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Novel Tubercular Therapeutic Agents: Need of the Day

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Introduction

Tuberculosis (TB), is an infectious disease caused by *Mycobacterium tuberculosis* and affects primarily the lungs and also can spread to other organs. *Mycobacterium tuberculosis* is an aerobic pathogenic bacterium that causes its infection usually in the lungs, but can also affect other organs of the body [1-4]. TB still represents a worldwide health threat with million new cases every year [5-7]. For this peculiar reason the first-line effective drugs presently available in market date back to several decades ago. The current drug resistant bacterial strains necessitated the invention for new anti-tubercular agents on urgent base [8-10]. Four first-line oral drugs viz., rifampicin, isoniazid, pyrazinamide, and ethombutol together are recommended for the minimum of two months therapy among nearly 6 month treatment of TB. Rifampicin and isoniazid are recommended for subsequent 4 months. Isoniazid is the most important and oldest anti-tubercular agent targets the biosynthesis of mycolic acids, basic constituent of the bacterial cell wall. Treatment of TB with these four first-line drugs leads to increased mortality and induce resistance. Multidrug resistant patients have to use second and third-line anti-tubercular agents, which are not affordable, less effective and more toxic than the first-line drugs. In this context, new anti-tubercular agents, as well as novel cellular targets, are the urgent need of the day to handle the spreading of TB worldwide as well as drug resistance. During the last few years, there have been many new anti-tubercular molecules are in preclinical and clinical trials.

Progress in anti-tubercular drug development

After a long four decade period a portfolio of promising new compounds is on the horizon. Some molecules have seems to be the potential to become the keystone drugs of future TB therapy [11,12]. The 10 to 15 new or repurposed anti-TB agents are in different phases of clinical investigation, some may be in safety and dose ranging study of phase 1, some in early bactericidal activity and sputum culture conversion of phase 2 and few in safety and efficacy trials of phase 3. The drugs in these trials are evaluating the possibility to reduce the drug resistant TB therapy to 4 months by the use of a third-generation fluoroquinolone, either gatifloxacin or moxifloxacin, to replace ethambutol or isoniazid [13,14]. A semi-synthetic form of rifampicin (Rifapentine) with a longer half-life is presently being tested in various clinical studies to evaluate its safety and ability to reduce the duration of therapy for drug-resistant TB in combination with isoniazid [15]. Other compounds have recently moved from phase 1 to phase 2 trials.

Challenges for fixing combination regimens in drug development process

Combination therapy has been proved to be better than a single therapy since 1943 when streptomycin came in existence with lot of excitement and hope to the world. However, very soon drug-resistance was observed and monotherapy could become ineffective and useless. Attempts for avoiding resistance and bring stable cure, combination therapy was needed. Since then, attempts for invention of newer molecules and optimization of effective drug combination regimens have been driven to improve the TB therapy. The longer duration, expensiveness and complexities of current clinical development pathway including fixation of proper combination trials of new and existing drugs need minimum of 2-3 decades to develop a new regimen of 3-4 drugs. The attempt to reduce the pathways to fix optimal drug combinations is therefore needed. In earlier days these studies were conducted by institutions funded by public and sponsored by various companies. The scenario has changed considerably today. The relatively unattractive market for anti-TB agents including large and lengthy trials to fix optimal drug combination are unlikely be willing to sponsor the studies, thus the problems related with TB therapy remained unresolved.

Conclusion

Fighting against most deadly disease TB is a battle for mankind that may not be easily won, but putting importunate effort and sustained support, it is quite anticipatory that the current deeds will provide fruit and lead to most effective TB treatment. After a long period of neglect, a strong momentum is gaining in the field of TB drug invention. The credit will go to diligence of many individual scientists and the organizations who involved in this noble endeavor for the betterment of mankind. Currently we are using very oldest anti-tubercular agents and there is a great need for development of effective new generation anti-tubercular molecules. Research on anti-tubercular agents is presently focusing on testing new or reformulated drugs, fixing the optimal combination of drugs to make effective regimen for reducing the treatment period, developing novel drug delivery systems to reduce the dosing frequency, and invention of molecular targets. The objectives of these researches are to find better and more effective molecules with reduced time of treatment and decreased toxicity. Better understanding of biological persistence, the factors responsible for tissue liquefaction and cavity formation, and the host immune mechanisms that control latent infection are the areas where today's research has to address. Such research outcomes may provide relevant biology-based targets for drug intervention along with better understanding of disease. During the recent decades significant progress has been made in reinvigorating of new molecules for the TB treatment. A number of anti-tubercular molecules are in preclinical and clinical stages show great promise. Better understanding of mycobacterial pathogenesis is helping to identify the new drug targets. The pursuit to invent more effective novel anti-tubercular agents is in process and many promising compounds are in the pipeline, there is a lot of exhilaration and even sanguinity in the area. And it is hoped that new more effective anti-

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tubercular agents will be invented in the very near future that could reduce the TB treatment from few months to a few weeks and improve control of this deadly human killer disease worldwide.

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