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N.A. Lytvynenko, H.O. Varytska, O.P. Chobotar, N.V. Grankina
SI «National Institute of Phthisiology and Pulmonology named by F.G. Yanovsky of NAMS of Ukraine», Kyiv, Ukraine

Analysis of the optimal duration and ATDs dosages between different short chemotherapy regimens for MDR-TB patients: comprehensive systematic review

Objective — a better understanding of the composition of optimal treatment regimens for multidrug-resistant tuberculosis is essential for expanding universal access to effective treatment and for developing new therapies for MDR-TB.

We conducted this systematic review to determine and justify the optimal duration and the dosages of antituberculosis drugs for short multidrug-resistant tuberculosis regimen.

Materials and methods. Three electronic databases (MEDLINE, EMBASE and PubMed) were searched to identify observational study, including «cohort studies» and «follow-up studies», that included results of using short — regimen for multidrug resistant tuberculosis treatment. We found only 3 relevant studies for this review: 1st — «High effectiveness of a 12-month regimen for MDR-TB patients in Cameroon» («Cameroon» regimen); 2nd — «High cure rate with standardized short-course multidrug-resistant tuberculosis treatment in Niger: no relapses» («Niger» regimen); 3rd — «Successful "9-month Bangladesh regimen" for multidrug-resistant tuberculosis among over 500 consecutive patients» («Bangladesh» regimen). The studies have low clinical & methodological heterogeneity, that allows make veracious conclusions for the results of comparison.

Results and discussion. All three short — regimens had identical composition and quantity of ATDs, but different duration and ATDs dosages. There was no found statistically significant difference between high ATDs dosages of the 9 — months and convenient ATDs dosages of the 12-months short MDR-TB regimen. Combined OR for unfavorable outcomes is 0.77(95 % CI 0.48—1.25). Sampling error, $I^2 = 0$ % (of 0 to 40 % is not important)

Conclusions. The 9 month «Bangladesh» regimen could be recommended (in addition — ATDs might be used in medium therapeutic doses for short-regimen) and this regimen reduce the health care burden.

Key words

Multidrug resistant tuberculosis, short chemotherapy regimen, optimal ATDs dosages.

The increasing burden of multidrug-resistant tuberculosis (MDR-TB), defined as tuberculosis with resistance to isoniazid and rifampicin (the two core drugs of the drug-sensitive TB regimen). In 2014, an estimated 480.000 people developed MDR-TB globally nevertheless only 123.000 were notified and 110.000 started treatment. Treatment outcomes for MDR-TB are poor, with less than half of cases having successful outcomes with no more than one in 10 MDR-TB patients being effectively identified and treated [9]. Currently applying treatment regimes continue till 20—24 months, but only half of the MDR-TB patients, who start treatment in 2012, were successful treated worldwide [3, 10].

In Ukraine today is also extremely unfavorable epidemiological situation for tuberculosis. According to the epidemiological surveillance of the

prevalence of drug-resistant strains the frequency of MDR-TB among new TB cases, 19.2 % among retreatment cases — 56.1 %. According to the WHO report, in 2013 among 27 countries around the world has been concentrated 85 % of cases of MDR-TB, while Ukraine is on the 4th place by the number of MDR/XDR-TB [9].

Present recommendations for MDR-TB treatment approach are tedious and has not been tested as a randomized clinical trial, being based largely on expert opinion. There is a lack of good evidence on optimal management [3]. A better understanding of the composition of optimal treatment regimens for MDR-TB is essential for expanding universal access to effective treatment and for developing new therapies for MDR-TB.

Analysis of observational data may inform the definition of an optimized duration of treatment and treatment regimen.

We have defined challenging «researchable» question — determine the optimal duration and the dosages of antituberculosis drugs (ATDs) for short MDR-TB regimen.

Materials and methods

We conducted this systematic review (SR) according to the CRD's guidance for undertaking reviews in health care [6].

The objective of this review is to assess the optimal duration and ATDs dosages for MDR-TB treatment.

Specifically, we used following PICOS approach:

— Population: Adults ≥ 18 years of age, with new MDR-TB cases, sensitive to quinolones (Q).
— Intervention: treatment with a short-regimen for MDR-TB.
— Comparison: treatment outcomes, duration of different short-regimens for MDR-TB, ATDs dosages and adverse events/serious adverse events (AE/SAE).
— Outcome: difference between favorable and unfavourable treatment outcomes dependiong on treatment duration and ATDs doseges.
— Study Design: prospective observational studies.

Search question and quality of assessment

Three electronic databases (MEDLINE, EMBASE and PubMed) were searched using full text and MeSH terms to identify articles discussing cohort studies designs, including «observational study with follow-up period». Where possible, all terms were included as full text, with truncation used where possible to capture variation in the terminology. The search was not limited to the English language, nor restricted by any other means.

The identified studies were assessed for quality of methodology viz: eligibility criteria, sample design, type of supervision exercised during study, type of regimen, treatment schedule, etc. Articles that provided general narrative approach, review and case report were excluded. Published WHO report were used for tools suitable for assessing quality.

The review question and the subsequent specification of the inclusion and exclusion criteria were tightly focused to determine relevant studies.

Study selection

Factors used in the assessment of the studies for potential bias included the study design, homogeneity of study population, duration of treatment, homogeneity of defined treatment outcomes, follow-up period.

To be included in the review, the eligibility criteria were as follow:

1) not limited to the English language;
2) observational prospective study;
3) study population (new MDR-TB patients);
4) patient characteristics (Adults ≥ 18 years of age, pulmonary TB cases, no history of previous TB treatment, susceptible to Q);
5) used short-regimen for MDR-TB patients;
6) standard definitions of the treatment outcomes and information about safety and tolerability of regimens;
7) 24 months follow-up period.

Exclusion criteria:

1) retrospective study;
2) follow up period is not finished yet;
3) use of new ATDs (bedaquiline, delamanid);
4) use standard 20-months treatment courses for MDR-TB.

From chosen 20 studies only 6 studies met the inclusion criteria, such as: from Uzbekistan [7], from 9 sub-Saharan African countries [8], STREAM trials [4], Bangladesh [1], Cameroon [2], Niger [5].

Data from Uzbekistan were excluded because researchers included children and they started trials in July 2014 (last updated was in November 2016) and the follow up period is not finished yet. We aimed to include only adult patients and 24 months follow up period [7].

We excluded observational study from 9 sub-Saharan African countries, because they reported data from May 1997 to December 2007 and we didn't find enough data for extraction from this research [8].

Also we excluded short-course treatment for multidrug resistant tuberculosis (STREAM trials had been done by Riya Moodley and Thomas R. Godec), because they compared 4 regimens: 20-month (standard) and three short regimens (two of them — with Bedaquiline) [4]. This study was excluded because it is not yet finalized. Riya and her team just

Table 1. **The specification of comparison of short MDR-TB regimens**

Varibles	«Cameroon» regimen	«Niger» regimen	«Bangladesh» regimen	Variances
Duration of treatment administration	12 months	12 months	9 months	different duration
Number of ATDs	7 ATDs daily	7 ATDs daily	7 ATDs daily	the same number
Dosages of ATDs				
Gatifloxacin	400 mg — for all patients	400—600—800 mg — by the weight	400—600—800 mg — by the weight	different dosages
Isoniazid	300 mg — for all patients	300—400—600 mg — by the weight	300—400—600 mg — by the weight	different dosages
Clofazimine	100 mg for all patients	50—100 mg — by the weight	50—100 mg — by the weight	different dosages
Kanamycin	15—20 mg/kg	15—20 mg/kg	15—20 mg/kg	the same dosages
Prothionamide	15—20 mg/kg	15—20 mg/kg	15—20 mg/kg	the same dosages
Ethambutol	25 mg/kg	25 mg/kg	25 mg/kg	the same dosages
Pyrazinamide	30—40 mg/kg	30—40 mg/kg	30—40 mg/kg	the same dosages

wanted to show the methodology. Stage I will be finalized after a year whereas stage II will be finalized after 3 or 4 years.

Only three studies were relevant and assessed for SR:

— «Cameroon» regimen — «High effectiveness of a 12-month regimen for MDR-TB patients in Cameroon» [2];
— «Niger» regimen — «High cure rate with standardized short-course multidrug-resistant tuberculosis treatment in Niger: no relapses») [5];
— «Bangladesh» regimen — «Successful "9-month Bangladesh regimen" for multidrug-resistant tuberculosis among over 500 consecutive patients» [1].

Data extraction

Data extracted from the trials included: study design, period of treatment, number of patients, study population, treatment duration, treatment outcomes and follow up period, as well as variables that might have an impact on treatment outcomes: AE/SAE, regimens (ATDs dosages), results. The studies were scored for their potential biases by means of a predetermined measurement of the validity of the study's design.

As for inclusion/exclusion criteria, on our opinion, potential clinical heterogeneity is because human immunodeficiency virus (HIV) infection was excluded only in «Bangladesh» study. In «Cameroon» study were included 30 patients and 25 (83.8 %) of those — cured. In «Niger» study one of 58 patients tested for HIV (1.7 %) infection was positive.

In Cameroon the patients had received a 12-month treatment regimen, with all drugs given daily throughout. An intensive phase of a minimum duration of 4 months with kanamycin (KM) 15—20 mg/kg, gatifloxacin 400 mg (GFX), prothionamide (PT) 15—20 mg/kg, clofazimine (CFZ) 100 mg, isoniazid (INH) 5 mg/kg, etambutol (EMB) 25 mg/kg and pyrazinamide (PZA) 30—40 mg/kg was followed by a fixed-duration continuation phase of 8 months with the same drugs, but omitting INH and KM.

In Niger the regimen was essentially the same as that used in the Bangladesh programme, but was slightly longer. The intensive phase regimen, consisting of high doses of KM, PTH, INH and GFX (Table 1), CFZ, EMB and PZA, lasted a minimum of 4 months. The intensive phase was extended up to a maximum of 6 months in the case of delayed sputum smear conversion at 4 or 5 months. The continuation phase regimen, comprising GFX, CFZ, EMB and PZA, was fixed at 8 months. The total duration of treatment was thus 12 months. No treatment was modified as a result of the initial drug resistance pattern.

The Bangladesh regimen was used throughout the 9 months period and comprised high-dose GFX, EMB, PZA, and CFZ, supplemented during the minimum 4-month intensive phase by KM, PTH and INH. The duration of the continuation phase was fixed at 5 months.

The difference between all 3 short MDR-TB regimens shown in Table 1. All three short regimens had identical composition and quantity of ATDs. In «Cameroon» regimen unlike of the two other regimens, were used medium-therapeutic dosages of GFX and H for all patients, but maximum — therapeutic dosages of CFZ. Those two regimens («Niger» and «Bangladesh») came with the maximal therapeutic dosages of GFX, H and CFZ for patients depending on weight. Only «Bangladesh» regimen differed from others two regimens through the duration of treatment and lasts 9 months instead 12 monthes. But in case the intensive phase was extended, due to sputum smear conversion delay, treatment was prolongated till 12 months also in «Bangladesh» regimen.

Consequently we faced with several key indicators of clinical heterogeneity:

1. Participants characteristics: studies including different sex, age group, ethnicity, and patients with different disease severity.
2. Intervention: studies are using different ATDs dosages and treatment duration (as shown in Table 1).
3. Outcome: all studies measuring the same outcomes as the result of the intervention: cure, completion, time to culture conversion, failure, relapse, death, default, lost of follow up (LTFU), except: transferred out to another jurisdiction, reinfection disease.
4. Adverse events: vomiting, hearing loss, hyperglycemia, gastritis, arthralgia, depression, peripheral neuropathy, skin pigmentation, optic neuritis), duration of follow up period and time of intervention.

Such outcome as «transferred out to another jurisdiction» defined as a patient who was transferred to another jurisdiction without known treatment outcome. Studies have been reported: no patients as «transferred out to another jurisdiction» — in «Cameroon» study; 4 patients (6.9 %) — in «Niger» study. However, that patients had left the country were alive when contacted by phone at 24 months» follow-up. In «Bangladesh» study didn»t have such outcome.

Such outcome as «Reinfection disease»: recurrent disease with a genotypically different strain reported only in «Bangladesh» study — 2 patients had confirmed reinfection disease during the 2-year follow-up.

We failed to extract one comparison item from PICOS approach — AE/SAE by the reason of significant clinical, methodological and statistical heterogeneity.

The «Bangladesh» study reported AE/SAE generally, but for Q-susceptible MDR-TB patients separately that data is not available. Every study reported different kinds AE/SAE, «Bangladesh» study had bad registration, that's why this factor was not considered.

Data synthesis

These are observational study describing a series of individuals, receiving the same intervention with no control group. Several tools have been used.

To assess confounding we used tests for categorical variables, odds ratios (OR), hazard ratios, mean value: OR for relapses and default depending on intervention (duration and treatment regimen); hazard ratio is constant across the follow-up period and we can use it for determining of relapses; mean value.

To deal with clinical heterogeneity were used: chi-square and P-value, quantify the heterogeneity: the I^2 test.

Results and discussion

The included studies were written in English; full texts of papers were analyzed. No limitations were defined among all 3 studies due to study design, period of treatment, follow up period, study population. Study population, inclusion/exclusion criteria, treatment regimens (ATDs combination), treatment outcomes and results could be calculated. Limitations of the studies are: the small sampling size in «Cameroon» and «Niger» studies, inclusion of HIV patients in «Cameroon» study and low level of AE/SAE registration; treatment outcomes are applicable.

Comparison analysis for estimating of heterogeneity for all studies included in SR has been presented in Table 2. The studies have low clinical & methodological heterogeneity that allows make veracious conclusions for the results of comparison. Those studies have similar inclusion and exclusion criteria, all prospective, the same follow-up period, the same 7 ATDs but with different dosages and treatment duration. They also have less statistical heterogeneity as shown by I^2, less than 25 %.

In addition, we found, if TB case is not complicated by extensive additional resistance, short-regimen is apparently effective even in a country with a generalized HIV epidemic, as it is shown by «Cameroon» study. That might mean the people living with HIV need to be given the same consideration for treatment with the short MDR-TB regimen as people who are HIV seronegative. This recommendation was given by researchers from Cameroon. On the other hand HIV infected patients were excluded from «Bangladesh» study and «Niger» study had included only one HIV positive patient. That's why, this finding has a significant limitation and can't be extrapolated to the general recommendations.

As for one of the core limitation we faced with: for active TB drug-safety monitoring and management needs to be applied more accurate registration level and appropriate action to respond promptly to adverse events alongside the monitoring for treatment outcomes. Therefore, the choice of optimal chemotherapy regimen can't be assessed based on the safety and tolerability. The duration of treatment and optimal ATDs dosages in different short — regimens were evaluated only on the basis of their efficacy.

Random effect model were conducted in the program Review Manager 5.3 software to compare

Table 2. **Comparison analysis for estimating of heterogeneity for all studies included in SR**

Variables	Types of the studies for comparison			Limitation
	High effectiveness of a 12-month regimen for MDR-TB patients in Cameroon [2]	**High cure rate with standardized short-course multidrug-resistant tuberculosis treatment in Niger: no relapses [1]**	**Successful «9-month Bangladesh regimen» for multidrug-resistant tuberculosis among over 500 consecutive patients [6]**	
Study design	Prospective study	Prospective study	Prospective study	No Limitations
Period of treatment	2008—2011	2008—2010	2005—2011	No Limitations
Follow up period	24 month	24 month	24 month	No Limitations
Number of patients	150	65	515	Not significant limitations*
Included patients	Pulmonary new MDR-TB cases (Q-susceptible)	Pulmonary new MDR-TB cases (Q-susceptible)	Pulmonary new MDR-TB cases (Q-susceptible)	No Limitations **
Excluded patients	1. Treatment SLD > 1mnth 2. Pregnant women 3. Patients with very poor clinical condition 4. Known hypersensitivity reactions to any of the study drugs 5. 2-nd line drug resistance	1. Treatment SLD > 1mnth 2. Diabetic patients 3. Pregnant women 4. Patients with severe liver Insufficiency 5. 2-nd line drug resistance	1. Treatment SLD > 1mnth 2. Isolates of environmental mycobacteria 3. Gailed to confirm MDR TB 4. Patients with severe liver Insufficiency 5. 2nd line drug resistance 6. HIV-infection	Significant limitation***
Treatment outcomes	Cure Completion Failure Death Default Transferred out to another jurisdiction Relapse time to culture conversion	Cure Completion Failure Death Default Transferred out to another jurisdiction Relapse time to culture conversion	Cure Completion Failure Death Default Reinfection disease Relapse time to culture conversion	Not significant limitations#
Definition	*Cure*: a patient who has completed treatment and has at least five consecutive negative cultures, each at least 30 days apart *Completion*: a patient who has completed treatment but does not meet the definition for cure or treatment failure due to missing culture results *Defaulted (lost)*: a patient whose treatment was interrupted for two or more consecutive months *Died*: a patient who dies for any reason during the course of treatment *Failed*: a positive culture at 5 months or later; bacteriological reversion to positive after conversion; evidence of additional acquired resistance to fluoro-quinolones or secondline injectable drugs, adverse drug reactions requiring permanent withdrawal of key study drugs	*Cured*: treatment completed with at least five consecutive negative cultures *Treatment completed*: treatment completed with documented bacteriological conversion but not meeting the definition for cure *Default*: interruption of treatment for > 2 con-secutive months without medical approval *Died*: death from any cause during the course of MDR-TB treatment *Failed*: two or more of the five cultures positive in the final 8 months of treatment, or one of the final three, or treatment stopped definitively due to adverse drug reactions *Relapse*: cured or completed treatment with at least one positive culture during post-treatment follow-up	*Cure*: completion of treatment with five or more negative cultures over at least 12 months (follow-up period included2) after the last positive culture. *Completion*: completion of treatment with docu- mented bacteriological conversion status persisting up to the end of treatment, but fewer than five negative cultures or,12 months of observation after the last positive culture. *Default*: interruption of treatment for at least 2 months not meeting the criteria for prior failure. *Death*: death from any cause during treatment not meeting the criteria for prior failure. *Failure*: one or more positive cultures during treatment after at least 150 days, or death or default with bacteriological evidence of active TB after the first 2 months of treatment, or a medical decision to definitively terminate treatment due to adverse drug reactions	No Limitations

Продовження table 2

Variables	Types of the studies for comparison			Limitation
	High effectiveness of a 12-month regimen for MDR-TB patients in Cameroon [2]	**High cure rate with standardized short-course multidrug-resistant tuberculosis treatment in Niger: no relapses [1]**	**Successful «9-month Bangladesh regimen» for multidrug-resistant tuberculosis among over 500 consecutive patients [6]**	
	Transferred out: a patient who was transferred to another jurisdiction without known treatment outcome		*Relapse*: cure or treatment completion, followed by at least one positive culture during post-treatment follow-up, unless the strain was proven to be genotypically different from the initial isolate. *Reinfection disease*: recurrent disease with a genotypically different strain	
Results	For all patients, included in study (150): Favorable outcomes (cure + completion) — 134 (89.3 %) Default — 5 (3.3 %) Relapse — 0	For all patients, included in study (65): Favorable outcomes (cure + completion) — 58 (89.2 %) Default — 4 (6.2 %) Relapse — 0	For Q-susceptible MDR-TB patients (439): Favorable outcomes (cure + completion) — 380 (86.6 %) Default — 33 (7.5 %) Relapse — 1 (0.2 %)	No limitations
AE/SAE	For all patients (150) Frequency of all AEs: 48 (32.0 %) Type of AE: abnormal audiogramme 46 (43.4 %) — among 106 patients with audiogramme; retrobulbar neuritis — 1 (1.5 %); elevated transaminases — 1 (1.5 %)	For all patients (65) Frequency of all AEs: 55 (94.8 %) Type of AE: Vomiting — 17 (26.2 %) Hearing loss — 13 (20.0 %) Hyperglycaemia — 6 (9.2 %) Gastritis — 5 (7.7 %) Arthralgia — 4 (6.2 %) Depression — 3 (4.6 %) Peripheral neuropathy — 3 (4.6 %) Skin pigmentation — 2 (3.1 %) Optic neuritis — 2 (3.1 %)	For all patients (515) Frequency of all AEs: 128 (24,9 %): Type of AE: vomiting — 111 (21.6 %); due to diabetes and glycosuria — 8 (1.6 %); all drugs temporarily interrupted — 2 (0.4 %); KM dose was reduced and stopped — 7 (1.4)	Significant limitations##

Note. * Small sample size; ** «Niger» study reported one case of resistance to Q; «Bangladesh» study were divided patients depending on Q-resistance or Q-susceptible MDR-TB, «Cameroon» study were not included patients with resistance to Q; *** «Cameroon» study included HIV patients; «Niger» study reported 1 HIV patient; «Bangladesh» study excluded HIV infected patients; # all studies have the same outcomes), except: transferred out to another jurisdiction, reinfection disease; ## low level of AE/SAE registration, not applicable for SR.

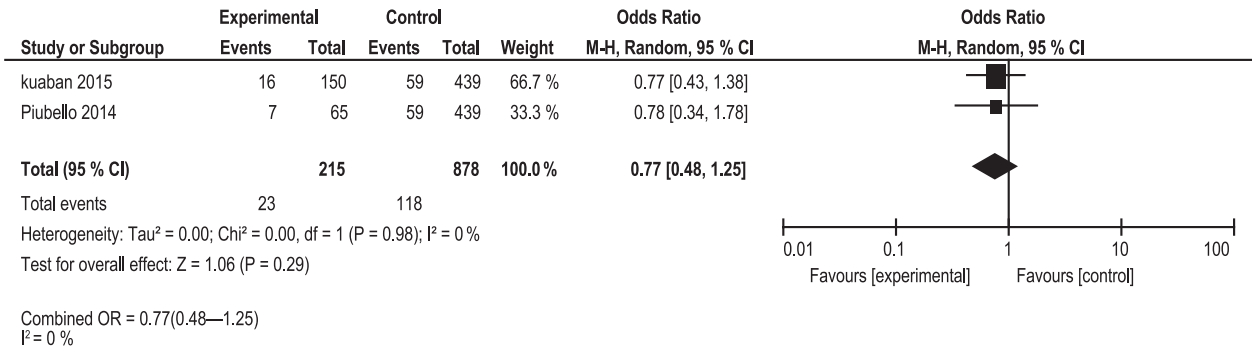

Figure. **Analysis of treatment outcome (unfavorable outcome) between different short-regimen for MDR-TB treatment**

treatment outcomes (success rate) between short MRD-TB regimens with different treatment duration, shown on Figure. For this we combine the data from «Cameroon» and «Niger» studies with 12-months duration of treatment to compare with «Bangladesh» 9-months study. The cure rate in «Bangladesh» was 84.4 %, «Cameroon» 89 % and «Niger» 89.2 %. All are obviously effective. Comparing both 12-months regimens of «Niger» and «Cameron» studies, the high weight was found in last one because of relatively larger sample size. There was no found statistically significant difference between high ATDs dosages of the 9 — months and convenient ATDs dosages of the 12-months short MDR-TB regimen. Combined OR for unfavorable outcomes is 0.77(95 %, CI, 0.48—1.25). Sampling error, I^2 = 0 % (of 0 % to 40 % is not important).

Conclusions

Comparing administration of high ATDs dosages from «Bangladesh» 9-month regimen with convenient ATDs dosages from «Cameroon» and «Niger» 12-month regimens, no significant difference was found. ATDs might be used in medium therapeutic doses for short-regimen, since administration of higher doses of fluoroquinolones, isoniazid and clofazimine associated with the same results.

Comparing the duration of «Bangladesh» short regimen with 12 months duration of the rest two (from Niger and Cameroon), no significant difference was found. The efficacy of 9-months and 12-months duration of short-regimens didn»t differ.

The 9 month «Bangladesh» regimen could be recommended (in addition — ATDs might be used in medium therapeutic doses for short-regimen) and this regimen reduce the health care burden.

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Н.А. Литвиненко, Г.О. Варицька, О.П. Чоботар, Н.В. Гранкіна
ДУ «Національний інститут фтизіатрії і пульмонології імені Ф.Г. Яновського НАМН України», Київ

Оптимальний скорочений режим антимікобактеріальної хіміотерапії для мультирезистентного туберкульозу за тривалістю та дозуванням протитуберкульозних препаратів: систематичний огляд

Мета роботи — краще розуміння оптимальних режимів антимікобактеріальної хіміотерапії туберкульозу з множинною лікарською стійкістю має важливе значення для розширення загального доступу до ефективного лікування і для розробки нових методів лікування мультирезистентного туберкульозу (МРТБ). Ми провели цей систематичний огляд, щоб визначити і обґрунтувати оптимальну тривалість і дозування протитуберкульозних препаратів (ПТП) у скороченому режимі антимікобактеріальної хіміотерапії для МРТБ.

Матеріали та методи. Пошук проводили у трьох електронних базах даних (MEDLINE, EMBASE і PubMed) для виявлення проспективних досліджень, які включали результати застосування скороченого режиму антимікобактеріальної хіміотерапії для МРТБ. Ми знайшли тільки 3 відповідних дослідження для цього огляду: 1-ше — «Висока ефективність 12-місячного курсу хіміотерапії для хворих на МРТБ в Камеруні» (режим «Камерун»); 2-ге — «Високий рівень успішного лікування стандартним коротким курсом хворих на туберкульоз із множинною лікарською стійкістю у Нігері: жодного рецидиву» (режим «Нігер»); 3-тє — «Успішний "9-місячний Бангладеський режим" для хворих на туберкульоз із множинною лікарською стійкістю серед більше ніж 500 пацієнтів» (режим «Бангладеш»). Дослідження мають незначну клінічну і методологічну гетерогенність, що дає змогу зробити достовірні висновки результатів порівняння.

Результати та обговорення. Всі три скорочених режими лікування мали однаковий склад і кількість ПТП у режимі, але застосовувались різні дозування фторхінолонів, ізоніазиду та клофазиміну та відрізнялись між собою за тривалістю лікування. Статистично значущої різниці між високими дозами ПТП, які застосовувались протягом 9 міс, і звичайними дозами ПТП, які застосовувалися протягом 12 міс для лікування МРТБ, не виявлено. Відношення ризиків складає 0,77 (95 % ДІ 0,48—1,25). Помилка вибірки, розрахована за коефіцієнтом I^2 = 0 % (від 0 до 40 % не має значення).

Висновки. Протитуберкульозні препарати можуть використовуватись у середніх терапевтичних дозах протягом 9 міс основного курсу лікування МРТБ, оскільки застосування більш високих доз фторхінолонів, ізоніазиду і клофазиміну не вплинули на ефективність лікування, як і більша тривалість основного курсу, — 12 міс відповідно.

Ключові слова: мультирезистентний туберкульоз, скорочений режим хіміотерапії, оптимальні дози ПТП.

Н.А. Литвиненко, Г.А. Варицкая, А.П. Чоботарь, Н.В. Гранкина
ГУ «Национальный институт фтизиатрии и пульмонологии имени Ф.Г. Яновского НАМН Украины», Киев

Оптимальный сокращенный режим антимикобактериальной химиотерапии для мультирезистентного туберкулеза по продолжительности и дозировкой противотуберкулезных препаратов: систематический обзор

Цель работы — лучшее понимание оптимальных режимов антимикобактериальной химиотерапии туберкулеза со множественной лекарственной устойчивостью имеет важное значение для расширения общего доступа к эффективному лечению и для разработки новых методов лечения мультирезистентного туберкулеза (МРТБ). Мы провели этот систематический обзор, чтобы определить и обосновать оптимальную продолжительность и дозировку противотуберкулезных препаратов (ПТП) в сокращенном режиме антимикобактериальной химиотерапии для МРТБ.

Материалы и методы. Поиск проводили в трех электронных базах данных (MEDLINE, EMBASE и PubMed) для выявления проспективных исследований, которые включали результаты применения сокращенного режима антимикобактериальной химиотерапии для МРТБ. Мы нашли только 3 соответствующие исследования для данного обзора: 1-е — «Высокая эффективность

12-месячного курса химиотерапии для больных МРТБ в Камеруне» (режим «Камерун»); 2-е — «Высокий уровень успешного лечения стандартным коротким курсом больных туберкулезом со множественной лекарственной устойчивостью в Нигере: ни одного рецидива» (режим «Нигер»); 3-е — «Успешный "9-месячный Бангладешский режим" для больных туберкулеза со множественной лекарственной устойчивостью среди более чем 500 пациентов» (режим «Бангладеш»). Исследования имеют незначительную клиническую и методологическую гетерогенность, что позволяет сделать достоверные выводы результатов сравнения.

Результаты и обсуждение. Все три сокращенных режимы лечения имели одинаковый состав и количество ПТП в режиме, но применялись различные дозы фторхинолонов, изониазида и клофазимина и отличались между собой по продолжительности лечения. Статистически значимой разницы между высокими дозами ПТП, которые применялись в течение 9 мес, и обычными дозами ПТП, которые применялись в течение 12 мес для лечения МРТБ, не обнаружено. Отношение рисков составляет 0,77 (95 % ДИ 0,48—1,25). Ошибка выборки, рассчитанная по коэффициенту I^2 = 0 % (от 0 до 40 % не имеет значения).

Выводы. Противотуберкулезные препараты могут использоваться в средних терапевтических дозах в течение 9 мес основного курса лечения МРТБ, поскольку применение более высоких доз фторхинолонов, изониазида и клофазимина не повлияли на эффективность лечения, как и большая продолжительность основного курса, — 12 мес соответственно.

Ключевые слова: мультирезистентный туберкулез, сокращенный режим химиотерапии, оптимальные дозировки ПТП.

Контактна інформація:

Литвиненко Наталія Анатоліївна, к. мед. н., ст. наук. співр. відділу хіміорезистентних форм туберкульозу
03038, м. Київ, вул. М. Амосова, 10
Тел. (044) 275-41-33
E-mail: dr.n.lytvynenko@gmail.coma

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