Treating More with Less: Effectiveness and Event Outcomes of Antituberculosis Fixed-dose Combination Drug versus Separate-drug Formulation (Ethambutol, Isoniazid, Rifampicin and Pyrazinamide) for Pulmonary Tuberculosis Patients in Real-world Clinical Practice

Jacqueline Mui Lan Lai, Su Lan Yang1, Richard Avoi2
Department of Pharmacy, Hospital Queen Elizabeth II, 1Clinical Research Centre, Hospital Queen Elizabeth II, 2Department of Community and Family Medicine, University Malaysia Sabah, Sabah, Malaysia

Abstract

Introduction: Conventionally, a combination of four separate drugs (ethambutol, isoniazid, rifampicin, and pyrazinamide [EHRZ]) is the first-line pharmacotherapy for pulmonary tuberculosis (TB). In recent years, fixed-dose combination (FDC) formulation, where a single tablet contains the active ingredients of four aforementioned drugs, is gaining popularity due to its ease of administration. Objective: To compare the real-world effectiveness of EHRZ and FDC treatment groups on a cohort registry by investigating the sputum conversion rate and treatment outcomes of both groups. Methods: A total of 11,489 patients’ data were extracted from the Sabah TB registry between January 2012 and June 2016, including EHRZ (n = 4188) and FDC (n = 7301) patients. Then, 1:1 propensity score matching was adopted to reduce the baseline bias. Caliper matching was conducted with maximum tolerance score set at 0.001. Confounders included in the propensity score matching were gender, nationality, diabetes, HIV status, smoking status, and chest X-ray status. Successful matching provided 4188 matched pairs (n = 8376) for final analysis. Results: In this matched cohort of 4188 pairs, the 2-month sputum conversion rate of FDC group was significantly higher than the EHRZ group (96.3% vs. 94.3%; P < 0.001) whereas 6-month sputum conversion of both groups showed no significant difference. Treatment outcomes such as noncompliance rate, failure rate, and success rate have no significant difference (P > 0.05) in both the treatment groups. There was an incidental finding of reduced death rate among FDC group compared to the EHRZ group (0.2% vs. 0.5%; P = 0.034). Conclusion: The FDC formulation has better sputum conversion rate at 2 months compared to conventional EHRZ regime as separate-drug formulation. It was also observed that FDC has a slight protective effect against all-cause death among TB patients. This protective effect of FDC, however, still needs to be proven further.

Keywords: Akurit-4, fixed-dose combination, intensive phase, propensity score, pulmonary tuberculosis, tuberculosis

INTRODUCTION

According to the WHO Global Tuberculosis (TB) Report 2017, Malaysia has 29,000 TB case notifications/year, and the incidence of TB is 92 cases/100,000 population.[1] In 2015, treatment success rate among the new and relapse cases in Malaysia is 78%, a rate that is similar to that of South East Asia region but lower than the global rate.[1] Among Malaysia states, Sabah state has the highest prevalence of TB.[2,3] Pressurized by the high TB prevalence and the urge to improve patient’s adherence, in 2012, the Ministry of Health, Malaysia, has launched the 3rd TB clinical practice guideline to make a Grade A recommendation that prefers fixed-dose combination (FDC) anti-TB drug as the first-line regime for intensive phase treatment.

Address for correspondence: Miss. Su Lan Yang, Clinical Research Centre, Hospital Queen Elizabeth II, Kota Kinabalu, Sabah, Malaysia. E-mail: yslan89@hotmail.com

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Lai JM, Yang SL, Avoi R. Treating more with less: Effectiveness and event outcomes of antituberculosis fixed-dose combination drug versus separate-drug formulation (Ethambutol, Isoniazid, Rifampicin and Pyrazinamide) for pulmonary tuberculosis patients in real-world clinical practice. J Global Infect Dis 2019;11:2-6.
The FDC brands that are currently used in Malaysia are Forecox-Trac film-coated tablet and Akurit-4, both are proven to be bioequivalent to separate-drug regime EHRZ at the same dose level. Some brands in the market that are not bioequivalent to the standard EHRZ may lead to a noncompliance problem, which may be managed with a FDC. The FDC brands that are currently used in Malaysia are Forecox-Trac film-coated tablet and Akurit-4, both are proven to be bioequivalent to separate-drug regime EHRZ at the same dose level. Since the Malaysian Clinical Practice Guideline recommendation of FDC as the first-line pharmacotherapy for pulmonary TB patients, there has yet to be any real-world analysis to compare its overall treatment outcome against conventional separate-pill EHRZ. Although RCTs are the gold standard to determine a treatment efficacy against a control, it is well recognized that the results of such studies may not accurately reflect effectiveness of therapies delivered in a real-world practice. Instead, registries are often used to compare real effectiveness of an intervention under routine clinical circumstances. Therefore, in our study, we mimicked the RCT design by applying propensity score analysis to control the effects of confounding factors and obtained a less biased estimation of the treatment effect of the anti-TB drugs.

**Objective**

The objectives of the study are to compare the sputum conversion rate of both treatment groups at 2nd and 6th months and to compare the treatment outcomes of both treatment groups at the end of 6th month. This study will establish the evidence on real-world effectiveness of FDC versus EHRZ, and it will serve as a scientific validation for Malaysian policymakers to support the first-line use of FDC in routine clinical practice.

**Methods**

This was a propensity-match cohort study carried out using population data.

**Database**

Data were obtained from the Tuberculosis Information System (TBIS), a mandatory registry that was established for the use nationwide since January 2003. It is a computerized registry since 2012, used by the Centre of Disease Control Division of Ministry of Health Malaysia to register all TB case notifications in Malaysia. TBIS contains comprehensive information for each notified TB patient in Malaysia. TBIS includes variables such as patient demographic, diagnostic result, disease characteristic, TB history, treatment regime, and outcome. Definition of the variables can be obtained from the TBIS manual. This database is maintained and audited by the state health department’s TB and Leprosy Unit to ensure completeness and accuracy. We were authorized to utilize data from the Sabah TBIS registry to conduct this study as Sabah state has the highest load (up to 20%) of TB patients in Malaysia.

**Treatment allocation**

Patient allocation to either EHRZ or FDC was based on the physician decision in each clinic.

**Patient selection**

There were 20,534 tuberculosis cases recorded in Sabah TBIS registry between January 2012 and June 2016. The cases were filtered according to the inclusion/exclusion criteria [Figure 1]. Main inclusion criteria were the pulmonary tuberculosis prescribed with either FDC or EHRZ, age ≥15, positive initial sputum smear and main exclusion criteria were missing data for treatment outcome and co-variates needed for propensity score matching. Patient selection process resulted in a total of 11,489 eligible cases for this research.

**Propensity score matching**

In the TBIS registry, patients were not randomized to either FDC or EHRZ. To reduce the patient’s baseline and treatment selection bias, we propensity-matched the FDC and EHRZ groups to the ratio of 1:1. Caliper matching was conducted using XLISTAT software using maximum tolerance score of 0.001. The matching characteristics included were:

- Total TB cases between 2012-2016 (n = 20,534)
- Exclude by exclusion criteria, n = 6380:
  1. Duplicated cases, n = 17
  2. Extra-pulmonary TB, n = 2310
  3. Multidrug resistant TB, n = 63
  4. Final diagnosis not TB, n = 133
  5. Paediatric cases where age <15, n = 580
  6. Negative/unknown baseline sputum, n = 2575
  7. Not treated with FDC or 2EHRZ, n = 564
  8. Unverify-able data entry error, n = 138
- Exclude due to incomplete data entry, n = 2665:
  1. No baseline X-ray status, n = 527
  2. No baseline HIV status, n = 228
  3. Without 2- and/or 6-month sputum result, n = 1910
- Eligible cases for matching, n = 11,489:
  FDC group, n = 7301
  EHRZ group, n = 4188
- 1:1 Propensity score matching
- Final matched pairs, n = 8376:
  FDC group, n = 4188
  EHRZ group, n = 4188

**Figure 1:** Patient selection for final analysis
gender, nationality, diabetes, HIV status, smoking status, and chest X-ray status. This resulted in 4188 matched pairs for statistical analysis. The differences between the two matched samples were tested with a standardized difference [Table 1].

**Statistical analysis**

The effectiveness and event outcomes between the FDC and EHRZ groups were assessed by the Chi-square test in SPSS v 19.0. All dichotomous variables were presented in n (%) and P < 0.05 was deemed statistically significant.

**Results**

From the TBIS registry, there were 20,534 patients between January 2012 and June 2016. Propensity score matching yielded 4188 pairs (n = 8376) in EHRZ and FDC groups for final analysis. As shown in Table 1, propensity score matching minimalized baseline biases in both treatment groups as standardized differences in two groups were smaller than 0.2. In this study, about two-third of the patients are Malaysian, male, and smokers; a majority of the patients have minimal and moderately advance chest X-ray lesion; and <10% of them are diabetic or HIV positive.

As presented in Table 2, patient’s sputum conversion rate after the 2-month intensive phase treatment was significantly higher among FDC group when compared to the EHRZ group (96.3% vs. 94.3%; P < 0.001). The sputum conversion rate at the end of the continuation phase treatment (6 months) was 0.1% higher in the FDC group, but this difference is not statistically significant.

In terms of treatment outcomes, noncompliance and failure rate were the same in both treatment groups. Noncompliance to treatment was defined as discontinuation of treatment for ≥2 months consecutively from the TB clinic. As presented in Table 3, treatment success rate at the end of the continuation phase was higher in the FDC group, but the 0.3% difference was not deemed statistically significant. Incidentally, it was found that patients who were on the FDC formulation suffered significantly lesser all-cause death compared to patients treated with conventional separate-tablet EHRZ.

**Discussion**

Despite the fact that previous studies showed noninferiority when compared the efficacy of FDC formulation to conventional EHRZ, our study with data of 8376 patients showed that FDC yielded significantly higher sputum conversion rate than EHRZ regime after 2 months of intensive phase pharmacotherapy. However, at the end of the continuation phase, both groups achieved similarly high 6-month sputum conversion rate that was just slightly low of 100%. This observation of no significant difference was expected as the use of FDC was only during intensive

---

**Table 1: Comparison of baseline characteristics between ethambutol, isoniazid, rifampicin, and pyrazinamid and fixed-dose combination treated subjects in the original sample and in the propensity score matched samples**

| Variable                | 2EHRZ (n=7301), n (%) | FDC (n=4188), n (%) | Standardized difference | 2EHRZ (n=4188), n (%) | FDC (n=4188), n (%) | Standardized difference |
|-------------------------|-----------------------|---------------------|-------------------------|-----------------------|---------------------|-------------------------|
| Gender male             | 2554 (61.0)           | 4402 (60.3)         | 0.016                   | 2554 (61.0)           | 2526 (60.3)         | 0.016                   |
| Malaysian               | 2817 (67.3)           | 5286 (72.4)         | 0.130                   | 2817 (67.3)           | 2832 (67.6)         | 0.003                   |
| Diabetes                | 291 (6.9)             | 581 (8.0)           | 0.088                   | 291 (6.9)             | 246 (5.9)           | 0.092                   |
| Smoking                 | 1412 (33.7)           | 2489 (34.1)         | 0.007                   | 1412 (33.7)           | 1424 (34.0)         | 0.007                   |
| HIV positive            | 42 (1.0)              | 56 (0.8)            | 0.124                   | 42 (1.0)              | 38 (0.9)            | 0.059                   |
| X-ray status            |                       |                     |                         |                       |                     |                         |
| No lesion               | 41 (1.0)              | 115 (1.6)           | 0.263                   | 41 (1.0)              | 36 (0.9)            | 0.059                   |
| Minimal lesion          | 1852 (44.2)           | 3498 (47.9)         | 0.082                   | 1852 (44.2)           | 1860 (44.4)         | 0.005                   |
| Moderately advanced     | 1992 (47.6)           | 3340 (45.7)         | 0.042                   | 1992 (47.6)           | 1993 (47.6)         | 0.000                   |
| Far advanced            | 303 (7.2)             | 348 (7.2)           | 0.238                   | 303 (7.2)             | 299 (7.1)           | 0.008                   |

Data from the Sabah state TBIS database between January 2012 and June 2016 were extracted and analyzed. All dichotomous variables are reported in n (%). EHRZ: Separate tablets of ethambutol, isoniazid, rifampicin, and pyrazinamide, FDC: Fixed-dose combination of 4 tuberculosis medications, TBIS: Tuberculosis Information System.

**Table 2: Sputum conversion rate of ethambutol, isoniazid, rifampicin, and pyrazinamid and fixed-dose combination treatment groups (n=8376) at the 2nd and 6th months**

| Sputum conversion to negative | Treatment arm | ² statistic * (df) | P     |
|------------------------------|--------------|--------------------|-------|
|                              | EHRZ          | FDC                |       |
| 2 months                     | 3949 (94.3)   | 4033 (96.3)        | 18.79 (1) | <0.001 |
| 6 months                     | 4175 (99.7)   | 4173 (99.6)        | 0.14 (1)  | 0.705  |

Data from the Sabah state TBIS database between January 2012 and June 2016 were extracted and analyzed. *Chi-square test, FDC: Fixed-dose combination, EHRZ: Ethambutol, isoniazid, rifampicin, and pyrazinamide.
phase (initial 2 months), and all the patients were kept on standard separate-drug regime of isoniazid and rifampicin during continuation phase (subsequent 4 months).

We wished to draw the reader’s attention to the definition of noncompliance in this research. The Malaysian Clinical Practice Guideline has made it mandatory for all TB patients to be supervised under “direct observed treatment” surveillance to ensure medication adherence. Hence, “noncompliance to treatment” is defined as lost to follow-up and discontinued treatment for ≥2 months. The noncompliance rate in this cohort was observed to be relatively low, at 0.8% (combined both groups), when compared to a state TB statistics report of <3%. One explanation given was that this study cohort was a selected group of patients according to a set of inclusion and exclusion criteria [Figure 1] where patients who are not suitable for FDC and EHRZ due to toxicity, intolerance, and contraindication as well as incomplete data were excluded from the analysis.

An intriguing incidental finding in this study was a significant lower death rate in the FDC group when compared to the EHRZ group. It was speculated that FDC has a protective effect against TB mortality. However, further investigation is needed before making any conclusion. It is suggested that the complete TBIS national database be examined in future to further confirm the association between anti-TB regimes (FDC or EHRZ) and mortality rate. As for now, there were 27 mortality cases in this 5-year cohort. The causes of death reported were infection and lung disease related (n = 20), cardiac cause (n = 2), malignancy (n = 2), and unknown (n = 3).

The strength of this study is the utilization of real-world population data, instead of RCT, to assess the medication effectiveness in clinical practice. The use of propensity score matching is also a powerful analysis to remove baseline biases before making a comparison of the treatment effect. However, we suggest that if the standardized difference of baseline variables is not >0.2 (no difference between 2 groups), we probably will not require a propensity score matching because we can retain more patients for final analysis.

The main limitation of this study, like most registry-based studies, is data incompleteness. We have to exclude 2665 patients from the analysis due to incomplete data [Figure 1]. The study result will not be affected by the exclusion of these patients, but the result can represent the population if the data were more comprehensive and larger.

**Conclusion**

The real-world effectiveness of FDC has been scientifically validated in this study. FDC formulation has extra advantages over conventional EHRZ in terms of 2-month sputum conversion and mortality rate. Two types of regimes were able to yield similarly good long-term treatment outcomes. These findings provide strong evidence for policymakers’ decision to switch from separate-drug regime to FDC, and thus the recommendation in Malaysian Clinical Practice Guideline should be followed.

**Ethical approval**

This study was conducted in accordance to the ethical principles outlined in the Declaration of Helsinki and the Malaysian Good Clinical Practice Guideline. The National Medical Research Registration (NMRR) code for this study is NMRR-16-2010-31262.

**Acknowledgment**

The authors would like to extend their gratitude to Dr. Christina Rundi for allowing the use of TBIS registry and Mr. William Lau for his expertise in propensity score matching technique. We also thank the Director General of Ministry of Health, Malaysia for his permission to publish this article.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

**References**

1. World Health Organization. Global Tuberculosis Report 2017. Geneva, Switzerland: World Health Organization; 2017. p. 1-262.
2. Iyawoo K. Tuberculosis in Malaysia: Problems and prospect of treatment and control. Tuberculosis (Edinb) 2004;84:4-7.
3. Dony JF, Ahmad J, Khen Tiong Y. Epidemiology of tuberculosis and leprosy, Sabah, Malaysia. Tuberculosis (Edinb) 2004;85:8-18.
4. Clinical Practice Guidelines on Management of Tuberculosis. 3rd ed. Putrajaya: Malaysia Health Technology Assessment Section (MaHTAS),
Lai, et al.: Fixed-dose combination versus separate-drug formulation

2012. Available from: http://www.moh.gov.my. [Last accessed on 2018 Feb 01].

5. Blomberg B, Spinaci S, Fourie B, Laing R. The rationale for recommending fixed-dose combination tablets for treatment of tuberculosis. Bull World Health Organ 2001;79:61-8.

6. World Health Organization, editor. Programme World Health Organization. Treatment of Tuberculosis: Guidelines for National Programmes. 3rd ed. Geneva, Switzerland: World Health Organization; 2003.

7. Bartacek A, Schütt D, Panosch B, Borek M, Rimstar 4-FDC Study Group. Comparison of a four-drug fixed-dose combination regimen with a single tablet regimen in smear-positive pulmonary tuberculosis. Int J Tuberc Lung Dis 2009;13:760-6.

8. Lienhardt C, Cook SV, Burgos M, Yorke-Edwards V, Rigouts L, Anyo G, et al. Efficacy and safety of a 4-drug fixed-dose combination regimen compared with separate drugs for treatment of pulmonary tuberculosis: The study C randomized controlled trial. JAMA 2011;305:1415-23.

9. Bangalore S, Kamalakkannan G, Parkar S, Messerli FH. Fixed-dose combinations improve medication compliance: A meta-analysis. Am J Med 2007;120:713-9.

10. Agrawal S, Kaur KJ, Singh I, Bhalde SR, Panchagnula R, et al. Assessment of bioequivalence of rifampicin, isoniazid and pyrazinamide in a four drug fixed dose combination with separate formulations at the same dose levels. Int J Pharm 2002;233:169-77.

11. Revicki DA, Frank L. Pharmaco-economic evaluation in the real world. Effectiveness versus efficacy studies. Pharmacoeconomics 1999;15:423-34.

12. Nallamothu BK, Hayward RA, Bates ER. Beyond the randomized clinical trial: The role of effectiveness studies in evaluating cardiovascular therapies. Circulation 2008;118:1294-303.

13. Saturni S, Bellini F, Braidio F, Paggiaro P, Sanduzzi A, Scchilone N, et al. Randomized controlled trials and real life studies. Approaches and methodologies: A clinical point of view. Palm Pharmacol Ther 2014;27:129-38.

14. Cohen AT, Goto S, Schreiber K, Torp-Pedersen C. Why do we need observational studies of everyday patients in the real-life setting? Eur Heart J Suppl 2015;17 Suppl D: D2-8. Available from: https://www.academic.oup.com/eurheartjsupp/article-lookup/doi/10.1093/eurheartj/suv035. [Last accessed on 2018 Feb 02].

15. Rosenbaum PR, Rubin DB. Reducing bias in observational studies using subclassification on the propensity score. Am Stat Assoc 1984;79:516-24. Available from: http://www.tandfonline.com/doi/abs/10.1080/01621459.1984.10478078. [Last accessed on 2018 Feb 02].

16. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. Biometrika 1983;70:41-55. Available from: http://www-links.jstor.org/sici?sici=0006-3444%28198304%2970%3A1%3C41%3ATCROTP%3E2.0.CO%3B2-Q. [Last accessed on 2018 Feb 02].

17. Perkins SM, Tu W, Underhill MG, Zhou XH, Murray MD. The use of propensity scores in pharmacoepidemiologic research. Pharmacoepidemiol Drug Saf 2000;9:93-101.

18. Infectious Diseases Prevention and Control Act. Malaysia; 1988. Available from: https://www.scribd.com/document/75615992/Prevention-and-Control-of-Infectious-Disease-Act-1988. [Last accessed on 2018 Aug 15].

19. Manual for National Tuberculosis Information System. Kuala Lumpur: Tuberculosis and Leprosy Control Unit, Ministry of Health; 2015. Available from: http://www.jknns.moh.gov.my/index.php/mengenai-kami/2017-03-23-07-41-27/pengenalan?id=186. [Last accessed on 2018 Feb 06].