



## NEW STRATEGIES FOR THE TREATMENT OF TUBERCULOSIS

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**Abstract.** The treatment of Tuberculosis may be associated with an emergence of mycobacterial resistance through chromosomal alterations, but also through a poor administration of treatment, leading to the emergence of multi-drug-resistant strains MDR-TB or extensively drug-resistant, XDR-TB, responsible for over one million illnesses. We aim at presenting current WHO recommendations for patients in treatment failure as well as information regarding the new compounds: TMC-207, OPC-67683, PA-824, LL-3858 and SQ-109, currently being evaluated in the treatment of tuberculosis.

**Keywords:** *Mycobacterium tuberculosis*, multi-drug-resistant strains

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### Tuberculosis – treatment – resistance

The emergence of resistance of *Mycobacterium tuberculosis* may be the result of spontaneous chromosome alteration, but most often it is attributed to the week pattern of administration of the tuberculosis medication, with the emergence of MDR-TB strains (multi-drug-resistant TB), resistant to two of the major tuberculostatics, INH isoniazid and RIF rifampicin, or XDR-TB strains (extensively drug-resistant), additional resistance to fluoroquinolones and one of the aminoglycosides used in tuberculosis treatment: kanamycin KM, amikacin AK, capreomycin CM, responsible since 2006 for important therapeutic failures [1,2].

Worldwide, WHO estimates the existence of a number of approximately 1 million illnesses with MDR-TB, respectively 40 000 illnesses with XDR-TB [3,4], influenced by poor administration of tuberculosis treatment, by sub-optimal doses and not least by the widespread use of fluoroquinolone therapy in respiratory, urinary infections, allowing the escalation of mycobacterial resistance to fluoroquinolones.

The presence of any of the following risk factors: treatment interruption, contact with persons known for treatment failure, alcoholism, poor socioeconomic conditions, migration of population from areas known with multi-resistance, requires the investigation of bacillary susceptibility through molecular tests of resistance.

Since 2008, WHO recommends a wider range of chemotherapy agents with anti-tuberculosis action [6,7], classified into 5 groups in relation to their efficiency (see table I), with warnings regarding the possible secondary effects correlated with their administration.

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The active substance	Side effects		
	Ordinary	Occasional	Rare
<b>Category A: first-line drugs</b>			
Isoniazid		Medicamentous hepatitis Skin hypersensitivity Peripheral neuropathy	Vertigo Seizures Optic neuritis Hemolytic anemia Aplastic anemia Lupoid reaction Arthralgia Gynaecomastia
Rifampicin		Medicamentous hepatitis Skin hypersensitivity Gastrointestinal disorders Thrombocytopenic purpura Febrile reactions Flu-like syndrome	Dyspnoea Shock Hemolytic anemia Acute renal failure
Ethambutol		Retrolbulbar neuritis Arthralgia	Medicamentous hepatitis Skin reactions Peripheral neuropathy
Pyrazinamide	Anorexia Nausea Flushing Photosensitivity	Hepatitis Vomiting Arthralgia Skin reactions	Sideroblastic anemia Gout
<b>Category B: parenteral administration agents</b>			
Streptomycin	Skin hypersensitivity Dizziness Paresthesia Tinnitus	Vertigo Ataxi Deafness	Renal affectation Aplastic anemia
Amikacin Kanamycin Capreomycin	Ototoxicity Nephrotoxicity	Clinically evident renal failure	Hypokalemia Hypocalcemia Hypomagnesemia
<b>Category C: fluoroquinolones</b>			
Ofloxacin	Gastrointestinal disorders Insomnia Dysmicrobism	Anxiety Dizziness Headache Tremor	Seizures Hemolysis Tendonitis / tendon rupture Arthropathies Colitis
Levofloxacin Moxifloxacin	Similar to Ofloxacin, more reduced effects on the CNS but potentially less cardiotoxic (Moxifloxacin)		
<b>Category D: bacteriostatic second-line agents</b>			
Ethionamide Prothionamide	Metallic taste Hyper-salivation Gastrointestinal disorders	Hepatitis Peripheral neuropathy Headache	Seizures Impotence Menstrual disorders Gynaecomastia Hypothyroidism Hypoglycemia Alopecia

Cycloserine	Dizziness	Agitation	Sideroblastic anemia
Terizidone	Headache	Psychoses	Stevens-Johnson syndrome
	Depression	Seizures	
	Memory disorders		
Para-aminosalicylic acid	Gastrointestinal disorders	Hepatitis	Hypothyroidism
		Medicamentous fever	Hematological reactions
		Skin allergic reactions	Hypokalemia
			Metabolic acidosis
			Hypernatremia
<b>Category E: agents with efficiency under evaluation (not recommended by WHO in routine therapy, used in patients with MDR-TB)</b>			
Clofazimine	Photosensitivity	Gastrointestinal disorders	Intestinal ileus
	Hyperpigmentation	Retinopathies	
	Skin reactions		
Amoxicillin-clavulanate	Gastrointestinal disorders	Headache	Hepatitis *
	Skin reactions	Hematological reactions *	Colitis *
		Vasculitis	Stevens-Johnson syndrome
			Seizures
Thiacetazone	Gastrointestinal reactions	Hepatitis	
	Hypersensitivity	Multiform Erythema	
	Vertigo	Exfoliative dermatitis	Agranulocytosis *
	Conjunctivitis	Hemolytic anemia	
Linezolid	Diarrhea	Thrombocytopenia *	Colitis
	Dyspepsia	Aplastic anemia *	Peripheral, optic neuropathy *
	Headache		
Imipenem / cilastatin	Nausea	Diarrhea *	Colitis *
		Skin reactions	Confusion
		Candidiasis *	Seizures
		Hepatitis *	Arrhythmias
		Neutropenia *	
High dose of isoniazid	(see footnotes) *		
Clarithromycin	Nausea	Eye irritation	Taste disorders
	Dizziness	Diarrhea	Postantibiotherapy Colitis
	Dry skin		

**Table 1.** WHO recommends of chemotherapy agents with anti-tuberculosis action

\* More frequent in extended administration

\* Hepatotoxicity and nephrotoxicity may be more frequent.

Ethambutol and pyrazinamide will be used in the **MDR-TB therapy**, if the resistance testing confirms the continued sensitivity to these drugs; supplementation with kanamycin or amikacin, from the second line, if there is resistance to streptomycin.

Regarding the administration of old **fluoroquinolones**, such as ciprofloxacin, the increase of resistance is envisaged, as well as the prolonged time of negatvation of sputum cultures, currently being preferred the moxifloxacin and the levofloxacin,

active against some strains resistant to ofloxacin.

The use of **linezolid**, initially 600 mg/day, then 300 mg/day, demonstrates its effectiveness on MDR-TB, XDR-TB, and the reduction of doses contributes to lowering the medulotoxic risk of linezolid, but with no long-term influence on neurotoxicity.

A different product from the oxazolidinone group, **PNU-100480**, has recently made its way into therapeutic practice, significantly increasing the bactericidal action of regimens containing first

line drugs and moxifloxacin, with the possibility of reducing the duration of therapy for persons with TB susceptible to PNU-100480.

**Amoxicillin-clavulanate** also demonstrates its early bactericidal efficiency in pulmonary tuberculosis with sensitive strains, respectively the inhibitory action on MDR-TB.

For the **MDR-TB** treatment, second line medication is used, respectively the injectable medication, streptomycin or kanamycin, amikacin or capreomycin associated with fluoroquinolones, ethambutol, ethionamide or prothionamide for strains resistant to INH and RFP. Cycloserine is associated with para-aminosalicylic acid for strains resistant to ethambutol, pyrazinamide, to aminoglycosides, fluoroquinolones, ethionamide or prothionamide. The minimum recommended duration in these cases is 18 months or 18 months from the negatization of cultures for BK.

In particular cases - patients with silicosis, diabetes mellitus, extensive radiological image, slow conversion rhythm of sputum, resistance of isolated strain, we encourage the extension of therapy to 24 months.

In **XDR-TB** strains therapy, we use medication in Group E that is amoxicillin-clavulanate, clofazimine, imipenem, linezolid and clarithromycin, combined, where suitable, with surgery.

In addition to the presented therapeutic regimens, since October 2008, the results of over 60 studies have been evaluated; for example phase III clinical studies regarding the effectiveness of moxifloxacin and gatifloxacin in the treatment of tuberculosis with drug-susceptible germs, but also phase II studies using new compounds: **TMC-207**, **OPC-67683** and **PA-824**, compounds that are in preclinical/ clinical stages of research, **LL-3858** and **SQ-109** effective in susceptible but also multidrug-resistant strains.

**TMC-207** is a new product, diarylquinoline, with action on the ATP - synthase BK, acting on mycobacteria being in the multiplication phase or hibernating. Its half-life is of approximately 24 hours, it is metabolized on the CYP3A4 level, the plasma being halved in combination with rifampicin. It acts synergistically with pyrazinamide, with bacteriological sterilization at 2 months after beginning therapy, and in combination pyrazinamide-rifampicin-TMC-207, with sterilization in a month after starting the treatment.

Administration in combination with amikacin, ethionamide, moxifloxacin and pyrazinamide dem-

onstrate its superiority compared with the combination of second-line treatment drugs.

**OPC-67683** is a nitroimidazole, extremely potent in vivo and in vitro, compared to BK with maintained sensitivity or MDR, with inhibitory action on the cell wall as the PA-824, 20 times more active than the latter and synergistic to first line medication. Its half-life is of 7-8 hours and it is used in doses of 100-200 mg/day.

**PA-824** is part of a new class of antibacterial agents, respectively **nitroimidazopiran**. It works through inhibition of protein synthesis and cell wall lipid biosynthesis, it does not significantly interact with the cytochrome P450, it is not mutagenic. It is bactericidal, comparable to the INH action within the first 8 weeks, highly potent in sputum sterilization, comparable to the INH-RFP association. Its action mechanism on the non-replicative bacilli has recently been ascertained: it acts by releasing intracellular nitric oxide.

The combination of moxifloxacin and pyrazinamide is expected to significantly reduce the duration of therapy in MDR-TB cases. PA-824 binds to serum proteins in percentage of 94% so that the administered doses may be associated to important side effects. Due to this disadvantage, the testing of PA-824 aerosols administering has been started.

**LL-3858** is a **pyrrole compound**, active against strains which are sensitive and resistant to BK, the action mechanism remains unknown, synergistic in vitro with rifampicin, more active compared with INH, in mono-therapy.

**SQ-109** is a **diamine**, active on sensitive and resistant strains by inhibition of cell wall synthesis, synergistic with INH and RFP, additive to streptomycin, potential replacement of ethambutol, highly potent in combination with IMC-207. It is administered in doses of 300 mg, with a half-life of 61 hours.

Other agents in tuberculosis therapy are also under evaluation: nitrofuranylamine, meropenem-clavulanate, pleuromutilin, malatsynthase inhibitors.

The general opinion is to associate **surgery** to drug therapy, classic or video-assisted thoracoscopy, collapse-therapy – thoracoplasty, filling or artificial pneumothorax that limits the risk of dissemination.

**Immunotherapy** is a complementary therapeutic method, IFN- $\gamma$ , IFN- $\alpha$ , IL-2, IL-12, the *Mycobacterium vaccae* vaccination, and the administration

of mono- and polyclonal antibodies being currently evaluated.

Other studies are focused on intracellular destruction of *M. tuberculosis* through the phenomenon of autophagy, homeostatic intracellular mechanism of clearance of cellular organelles, of cellular proteins, increased by administering Rapamycin.

MDR TB therapy is far from being solved, the costs being 100 times greater than the costs for atypical mycobacterial infections, while the chances of healing are still low. Among the presented therapeutic products, 8-methoxy-fluoroquinolones remain the most accessible option, given that their use should be restricted to the therapy of pneumonia or community urinary infections.

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