holes burned into the second sheet of tissue.

2. Roll the moxa as tightly as you can and see if it burns hotter or softer than a lightly rolled moxa cone.
3. Get your fingers wet and roll a cone (note this ruins the mogusa so please only handle a little bit of mogusa when trying this experiment). Does the cone burn differently than when it is dry?
4. All of these factors really do affect how the heat transfers through the cones and hence into the patient.

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Moxafrica Update Summary of Moxa-TB Study at Kiswa Health Centre, Kampala, Uganda, August 2015

by Merlin Young

Introduction

Multi drug-resistant TB (MDR-TB) is an infection that is resistant to two of the first line drugs (Isoniazid and Rifampicin). Extensively drug-resistant TB (XDR-TB) is an infection that is MDR with further resistance to at least two clinically important types of second line drugs as well. Worldwide at least 3.5% of new cases of TB and 20% of the retreatment cases are MDR-TB, and around 10% of MDR infections are estimated to be XDR. Rates of successful treatment of drug-resistant disease are dramatically less than those for drug-susceptible strains, meaning that DR-TB is now a very serious public health threat.

Current rates of MDR-TB estimated for the African region are quoted as being significantly below the global average, but this is unlikely to reflect reality given that more than three-quarters of African countries were unable to provide usable data for the most recent analysis.[1] In fact the probability is that they will be much higher given that generally the regional rates of drug-susceptible TB (DS-TB) are much higher than the global average whilst medical resources are more deficient, and especially because poor management of TB drugs due to inadequate medical resources is known to contribute to national MDR-TB epidemics.

There is emerging concern that the WHO is reluctant to present data that promotes the idea that the proportion of DR-TB is rising within the global pandemic. It recorded in 2014 that enrolment of MDR-TB patients worldwide had increased "by 150% between 2009 and 2012"[2] which certainly provided evidence that more patients were being treated. It stated in the same year, however, that "the percentage of new TB cases that have MDR-TB... has not changed compared with recent years."[3] This conclusion appears illogical given the proportional treatment success rates quoted by the WHO itself in which treatments of drug-resistant cases are significantly less successful than the drug-susceptible ones. In fact there is every reason to suspect that that the proportion of DR-TB within the wider pandemic is rising. This concern has recently been effectively confirmed by the Barcelona Declaration which unequivocally identified that the existence of a pandemic of "drug-resistant TB demonstrates a collective failure to address the disease properly,"[4] as well as by a report commissioned by the UK government suggesting that as many as 76 million people will have died prematurely from DR-TB by 2050 based on current data and knowledge, mostly in Africa and Asia.[5]

The Stop TB Partnership (which uses the WHO estimates in its extrapolations) states that "only 54% of 9 million people who fall ill with TB can be certain to get cured each year through medical treatment." Furthermore, according to the WHO's own numbers it has been conjectured that more than a third of those who currently die from TB die from drug-resistant infections. In spite of this, the WHO in 2014 ambitiously targeted "ending the global tuberculosis epidemic" (defined as a global incidence rate of 10/100,000 or less) by 2035, but did so without setting any discrete targets for either MDR- or XDR-TB. This is a short time period in terms of TB epidemiology and so will require new approaches to TB control and particularly to dealing with drug-resistance. Whilst this could include new drugs and vaccines, it may also require better prevention methods and alternative or innovative approaches to treatment.

The existing treatment of MDR-TB is prohibitively expensive for the strained health systems that are typical in Sub-Sahara Africa. This is due to the costs of initial diagnosis, of second-line drugs and also of the vital follow-up investigation of contacts. It is imperative therefore that additional measures to lower, eliminate or contain MDR-TB in this vulnerable region should be being looked for urgently. Such measures could include those that either increase the efficacy of the drugs used or improve the host immunity to fight off the disease (given a far higher incidence of the disease among the immune suppressed).

It was with all of this in mind that the current study was developed.

This report reflects a preliminary detailed analysis of the first two months' bacteriological responses of all 180 enrolled patients in the moxa-TB study in Uganda. This data was released by Makerere University in August 2015.

Moxa is a very simple treatment that utilises the smouldering of a refined herb (*Artemisia princeps*) on the skin. Substantial documentary evidence exists of its use in Japan in the decades immediately prior to the discovery of the first TB drug. Research has also been conducted to confirm its assumed immunotherapeutic effects.[6]

First of all this report describes the general characteristics of the overall cohort (table 1); secondly

it compares the respective rates of bacteriological conversion seen in the first two months of the multi-drug chemotherapy between those patients using moxa and those not using moxa (table 2). Two further tables appear later, one re-recording the study's earlier report of a significantly reduced drug side effect in the moxa patients among the first 90 enrolled patients at their six month way point (table 3), and the last identifying distinct critical treatment issues relating to treating drug-susceptible and drug-resistant types of tuberculosis (table 4).

It should be noted that the overall TB drug treatment period in Uganda at the time of the study was eight months (which therefore is also the study's duration period for each patient), and that further more extensive analyses are to be expected quite soon after the final enrolled patient has completed treatment in early January.

Patient Characteristics

The study enrolled 180 study drug-susceptible participants of which 90 were randomly assigned to drug-only TB treatment and 90 were randomly assigned to TB drug treatment with adjunctive moxa.

Table 1: Patient Characteristics

Patient Characteristics		Overall number	Randomization		p-value
		180	Moxa 90	No Moxa 90	
Gender					0.356
	Male	112	53	59	
	Female	68	37	31	
Age (years)					0.297
	15-30	103	47	56	
	31-45	64	37	27	
	>45	13	6	7	
Body mass index					0.102
	Under-weight	91	51	40	
	Normal	80	37	43	
	over-weight	9	2	7	
HIV sero status					0.350
	Positive	49	25	24	
	Negative	128	65	63	
	Not done / unknown	3	0	3	

As table 1 shows, both arms of the study were similar in terms of body mass index (BMI), proportion of HIV positive participants, age, and gender. This means that these characteristics were not confounding factors – i.e. they did not in themselves present any bias that could have affected the outcome.

This absence of confounding factors is particularly promising in respect of subsequent interpretations of data, particularly in relation to future analysis of outcomes for HIV positive cases and for those with higher bacteriological loads.

The percentage of HIV co-infected cases is less than might generally be expected among TB patients in a country like Uganda with high incidence of both diseases – but is predictable because such co-infected cases are often sputum negative (i.e. they are diagnosed by symptomatology only or by X-ray because the sputum diagnosis is inadequate to identify the limited TB mycobacteria in their sputum). Such HIV infected patients are also more likely to develop extra-pulmonary TB which is rarely diagnosed by sputum microscopy. In fact, given these two phenomena, this percentage of HIV co-infections in the cohort (at 27.2%) is probably as much as could have been hoped for. (Two fundamental criteria for eligibility for enrolment in the study were diagnosis by being sputum positive and a recent diagnosis of pulmonary TB.)

Sputum Conversion Rates

Sputum conversion was identified from the outset as a primary outcome measure in the study design.

The sputum test is a microscopic examination of a sputum sample that identifies the visible presence or absence of TB bacteria. All enrolled patients tested 'sputum positive' at the start of treatment. A change to negative status (i.e. no bacteria visible) indicates early recovery and reduced infectivity, but does not mean that the patient is cured. Usually a conversion to negative status is seen after the first two months of intensive chemotherapy using the four "first line" drugs, in around 75% of patients. Subsequent to this, treatment continues with the lengthier continuation phase (with only two drugs) in order to finally clear and cure the disease.

A comparison of the performance of the two treatment arms (moxa and no moxa) in terms of sputum conversion was made using a chi square test statistic at a 5% level of significance. Any resultant 'p-value' that is less than or equal to 0.05 is statistically accepted to be significant.

Table 2: *Sputum conversion rates during the first 2 months*

Duration of treatment		Moxa n=90 (%)	No Moxa n=90 (%)	p-value
1 month	Negative	10 (11.2)	2 (2.2)	0.015
	Still positive	79 (88.8)	88 (97.8)	
2 months	Negative	79 (87.8)	72 (80.0)	0.156
	Still positive	11 (12.2)	18 (20.0)	

By the end of the first month of treatment, 11.2% of the participants assigned to moxa were sputum negative compared with only 2.2% of the patients assigned to only TB treatment (no moxa). This difference was statistically significant (p=0.015).

By the end of the second month of treatment, most patients had, as expected, converted to sputum negative status. The conversion rate was higher in those using moxa (87.8%), but this time the difference was not statistically different (p>0.05).

These data suggest that the use of moxa can increase the sputum conversion rate during the intensive phase of drug treatment. It is important to note that in this instance only drug-susceptible TB is being considered, which in Uganda is treated using an intensive phase of two months followed by a continuation phase of a further six months. If these results are considered in the light of the much longer treatment regimen for drug-resistant tuberculosis (DR-TB) they throw up some interesting possibilities.

MDR- and XDR-TB patients experience a much longer intensive phase of treatment with more drugs used. Treatment comprises a minimum six-month intensive phase with six drugs (including daily injections), and then (subject to successful bacteriological conversion) a subsequent 18-month continuation phase using four drugs. This extended treatment is well recognised as having a much lower success rate than standard DOTS (Directly Observed Treatment Short-Course) for DS-TB (see Table 4). Non-completion of treatment is considered to be frequently caused by the side effects of the drugs, whilst unsuccessful treatment is often considered to be because of their lesser efficacy.

What the conversion rates in Table 1 suggest is that there is a statistically significant moxa-induced host response in the early stages of standard DOTS therapy in a proportion of the moxa patients. (It should be noted that this effect could quite possibly be enhanced if the moxa dosage was increased. The dosage used in this study was deliberately minimised in order to encourage treatment adherence in moxa patients and therefore render the study statistically viable.)

It is possible therefore that a similar response might be seen in patients undergoing second line drug treatment for DR-TB with adjunctive moxa regardless of the extent of the drug-resistance of the tuberculosis strain. If this were to occur in DR patients on longer treatment regimens with weaker drugs this effect could be much more clinically significant than in the current cohort of DS-TB cases. It might even contribute to improved treatment outcomes.

Quality of Life

The experience of treatment might also prove less pernicious to the patient if reductions in adverse reactions to the treatment regimen were seen and this might also result in better adherence rates. This phenomenon was observed in the very first sweep of the data when there were significant reductions in arthralgia (caused most probably by Pyrazinamide, one ofthe four firstline drugs) in moxa patients (see table below).

TABLE 3: *An earlier survey of first 90 enrolled and randomised patients at six month stage who had experienced joint pains.*

	Patients on moxa	Patients not on moxa
Number sur–veyed	40	50
Joint pains	6	21
% with pain	15%	42%

The proportion of patients who suffered from joint pains was higher in the control arm than in intervention arm (42% vs 15%, P<0.05) and this was statistically significant.

Based on patient interviews we believe that arthralgia (in particular knee pain) is a significant problem for patients who use latrines since squatting becomes extremely challenging and therefore might well be a significant contributor to non-adherence. Pyrazinamide(whichis the most likely cause of the complaint) is a first-line drug that is also used for the entire 24 months of most DOT-plus DR-TB protocols. These results suggest that adjunctive moxa therapy might: (1) improve adherence rates in DR-TB, (2) shorten sputum conversion time and, (3) reduce the risk of consequential infections. This last effect could be because of the reduced periods of infection during the early stages of treatment, but could also be a consequence of improved adherence which could reduce the risk of MDR-TB developing.

To obtain an overall assessment of quality of life changes throughout the whole treatment period, Karnovsky scores were taken at monthly intervals. These were analysed for all 180 patients using the Kruskal-Wallis test, but no differences were seen between the two treatment groups after Month 1 or Month 2. Karnofsky scores are a widely recognised method for measuring quality of life in patients with severely life-limiting disease. This result is therefore something of a disappointment – particularly because positive differences were expected given the earlier reports from a preliminary analysis of the first 90 patients during the first six months of treatment. The opinion of the professor who is leading the study, however, is that differences may show up more clearly when these numbers are first reviewed for all 180 patients at the six month waypoint – probably in November.

Conclusions

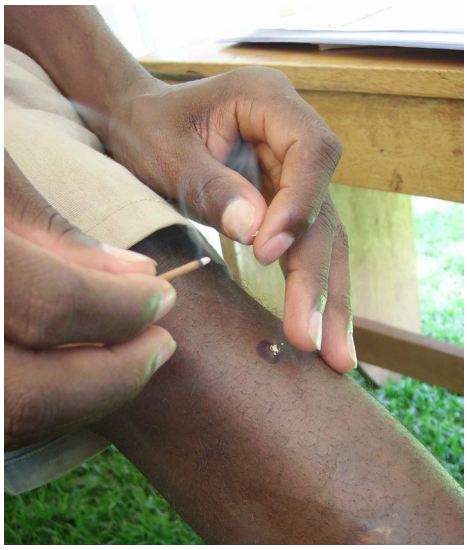
From these early numbers there is reason to be optimistic that moxa might have a part to play in the ongoing struggle to contain the rising tide of drug-resistant disease in resource-poor environments, and even possibly with otherwise functionally untreatable strains of XDR-TB. This could be particularly relevant because moxa has so far been found to be safe, is cheap and sustainable, and is highly adaptable to the most resource-poor environments. The most regularly identified problems with existing second-line treatments for DR-TB are that they are too expensive, too lengthy, very challenging to manage, and too toxic for the patient. Moxa might well be shown to attenuate one or more of these problems without the risk of stoking further drug-resistances in the mycobacterium.

Table 4: Comparisons of treatment complexities between different types of TB

	Drug–susceptible TB	MDR–TB	XDR–TB
Resistance to:	n/a	2 drugs	4 + drugs
Total treat–ment time	6–8 months	24 month	24 + months
Intensive phase	2 months (4 drugs)	6 months (6 drugs)	6 months (6 drugs)
Continua–tion phase	4–6 months (2 drugs)	18 months (4 drugs)	18 + months (6 drugs)
Success rate	86%	48%	18%
Drug and costs[7]	$257	$6,772	$26,392
Adjunctive moxa cost	<$10	c. $20	c. $20

(Note that the estimated drug costs include diagnostic costs and treatment management costs as estimated in 2012 for South Africa).

Further data are anticipated soon. These will include more comparative details of immunological responses, and specific comparisons between the important sub-groups within this same cohort (including those who are HIV positive, and those with higher sputum bacteriological load – both of which are recognised as significant contributors to the ongoing pandemic and as promoting rates of drug-resistance). If these analyses complement and confirm the existing findings, there will be an imperative to develop further investigations into the effects of adjunctive moxa treatment on both MDR and XDR cases.



Notes

1. WHO Global Tuberculosis Report 2014 – 'Recent trends in MDR-TB: a new analysis'.
2. WHO Antimicrobial Resistance Global Report on Surveillance 2014, page 47.
3. WHO Global Tuberculosis Report 2014, page 56.
4. Barcelona Declaration, made at the 45th Union World Conference on Lung Health in October 2014.
5. The Review on Antimicrobial Resistance, Tackling a Crisis for the Health and Wealth of Nations – chaired by Jim O'Neill 2014.
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