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NTM-TB INSIGHTS

November 2015

Living with NTM - A Patient's Perspective

The year 2000 and the new millennium brought some new challenges. I was excited to be planning for my daughter's wedding. During the planning period, I experienced mysterious symptoms. A chronic cough, weight loss (ok, not so bad so I thought…maybe I'll look better in my mother-of-the-bride dress), and severe exhaustion. A few months before the wedding at a family dinner, I was suddenly unable to function and had to lie down in bed. I was unable to partake in the family dinner which was very disappointing. This was my "wake-up" call. It was the time to take action. Ignoring my ill health didn't make it go away, as I had hoped.

A few days later my local internist took a series of x-rays and diagnosed pneumonia. He noticed some abnormalities on the first set of x-rays as well as a number of follow up scans. After the third set of x-rays, he referred me to a local pulmonologist booking an appointment for the following day. His hunch was that lung cancer was the cause.

The pulmonologist was perplexed by the shadings on the films, but said those shadings didn't look like lung cancer. Not knowing the cause, he ordered a bronchoscopy, and sent the samples to National Jewish Health. The diagnosis was made very shortly thereafter. It was *Mycobacterium avium* complex (MAC), a form of nontuberculous mycobacteria (NTM).

"What is that?" I asked. He explained it is a resistant bacterial infection found in the lung, a condition in the same family as tuberculosis except non-contagious and more difficult to cure. Even with treatment, most people are not cured, but the infection may be able to be controlled with mega-doses of antibiotics. Left untreated, the lungs could become irreversibly damaged. There is no "cookie cutter" plan of treatment. Treatment is fine tuned for each patient. Symptoms can include pneumonia, chronic exhaustion, weight loss, fever, chills, night sweats, shortness of breath and bloody sputum among others.

Wow, how can a healthy person like me be diagnosed with something like this? I was TERRIFIED! This was a big mystery. My doctor couldn't answer my many questions, and I learned quickly that most physicians knew nothing or very little about NTM. Does lack of information mean bad news? Initially, I felt isolated, depressed and questioned my mortality.

Fortunately, my local pulmonologist had been in contact with National Jewish Health and knew the basic treatment protocol. He gave me the choice of being treated by him, or by the doctors at National Jewish Health. My decision was to allow him to treat me for that first year, and if I were not "cured", I would check into National Jewish for further evaluation. After being on the antibiotics for a few weeks, my symptoms disappeared. I was convinced I was responding to the treatment. However, upon being retested, the resistant bacteria remained in my lungs.

The next step of my journey was an evaluation at National Jewish Health. I was evaluated extensively, and the diagnosis now revealed *Mycobacterium abscessus*, another form of NTM, even more resistant and more of a rapid grower than MAC. My lead physician at National Jewish Health, Dr. Huitt, and her knowledgeable staff worked me over, checking not only my lungs, but also the other systems in my body for underlying conditions which could aggravate the NTM. I was also provided with a great deal of information and training on how to best proceed with my treatment. Hooray, I finally

found my “army of team members” fighting the army of bugs in my lungs! For the first time I felt like I was in control. THIS WILL NOT GET ME! I WILL OVERCOME IT!

I became more diligent and involved in my treatment. I took my antibiotics regularly and as instructed, as well as using a bronchodilator. In addition, a nasal rinse was part of my daily regimen. The use of the airway clearance device (originally the Acapella replaced several years later by newer technology, the AerobiKa) helped clear my airways, hopefully loosening secretions and enabling me to expel some of the bacteria. I also rested when needed, a concept foreign to me up to that point.

I was so immersed in my treatment, I eventually realized that something was lacking. I was doing all the right things medically, but realized I had been overlooking activities aside from NTM. I needed to add back the fun that was missing in my life. I began to refocus, and with some conscious planning and organization, was able to integrate my care into my day-to-day living.

Here were some of the things that helped me. Modifying my expectations was a challenge I eventually overcame. I realize I can’t control others or every situation. A perfectionist who is not perfect? That was me. Mistakes are acceptable. I needed to judge myself more kindly, or judge not at all. I could take control of my own actions, learn from my mistakes and make improvements. No more brooding over past problems. My outlook on life was changing in positive ways. I became more open, more charitable and more empathetic.

How did I accomplish this? I modified my environment, eliminating a great deal of responsibility. Less pressure became an important goal. We downsized from a large house to more peaceful and manageable surroundings. My priorities were redefined, scheduling time for important things and eliminating what was not really important. I treasure relationships more, and I’m less goal-oriented. I realize it is ok to give myself the gift of more leisure time and partake in activities enjoyable to me. I have set boundaries on commitments and can now say “no” when asked to assume a project with overwhelming responsibility. I find myself more at ease when I plan ahead to avoid “crunch time”, and if I think I will need to wait for someone, I carry my favorite book or iPad to keep my mind occupied. Sleep makes a big difference. Not setting an alarm clock if possible to wake up naturally, avoiding alcohol, cutting caffeine, and exercising promote better sleep.

I have channeled my energies into interacting with other NTM patients, helping to provide information and support so that we can cope more effectively with our condition. Our New York support group that was established in 2003 has grown exponentially. My co-leader presently chairs most of the New York meetings since I have moved to the California desert for a good part of the year. When I am back in the New York area during the summer season, I am able to chair a few meetings, which enables me to keep up with my New York area friends. Our Palm Springs area support group was established in 2012. Since last year, the Connecticut/Massachusetts/Westchester County group has been getting together for lunch and chat. Our groups are growing rapidly as more physicians are being educated. I am fortunate to have met wonderfully compassionate and intelligent people who are always willing to help others.

My recommendation for NTM patients is to find an interest and embrace it with a passion. Although your life may not be the same as it was before your diagnosis, look at this time as a new phase and run with an interest based on your physical and emotional capabilities. I enjoy getting together with friends and family, working my mind with daily crossword and number puzzles, and reading books and newspapers. My daily walks provide me with needed exercise for my lungs as well as providing time to clear my head. My involvement with NTM, especially with like-minded people who understand our issues has provided me with a new lease on life, for which I am grateful.

Debbie Breslawsky

A Message from United States Food and Drug Administration (FDA)

On October 15, 2015, the FDA held a public meeting on NTM Lung Infections Patient-Focused Drug Development. The FDA letter below includes information of interest to NTM physicians, researchers and patients.

Dear meeting attendees,
Thank you for attending the public meeting on **NTM Lung Infections Patient-Focused Drug Development** last week! FDA collected valuable information on NTM lung infections, the impact it has on patients' lives, and patients' perspectives on treatment options. We truly appreciate the courage, effort and time invested from everyone who was able to attend the meeting in person or on the web.

We know that not everyone who wanted to come to this meeting was able to attend. For anyone who missed the meeting or is interested in what was discussed, **we have posted a full recording of the meeting on our website**: http://www.fda.gov/Drugs/NewsEvents/ucm453877.htm.

In addition to the input we gathered at the October 15th meeting, we encourage NTM lung infection patients and other stakeholders to submit written comments to the online public docket. **The comment period closes on December 15, 2015.** Submit your comments through this website: http://www.regulations.gov/#!documentDetail;D=FDA-2012-N-0967-0748.

FDA is particularly interested in hearing patients' perspectives on the questions outlined in the Federal Register Notice that announced this meeting. These questions are pasted below for your reference, and the Federal Register Notice can be found here: https://federalregister.gov/a/2015-18919.

Again, thank you to everyone who attended the meeting! If you have any questions, please email PatientFocused@fda.hhs.gov.

Discussion Questions

Topic 1: Disease Symptoms and Daily Impacts That Matter Most to Patients

1. Of all the symptoms that you experience because of your condition, which 1-3 symptoms have the most significant impact on your life? (Examples may include cough, increased sputum production, shortness of breath, difficulty breathing, chest pain)
2. Are there specific activities that are important to you but that you cannot do at all or as fully as you would like because of your condition? (Examples of activities may include sleeping through the night, daily hygiene, driving, walking/running, exercising, etc.)
   - How do your symptoms and their negative impacts affect your daily life on the best days? On the worst days? (Examples may include limitations on the ability to undertake physically strenuous activities, restrictions on the ability to travel, inability to sleep, lack of appetite, fatigue, etc.)
3. How has your condition and its symptoms changed over time?
   - Do your symptoms come and go? If so, do you know of anything that makes your symptoms better? Worse?
4. What worries you most about your condition?

Topic 2: Patients' Perspectives on Current Approaches to Treating NTM Lung Infections

1. What are you currently doing to help treat your condition or its symptoms? (Examples may include prescription medicines, over-the-counter products, nebulizers, and other therapies including non-drug therapies)
   - What specific symptoms do your treatments address?

- How has your treatment regimen changed over time, and why?

2. How well does your current treatment regimen treat the most significant symptoms of your disease?
   - How well do these treatments stop or slow the progression of your disease?
   - How well do these therapies improve your ability to do specific activities that are important to you in your daily life?
   - How well have these treatments worked for you as your condition has changed over time?
3. What are the most significant downsides to your current treatments, and how do they affect your daily life? (Examples of downsides may include bothersome side effects, need for multiple medications, need for injections, going to the hospital for treatment, etc.)
4. Assuming there is no complete cure for your condition, what specific things would you look for in an ideal treatment for your condition?

Fluoroquinolones for Shortening Treatment of Tuberculosis: Promises, but not Reality

Last year, three large phase 3 randomized, comparative trials which assessed the efficacy and safety of fluoroquinolones in shortening the length of anti-tuberculosis therapy from 6 months to 4 months were published in the same edition of the *New England Journal of Medicine* ("the quinolone trifecta") [1-3]. These trials were based on prior *in vitro* studies showing that moxifloxacin and gatifloxacin have potent antimicrobial activity against *Mycobacterium tuberculosis,* murine model studies showing that moxifloxacin in combination with isoniazid, rifampin and pyrazinamide or with high-dose rifapentine led to reduced time to lung sterilization and cure with 4-month regimens, human studies showing potent early bactericidal activity in sputum with moxifloxacin monotherapy, and one observational study in India using ofloxacin.

The experimental and control regimens used in the three trials, REMoxTB (Rapid Evaluation of Moxifloxacin in Tuberculosis), RIFAQUIN, and OFLOTUB/Gatifloxacin for Tuberculosis, are shown below in Table 1. REMoxTB was conducted in South Africa, India, Tanzania, Thailand, Kenya, Malaysia, Zambia, China and Mexico; RIFAQUIN in South Africa, Zimbabwe, Botswana and Zambia; and OFLOTUB in South Africa, Guinea, Senegal, Benin and Kenya. Patients enrolled were ≥18 years old with acid-fast bacilli smear-positive, culture-positive, drug-susceptible pulmonary tuberculosis.

The primary efficacy analyses of the trials are shown below in Table 2, by per-protocol and modified intention-to-treat populations. All the studies were designed to demonstrate non-inferiority of the experimental regimens compared to the control regimen, by comparing margins of percentage point differences of unfavorable outcomes. As in other randomized clinical trials of tuberculosis, the majority of unfavorable outcomes were bacteriologic relapses which occurred in follow-up after patents became culture-negative during treatment.

In the REMoxTB trial neither of the 4-month moxifloxacin-containing regimens were found to be as effective as the 6-month regimen. In the RIFAQUIN trial the 6-month moxifloxacin-rifapentine regimen was non-inferior to the control arm, but the 4-month regimen was not. Similarly, in the OFLOTUB trial the 4-month gatifloxacin-containing regimen was not as effective as the 6-month control regimen.

Each of the studies evaluated time to culture conversion as secondary endpoints. Of note, in the REMoxTB trial, both of the 4-month regimens had culture conversion sooner that the control arm in both solid and liquid culture media, but the proportion of negative cultures at 8 weeks was not significantly different between the groups. In the RIFAQUIN trial, patients who received isoniazid in the first 2 months had a slightly lower proportion of negative cultures at 2 months (85%) compared with those who received moxifloxacin (90%), but the difference was not significant. In the OFLOTUB trial, culture conversion at 2 months was not different in the two arms of the study.

There were no significant differences in severe or grade 3/4 adverse events in any of the trials. In particular, adverse events of special interest, i.e., tendinopathy, cardiac toxicity, Q-T prolongations, hyper- or hypoglycemia, and peripheral neuropathy did not occur more frequently in the fluoroquinolone arms.

The results of these three large multicenter randomized (and complementary) clinical trials were disappointing, in that the fluoroquinolones as used in these regimens did not achieve the holy grail of treatment shortening that had been anticipated. In retrospect one might have predicted these results from the prior phase 2 trials, but hindsight is 20-20. In addition to the aforementioned *in vitro* and animal model data, the initial enthusiasm for moving into phase 3 trials came from the OFLOTUB group, who conducted a phase 2 trial in South Africa in 2004-2005, in which moxifloxacin, gatifloxacin, and ofloxacin were substituted for ethambutol in the first 2 months of therapy [4]. The study had promising results in which both moxifloxacin and gatifloxacin showed greater bactericidal activity than isoniazid based on serial sputum colony counts. Simultaneously and thereafter, the Tuberculosis Trials Consortium (TBTC) conducted two larger phase 2 trials, in which moxifloxacin was substituted for ethambutol in the intensive phase (TBTC Study 27) in 2003-2005, or for isoniazid (TBTC Study 28) in 2006-2007 [5,6]. In both studies, the substitution of moxifloxacin did not result in different proportions of negative sputum cultures after 8 weeks of therapy; each study concluded that treatment shortening would not be achieved with moxifloxacin, assuming 2-month culture conversion as a surrogate endpoint for predicting outcome. Either way, is it now appreciated that the bactericidal activity of potent regimens shown by 2-month culture conversion by itself does not serve as an ideal surrogate marker to predict the final outcome and length of therapy, i.e., sterilizing activity throughout the entire course of therapy and risk of relapse [7].

Another lesson is that mice and humans are not the same. A great deal has been learned from murine models, to inform about potency and activity of individual drugs, their use in different combinations, length of therapy and the design of human studies. There may be other newer animal models that might improve further what we can learn from mice, with different pathologic characteristics and pharmacokinetics and pharmacodynamics, but that remains to be seen.

There is one silver lining from the above data. In the RIFAQUIN trial, the 6-month regimen using moxifloxacin and rifapentine once a week in the continuation phase was very effective. True directly observed therapy (DOT) is rarely utilized during the continuation phase in resource-limited settings. If these drugs were available, a once-weekly DOT regimen for the last 4 months of therapy could be quite beneficial in certain settings. And it should be remembered that both moxifloxacin and levofloxacin are very important drugs in the treatment of multidrug-resistant tuberculosis, and as substitutes for 1st-line drugs when they are not tolerated in the treatment of drug-susceptible tuberculosis.

What's next? The use of higher doses of both rifampin and rifapentine, novel combinations such as pyrazinamide, pretomanid (PA-824, an investigational nitroimidazole) and moxifloxacin, and other new anti-tuberculosis drugs in the pipeline hold promise for treatment-shortening regimens. Innovative approaches to clinical trial design have been suggested, i.e., the "multi-arm, multi-stage" trial, where several experimental arms are simultaneously compared with a common control arm and interim analyses allow for poorly performing arms to be dropped early [8]. As we have learned from "the quinolone trifecta", careful decisions need to be made before embarking on large, expensive phase 3 randomized controlled trials. And more funding for both basic science and clinical research for combating tuberculosis wouldn't hurt. It is high time to have shorter, better tolerated drug regimens than good ol' 2EHRZ/4HR that has been the standard in clinical practice for over 25 years. Stay tuned.

Table 1. Study regimens of REMoxTB, RIFAQUIN and OLFLOTUB trials

REMoxTB		
Regimen	***Intensive Phase***	***Continuation Phase***
2MHRZ/2MHR (Isoniazid arm) - 17 weeks of drugs, 9 weeks placebo	MHRZ - 8 weeks E placebo	MHR - 9 weeks HR placebo - 9 weeks
2EMRZ/2MR (Ethambutol arm) - 17 weeks of drugs, 9 weeks placebo	EMRZ - 8 weeks H placebo	MR - 9 weeks HR placebo - 9 weeks
2EHRZ/4HR (Control arm) -26 weeks	EHRZ - 8 weeks M placebo	HR -18 weeks M placebo
All doses given daily, observed based on local guidelines. Moxifloxacin = 400mg, EHR and Z World Health Organization (WHO)-recommended doses. All groups followed an additional 52 weeks after completion of treatment (78 weeks total, i.e., 18 months)		

RIFAQUIN		
Regimen	***Intensive Phase***	***Continuation Phase***
2EMRZ/2M_2P_2 (4-month study arm)	EMRZ - 2 months	MP (900mg), twice-weekly - 2 months (9 weeks)
2EMRZ/4M_1P_1 (6-month study arm)	EMRZ - 2 months	MP (1200 mg), once-weekly - 4 months (18 weeks)
2EHRZ/4HR (6-month control arm)	EHRZ - 2 months	HR - 4 months (18 weeks)
All doses given daily unless otherwise stated, directly observed at a health care facility, except continuation phase of control arm (observed by a relative). M= 400mg, EHR and Z WHO-recommended doses. All groups followed for 15-18 months after randomization.		

OFLOTUB		
Regimen	***Intensive Phase***	***Continuation Phase***
2GMRZ/2GHR (4-month study arm)	GMRZ - 2 months	GHR - 2 months (9 weeks)
2EHRZ/4HR (6-month control arm)	EHRZ - 2 months	HR - 4 months (18 weeks)
All doses given 6 days per week, directly observed in intensive phase. G=400mg, EHR and Z WHO-recommended doses. Both groups followed for 24 months from the end of treatment.		

Abbreviations of drugs: **E**=ethambutol, **H**=isoniazid, **R**=rifampin, **Z**=pyrazinamide, **M**=moxifloxacin, **P**=rifapentine, **G**=gatifloxacin

Table 2. Primary Efficacy Analyses by Per-Protocol and Intention-to-Treat Populations

REMoxTB		
Regimen	***N, % Unfavorable outcome* Difference from control in unfavorable rate (97.5% Confidence Interval (CI)†***	
	Per Protocol	**Intention to Treat**
2MHRZ/2MHR (Isoniazid arm)	514, 15% 6.1 (1.7-10.5)	568, 23% 7.8 (2.7-13.0)
2EMRZ/2MR (Ethambutol arm)	524, 20% 11.4 (6.7-16.1)	551, 24% 9.0 (3.8-14.2)
2EHRZ/4HR (Control arm)	510, 8%	555, 16%
Enrolled 2008-2012, 7% HIV-infected (CD4 >250/µL, not on ART)		

RIFAQUIN		
Regimen	***N, % unfavorable outcome* Difference from control in unfavorable rate (95% CI)†***	
	Per Protocol	**Intention-to-treat**
2EMRZ/2M_2P_2 (4-month study arm)	165, 18% 13.6 (7.0-20.2)	141, 27% 13.1 (5.6-20.6)
2EMRZ/4M_1P_1 (6-month study arm)	186, 3% -1.8 (-6.9-3.3)	183, 14% 0.4 (-5.7-6.6)
2EHRZ/4HR (6-month control arm)	163, 5%	161, 14%
Enrolled 2008-2011, 27% HIV-infected (CD4>150/µL, on ART)		

OFLOTUB		
Regimen	***N, % unfavorable outcome* Difference from control in unfavorable rate (95% CI)†***	
	Per Protocol	**Intention-to-treat**
2GMRZ/2GHR (4-month study arm)	651, 18% 5.5 (1.6-9.4)	694, 21% 3.5 (-0.7-7.7)
2EHRZ/4HR (6-month control arm)	601, 11%	662, 17%
Enrolled 2005-2007, 18% HIV-infected (WHO stage 1-2)		

*Unfavorable outcomes include treatment failures, death during treatment, and relapses after treatment. Intention to treat analyses additionally include patients who withdrew consent, had limited bacteriologic confirmation, were lost to follow-up, relocated, or had inadequate treatment.

†Difference rate adjusted for study center.

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Meetings

- **46th Union World Conference on Lung Health – A New Agenda: Lung Health Beyond 2015**, December 2-6, 2015, Cape Town, South Africa
- **20th Annual Conference of the International Union Against Tuberculosis and Lung Disease – North American Region**, February 24-27, 2016. Sheraton Denver Downtown Hotel, Denver, CO
- **National Tuberculosis Controllers Association Meeting**, February 24-27, 2016, Sheraton Denver Downtown Hotel, Denver, CO
- **Tuberculosis Co-Morbidities and Immunopathogenesis**, February 28-March 3, 2016, Keystone Resort, Keystone, CO
- **World Tuberculosis Day,** March 24, 2016
- **The 53rd Semi-Annual Denver TB Course**, April 6-9, 2016; Molly Blank Conference Center at National Jewish Health Main Campus. Click here for more information and registration.
- **Front Range Mycobacteriology**, June 7-10, 2016, Colorado State University, Fort Collins, CO

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