitution inflammatory syndrome (Mpagama et al. 2013; Lawn et al. 2013).

BIOMARKERS TO PREDICT DISEASE PROGRESSION

Biomarkers may be used as predictor, to predict favourable or unfavourable clinical outcome. The role of serrogate biomarker in translational studies

are important because they help in decision-making to move a new regimen or drug into the confirmatory phase III randomised controlled trial which is more time-consuming and expensive. Therefore, improvement in markers remains as one of the main focus.

Selection of the best biomarkers is challenging due to heterogenicity in the pathology of tuberculosis, i.e. difference in clinical presentation, site and type of tuberculosis e.g. LTBI versus active TB, difference in host immune response e.g. immunocompromised versus immunocompetent, children versus adult response, as well as difference in sociodemographic factors e.g. endemic versus non-endemic. So far, there is no single biomarker that applicable and feasible to all groups. For example, tuberculin skin test (TST) and IFN-γ release assays (IGRA) can be false-negative in HIV-coinfected person therefore unreliable in screening and monitoring LTBI treatment efficacy (Pullar et al. 2014). Other example is bacterial confirmation which is not always feasible in children.

In a prospective cohort study in low-endemic setting using QuantiFERON TB-Gold In-tube®essay (QFT) to measure interferon-gamma (IFN-γ) level in LTBI/HIV co-infected patients on preventive treatment, it was found that the conversion of QFT to negative independent of the preventive anti-TB treatment indicating false positive results therefore QFT is unreliable in monitoring LTBI preventive treatment efficacy in TB low-endemic setting (Pullar et al. 2014). Indeed, attempts were made to improve the reliability of diagnostic tool as well as to know the factors that contribute to false positive or false negative results. For instance, a prospective study by Ma et al. (2014) among household contact of smear positive TB on standard TB regimen in Uganda found that 5-15 years old age group had tendency to have persistently negative TST (Ma et al. 2014). Furthermore, Oberhelman et al. (2015) compared the used of culture and/or microscopic evaluation against PCR method for bacteriological confirmation of TB. This study reported that PCR is prone to have false positive indicating culture and/or microscopic evaluation for diagnosis of TB as still superior.

A previous study by Phillips et al. 2016 reported that time-to-culture/smear negative and daily rate of change in bacillary overload (time-to-positivity on mycobacteria growth indicator tube, MGIT) are all independent predictor of clinical outcome therefore suggesting that these markers are not suitable as primary end-point. Indeed, serrogate end-point which defined as "a laboratory measurement or a physical sign used to substitute for a clinically meaningful end-point" should be interpreted with caution especially on assessing the efficacy of treatment regimens. Definitive clinical end-point remains as gold standard as the primary end point in the confirmatory trial (Crook et al. 2016).

FUTURE DIRECTIONS OF RESEARCH IN TUBERCULOSIS

Figure 1 illustrates the clinical spectrum of tuberculosis and where risk of the

disease progression as well as the diagnostic and predictive marker leave us a gap in knowledge to be improved. So far, no single biomarker can be considered perfect neither truly conclusive on its own. Therefore, finding a highly specific and sentitive biomarkers is our future directions.

To date, no regimen has been proved able to replace the 1st-line 6-month regimen for drug sensitive tuberculosis, consisting of 2 months of four-drug combination (isoniazid, rifampicin, ethambutol and pyrazinamide) and followed by additional 4 months of isoniazid, rifampicin and ethambutol (World Health Organization 2014). However, this regimen is not always adequate to control the epidemic. Furthermore, if rifampicin is to be discontinued due to rifampicin-related adverse drug reaction, the disease progression could be poor. Therefore, there is an urgency to discover new drugs and treatment regimen to improve patient's quality of life and to reduce adverse effects of rifampicin.

THE ROLE OF RIFABUTIN AS SUBSTITUTION FOR RIFAMPICIN IN TUBERCULOSIS

Rifampicin has an excellent sterilizing capacity therefore contained in the first line standard 6-months drug susceptible TB (Chien et al. 2013). However, if rifampicin should be discontinued due to rifampicin-related adverse drug reactions or resistance to rifampicin, current recommendation suggest a higher doses and prolonged treatment for at least 12-18 months with isoniazid, ethambutol and fluoroquinolone (World Health Organization 2014). Rifampicin-related adverse drug reactions is accelerated

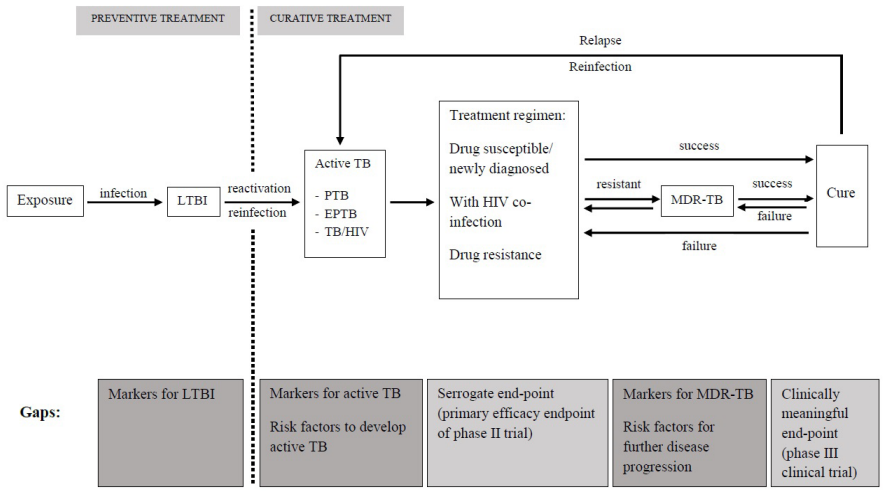

Figure 1: Clinical spectrum of tuberculosis and where some gaps in knowledge regarding the diagnostic and predictive marker as well as the risk of the disease progression could be our future directions. Abbreviations: TB=tuberculosis; PTB=pulmonary tuberculosis; LTBI=latent TB infection; EPTB=extrapulmonary tuberculosis; HIV=human immunodeficiency virus; MDR-TB=multidrug resistance tuberculosis.

when combining rifampicin with protease inhibitor based- antiretroviral therapy in HIV co-infected TB patients (Naiker et al. 2014).

The use of rifabutin, a rifamycin to replace rifampicin in the conditions where rifampicin is to be discontinued, was reported successful as it results in a comparable activity against *Mycobacterium tuberculosis* and lower incidence of adverse drug reactions (Tattevin et al. 2003; Martinez et al. 1999; Mancini et al. 1992). Substitutions of rifampicin by rifabutin was reported safe with no development of new drug resistance and no relapse cases during 2 years of follow up (Chien et al. 2013) as well as reported effective in treating rifabutin-susceptible, MDR-TB patients (Jo et al. 2013).

However, there are uncertainties issued in the use of rifabutin as alternative to rifampicin. Previous study by Schon et al. (2013) reported that rifampicin-resistant strains was associated with *rpo*B mutations but treatment with rifabutin shows that rifabutin minimum inhibitory concentration (MIC) was significantly higher in *rpo*B mutant strains compared to the strains without *rpo*B mutations therefore criticize the efficacy of rifabutin in this setting with lack in data to confirm that such mutant strains can be treated with rifabutin.

Rifabutin dose of 150 mg daily in adult HIV-infected TB patients receiving protease inhibitor based antiretroviral therapy was able to safely maintained rifabutin plasma concentrations and prevents the sub-optimal dosing-related acquired rifamycin resistance (Lan et al. 2014; Naiker et al. 2014). However, the safe and effective dose of 5 mg/kg/dose of rifabutin in young TB-HIV co-infected children (5 years old) receiving lopinavir/ritonavir is still uncertain. Moreover, it seems that young children were more prone to get severe transient neutropenia associated with rifabutin despite the resulted lower plasma concentration as compared to adults (Moultrie et al. 2014).

A recent case report in United Kingdom highlighted that moxifloxacin, a fluroquinolone is superior than rifabutin in treating a 12-year old African boy with TB-HIV co-infection. This boy was initially treated with isoniazid, rifabutin, ethambutol and pyrazinamide. However, he had persistent sputum smear positive despite no evidence of resistance to the mentioned drugs. Subsequently, his treatment regimen was modified to moxifloxacin, isoniazid, pyrazinamide and ethambutol. His repeated sputum and nasopharyngeal aspiration was sent for molecular bacterial load (MBL) assay in addition to mycobacterium culture via MGIT and drug susceptibility testing. The MBL assay reported very low bacterial load and no drug resistance. After changed to moxifloxacin in substitutions for rifabutin, he clinically improved with no raise in bacterial load and further smear and culture test was negative. He completed treatment for 9 months without further recurrence reported (Evangelopoulos et al. 2017). Therefore, this report suggest that rifabutin may not be superior than moxifloxacin in term of bactericidal activity and warrants the need for more reliable

tool to monitor disease progression such as MBL essay.

Although there is currently no regimen that is able to replace the standard 6-month regimen for drug sensitive tuberculosis, rifabutin could possibly go a long way towards achieving the aims of TB treatment; cure, prevent death, prevent relapse, prevent MDR-TB and reduced toxicity. Although rifabutin was well tolerated in most adults who previously had rifampicin-related adverse reactions (Chien et al. 2013), more studies on its safety and efficacy particularly in other groups having different risk factors are needed. (ClinicalTrials.gov Identifier: NCT01601626)

CONCLUSION

In conclusion, understanding the disease progression of TB and the relationship between biomarkers measured during treatment as well as risk factors involved are important so that prevention and curative interventions will become more focused to individual patient based on the risk factors one acquired and their predicted disease progression. Indeed, the evaluations of rifampicin versus rifabutin in the treatment of tuberculosis are still ongoing. Although both agents seem to have comparable rates of cure and relapse in adults tuberculosis patients, they have difference in adverse effect profile which favour the use of rifabutin in patients who are rifampicin intolerant. However, the evaluations on efficacy and side effects profile particulary in HIV-coinfected populations and children are still limited. Therefore rifabutin require further evaluations as a potential candidate replacing rifampicin in the standard regimen.

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