REVIEW
DERLEME

New aspects of pulmonary tuberculosis
Akciğer tüberkülozunda güncel yaklaşımlar

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SUMMARY

There is a worldwide rise in tuberculosis (TB) cases with drug resistant strains being a threat to disease control with the current measures. In recent years novel antituberculosis drug candidates and vaccines have entered clinical trials. Besides their activity against multi drug and extensively drug resistant strains they also target to reduce the treatment period and dosing. In this article recent developments in tuberculosis diagnostics, new anti tuberculosis drugs and vaccines for tuberculosis have been summarized.

Keywords: drug resistance, new antituberculosis drugs, pulmonary tuberculosis, vaccination

ÖZET

İlaçlara dirençli tüberküloz olgularında dünya genelindeki artış günümüzdeki tedbirler ile hastalığın kontrolünde bir tehdit unsuru oluşturmaktadır. Son yıllarda yeni antitüberküloz ilaç adayları ve aşılar ile ilgili klinik araştırmalar yürütülmektedir. Çok ilaca dirençli ve yaygın ilaç direnci olan türler üzerindeki etkinlikleri yanında tedavi süresi ve ilaç dozlarını azaltmak da hedeflenmektedir. Makalede tüberküloz tanı yöntemlerindeki son gelişmeler, yeni antitüberküloz ilaçlar ve aşılar özetlenmiştir.

Anahtar kelimeler: akciğer tüberkülozu, aşılama, ilaç direnci, yeni antitüberküloz ilaçlar

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INTRODUCTION

The post-2015 global Tuberculosis strategy aims to end Tuberculosis (TB) epidemic targeting reductions in TB deaths and TB incidence (1). Today, Mycobacterium tuberculosis – the microscopic enemy- is stil a great threat to mankind being responsible for two million deaths per year. It is estimated that one third of the world population is infected by M. Tuberculosis and statistics predict that 5-10% of this population has the potential to develop active disease in the future (2-5).

Even in the current century we have many problems awaiting solutions. Emergence of Extensively Drug Resistant Tuberculosis (XDR-TB) brought the problem of untreatable TB (6). Its overlap with HIV infection and probable nosocomial spread especially in poor income countries have made the problems even more difficult to solve (7,8). The global assessment has remarked that those challenges of the century should be managed with novel strategies including; New and easy to access methods for quick diagnosis of all forms of M. Tuberculosis, drug susceptibility tests at the first microscopic evaluation, novel drugs for resistant cases (Multi Drug Resistant TB:MDR-TB and XDR-TB), drug regimens to shorten the classical treatment period in drug susceptible cases, methods to shorten culture results period, new vaccines to protect children, adults and even the diseased, and methods that would prevent spread of the disease throughout the world. At this point, health care system strategies on research and development regarding TB have critical roles. Although there are studies on new TB diagnostics, drugs and vaccines in the past decade, results and applications are limited when considered worldwide.

Recent developments in Tuberculosis diagnostics:
The development of new TB diagnostics are of great importance to reach the targets of the post-2015 global TB strategy. An ideal test should be practically used at lower levels of the health care system and not only at reference laboratory level by experienced teams. Methods to diagnose TB in children, to differentiate latent infection from active disease, to achieve quick culture results, to get information about drug susceptibility at the start of the treatment are still insufficient and necessitate improvement.

Genotype MTB-DR plus assay is an example for line-probe assay (Hain Lifescience) which is one of the molecular methods and it can detect M. Tuberculosis gene mutations related to tuberculosis drugs; rifampicin, isoniazide, floroquinolones and second line injectable drugs (1,2). In 2012, the Hain Lifescience MTB-DR assay has been proposed as an alternative for drug susceptibility test (DST) to determine resistant related mutations (1,2).

As an example for culture-based methods, Liquid culture (Mycobacteria Growth indicator Tube: MGIT) is faster and more sensitive when compared to solid media. Microscopic observation drug susceptibility assay and thin layer agar methodology are both culture-based methods that yield faster culture and DST results when compared to liquid and solid media (9).

T cell interferon gama release assays can be useful in settings where TB incidence is low. It is more specific than tuberculin skin test but it can neither differentiate active from treated disease nor latent TB infection (3). There are technologies planned for evaluation by World Health Organization (WHO) and can be categorized as molecular and non-molecular. Examples are; TB LAMP and Urinary LAM, respectively (1).

TB LAMP (Eiken Japan / Loop mediated isothermal amplification): This test is aimed to replace acid fast bacilli (AFB) microscopy. Although WHO reviewed the evidence for its use in 2012 there is insufficient evidence for its broadened applications. Re-evaluations have been made by comparing it with flourescent smear microscopy, Xpert MTB/RIF and culture (1).

Urinary LAM (Alere USA/Lipoarabinomannan): Studies have been made about its use for the detection of active TB in severely immunosupressed people(1). High priority TB diagnostic tests are grouped as target product profiles during a meeting convened by WHO in 2014. Global Laboratory Initiative (GLI) and New Diagnostic Working Group (NDWG) have taken the responsibility to develop consensus on these novel TB diagnostics (1).

New drugs for Tuberculosis:
New drugs are necessary to provide shorter treatment periods for drug susceptible TB as alternatives to classical 6-month treatment protocol. Another target is to shorten regimens for MDR-TB and XDR-TB with less toxic and more effective anti-TB medications. Today, as WHO recommended a treatment duration of $\geq$ 18 months after culture conversion by applying Directly Observed Treatment (DOT), this regimen is accepted as the standard treatment for XDR-TB and MDR-TB.

Discovery of new molecules and antibiotics is quite a difficult task. Furthermore, it necessitates suitable

animal models for preclinical studies and long follow-up periods for drug combination protocols to achieve satisfactory results that support their use in the field. There are novel drugs that undergo clinical evaluation. Global WHO Report 2014 has declared 10 drugs in phase II and phase III trials and has published results till September 2014 related to drug susceptible TB, MDR-TB and latent TB infection (1).

Treatment of drug susceptible Tuberculosis:

*Fluoroquinolone containing regimens (gatifloxacin and moxifloxacin- OFLUTUB trial and REMOX trial) (1).

*Rifapentine: Is a rifamycine that has a longer half life than rifampicin (1,5,10). Phase I and Phase II trials have been conducted. Examples for phase II trials; RIOMAR study in Rio de Janeiro, Brasil and the second phase II trial in Cape Town, South Africa (1). Another planned study is TB Trials Consortium (TBTC) Study 31, that enrolled 2500 people and will be completed in 2020 (1). These studies on Rifapentine aim to clarify whether high and daily doses of this drug could allow shortened treatment regimens for drug susceptible TB.

Treatment of multi-drug resistant Tuberculosis:

*TMC-270 / Bedaquiline: It shows its effect by inhibiting Mycobacterium membrane bound ATP synthase. In 2012 US FDA approved Bedaquiline "as part of combination therapy to treat adults with multi-drug resistant pulmonary TB when other alternatives are not available" (1). In 2013 WHO declared a policy guidance for the use of the drug in MDR-TB treatment (11).

*OPC-67683 / Delamanid: It inhibits methoxy-mycolic and keto-mycolic acid synthesis in the cell wall of mycobacteria. A phase III clinical trial is being conducted as an adjunct to an optimized background regimen for the treatment of MDR-TB in adults. Two other trials are being conducted to evaluate delamanid in children with MDR-TB (1,2,10).

New drug regimens for drug susceptible and / or drug resistant Tuberculosis:

New combinations of drugs are being tested in various phase II trials as NC-002, NC-003, and NAMS-TB-01 (1).

*NC-002: It investigated the efficacy, safety and tolerability of a combination therapy: PA-824 (a nitroimidazole) + moxifloxacin + pyrazinamide (Pa-M-Z). It is being conducted in adults with newly diagnosed drug susceptible or smear positive pulmonary MDR-TB (1).

PA 824 is a nitroimidazopyran, derived from 5- nitroimidazoles. It is highly active against M. Tuberculosis and MDR-TB. It is prodrug and requires activation by a bacterial F420 dependent glucose-6-phosphate dehydrogenase and nitroreductase to activate components which inhibit bacterial mycolic acid and protein synthesis. Its ability to shorten TB therapy in combination with other drugs is currently being tested in clinical trials (5).

*NC-003: This trial is being conducted in patients with drug susceptible TB. It investigated the 2-week early bactericidal activity of various combinations of clofazimine, bedaquiline, PA-824 and pyrazinamide (1).

*MAMS-TB-01: This trial is funded by the European and Developing Countries Clinical Trials Partnership (EDCTP). It evaluated new combination regimens to shorten treatment. The drugs are H, R, Z, E, M and SQ-109 (a synthesized derivative of ethambutol) (1).

New vaccines for Tuberculosis:

An effective vaccine for Tuberculosis is stil lacking. Global coordination is necessary to achieve targets in developing new effective TB vaccines. There are candidates designed for prevention of TB infection and progression of disease in infected individuals. An improved version of BCG for infants and a new vaccine for adults for long term protection as a booster dose could be a problem solving strategy. TB vaccine candidates in clinical trials are; viral vectored, protein/ adjuvant, attenuated M. tuberculosis and mycobacterial- whole cell or extract types (1).

MVA85A is an attenuated vaccine candidate which entered phase III study. It is a vaccinia –virus vectored vaccine expressing Ag 85A. Studies on this vaccine candidate are made on infants as a booster vaccine and also on adults with HIV (in South Africa and Senegal) (1,2).

MT2+ AS01 is a vaccine formulated in an adjunct to increase immunogenicity using fusion protein of M. Tuberculosis antigens 32A and 39A. A large phase II b study is conducted in TB endemic countries in Zambia, Kenya and South Africa (1).

A phase III trial is conducted to study the efficacy of a lysate of M. Vaccae. It has been tried as an adjunctive treatment in MDR-TB, previously treated TB or in the prevention of TB in high risk individuals and in BCG vaccinated HIV infected people. It is licensed in China and is used as an adjunct to standard TB chemotherapy (1,4,12)

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Phase II studies:

VPM 1002: A live recombinant vaccine to improve immunogenicity

H1+ IC31: Protein subunit adjuvant vaccine (Ag 85B, ESAT-6 Ag)

H4: IC31: Protein subunit adjuvant vaccine (Ag 85B, ESAT-6, AgRv2660c: latency Ag) Adolescent HIV (-), Igra (-) South africans at high risk for TB infection

H56: IC31: Fusion protein that express Ag 85B, TB10.4

RUTI: Immunotherapeutic vaccine, a non-live vaccine.

Crucell Ad35/AERAS-402: An Adenovirus vectored vaccine including Ag 85A, Ag 85B and TB10.4. (a booster vaccine for neonates, adolescents and adults) (1,4).

Phase I studies:

Ad Ag 85A (Adenovirus serotype 5 vector expressing Ad Ag 85A), MTBVAC, ID93+GLA-SE, Crucell Ad35/ MVA85A, DAR901 (heat inactivated M. Obuense strain), TB/FLU-04L (a recombinant influenza vectored vaccine) (1).

In conclusion; we expect that wider incorporation of recent advances on TB diagnostics, drugs and vaccines will provide quick and better diagnosis, treatment and prevention of the disease allowing targeted reductions in TB mortality and incidence.

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