

Recent advances in treatment of drug resistant Tuberculosis

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CASE FINDING

- Patients at risk of DR-TB should be screened for drug resistance
- In pts with HIV, when possible, DST should be performed at the start of anti-TB therapy to avoid mortality due to unrecognized DR-TB
- For the initial screening of DR-TB, rapid DST methods should be used whenever possible
- Patients at increased risk of XDR-TB should be screened for resistance with DST of isoniazid, rifampicin, the second-line injectable agents and a fluoroquinolone.

- Design treatment regimens based on the hierarchy.
- Use at least 4 drugs with either certain, or almost certain, effectiveness.
- DST should generally be used to guide therapy; however do not depend on DST in individual regimen design for ethambutol, pyrazinamide, and Group 4 and 5 drugs
- Treat for 18 months past culture conversion
- Use adjunctive measures -surgery and nutritional social support
- Treat adverse effects immediately and adequately.

- In Seven-year DOTS-Plus pilot experience in India: Of the 126 patients enrolled, 61% were cured, 19% died, 18% defaulted and 3% failed treatment.

Singla et al. Int J Tuberc Lung Dis. 2009 Aug;13(8):976-8

- MDR-TB case fatality in NON HIV Pts is 26%(16-58%).
- XDR-TB has been reported on 6 continents in at least 37 countries, constituting up to 10% of all MDR-TB strains.
- Much more difficult to treat than MDR-TB and is extremely difficult to treat in HIV-positive patients.
- Reports of HIV positive patients being promptly diagnosed with XDR-TB and placed on an adequate regimen are non-existent to date
- Cohorts of HIV-negative XDR patients have been shown to have cure rates that exceed 50%

Fluoroquinolones

- Against DNA gyrase
- second-line therapy for the treatment of MDR-TB.
- comparable with the bactericidal activity of rifampicin

Alvarez-Freites Ejet al. Antimicrobial Agents Chemother 2002;46:1022–5.

- Moxi>> Oflox> cipro

- In a Phase 2 controlled trial in which patients were randomized to receive 8 weeks of therapy with either standard treatment or the combination of H,R,Z and with either ofloxacin, moxifloxacin, or gatifloxacin, the rates of elimination of M tuberculosis from serial sputum cultures were more rapid in the gatifloxacin- and moxifloxacin-containing regimens than in the ofloxacin-containing or the standard regimen.

Rustomjee R et al Int J Tuberc Lung Dis 2008;12(2):128–38.

- When given in combination with R and Z, moxifloxacin has been reported to reduce treatment time by up to 2 months compared with an H,R and Z combination.

Nuermberger EL et al. Am J Respir Crit Care Med 2004;169:421–6.

- In a Phase 2a EBA study conducted in Tanzania, moxifloxacin (400 mg daily) was as efficacious as isoniazid (300 mg daily) and more efficacious than rifampicin (600 mg daily).

Gosling RD et al. Am J Respir Crit Care Med 2003;168:1342–5.

- Phase 2b trial conducted in Brazil, the moxifloxacin-containing regimen achieved a higher rate of culture conversion at 2 months compared with the standard ethambutol-containing regimen.
- Two Phase 3 randomized controlled trials are presently underway which investigate the safety and efficacy of 4-month treatment regimens including those that replace ethambutol or isoniazid with gatifloxacin or moxifloxacin.

Ginsberg Am et al. Nat Med 2007;13(3):290–4.

RIFAPENTINE

- selective inhibitors of bacterial RNA polymerase, an essential enzyme for DNA transcription.
- Close analogue of rifampicin ;not active against rifampicin resistant mutants.
- Extended terminal half life ;can be used in intermittent therapy.
- Poor inducer of CYP450
- But underrepresented in clinical trials of HIV pts

- Rifapentine +Mxfl +Z daily or thrice-weekly therapy allowed shortening of treatment from 6 to 3 months or less in mice.

Rosenthal et al. PLoS Med 2007;4(12):e344

- Daily regimens rifapentine +H+ Z produced a stable cure in mice after 10 weeks of therapy, whereas mice receiving standard RHZ regimen relapsed after 12 weeks of treatment.

Rosenthal IM et al. Am J Respir Crit Care Med 2008;178(9):989–93

Diarylquinoline: TMC-207

- Most advanced compound presently in clinical development.
- Target of TMC-207 is ATP synthase, the powerhouse of the tubercle bacillus.
- Potent against both sensitive & resistant MTB strains.
- Potent activity against *M avium*, *M marinum*, *M fortuitum*, *M abscessus*, and *M smegmatis*
- Killing is time dependent but not concentration dependent.

- Potent late bactericidal activity.
- Long tissue half life & high tissue penetration
- Linear pharmacokinetics
- Absorption ↑es with food.
- CyP450 3A4 → interaction with R.

- TMC-207/HZ and TMC-207/RZ combinations cleared the infections in the lungs of all mice after 2 months of therapy.
- Phase 2b placebo-controlled, double-blind, randomized trial preliminary results of the 2-month treatment Phase showed that the combination of the background MDR-TB treatment with TMC-207 provided a higher sputum culture conversion (48%) in patients than the background regimen combined with placebo (9%).

Diacon AH et al. N Engl J Med 2009;360:2397–405.

- Compared with the standard combination RHZ, TMC-207 at 5, 10, and 15 mg/kg exhibited better bactericidal activity than the 3-drug combination after 6 weeks of therapy.

Lenaerts AJ et al. *Chemother* 2007;51(9):3338–45

Nitroimidazoles

bioreduction of the nitroimidazole pharmacophore



Reactive chemical species generated



through this bioreduction process is presumed

PA-824

- highly specific with potent activity only against bacillus Calmette-Guerin and M tuberculosis among mycobacterial species tested
- without significant activity against a broad range of gram-positive and gram-negative bacteria (with the exception of Helicobacter pylori and some anaerobes).
- has activity against nonreplicating bacilli, indicating its potential for activity against persisting organisms and shortening duration of treatment
- Nonmutagenic ; excellent tissue penetration
- Orally bioavailable → OD or less frequent dosing

- promising bactericidal activity in mice during the initial intensive Phase of therapy, similar to that of the equipotent dose of INH in humans.
- potent activity during the continuation Phase of therapy in mice, during which it targeted bacilli that had persisted through an initial 2-month intensive Phase of treatment with RHZ.

Tyagi S et al. *Chemother* 2005;49(6):2289-93.

- Phase 1 trial demonstrated clinically significant bactericidal activity for this drug over a 14-day dosing period when administered orally at 200 to 1200 mg per day.

Ginsberg AM. Symposium12: 39th Union World Conference on Lung Health 2008; Paris.

OPC-67683

- No cross resistance with any first line drugs
- Nonmutagenic
- No P450 drug interactions
- In a mouse model of established infection, the efficacy of OPC-67683 is superior to that of currently used TB drugs.

OPC-67683

- human equipotent dose (to rifampicin)0.625 mg/kg.
- The combination of OPC-67683+ R+Z→ quicker eradication of viable TB bacilli in the mouse lung in comparison with the standard regimen consisting of RHZE.

Matsumoto Met al.PLoS Med 2006;3(11):e466

Ethylenediamine: SQ109

- derivative of ethambutol
- different mode of action from that of ethambutol, and is believed to have synergistic interactions with both INH & R.
- In a mouse model of established infection, substituting SQ109 for ethambutol in the standard regimen demonstrated an improved efficacy.
- A Phase 1 single-dose, dose-escalation study has been completed and a Phase 1 multiple-dose study has been planned.

Oxazolidinones: Linezolid and PNU-100480

- Broad spectrum coverage
- inhibiting protein synthesis through binding to the 70S ribosomal initiation complex
- Linezolid – used in MDR TB
- ? Unclear role
- S/E- peripheral & optic neuropathy.
- PNU-100480 is close analogue of linezolid.
- slightly better in vitro activity against M tuberculosis than linezolid.

Oxazolidinones: PNU-100480

- incorporation of PNU- 100480 dramatically improved the bactericidal activity of regimens containing current first-line TB drugs and moxifloxacin.
- A regimen combining PNU-100480, moxifloxacin, and Z, which contains neither INH nor R, was more active than the RHZ combination.

Williams et al. Antimicrobial Agents Chemother 2009;53(4):1314–9.

- May have the potential to significantly shorten the duration of therapy for both drug-susceptible and drug-resistant TB

Preclinical Discovery Pipeline

- There are about 43 compounds and projects in the global pipeline.
- 34 are in preclinical and discovery stage, including 6 compounds in preclinical development, 8 projects in lead optimization, 6 projects in lead identification, and 14 projects in screening stage

ROLE OF IMMUNOTHERAPY

- The nature of the immune response to TB infection determines whether protective immunity or active disease will be the result.
- Protective immunity is comprised of bacteriostatic and bacteriocidal components.
- Although a bacteriostatic response may transiently protect the host from an invasive pathogen, it does so at the cost of creating dormancy, a source of recurrent infection that can be difficult to eradicate.
- The challenge for immunotherapy is to convert a predominantly bacteriostatic immune response into a bacteriocidal response, or, alternatively, to modify the bacteriostatic response so that it no longer interferes with chemotherapy.

- Optimal bacteriocidal immunity is probably achieved by a combination of the classic type 1 IFN- γ -mediated response plus Cytotoxic-T Lymphocytes.
- \uparrow proportion of antigen-specific IL-4- producing T cells, and skewed toward a Th2- type cellular response \rightarrow increased immunopathology rather than protection

- The aim of immunotherapy is to “realign” or improve the immune response by either promoting protective Th1 immunity or blocking harmful immune (Th2) responses.
- Boosting Th1 responses may induce systemic release of Th1-associated cytokines, resulting in necrosis of TB lesions (Koch phenomenon).
- A better approach may be to optimize the balance between the Th1/Th2 immune response by downregulating the Th2 response

HIGH DOSE IVIg

- high-dose IVIg given in mouse model of TB showed marked therapeutic effect whether administered early or during infection.
- Excellent safety

HE2000 (16a-BROMOEPIANDROSTERONE)

- HE2000 is a modified form of DHEA that cannot go into the sex steroid pathways .
- HE2000 was therapeutic in a mouse model of pulmonary TB, even when given late in the infection, without any chemotherapy. The molecule also showed synergy with antibacterial drugs, leading to accelerated bacillary clearance

Studies of HE2000 in HIV Pts

- well tolerated and safe in HIV.
- significant decrease in viral load ($P < .01$).
- reduce the incidence of TB coinfection by 42.2% ($P < .05$)
in a cohort of antiretroviral therapy-naive HIV-infected
subjects with advanced HIV disease.

Stickney Dr et al. Antimicrobial Agents Chemother 2007;51(7):2639–41.

Multidose heat-killed *M vaccae*

- preparation of an environmental saprophyte.
- inhibit Th2 responses and driving a Th1 response that results in activation of cytotoxic T cells that kill *M tuberculosis*-infected macrophages.

- In China, multiple injections of M vaccae have been given to patients with recurrent or drug-resistant TB. Significant improvements in sputum conversion rates were claimed.

Fan Met al:Chinese Journal of Evidence-Based Medicine 2007;7(6):449–55.

- Commercially available and licensed as a therapy for TB in China, and a recent meta-analysis of 11 trials of multidose M vaccae undertaken in China concluded that it is effective as an adjunctive treatment in MDR-TB.

DARDAR study

- 5 doses of M vaccae were given to more than 2000 Tanzanians infected with HIV, which resulted in a significant decrease in definite TB in the M vaccae recipients ($P = .027$).most patients were already TB-infected, even if their disease was latent.

von Reyn et al. [PS-81689-20] Int J Tuberc Lung Dis 2008;12(11 Suppl 2):S318.

- Need for a randomised ,blinded trial.

Neutralizing antibodies to IL-4, leading to reduced IL-4 and TGF- β

- \downarrow IL-4 \rightarrow \downarrow TGF- β \rightarrow \downarrow TB
- TGF- β blocker \rightarrow \downarrow TGF- β \rightarrow \uparrow inflammation
- modest decrease in TGF- β caused by blocking IL-4 might be a part of the therapeutic effect.
- Pascolizumab (M Ab to IL-4) \rightarrow likely to be effective in patients with high IL-4.

DNA vaccine encoding a mycobacterial protein (HSP65)

- major target of the immune response to mycobacteria, profound immunoregulatory properties.
- HSP65 DNA vaccine is effective alone and enhances cytotoxic T cells, while inhibiting the IL-4 response.
- Synergy with antibacterials (Mflx)
- ? S/E → immunopathology in lung lesions in guinea pigs

DNA VACCINE

- DNA vaccine encoding 3 other antigens of MTB: Ag85B, MPT-64, and MPT-83. Used together with antibacterial drugs, this vaccine significantly reduced CFU 3 to 5 months after treatment of infected mice ($P < .001$).

Hu D H et al Gene Ther 2008;15(9):652–9

DZHERELO

- Plant extract
- Used in ukraine
- Striking claims when used as adjunct immunotherapy against MDRTB & XDR TB.
- Need for randomised trials.

SCV-07 SciCLone

- Gamma glutamyl-tryptophan
- Immunostimulatory with unknown actions

RUTI

- liposome preparation of M tuberculosis cell wall skeleton.
- RUTI accelerates bacterial clearance when given late in T/t as an adjunct to conventional chemotherapy.

Cardona PJ. Tuberculosis 2006;86(3-4):273-89.

- Phase 1 study

IMMUNOSUPPRESSIVE

- Current AB kill rapidly growing ,not nonreplicating bacilli→ dormant
altered biosynthetic pathway
- Immune system modulation may render dormant bacilli more susceptible to drugs
- S/E→opportunistic infections
disease flare up

ROLE OF TNF α

- TNF α is essential for granuloma
- \downarrow TNF α \rightarrow \downarrow granuloma \rightarrow bacilli in open active state & more susceptible to AB
- Thalidomide \rightarrow partially block TNF α but not T cells \rightarrow immunomodulatory & anti immunomodulatory effects
- $\uparrow\uparrow$ mortality in TBM in HIV uninfected children
- Teratogenic; peripheral neuropathy

THALIDOMIDE ANALOGS

- selective cytokine inhibitory drugs (SelCiDs), has been shown to act via inhibition of PDE4.
- TNF- α PDE4 inhibitor (thalidomide analog)CC 3052→cotreatment of infected mice with CC-3052 and INH resulted in improved bacilli killing & clearance.
- T/t with only CC-3052 alone was associated with control of M tuberculosis growth in the lungs during infection similar to that seen in the untreated control mice indicating that the drug is not genuinely immunosuppressive.

anti-TNF- α monoclonal antibody TN3-19.12

- highly immune suppressive
- $\uparrow\uparrow$ morbidity & mortality
- Didn't enhance the efficacy of INH.

Etanercept (soluble TNF- α receptor)

- Adjunctive treatment with etanercept, together with conventional TB chemotherapy, can accelerate the microbiologic response and improve outcome in patients with HIV/TB coinfection.
- Adjunctive etanercept treatment resulted in a trend toward increased CD4+ T cell counts, but there was no effect on plasma HIV RNA levels.

HIGH DOSE PREDNISOLONE

- Phase 2 trial → 187 HIV-infected TB patients (CD4 counts > 200 cells/mm³) were treated with either prednisolone (at 2.75 mg/kg/d) or placebo during the first month of standard TB chemotherapy. Sputum culture conversion rates after 1 month of treatment were 62% & 37% in subjects treated with prednisolone versus placebo, respectively (P < .001), and is the greatest effect on sputum culture conversion observed in any trial of adjunctive therapy in TB, whether chemotherapy or immunotherapy.
- Minor side effects

- Two other prospective clinical trials of adjunctive corticosteroids administered at much lower doses in TB patients have shown acceleration of sputum culture conversion providing further support for the hypothesis of an association between release of immune pressure and improved antibiotic-mediated bacillary clearance.

Bilaeroglu S et al. *Int J Tuberc Lung Dis* 1999;3(1):47–54.

Horne NW. *Br Med J* 1960;2(5215):1751–6.

- Future - ? Inhaled delivery of steroids

Recombinant Human IFN- γ

- 5 small trials of aerosolized, s/c or i/m rh IFN- γ or α among patients with multi- or drug-resistant TB.
- minimal to moderate benefit that was not sustained

IL-12

- \uparrow es IFN γ response in MTB stimulated human peripheral mononuclear cells & alveolar macrophages.
- Therapeutic efficacy shown in murine model of PTB

rh IL-2

- promotes T cell proliferation, differentiation, and activation, and is essential for cellular immune function and granuloma formation.
- In 1997, a small, unblinded study in MDR-TB patients of 2 lowdose IL-2 regimens (daily or in 5-day “pulses”) found that the daily regimen appeared to decrease sputum AFB counts.

rh IL-2

- A randomized, double-blind, placebo-controlled trial of the effect of IL-2 on sputum culture conversion was conducted in 110 HIV-uninfected drug-susceptible Ugandan TB cases. Contrary to expectations, the study found reduced clearance of viable M tuberculosis sputum counts and delayed sputum culture conversion in the IL-2 arm. These results suggest that IL-2 may only be beneficial when given adjunctively with MDR-TB drug regimens.

Johnson JLA *Am J Respir Crit Care Med* 2003;168(2):185–91

rh- GMCSF

- ↓replication of MTB
- Only 1 small (n 531) randomized controlled trial of adjunctive rh-GMCSF in patients with newly diagnosed HIV uninfected PTB in Brazil was shown to be safe and well tolerated and showed a trend towards faster sputum conversion.
- BCG-derived GM-CSF resulted in tenfold increased protection against disseminated TB compared with standard BCG alone.

TIME TO RETHINK??

WHO GUIDELINES

- Pt can be empirically started on Cat IV
- T/t can be standardised/individualised.
- BD dose
- Change in T/t if mono/poly resistance
- DST at start of T/t in HIV with PTB

RNTCP-DOTS PLUS

- Only if DST is positive
 - Cat IV in R resistance
 - T/t is standardised
- 6 (9) Km Ofx (Lvx) Eto Cs Z E / 18
Ofx (Lvx)Eto Cs E
- OD dose of PAS, Eth, Cs
 - No change in T/t if mono/poly resistance

SUMMARY

- Potential to cure
- Potential to shorten
- Too early
- Prevention is cure