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Review

Nevirapine versus efavirenz for patients co-infected with HIV and tuberculosis: a systematic review and meta-analysis

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SUMMARY

Objectives: Antiretroviral therapy (ART) reduces the morbidity and mortality of patients infected with HIV. Standard ART includes either nevirapine or efavirenz, however the efficacy of these drugs is limited in patients receiving rifampin treatment for tuberculosis (TB). We compared the efficacy and safety of nevirapine- and efavirenz-based ART regimens in patients co-infected with both HIV and TB through a systematic review and meta-analysis.

Methods: A comprehensive search of the literature was carried out to identify clinical trials comparing the efficacy and safety of nevirapine- and efavirenz-based ART regimens in HIV-associated TB. Eligible clinical studies included at least one primary or secondary event; the primary event was virological response and secondary events were TB treatment outcomes, mortality, and safety profile.

Results: This meta-analysis compared five randomized clinical trials and four retrospective clinical trials. Both included patients co-infected with HIV and TB; 833 received nevirapine, while 1424 received efavirenz. The proportion of patients achieving a virological response by the end of the follow-up was higher in the efavirenz group: plasma viral load <400 copies/ml, risk ratio (RR) 1.10, 95% confidence interval (CI) 1.03–1.17 ($p = 0.004$); plasma viral load<50 copies/ml, RR 1.07, 95% CI 0.98–1.16 ($p = 0.146$). No significant differences were found in either mortality (RR 0.70, 95% CI 0.44–1.13, $p = 0.142$) or TB treatment outcomes (RR 1.01, 95% CI 0.96–1.06, $p = 0.766$). Due to adverse advents, nevirapine-based regimens significantly increased the risk of discontinuation of assigned ART (RR 0.43, 95% CI 0.23–0.81, $p = 0.009$).

Conclusions: Although efavirenz-based ART was associated with more satisfactory virological outcomes, nevirapine-based ART could be considered an acceptable alternative for patients for whom efavirenz cannot be administered.

1. Introduction

The advent of highly active antiretroviral therapy (ART) has greatly reduced both the mortality and morbidity caused by HIV.[1] Among HIV-infected individuals, tuberculosis (TB) has emerged as one of the most frequent opportunistic infections, and is a leading cause of death in resource-limited areas.[2] Although both ART and anti-TB therapy (ATT) have been shown to improve survival in co-infected patients, the use of certain ART regimens remains controversial due to concerns over adverse drug interactions.

Nevirapine and efavirenz, two classes of non-nucleoside reverse transcriptase inhibitor (NNRTI), are recommended as first-line ART regimens in resource-limited settings.[3] Rifampin, a key component of ATT, is a potent inducer of the cytochrome P450 enzyme system; activation of this system leads to enhanced clearance of NNRTIs.[4,5] Efavirenz is recommended by the World Health Organization (WHO) for patients infected with HIV and TB due to a lower risk of sub-therapeutic concentration than nevirapine or protease inhibitors (PIs).[6] The preferred antiretroviral regimen for co-administration with rifampin is two nucleoside reverse transcriptase inhibitors plus efavirenz, however, nevirapine is more widely used

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than efavirenz in resource-limited areas due to lower costs, fewer food restrictions, and more convenient dosing. Moreover, nevirapine is effective for preventing mother-to-child transmission of HIV.[7]

Although several randomized trials have been conducted to compare the efficacies of nevirapine- and efavirenz-based regimens, the use of these drugs remains controversial. Due to differences in methodology, including retrospective designs, non-randomized designs, small sample sizes, and differences in the criteria used for scaling adverse events, definitive conclusions remain elusive. To address these issues, we performed a systematic review and meta-analysis of the existing data to compare the efficacy and safety of nevirapine- to efavirenz-based ART when administered with rifampin-based ATT.

2. Methods

2.1. Literature search

We searched the medical literature published between January 1990 and February 2014 using PubMed, Embase, and the Cochrane Database. We conducted the search using the terms 'efavirenz', 'nevirapine', and 'rifampin or tuberculosis or TB'. In addition, we examined the bibliographies of reviews, original studies, and relevant conference articles, and directly contacted some investigators.

2.2. Inclusion and exclusion criteria

Criteria for inclusion were: (1) study design was a randomized controlled trial (RCT) or cohort study; (2) study subjects were HIV patients presenting with concomitant TB; (3) two study arms included standard doses of nevirapine- versus efavirenz-based ART; and (4) the ATT was rifampin-based.

The primary outcome was the virological response at the end of follow-up. Plasma viral load (pVL) is a globally accepted endpoint used to measure the efficacy of ART. Available data on the virological response in the studies included were recorded as a plasma HIV RNA level <50 and <400 copies/ml. It should be noted that suppression of pVL to 50 copies/ml is a better generalized predictor of durable virological success.[8,9] The secondary outcomes were mortality, TB treatment, and safety profile (risk of adverse events and discontinuation of the study because of adverse events). TB treatment outcomes were defined as per the WHO guidelines.[10] Studies including at least one primary or secondary event were eligible for the analysis. Studies published in a language other than English were not included, nor were articles published as comments, reviews, or editorials. Data from the same trial were skimmed for relevant information.

2.3. Quality assessment and data extraction

Two authors independently assessed the methodological quality of the selected studies. To assess the methodological quality of the included RCTs we used the Cochrane risk of bias assessment tool. For observational studies we used the Newcastle–Ottawa quality assessment scale. All relevant information was collected, including patient demographics, year of publication, study location, study design, characteristics of the study population (age, gender, baseline viral load, and CD4 cell count), ART and ATT regimens, and follow-up time. To ensure accuracy, two authors working independently extracted the target data.

2.4. Statistical analysis

Relative risks (RR) with 95% confidence intervals (CI) were used to estimate the strength of association between dichotomous variables. Patients lost to follow-up in retrospective studies were not included in our virological analysis. For RCTs, the RR for primary and secondary outcomes were calculated on an intention-to-treat basis. We assessed heterogeneity using the Chi-square-based Q-test, with I^2 as a measure of inconsistency; a random-effects model was used for comparisons exhibiting a Q-test p value of <0.10 or $I^2 > 50\%$.[11,12] A subgroup analysis of RCTs and non-randomized controlled trials (nonRCTs) was carried out to identify differences between the two study types and verify the accuracy of our results. Where sufficient studies were available, publication bias was assessed visually using funnel plots.[13] All of the above analyses were conducted using Stata 11.0 software (StataCorp LP, College Station, TX, USA).

3. Results

3.1. Search results

Following a search of three databases and the bibliographies of relevant publications, a total of 802 potentially eligible articles were identified. Fifty-six duplicate articles were excluded from the analysis, along with 718 articles deemed irrelevant after reading the title and abstract. The remaining 28 potentially relevant papers were examined thoroughly. Articles were excluded based on the inclusion criteria listed in the Methods section, resulting in a total of 11 publications referring to nine trials.[14–24] A flow diagram of the literature search and selection process is given in Figure 1.

3.2. Characteristics of the studies included

The characteristics of the nine studies considered in this analysis are presented in Table 1. Four studies[16,21,22,24] were conducted in Asia, four[17–19,23] in Africa, and one[20] in Spain. The total number of patients was 2257. The mean age of participants ranged from 32 to 38 years, and the proportion of male participants ranged from 24% to 85%. The duration of ART was 24 to 96 weeks. The sample size varied from 33 to 849 patients.

All trials involved patients co-infected with both HIV and TB. Mean baseline viral loads ranged from 5.3 to 5.7 copies/ml, and mean baseline CD4 cell counts ranged from 36 to 139 cells/μl. Most trials included patients with pulmonary TB, all of whom received rifampin-containing anti-TB regimens. The patients in one study[21] initiated nevirapine at the full dose (400 mg/day) without the 2-week lead in dose (200 mg) in order to limit the risk of sub-therapeutic nevirapine concentrations during the initiation of treatment. Thirty patients in one study,[20] treated with 800 mg efavirenz daily, were excluded from our analysis.

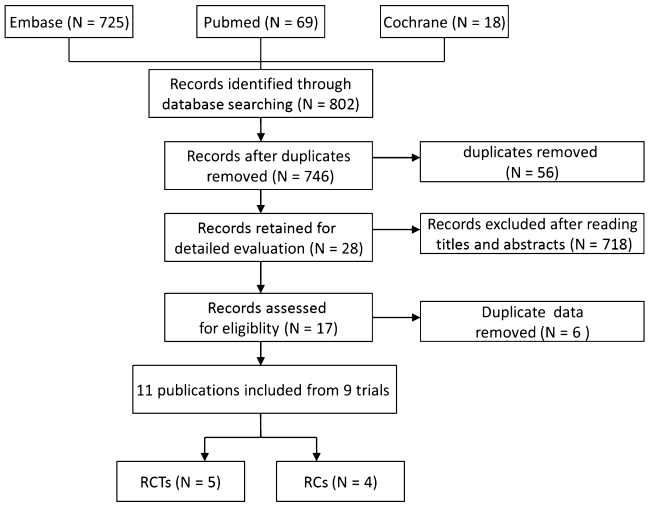

Figure 1. Flow chart of study selection.