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MALLA REDDY COLLEGE OF PHARMACY

THE INQUEST

DELAMANID– new drug to combat multi drug resistant tuberculosis (MDR– TB)

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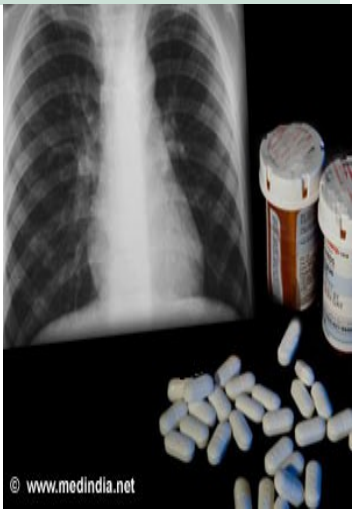
- **Anti-TB drug resistance major public health problem.**
- **Use of current therapy for up to 2 years.**
- **Poorer rates of compliance.**
- **Improved rates with DELAMANID—improvement within 2 months.**
- **New ray of hope to overcome MDR TB.**

Anti-tuberculosis (TB) drug resistance is a major public health problem that threatens progress made in TB care and control worldwide. Drug resistance arises due to improper use of antibiotics in chemotherapy of drug-susceptible TB patients. This improper use is a result of a number of actions including, administration of improper treatment regimens and failure to ensure that patients complete the whole course of treatment. Essentially, drug resistance arises in areas with weak TB control programmes. A patient who develops active disease with a drug-resistant TB strain can transmit this form of TB to other individuals.

The term **MDR-TB** has a very specific definition in the field of medicine. A strain of *Mycobacterium tuberculosis* that is resistant to the effects of at least isoniazid and rifampicin is defined as a MDR-TB, with or without resistance to any other drugs, with isoniazid and rifampicin being the two most potent drugs available for TB treatment.

The problem arises at this point. How to treat this condition of MDR- TB? By far, the available treatment has been the use of a combination of nearly six drugs (Isoniazid, Rifampin, Ethambutol, Pyrazinamide and Streptomycin), including more toxic and less potent second line agents, with a further disadvantage of having to use these medications for up to 2 years. This prolonged treatment and the use of multiple medications will reduce the patient's medication adherence and thus results in poorer rates of cure.

What is the solution now? Although we cannot term it a solution yet, Phase III trials on a new chemical entity DELAMANID are in progress. These trials are being carried out by the Otsuka Pharmaceutical Development & Commercialization, Inc, under the guidance of its MD, Mr. Charles Wells. Currently this study is being carried out in 17 centers, in 9 countries – the Philippines, Peru, Latvia, Estonia, China, Japan, Korea, Egypt, and the United States.



Delamanid is a nitro-dihyroimidaz-oxazole derivative that inhibits mycolic acid synthesis, inhibiting formation of the mycobacterial cell envelope, in both drug-susceptible and drug-resistant strains of *M. tuberculosis* and was thus found to be effective in the treatment of MDR- TB.

Inside this issue:

It is being available for the trial in the dose of 50 mg tablets and a dosage of 100mg and 200mg twice daily plus a background regimen in accordance with WHO guidelines is given in different set of groups, and the subjects are being compared with the subjects receiving placebo and the background regimen alone. Systemic exposure increases with food, and thus the drug was administered in the morning and evening with food, with a time gap of 10 hours (Half life: 38 hours). This treatment was continued for 6 months in patients with pulmonary sputum culture-positive, multidrug-resistant TB. The primary outcome measure is the proportion of patients who achieve sputum culture conversion at 2 months.

Results from PII trial (n=481) showed a 53% increase in sputum culture conversion (SCC) after two months between study subjects receiving delamanid 100 mg BD plus a background regimen consistent with WHO treatment guidelines compared with subjects receiving placebo plus background regimen alone. 45.4% of subjects in the delamanid 100 mg BD group and 41.9% of subjects in the delamanid 200 mg BD group, vs. 29.6% in the placebo group, achieved SCC in the Mycobacterial Growth Indicator Tube (MGIT) system after two months of treatment (p=0.008 and 0.039 respectively).

Delamanid was generally well tolerated overall. However, 3% of participants stopped treatment due to adverse events. The most common side effects were gastrointestinal symptoms such as nausea or vomiting, mostly mild to moderate. 10% of patients receiving 100 mg and 13% receiving 200 mg delamanid developed prolonged QT interval (a type of abnormal heartbeat), versus 3.8% of placebo recipients. QT prolongation was not associated with clinical events such as syncope (fainting) or arrhythmias in this short study. The other adverse effects observed in lesser proportions were anemia, reticulocytosis, head ache and insomnia.

This well conducted study shows that delamanid is a potentially useful additional drug for MDR-TB, although cardiotoxicity is a potential concern. Long-term studies are now needed to evaluate treatment outcome efficacy. Once the efficacy and the other essential parameters are established, it may be used for the treatment of MDR- TB.

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PHARMACOEPIDEMIOLOGY AND TREATMENT STRATEGIES– MDR TB

Shreya Sangam & Navya Pakalapati, Pharm,D V year, MRCP

Drug-resistant TB can occur when the drugs used to treat TB are misused or mismanaged like,

- When people do not complete the full course of treatment;
- When health care providers prescribe the wrong treatment, the wrong dose, or wrong length of time for taking the drugs;
- When the supply of drugs is not always available; or
- When the drugs are of poor quality.

Five different categories of drug resistance have been established:

Mono-resistance*:* resistance to one antituberculosis drug;

Poly-resistance: resistance to more than one antituberculosis drug, other than both isoniazid and rifampicin;

Multidrug-Resistant TB (MDR TB): It is caused by an organism that is resistant to at least isoniazid and rifampin, the two most potent TB drugs. These drugs are used to treat all persons with TB disease.

Extensively Drug-resistant TB (XDR TB): It is a rare type of MDR TB that is resistant to isoniazid and rifampin, plus any fluoroquinolone and at least one of the three injectable second-line drugs (i.e., amikacin, kanamycin, or capreomycin).

Because XDR TB is resistant to the most potent TB drugs, patients are left with treatment options that are much less effective.

Total drug resistant TB (XXDR): Totally drug resistant TB which is sometimes referred to as extremely drug resistant TB, is TB which is resistant to all the first and second line TB drugs. This makes it almost but not totally impossible to treat.

The **epidemiology** of MDR-TB is complicated by the fact that Mycobacterium *tuberculosis*, unlike many other infectious diseases, causes disease in only a minority of patients infected and has a lifetime potential for activation after infection. MDR-TB incidence varies considerably in different populations and geographical regions. Most of these differences can be attributed to underlying variation in the prevalence of infection.

The geographical distribution of MDR-TB in the world shows that many areas face endemic and epidemic MDRTB, with rates in several settings being alarmingly high.

MDR-TB prevalence may be three times greater than its incidence, suggesting that the actual number of MDR-TB cases in the world today may approach or exceed **one million cases.**

The social and economic burden of this problem is already evident, given that the cost of treating a case of MDR-TB is **up to 100 times** the cost of treating an uncomplicated drug-susceptible TB case.

Within a year of the first reports of extensively resistant TB (XDR-TB) in 2006, isolated cases were reported in Italy that had resistance to all first-line anti -TB drugs (FLD) and second-line anti-TB drugs (SLD) that were tested. In 2009, a cohort of 15 patients in Iran was reported which were resistant to all anti-TB drugs tested. The terms 'extremely drug resistant' ('XXDR-TB') and 'totally drug-resistant TB' ('TDR-TB') were given by the respective authors reporting this group of patients. Recently, a further 4 patients from India with 'totally drug resistant tuberculosis ('TDR-TB') were described, with subsequent media reports of a further 8 cases.

Treatment Strategies for MDR-TB

• Drug dosage should be determined by patient weight.

• An injectable agent (an aminoglycoside or capreomycin) is used for a minimum of six months and at least four months past culture conversion.

• The minimum length of treatment is 18 months past culture conversion.

• Each dose should be given under directly observed therapy (DOT) throughout treatment.

• DST, when available from a reliable laboratory, can be used to guide therapy. It should, however, be noted that DST does not predict with 100% certainty the effectiveness or ineffectiveness of a drug. In particular, the reliability and clinical value of DST for ethambutol, and groups 4 and 5 second-line anti-tuberculosis drugs have to date not been fully established.

• Pyrazinamide may be used for the entire treatment period if the strain is thought to be susceptible.

Many MDR-TB patients have chronically inflamed lungs which theoretically produce the acidic environment in which pyrazinamide is active.

• Treatment of adverse drug effects should be immediate and adequate in order to minimize the risk of treatment interruptions and prevent increased morbidity and mortality due to serious adverse effects.

• Early MDR-TB detection and prompt initiation of treatment are important factors in determining successful outcomes.

In order to control drug resistant TB worldwide, **WHO** and its partners recommend the treatment of MDR-TB as a priority in expanded DOTS programmes, now called the Stop TB Strategy.

"The treatment of MDR-TB as a priority in expanded DOTS programmes, now called the Stop TB Strategy."

1. Pursuing high-quality DOTS expansion and enhancement
2. Address TB-HIV, MDR-TB, and the needs of poor and vulnerable populations
3. Contribute to health system strengthening based on primary health care
4. Engaging all care providers
5. Empower people with TB, and communities through partnership
6.Enable and promote research

To ensure the proper management of MDR-TB cases and prevent the emergence of drug resistance to second-line drugs, MDR-TB treatment should be fully integrated with the TB control programme in the country.

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SNAPSHOT OF CONTINUOUS MEDICAL EDUCATION (CME)
Irrational Use of Pantoprazole
by Srikar Desiraju, Pharm D V yr

Continuous Medical Education (CME) refers to a specific form of continuing education, that helps those in the medical field maintain competence and learn about new and developing areas of their field. Here in this section we focus on bringing out the gist of CME discussions made in our institute– Malla Reddy Hospital, such that it helps both the practicing physicians and the pharmacists be more vigilant. A brief summary on the irrationality of Pantoprazole, presented by Mrs. Richa Saxena, faculty MRCP and Mr. Srikar Desiraju , student of Pharm D V yr, is being put forward in this issue.

Pantoprazole is the most widely used agent of the proton pump inhibitor class due to its better bioavailability and cost effectiveness. It does not often cause any serious side effects. It acts by blocking the H^+/K^+ATPase enzyme and thereby reduces the gastric acid secretions, and it is this mechanism that finds its use in the treatment of Gastro esophageal reflux disease (20-40mg), peptic ulcer (40mg), prophylaxis of NSAID induced ulcers (20mg).

Although a relatively safe drug, long term therapy may lead to bacterial overgrowth in the GI tract, atrophic gastritis, hepatic impairment; and also caution is advised in pregnancy and is not recommended in children under 18 years and in lactation. It is also associated with an increased tendency for fractures, and thus must not be prescribed for longer time in post menopausal women. If long term therapy is required, the liver function has to be regularly assessed and in case there is an increase in the enzymes, the usage of the drug must be discontinued.

> "Clostridium *difficile* associated diarrhea (CDAD), achlorhydremia– two most potential ADEs of pantoprazole."

SPECIAL ALERT :
FDA notified the public that the use of proton pump inhibitors (PPIs) may be associated with an increased risk of Clostridium difficile–associated diarrhea (CDAD). A diagnosis of CDAD should be considered for patients taking PPIs who develop diarrhea that does not improve.
Lab Interaction : The administration of pantorprozole on the same day as the urine test produces false positive urine screening tests for tetrahydrocannabinol. Due to THC inference assay.
Food Interaction : Long term use (>3 yr) may lead to vitamin B12 malabsorption. May decrease oral absorption of iron salts.

A ***critical statistical evaluation*** of the prescriptions containing pantoprazole in the surgical ward was done. A total number of 17 prescriptions were audited out of which, pantoprazole was prescribed in 11 prescriptions, other proton pump inhibitors in 2 pre-

scriptions, H2 receptor antagonists in 3 prescriptions and only 1 prescription was devoid of antacid therapy. The number of prescriptions with IV pantoprazole were 7 and oral pantoprazole were 4.

The recommendations ranged from switching to oral therapy when IV therapy is not required to identifying the potential adverse events and suggesting a suitable management. Of all the interventions, 2 cases are brought to light here.

A 35 yr old lady suffering from Ileal perforation with secondary suturing and wound GAPING, was given pantoprazole for a longer duration. She eventually developed diarrhea and passed loose watery stools. This is a potential adverse event caused by the drug. It may be attributed to its mechanism of blocking the release of gastric acid and there by altering the gastric pH. This alterations in the gastric pH cause an increased sensitivity to developing GI infections, one of which is Clostridium *difficile* associated diarrhoea. (CDAD). A suitable management for this would be a switch to a H2RA.

The second possible adverse event with pantoprazole is hypochlorhydria. This condition is again linked to the mechanism of pantoprazole, where a constant decrease in the gastric acid secretion results in this condition and makes the individual more susceptible to infections and thus it must be borne in the mind at all times. A 65 yr old male patient suffering from strangled left indirect inguinal hernia with malaria was prescribed pantoprazole and was on it for nearly 2 weeks. So as a preventive measure the use of pantoprazole was stopped to prevent hypochlorhydria from manifesting.

On an ending note, although pantoprazole is a relatively safe drug, it just as any other agent has its own set of side effects and these effects must be borne in the mind and a safe and judicious use of this agent must be made. Long term use must be avoided, particularly in post menopausal women. If long term therapy is required switching between PPIs and H2RAs may be done.

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By : R.Cunnigham* * S.dial

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NOW, DETECT DENGUE IN 10– 15 MINUTES

A software tool that can rapidly diagnose dengue fever based on symptoms and clinical parameters has been developed and validated by scientists of CSIR- Indian Institute of Chemical Technology, Hyderabad.

Dengue fever is an infectious tropical disease and is caused by dengue virus. It is estimated that the mosquito-borne pathogen infects approximately 50-100 million people every year.

The Dengue Decision Support System (DDSS) has been developed by Dr. U.S.N.Murty, Chief Scientist and Head of Biology Division and his group. This diagnostic software system is ready for release and would be handed over to the state government soon. This is a simple and accurate tool and it was tested and validated in a few hundred cases at the Sir Ronald Ross Institute of Tropical Diseases, Hyderabad.

The DDSS would help health authorities in detecting the disease within 10-15 minutes, which was vital in saving the life of the patient. It could be used on a desktop computer with any operating system or server-based network for remote areas.

This diagnostic tool serves as a ray of hope in the diagnosis of dengue and may be utilised by the health care providers in the diagnosis of dengue.

VIGILANT– ADRs & ADEs

Reported by Sujitha Katragadda, Pharm.D P.B III year, MRCP

The vigilant is a column dedicated to the adverse drug reactions and adverse drug events observed in Narayana Hrudayalaya and Malla Reddy Hospital.

The current issue features the ADE observed with Myospaz (Chloroxazone+ Paracetamol).

An anaphylactic reaction was observed in a 23 yr old female patient, admitted to the hospital with pregnancy induced hypertension and oligohydraminos at 37 weeks of gestation.

She was administered myospaz (Chlorzoxazone 250mg and Paracetamol 500mg) for neck pain on 22nd Jan at 8 PM. Within 2 hours of taking this drug, she developed an acute anaphylactic reaction with puffiness, periorbital edema, ear lobe edema, excessive tearing, rashes all over the body and itching. Vital signs were recorded: BP-110/80mmHg; Pulse rate- 82 beats/min and the patient was diagnosed as anaphylactic reaction to chlorzoxazone. The patient was started on tablet Avil.

By 11:00p.m. blood pressure was 80/60 mmhg and pulse rate was 90 bpm. The patient was then given Inj Avil I.M stat and hydrocortisone was added at 11:45 p.m.

Moxifur and lacrimos eyedrops were administered to the patient to reduce excessive tearing.

The concomitant medications used were-Tab. Taxim-O 200mg BD, Tab. Rantac 150mg BD, Tab. Metrogyl 400mg TID, Tab. Emanzen D 1 tab, and Tab. Zincovit.

After withdrawing the drug, the patients conditions started getting stable and there was a decrease in the swelling and itching by 23rd of January. It must be mentioned in all her records regarding her sensitivity towards this agent along with educating her about the condition, such that she may avoid taking the medication.

Therefore, health care providers should be vigilant and should educate the patients administered with this drug about the adverse effects and should be advised to report to the physician immediately if any adverse effect is observed so that a suitable management can be made and prevent any mishaps.

MALLA REDDY COLLEGE OF PHARMACY

DRUG INFORMATION CENTER.

Room No. 304,
Malla Reddy Hospital

The pharmacy practice department of Malla Reddy College of Pharmacy(MRCP) has initiated the Drug Information Center in the year 2011, under the guidance of Principal Dr. M. Sudhakar, MRCP.

The Drug Information Centre's mission is to provide a central and unbiased source of current information and specific responses about medicines and medicine-based therapy to the healthcare providers and community regarding the related issues.

The centre is open seven hours a day between **9.00 am to 4.00 pm**.