Successful MDR-TB treatment regimens – are 9 months long enough?

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26e Symposium Tuberculose de Macolin, 23 March 2017

Slide 1

After publishing the results with a regimen for multidrug-resistant tuberculosis of a minimum duration of 9 months in 2010 and 2014, the World Health Organization (WHO) recommended its use with some restrictions in 2016. The ensuing discourse reflects the interest in this regimen. It also shows that not all considerations that entered the design of this colloquially called "Bangladesh regimen" have been fully understood. The purpose of this presentation is to summarize the treatment results with the regimen in a first part, and to discuss the composition of the regimen in more detail in the second.

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From 1997 to 2011 a series of 6 sequentially adaptive regimens was used among patients with laboratory-confirmed resistance to both isoniazid and rifampicin, i.e. multidrug-resistant (MDR) tuberculosis. The first regimen was closely similar to a then recommended 21-month regimen of WHO, the second was the same shortened to 15 months. The major problem with these two regimens was drug intolerance, mainly vomiting attributed to the thioamide in the regimen, leading to premature absconding of patients from treatment. In subsequent regimens, the objective was to find a balance between tolerance and bacteriological effectiveness. Up to regimen 5, all were based on the core drug ofloxacin. In the final regimen the latter drug was replaced by gatifloxacin, a fourth-generation fluoroquinolone.

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The lowest success was obtained with regimen 3. In the subsequent regimens the results were successively and successfully improved. Details about each regimen will be discussed in more detail.

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The so-called 9-month regimen is actually a regimen of a minimum duration of 9 months. The intensive phase lasts for a minimum of 4 months and its actual duration depends on the direct sputum smear microscopy result. If positive at 4 months, the intensive phase is extended by up to 2 months. The continuation phase is of a fixed duration of 5 months. Seven drugs are used, of which three, kanamycin, prothionamide, and isoniazid are given only in the intensive phase. Gatifloxacin, ethambutol, pyrazinamide, and clofazimine are given throughout.

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The actual time to treatment completion was 9 months for 50% of the patients. 75% completed treatment in 10 months, 90% in 11, and 95% in 1 year. This slide thus partially answers the title question: 9 months are not sufficiently long for every patient.

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Sputum culture conversion was swift: by the end of the second month, more than 93% had converted. The speed of sputum smear microscopy conversion depended on the initial bacillary load and lagged behind culture conversion.

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Of the total 515 consecutive, unselected patients meeting the inclusion criteria, 501 had an initial fluoroquinolone drug susceptibility test result, using the then laboratory standard ofloxacin for phenotypic testing. For strains with initial ofloxacin resistance (resistant at 2 mg/L), the minimum inhibitory concentration (MIC) for gatifloxacin was determined. "Low-level" gatifloxacin resistance was defined as an MIC of 0.5 to 1.0 and "high-level" as an MIC of ≥2 mg/L. Stratification by fluoroquinolone resistance level in the survival analysis showed equally good results for patients with an ofloxacin-resistant / low-level gatifloxacin-resistant strain as for patients with an ofloxacin-susceptible strain, with over 85% successful treatment outcome. Among patients with a high-level gatifloxacin-resistant strain, the outcome was much poorer with just 50% successes and 8 failures or relapses among the 29 patients. We will examine later why the bacteriological results were not even poorer.

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Given the good results obtained with the regimen in Bangladesh, a very large multi-country study in 9 francophone African countries was initiated by The Union, using the same regimen with the exception of replacing gatifloxacin by moxifloxacin. By mid-2016 over 1,000 patients should have completed their treatment. Close to 85% of patients without HIV infection had a successful treatment outcome. Results were somewhat poorer for the 200 patients with HIV infection. This lower success was due to the higher frequency of deaths on treatment and not a difference in failure frequency. It may be noted that in some of the collaborating countries the organization of treatment services has been very difficult to implement, thus even more emphasizing the sturdiness of the regimen.

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The standard WHO treatment outcome categories are shown here for all 6 regimens in Bangladesh. The lowest success was achieved with regimen 3. It had the largest proportion of patients absconding from treatment. This regimen used prothionamide throughout like its predecessors. Two thirds of patients reported vomiting, leading to abandonment of treatment. In contrast to regimen 2, regimen 3 also used no isoniazid and gave a higher proportion of treatment failures than the former. From regimen 3 to 4, two changes were made: prothionamide was dropped from the continuation phase and isoniazid was re-introduced throughout. Default decreased, yet the proportion of treatment failures increased. The decrease in default seemed to be linked to dropping prothionamide as now only 30% reported vomiting. However, the thioamide has good bacteriological activity and its omission from the continuation phase increased the risk of treatment failure. Regimen 5 was the same regimen as regimen 4 except that clofazimine was given throughout instead of only during the intensive phase. The smaller proportion of absconding from treatment was retained, but now the proportion of treatment failures was substantially reduced. Treatment success with this 15-month regimen based on ofloxacin was about 85%. Subsequently, gatifloxacin became generically available. There was a large body of evidence that this generation of fluoroquinolones was substantially more active against *M tuberculosis* on a weight basis than earlier generations and likely allowed shortening the treatment duration substantially without sacrificing activity. In regimen 6, the regimen known as the "Bangladesh regimen", four changes were made: 1) gatifloxacin replaced ofloxacin; 2) the total treatment duration was cut to a minimum

of 9 months; 3) isoniazid was retained only in the intensive phase; and 4) the minimum duration of the intensive phase was extended to 4 months. Post-treatment follow-up was to be two years to ascertain occurrence of relapses. As shown in Slide 7, only 1 treatment failure and 1 relapse were observed among the 439 patients with a fluoroquinolone-susceptible strain. In other words, when it was said above that 9 months are not sufficient for every patient, one might add here that seemingly 9 months are overkill for some patients.

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We get now to the individual drugs. A high dose of gatifloxacin was given. The thioamide was given in combination with a high dose of isoniazid. The other four drugs were given in their normal dosages.

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The MICs of gatifloxacin and ofloxacin were compared. This analysis provides an explanation why gatifloxacin is microbiologically superior to ofloxacin: the former is 4 to 6 times more active on a weight basis than the latter. The high dose is designed to overcome low-level gatifloxacin resistance with a higher probability. In part it may explain why ofloxacin resistance that turns out to be low-level resistance in the MIC distribution of gatifloxacin was seemingly overcome without difficulties.

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Gatifloxacin has unfortunately been retracted from the market by its manufacturer and the alternative is moxifloxacin. The comparison of the MICs of ofloxacin and moxifloxacin shows that the latter has similar activity as gatifloxacin, perhaps somewhat less, if comparing here the MIC ratios, a finding supported by studies examining the area under the curve parameter.

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Failures might be missed if transport times in the tropics adversely affect bacillary survival. Obtaining multiple cultures partially remediates this, but such a problem is best revealed as relapses during the post-treatment period after stopping all drugs. However, we also have an internal, unbiased validation that missing failures was not actually a substantial problem. Drug susceptibility results and MICs for fluoroquinolones from the Antwerp laboratory were only known after study closure before data analysis. The odds ratio of failure or relapse given high-level gatifloxacin resistance relative to low-level or susceptibility is very high. This convincingly demonstrates that failures and relapses were indeed discovered by serial cultures if there was a reason for the regimen to fail.

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In the final regimen, prothioamide and isoniazid were paired and given only during the intensive phase. Two major mechanisms for isoniazid resistance are related to mutations in the *katG* and *inhA* promoter genes. For thioamides a known resistance mechanism is the latter but not the former. The argument for pairing the two drugs is that if isoniazid resistance is due to a mutation in the *katG* gene, chances are good that a thioamide is still effective. Conversely, resistance due to a mutation in the *inhA* promoter gene is usually low-level resistance and is overcome by isoniazid. Not infrequently, one hears that the rationale for high-dose isoniazid is to overcome resistance due

to mutations in the *inhA* promoter gene. This is not the case: to overcome this low-level resistance, a normal dose of isoniazid suffices because the very large therapeutic range of isoniazid.

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The rationale for high-dose isoniazid becomes evident in this paper by Böttger that is worth consulting. Most laboratories still use a critical drug concentration in phenotypic testing, dichotomizing strains into susceptible or resistant. For isoniazid this is commonly 0.2 mg/L. Achievable serum peak drug concentrations of isoniazid are 5 to 10 mg/L, and thus bactericidal for an organism resistant to 0.2, but say susceptible to 1.0 mg/L. Many strains with resistance due to mutations in the *inhA* promoter gene are resistant around these values. One frequent mutation in the *katG* gene leading to isoniazid resistance is the 315Thr mutation. If the MIC distributions are determined for this mutation, then it shows the large variation in bactericidal concentrations. The rationale for the high dose of isoniazid are thus precisely certain mutations in the *katG* gene.

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The role of pyrazinamide in general and in the treatment of MDR tuberculosis in particular still remains largely elusive. There where virtually no failures or relapses in patients with strains susceptible or low-level resistant to gatifloxacin. Thus, it was irrelevant in such cases whether the strain was susceptible or resistant to pyrazinamide. However, when evaluating possible predictors for treatment success among patients with high-level gatifloxacin resistance, we found a strong association with absence of documented pyrazinamide resistance. Among 14 patients with high-level gatifloxacin resistance, 7 who also had pyrazinamide resistance failed, but only 1 of 8 such patients failed if pyrazinamide resistance had not been demonstrated. This strongly suggests that pyrazinamide can reduce the risk of treatment failure or relapse if patients receiving this regimen have a high-level gatifloxacin-resistant strain.

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In South Africa, about 40% of patients with MDR seemingly still harbored a pyrazinamide-susceptible strain.

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One might expect that all patients with initial MDR would also have acquired pyrazinamide resistance when receiving all three drugs in the intensive phase. The hypothesis here could partially explain why this may not be so. According to the prevailing concept drug resistance emerges as a result of selection of naturally occurring resistant mutants. As the spontaneous mutation frequency leading to clinically relevant resistance is approximately in the order of 1 per million organisms, the probability of selection increases with the number of bacilli. Such are present in abundance in cavitary lesions which tend to have a neutral pH where pyrazinamide is likely inactive. The acidic lesions in which pyrazinamide best exerts its action tend to be paucibacillary and selection of spontaneously pyrazinamide-resistant mutants is therefore less likely.

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In the international laboratory network on drug susceptibility proficiency testing, phenotypic ethambutol testing performs poorest among first-line drugs. As a bacteriologically weak drug it also exerts less selection pressure on resistant mutants than highly active drugs. There are thus good reasons to retain this well-tolerated drug in an MDR regimen. There are also poorly

understood observations, such as in this study from Sweden where ethambutol was given at concentrations of one quarter of its MIC. The beta-lactam amoxicillin is not expected to inhibit growth of *M tuberculosis* and the growth here is thus expected. It is also expected that ethambutol at sub-inhibitory concentrations may suppress growth somewhat as it does here in comparison to amoxicillin alone. What is nevertheless not easily explained is why the combination of amoxicillin plus a sub-inhibitory concentration of ethambutol exerts most growth suppression. Very few laboratories in the world actually test the activity of drug combinations as part of their routine services. Dismissing the role of ethambutol said to be resistant in the laboratory thus might not be the wisest course of action.

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Which injectable to choose is a bit of a toss-up. The main reason for the choice of kanamycin in Bangladesh was based on cost considerations. There is perhaps some argument that might be made microbiologically as cross-resistance between polypeptides and aminoglycosides is not complete, but we would not argue strongly based on this argument. The bigger problem for the time being is that this toxic class of drugs is unfortunately still required.

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Regimen efficacy, i.e. prevention of bacteriologic failure and relapse is of utmost importance. In the treatment of MDR tuberculosis this aspect has been dwarfed by the issue of premature absconding from treatment, often due to adverse drug events. Quite possibly, the regimen as a whole including the interplay between different drugs and drug classes has been of major importance in addition to the primordial role of the choice of the fluoroquinolone generation. Being selective for one or the other drug because of appeal or lack thereof must thus be cautioned against. It is imperative to develop an equally effective regimen not requiring the two least desirable drug classes, i.e. thioamides and injectable drugs. The STREAM 2 trial for The Union will address this question, but results will have to wait for quite some time to come.

The regimen presented here was developed with the primary objective of providing an effective and affordable regimen for the most common form of MDR for the poorest countries in the world, a regimen that is so simple as to allow its implementation in the periphery without the need on relying on specialized services far from home of the patient. All the better if the experience made in Bangladesh and numerous countries in Africa is also having a positive effect on the management of tuberculosis in affluent countries like ours.