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Research Article

Shorter Treatment Regimens for Multidrug-Resistant Tuberculosis: A Great Challenge

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Abstract

Since the introduction of streptomycin, development of anti-tuberculous drug resistance was identified and frequently leads to failure of TB chemotherapy. Amplifier effect of short-course chemotherapy for TB is the phenomenon that patients infected with *Mycobacterium* strains resistant to at least one anti-tuberculous drug not only fail short-course chemotherapy, but may develop additional resistance to other anti-tuberculous drugs. The previously conventional WHO guidelines on MDR-TB management recommended 8-month intensive phase and a total treatment duration of not less than 20 months is conditional with "very low-quality evidence" to support its recommendations. These conventional long-duration regimens are suboptimal and poor treatment outcomes. In May 2016, the WHO has started a clinical trial of the shorter MDR-TB treatment regimen (4-6K(Mfx)(PTH)(Clf)ZH(high dose)E/5(Mfx)(Clf)ZE in Bangladesh, Benin, Burkina Faso, Burundi, Cameroon, Central African Republic, Cộte d'Ivoire, DR Congo, Guinea, Niger, Rwanda, Senegal, Swaziland, Uzbekistan, Ethiopia, South Africa, Viet Nam, and Mongolia. The WHO claimed that this shorter regimen indicated conditionally in MDR-TB or rifampicin-resistant TB (regardless of patient age or HIV status), monitored for effectiveness, harms and relapse (with patient-centered care and social support to enable adherence), feasibly programmatic use in most setting globally, lowered cost (less than US$ 1,000 in drug costs/patient) and reduced patient loss expected. Some Southeast Asian countries have implemented the 9-month Bangladesh gatifloxacin (or moxifloxacin)/isoniazid (high dose)-containing regimen which was proved to be cost-effective.

Keywords: *Multidrug-Resistant; Shorter Regimens; Treatment; Tuberculosis*

Abbreviations

Bdq: Bedaquiline; C: Cycloserine; CI: Confidential Interval; Clf: Clofazimine; DM: Diabetes Mellitus; DNA: Deoxyribonucleic Acid; DOT: Directly Observed Treatment; DOTS: Directly Observed Treatment-Short Course; E: Ethambutol; Eth/ETH: Ethionamide; H: Isoniazid; HIV: Human Immunodeficiency Virus; IS6110-RFLP: Insertion Sequence IS6110-based Restriction Fragment Length Polymorphism; IUATLD: International Union Against Tuberculosis and Lung Disease; K: Kanamycin; Lfx: Levofloxacin; MDR-TB: Multidrug-Resistant Tuberculosis; MIRU-VNTRs: Mycobacterial Interspersed Repetitive Units- Variable Numbers of Tandem Repeats; Mxf: Moxifloxacin; *M tb: Mycobacterium tuberculosis*; NA: Not Available; O: Ofloxacin; PTH: Prothionamide; Q: Quinolone; R: Rifampicin; RR: Rifampicin Resistance; S: Streptomycin; SCC: Short-Course Chemotherapy; STREAM: Standardized Treatment Regimen of Anti-tuberculosis Drugs for Patients with Multidrug-resistant Tuberculosis; TB: Tuberculosis; UK: United Kingdom; USA: United States of America; VNTRs: Variable Numbers of Tandem Repeats; WHO: World Health Organization; Z: Pyrazinamide

Objective of the Study

This study was aimed to compare and review the results of various MDR-TB regimens which previously recommended by the WHO with the current recommended shorter regimens.

Introduction

Nearly 40 years since 1968 that rifampicin was introduced and provide several effective anti-tuberculous agents [1,2]. Operational study by Karel Styblo and the International Union Against Tuberculosis and Lung Disease (IUATLD) and the clinical trials by the British Medical Research Council demonstrated that short-course chemotherapy (SCC) administered under direct observation could reach the success of tuberculosis (TB) treatment, but these tools have not been used appropriately for controlling TB [3]. Development of anti-tuberculous drug resistance was identified since the introduction of streptomycin (S) for TB treatment and frequently contributes to failure of TB chemotherapy [4]. Approximately, 28% of global TB cases are in India [4]. In 1998, globally, the overall resistance to any one anti-tuberculous drug varied from 12.7% to 34%; to any two drugs 1.8% to 15.8%; and to rifampicin (R) and isoniazid (H) 0.4% to 3.1% [4]. Currently, the World Health Organization (WHO) defines the multidrug-resistant TB (MDR-TB) as disease with organisms resistant to both R and H, with possible resistant to other anti-tuberculous drugs as well [4]. Due to being less likely to be cured and more likely to be dead, MDR-TB might take us to the era when TB was considered non-curable. A previous study in India revealed that the favorable treatment outcomes for the regimen $2HRZ_2/4H_2R$ with resistance to H or SH was 38% and with resistance to HR or SHR was 8%, for the regimen $2HRZ_2E/4H_2RE$ with resistance to H or SH was 80% and with resistance to HR or SHR was 0%; and for the regimen $2HRZ_7/6H_7E$ with resistance to H or SH was 83% and with resistance to HR or SHR was 12% [5]. Favorable response of patients with failure on SCC to the retreatment regimen K+R+E was 90%; and to the retreatment regimen C+Eth+E was 64% [5]. Favorable response of patients with failure to SCC to the retreatment regimen (according to drug susceptibility pattern) SRZ_2E/RZ_2E with resistance to H was 75%; to the retreatment regimen (according to drug susceptibility pattern) $SKRZ_2E/6Z_2E$ with resistance to S and H was 73%; to the retreatment regimen (according to drug susceptibility pattern) $3S_3EthZ_7E/9EthZ_7E$ with resistance to H and R was 37.5%; and to the retreatment regimen (according to drug susceptibility pattern) $3K_3Eth_7E/7EthZ_7E$ with resistance to SHR was 42% [5]. Response of MDR-TB patients to retreatment or salvage regimen O (400 mg/day for a minimum of 12 months) plus three or more drugs (Cycloserine, Thioacetazone or high dose of Isoniazid (600 mg/day) or Amik/K/S/Eth/Z/PAS) [5]. The total duration of treatment varied from 12 to 20 months [5]. Patients treated with ofloxacin-containing salvage regimens had 47% of favorable response, 40% of failed treatment, and 13% of defaulted treatment outcome [5]. As the side effects was almost nil or absent, ofloxacin was more acceptable to the patients [5]. The final treatment outcomes despite 2 or 3 full courses of proper treatment regimens for MDR-TB cases was as the following: 33% of overall favorable response, 26% of default, and 34% of death [5]. Intolerance to cycloserine, thioacetazone, and ethionamide was the main cause of default of treatment [5]. Amplifier effect of SCC is described the phenomenon or process by which patients infected with strains resistant to at least one anti-tuberculous drug not only fail SCC, but in the process may develop additional resistance to other anti-tuberculous drugs [6,7].

The development of DNA-fingerprint tools in the last three decades has considerably increased the capability to differentiate both susceptible and resistant *Mycobacterium tuberculosis* (*M tb*) strains, thus enabling tracing of strains in the community, and was able to design the prevention and control strategies to block further possible transmission [8-10]. These diagnostic tools include typing based on variable numbers of tandem repeats (VNTRs) of mycobacterial interspersed repetitive units (MIRU-VNTRs), spoligotyping, and the insertion sequence IS6110-based restriction fragment length polymorphism (IS6110-RFLP) [11-15]. MIRU-VNTRs have an advantage over IS6110-RFLP due to being less labor intensive, requiring very little DNA-amplification step, and easy interpretation [16-18].

According to the introduction of rifampicin and pyrazinamide into combined chemotherapy, the duration of treatment was decreased significantly from a mean of 18 - 24 months in the 1970s to 6 months for fully susceptible strains with relapse rates of < 2% [19]. Inadequacy of drug prescription by physicians and patients' non-adherence to advised treatment regimens, in addition to receiving monotherapy contribute to acquired drug resistance and transmission of drug-resistant *M tb* to contacts induced new cases with primary

and multidrug resistance. Until the 1990s, when several MDR-TB outbreaks were identified in different regions of the world, this was considered as a major health problem [20-22]. MDR-TB spreading was further increased inadequate isolation and ventilation measures, delayed recognition of MDR-TB, a lack of financial supports, including insufficient TB control programs [23,24]. Due to rapidly development of drug resistance, non-adherence to treatment commonly contribute to the development of drug-resistant TB with subsequent transmission of drug-resistant strains within the community. The spread of MDR-TB may be the results of several overlapping programmatic factors, such as use of substandard quality drugs with inferior bioavailability, interrupted drug supply, widespread availability of anti-tuberculous drugs without prescription, non-establishment of recommended treatment regimens, the lack of supervised treatment, poor medical management of treatment, and poorly managed and supported national TB control programs [25-27]. Several risk factors include a history of imprisonment, previous treatment or relapse, originating from "hot spot" regions, and possibly immunosuppressive conditions or diseases, such as human immunodeficiency virus (HIV) infection [28-30] and diabetes mellitus (DM) [31]. A previous study in different settings demonstrated a high rate of infection with Beijing strains (70.8%) associated with high rate of MDR-TB (60.9%) in prisons in Azerbaijan (n = 65) [32].

TB control strategies

TB control strategies are aimed at decreasing transmission through rapid identification of infectious cases and rapid adequate diagnostic measures, followed by immediate treatment with effective drugs due to resistance, while long sufficient protection by vaccination is not available. The basis of preventing and containing the further spread of MDR-TB recommended by the WHO, besides poverty reduction is the expansion of the directly observed treatment (DOT), short-course (DOTS) strategy with all of its five constituent elements; 1) Political commitment; 2) Case finding; Standardized and supervised short-course chemotherapy (DOTS); 4) A steady supply of high-quality effective drugs; and 5) A standardized surveillance system including treatment outcome monitoring. Short-course chemotherapy with four drugs (isoniazid, rifampicin, pyrazinamide and ethambutol/streptomycin in the intensive phase) is only suggested in the epidemiological situations with total resistance rates of less than 10%, but in settings with higher resistance rates, five drugs should be prescribed initially [33] accompanying drug susceptibility test performing, allowing the extension of the second-line drug treatment regimens [34-36]. Five or six drugs should be recommended in cases of the retreatment of MDR-TB [29]. Absence of epidemiological data about the extension of drug resistance, high cost of second-line drugs and their rational use, clinical management problems, as well as the lack of management of MDR-TB on a national scale are the main obstacles to the management of MDR-TB in resource-limited settings [37]. Enhanced surveillance of drug resistance patterns and TB cases, including better and faster reporting by the medical and laboratory personnel needs to be established. Urgently requirement of efficient monitoring of global drug resistance and the modification of successful treatment regimens had contributed to the designation of a MDR-TB case-management strategy using second-line drugs within the DOTS strategy (DOTS-Plus) in the low- and middle-income countries. These DOTS-Plus programs should be implemented in settings with well-established and well-functioning national TB-control programs that promote sound TB control practices for all patients [38]. Additionally, certain aspects must be considered as the following: 1) the diagnostic prerequisites of microscopic and cultural proof of *M tb* as well as drug susceptibility testing; 2) the regional resistance rates of *M tb*; 3) direct scientific evaluation of treatment regimens and alternative treatment regimens for polyresistant and MDR-TB cases that met the regional requirement; and 4) polyresistant and MDR-TB cases should preferably only treated by specially qualified experts in centers of expertise and specialization [39]. In countries with inappropriate TB control programs and already purchasing and using second-line drugs, establishment of proper TB control programs for prevention of the further development of drug resistance is urgently needed [38].

TB Costs

Several previous studies demonstrated that 3 - 4 months of work time are lost due to TB, by average, resulting in mean lost potential earnings of 20% - 30% of the annual household income. A further income loss of about 15 years due to premature death due to TB for these families is estimated by WHO [40]. In countries with unstable TB control programs, treatment regimens should use rifampicin only in the form of combined tablets of proven bioavailability to avoid monotherapy and to control the sale of anti-tuberculous drugs on the

private market [41]. The provision of four-first-line-drug fixed-dose combination tablets through the global drug facility for less than US $ 10 per treatment is practical approach to the treatment of susceptible TB to prevent the further spread of drug-resistant *M tb* [38]. The costs of MDR-TB treatment is 100 times more expensive than of fully susceptible TB. Considering cost effectiveness of DOT for MDR-TB was revealed in an assessment between South Africa and the USA. Cost savings of US $ 2,215 and US $ 1,788 per patient treated with conventional treatment (non-DOT) compared with DOT, respectively. A saving of 8% was demonstrated in the USA although conventional treatment (non-DOT) was about twice the cost of DOT in South Africa (1.5 times with the second-line drugs) [42], whereas White., *et al.* estimated the overall cost of MDR-TB treatment at 60,000 UK pounds compared to 6,040 UK pounds for drug-susceptible TB [43]. Laing., *et al*. demonstrated dramatic variations in drug price between different countries. They concluded that "free market" seems to be functioning for the first-line drugs, but it was not functioning for the second-line drugs. They reasoned that this was due to the lack of large-scale tenders and the limited number of the suppliers. Nevertheless, they expected a decrease in price with an increase in DOTS-Plus projects [44]. For reduction of the immensely high costs and foster the rational use of the second-line drugs, the WHO has established a multi-institutional working group for the DOTS-Plus approach, namely "Green Light Committee" [38]. So the countries that include budgets for purchasing the second-line drugs could save up to 57.5% of their overall budget for TB control activities [38].

Regimens[b] (US$/month)	Z (US$2.63)	E (US$2.60)	Ciprofloxacin[c] (US$7.34)	K[d] (US$13.50)	ETH (US$76.05)	C (US$318.05)	PAS (US$239.40)	Total cost (US$)
3K(ETH)ZQE/18ETHQE	7.90	54.68	154.22	40.50	1597.05	-	-	1,854.36 (53.5)[e]
3K(ETH)ZQC/18ETHQC	7.90	-	154.22	40.50	1597.05	6678.97	-	8478.65 (244.4)
3K(ETH)EQC/18EQETH	-	54.68	154.22	40.50	1597.05	954.14	-	2800.60 (80.7)
3K(ETH)QCP/18ETHQC	-	-	154.22	40.50	1597.05	6678.97	718.20	9188.95 (264.9)

Table 1: *Costs of Various MDR-TB Treatment Regimens*[a]

[a]*Free-on-board drug prices obtained from the International Drug Price Indicator Guide [45] for isoniazid, rifampicin, ethambutol, pyrazinamide, kanamycin and ciprofloxacin (calculations based on the average vendor price), from ECHO International Health Services Limited for cycloserine, and from pharmaceutical companies and reference 46 for ethionamide and para-aminosalicylic acid.*

[b]*Various treatment regimens recommended for MDR-TB treatment with/without associated pyrazinamide and ethambutol resistance [46-48]; K: Kanamycin; ETH: Ethionamide; Z: Pyrazinamide; E: Ethambutol; Q: Quinolone; C: Cycloserine; P: Para-Aminosalicylic Acid.*

[c]*Ciproflozxacin selected as cheapest available quinolone, ofloxacin costed at US$ 196.95 per month.*

[d]*Kanamycin selected as cheapest injectable agent (assuming streptomycin resistance); amikacin and capreomycin costed at US$ 641 and US$ 828 per month, respectively; additional price of needles and syringes must be added to the costings for the injectable agents.*

[e]*Figures in parentheses are the costings for the MDR-TB treatment regimens compared with the price of the WHO-recommended category 1 first-line treatment regimens (for example: 2HRZE/4HR) [49].*

Treatment and Treatment Outcomes of MDR-TB

Early detection of MDR-TB can improve treatment outcomes. A significant delay in MDR-TB patients receiving adequate treatment can be due to taking at least 3 - 4 weeks of conventional drug susceptibility testing [50]. FASTPlaqueTB-RIF™ Rapid test can detect rifampicin resistance that represent an indicator for MDR-TB with overall accuracy of 98% and the results are available after 48 hours from *M tb* cultures [51, 52].

Drug Resistance	Initial Phase		Continuation Phase	
	Duration (months)	Drug	Duration (months)	Drug
H+S	3	R, Z, E	6	R,E
H+E+S	2 1	R, Z, amikacin, PTH followed by R, Z, PTH	6	R, PTH
H+R+/-S	3-6	Z, E, PTH, amikacin, fluoroquinolone	18	E, PTH, fluoroquinolone
H+R+E+S	3-6	Z, PTH, amikacin, fluoroquinolone, cycloserine	18	PTH, fluoroquinolone, cycloserine
H+R+Z+E+S	3-6	PTH, amikacin, fluoroquinolone, cycloserine, PAS	18	PTH, fluoroquinolone, cycloserine

Table 2: *Treatment of drug-resistant TB, recommended by the WHO*[*].

H: Isoniazid; R: Rifampicin; Z: Pyrazinamide; E: Ethambutol; S: Streptomycin; PTH: Prothionamide/Ethionamide; PAS: p-Aminosalicylic Acid; [*]: treatment options for known drug resistance. If there is assumed polydrug resistance (treatment failure after standard short-course chemotherapy and DOT, treat for 3 months with pyrazinamide, aminoglycoside, prothionamide and fluoroquinolone followed by 18 months with prothionamide and fluoroquinolone [53-55].

Van Rie., *et al.* demonstrated on their study in 42 MDR-TB patients in South Africa that the sputum conversion occurred in 32 patients and treatment success was reported in 25 patients [56]. Five cases were treatment failure and 11 patients were dead within 5 years [56]. Tahaoglu., *et al.* reported their study results among 158 MDR-TB patients that the sputum conversion achieved in 150 patients and treatment success in 121 cases, particularly in cases of absence of previous treatment with ofloxacin and the younger age [57]. Thirty-six cases were performed lung resection [57]. Park., *et al.* demonstrated their study on 107 pulmonary MDR-TB patients that 52 patients achieved sputum conversion among included 63 cases due to 20 patients with loss to

follow-up, 22 cases with additional lung resection, and 2 cases with treatment interruption [58]. If including treatment success in patients with lung resection (21 in 22 cases), 73 of 107 cases could be achieved the treatment success of 68% [58]. Currently, adjuvant surgery is again considered for selected MDR-TB patients and pulmonary TB if treatment with the second-line drugs is not effective since surgical interventions were a major therapeutic approach before the era of introduction of antibiotics. Major surgical indications include failure to sputum conversion, a high potential risk of relapse, previous relapses, destruction of one lobe or one lung, persistent cavitations if surgical contraindications are absent. Achievement of bacteriological cure rates more than 90% was found in experienced and specialized centers and in combination with adequate and effective chemotherapy [59-62]. Nevertheless, anti-tuberculous drugs must be continued 18 - 24 months after surgical interventions [28,62-64], but the duration remains controversial [65]. Chang., *et al*. reported their study on 83 users with pyrazinamide-susceptible MDR-TB, 24 users with pyrazinamide-resistant MDR-TB, 40 nonusers with pyrazinamide-susceptible MDR-TB, and 47 nonusers with pyrazinamide-resistant MDR-TB from a Hong Kong territory-wide registry of MDR-TB cases diagnosed between 1995 and 2009 and concluded that pyrazinamide increased the incidence proportion of early culture conversion and that of treatment completion or of cure by a best estimate of 38% for both (95% CI, 26% to 133%) [66]. These study results imply that pyrazinamide plays significant role in fluoroquinolone-based treatment of MDR-TB [66]. The standard short-course first-line chemotherapy although with DOT is inadequate treatment for some patients with drug-resistant TB [67].

The Shorter MDR-TB Treatment Regimens

In 2014, the WHO estimated that 480,000 persons developed MDR-TB, worldwide [68]. Nevertheless, only about 123,000 persons (26%) were identified and around 111,000 persons (23%) received MDR-TB treatment [68]. Less than 10% of MDR-TB cases are being effectively identified and treated [68]. The previous WHO guidance on the management of MDR-TB recommended 8-month intensive phase and a total duration of not less than 20 months of treatment is conditional with "very low-quality evidence" to support its recommendations [69,70]. These conventional long-duration MDR-TB treatment regimens are suboptimal, costly, and high pill burden that contribute to poor treatment compliance and treatment outcomes. The limited treatment options available to MDR-TB patients and poor treatment outcomes contributed to the initiation of a series of 6 prospective observational cohort studies over a period of 12 years in Bangladesh to evaluate outcomes using fluoroquinolone-based regimens [71]. The 9-month regimen used in the last cohort of 206 patients showed the most promising results of a relapse-free cure rate of 87.9%, compared to the sequentially adapted regimens that based on the results of each preceding cohort [72]. This 9-month regimen or "Bangladesh regimen" included gatifloxacin and isoniazid at a higher than usual dose and proved to be cost-effective [73,74]. This regimen included at least four effective drugs (gatifloxacin or moxifloxacin (400 - 800 mg), isoniazid (300 - 600 mg), prothionamide (250 - 750 mg) or ethionamide, clofazimine (50 - 100 mg), ethambutol (800 - 1,200 mg), pyrazinamide (1,000 - 2,000 mg), and kanamycin (15 mg/kg-1 g)) in the 4-month (16 weeks) initial phase and at least three effective drugs (gatifloxacin or moxifloxacin (400 - 800 mg), clofazimine (50 - 100 mg), ethambutol (800-1,200 mg), and pyrazinamide (1,000 - 2,000 mg)) in the 5-month (24 weeks) continuation phase [71]. The STREAM trials have conducted a study in 2016 that will compare the treatment outcomes of the WHO individualized (conventional) MDR-TB treatment regimen (4 or more second-line drugs, up to 8 months of the intensive phase/3 or more second-line drugs, 12 months or more of the continuation phase) to the Bangladesh regimen, oral 9-month bedaquiline which replaces kanamycin (4 months (16 weeks) of bedaquiline+isoniazid+prothionamide+levofloxacin+clofazimine+ethambutol+pyrazinamide and 5 months (24 weeks) of bedaquiline+levofloxacin+clofazimine+ethambutol+pyrazinamide) regimen, and 2 months (8 weeks) of kanamycin+isoniazid+bedaquiline+levofloxacin+clofazimine+pyrazinamide and 5 months (20 weeks) of bed aquiline+levoflozxacin+clofazimine+pyrazinamide regimen. The patient enrolment is expected to continue for 3 years and the primary results will be expected in 2020 [71]. Although it has not been assessed in a randomized controlled trial, a number of countries including some Southeast Asian countries have started introduction of the "Bangladesh regimen" or a variant of it into their TB control programmes [71].

In May 2016, the WHO has launched a clinical trial of the shorter MDR-TB treatment regimen (4 - 6 months of kanamycin+moxifloxacin+prothionamide+clofazimine+pyrazinamide+isoniazid (high dose)+ethambutol/5 months of moxifloxacin+clofazimine+pyrazinamide

+ethambutol) in Bangladesh (as mentioned above), Benin, Burkina Faso, Burundi, Cameroon, Central African Republic, Cộte d'Ivoire, DR Congo, Guinea, Niger, Rwanda, Senegal, Swaziland, Uzbekistan, Ethiopia, South Africa, Viet Nam, and Mongolia [75]. The criteria for inclusion in this clinical trial are as the following: 1) no confirmed resistance or suspected ineffectiveness to a medicine in the shorter MDR-TB treatment regimen (except isoniazid resistance), 2) no exposure to at least one second-line medicines in the shorter MDR-TB treatment regimen for more than one month, 3) no intolerance to at least one medicines in the shorter MDR-TB treatment regimen or risk of toxicity (e.g. drug-drug interactions), 4) no pregnancy, 5) no extrapulmonary disease, and 6) no at least one medicine in the shorter MDR-TB treatment regimen not available in the programme [75]. If these criteria are yes, then individualized (conventional) MDR/RR-TB treatment regimens will be applied [75]. The WHO claimed that this shorter MDR-TB treatment regimen will be standardized with seven drugs and a treatment duration of 9 - 12 months, indicated conditionally in MDR-TB or rifampicin-resistant TB (regardless of patient age or HIV status), monitored for effectiveness, harms and relapse (with patient-centered care and social support to enable adherence), feasibly programmatic use in most setting globally, lowered cost (less than US$ 1,000 in drug costs/patient) and reduced patient loss expected [75].

Discussion

DOTS has been successful in preventing increases in cases of MDR-TB in many countries with a low incidence, but it is not clear whether a good DOTS programme would be enough to control MDR-TB in those countries where it was already established. In DOTS-Plus programmes, drug distribution might prove difficult for MDR-TB patients scattered over a wide geographic areas. The laboratory equipment and reagents required by the diagnostic facilities supporting DOTS-Plus programmes must be provided by the supply services. The cost of the second-line drugs used in the MDR-TB treatment regimens is the most important problem confronting the procurement services of DOTS-Plus programmes. An injectable agent and a quinolone that form the basis for successful MDR-TB treatment regimens are both expensive. The other second-line agents are excessively expensive due to limitation of available supplies or existence of production monopolies. The WHO's previously recommended MDR-TB treatment regimen has unpleasant treatment outcomes due to its suboptimum and toxicity. The absence of accurate data from randomized clinical trials for MDR-TB has prevented the WHO from being able to produce strong and proper MDR-TB treatment guidelines. Better treatment outcomes are possible using alternative shorter regimens of currently available drugs like "Bangladesh regimen". Use of pyrazinamide with susceptibility among pyrazinamide users markedly increases the incidence proportion of early sputum culture conversion and that of the treatment success in MDR-TB patients treated with fluoroquinolone-based regimens. The potential toxicity of the MDR-TB drugs contribute to the evaluation of regimen safety in a randomized comparison clinical trial, especially important for patients' treatment programmes. STREAM stage 2 compares the effectiveness of a shorter 6-month regimen, an all-oral regimen, and two new bedaquiline-containing short-course regimens. If the results demonstrate to be at least non-inferior to the STREAM stage 1 study regimen, this would indicate a greater advance for MDR-TB treatment and TB control programmes worldwide. With the explosion in population, urban migration, the rapid increase in national and international travel, and increasing poverty, there is a need to focus on the chemotherapy of resistant TB in view of the anticipated increase in anti-tuberculous drug resistance.

Conclusion

The implementation of shorter MDR-TB treatment regimens whether 6, 9 or 12 months of the treatment course along with DOTS-Plus programmes will be definitely cost-effective treatment for MDR-TB patients.

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Conflict of Interest

No conflict of interest declared.

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