From Scylla to Charybdis: Fixed drug combinations for tuberculosis and increased ethambutol-induced optic neuropathy in India

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Purpose: To describe the increase in prevalence of ethambutol-induced optic neuropathy (EON) in patients presenting to a single tertiary referral eye care center in India after introduction of weight-based fixed dose combinations and an increase in duration of ethambutol use from 2016 in the Revised National Tuberculosis Control Program. Methods: This was a retrospective, observational, referral hospital-based study of 156 patients with a diagnosis of EON presenting to a single tertiary referral eye care center between January 2016 and December 2019. The main outcome measure was to assess the increase in prevalence of EON cases presenting to our tertiary care institute. Results: During the 4-year study period, 156 new patients were diagnosed with EON. A total of 101 patients (64.7%) were males and 55 (35.3%) were females. The most common age group affected was 41–60 years. The significant complaint at presentation was decreased vision in all the patients. A rising trend in the number of patients diagnosed as EON was seen, with the prevalence increasing from 16 cases in 2016, 13 cases in 2017, and 31 cases in 2018 to 96 cases in 2019. Conclusion: The results of this study indicated an alarming increase in the trend of EON cases presenting to our tertiary care institute.

Key words: Antitubercular Therapy, ethambutol toxicity, fixed dose combination, Revised National Tuberculosis Control Program, RNTCP

The estimated prevalence of tuberculosis (TB) in India is around 2.7 million. India also happens to contribute around 27% of global burden of TB as per the Global TB Report 2018.[1,2] A major population affected by the burden of TB consists of those in the working age group of 15–69 years, and therefore, its treatment assumes ramifications for both public health as well as national economy. To tackle this problem, the National Tuberculosis Program (NTP) of India was initiated in 1962, which was revised in 1997 as Revised National Tuberculosis Control Program (RNTCP) that used the World Health Organization (WHO)-recommended Directly Observed Treatment, Short-course chemotherapy (DOTS) strategy. In July 2016, the RNTCP revised its technical and operational guidelines and initiated a daily regimen of treatment for new drug-sensitive TB cases, which included a weight-based fixed dose combination (FDC) of first-line anti-TB drugs. The implementation of daily regimen was meant to ensure optimum dosage and reduced pill burden with expectedly improved treatment outcomes.

The RNTCP guidelines were released on July 21, 2016, and initially covered five states, that is, Bihar, Maharashtra, Sikkim, Himachal Pradesh, and Kerala, in a phased manner. The rest of the country was covered over a period of time starting from July 2016 till 2017. The new DOTS strategy was finally implemented all across India by October 2017.[3] The new regimen now involves taking ethambutol daily for the entire 6 months duration of treatment, as opposed to three times a week for 2 months in the earlier regimen [Table 1]. Ethambutol, however, has associated adverse effects, which include visual impairment, liver problems, and allergies.[4] Ethambutol-induced optic neuropathy (EON) is an extensively known ocular complication which may lead to permanent vision loss, although its severity depends on its dosage.[5] Based on this, we hypothesize that higher dose administration with the FDC could increase the risk of EON.

Ancient Greek mythology mentions two mythical monsters Scylla and Charybdis, and avoiding Charybdis meant passing too close to Scylla and vice versa, and thus, having to navigate between the two hazards meant choosing between the two evils. The increase in duration of ethambutol usage for 6 months is like navigating between the Scylla of TB and the Charybdis of EON.

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This study aims to investigate the increased prevalence of EON, its demographic distribution, clinical findings, and association of ethambutol with optic neuropathy in a tertiary referral eye care center in India over a 4-year period.

Methods

Study design, period, location, and approval
This was a retrospective, observational, hospital-based study of 156 patients diagnosed with EON, who presented between January 2016 and December 2019 at a single tertiary eye care center. A standard consent form for electronic data privacy was filled by the patients or their parents or guardians at the time of registration. No identifiable information of the patient was used for analytical purposes. The study adhered to the Declaration of Helsinki and was approved by the Institutional Ethics Committee (LEC BHR-R-03-21-598).

Each patient underwent a comprehensive ophthalmic examination, and data were entered into a browser-based electronic medical records system (eyeSmart EMR).

Data retrieval
Data of patients diagnosed with toxic optic neuropathy were retrieved from the electronic medical record database at a single tertiary eye care center in Hyderabad. Of these, patients who had a documented history of the use of antitubercular treatment and a systemic diagnosis of TB were included in the study. Data on demographics, ocular diagnosis, clinical examination, and visual field reports of these patients were exported for analysis.

Variables’ description
The variables included were age, gender, location, socioeconomic status of the patient, chief complaint, complete diagnosis of each eye, systemic comorbidities, type of TB, regimen of ethambutol treatment, onset of optic neuropathy after using the course of ethambutol, onset of decrease in vision after using the course of ethambutol, best corrected visual acuity (BCVA), and Humphrey visual field test findings.

Table 1: Daily dose schedule of FDCs according to the RNTCP (number of tablets)\(^3\)

| Weight bands (kg) | Number of tablets |
|-------------------|-------------------|
|                   | Intensive phase (2 months) | Continuation phase (4 months) |
|                   | HRZE (four FDCs) | HRE (three FDCs) |
|                   | H-75/R-150/ Z-400/E-275 (in mg) | H-75/ R-150/E-275 (in mg) |
| 24-39             | 2                 | 2 |
| 40-54             | 3                 | 3 |
| 55-69             | 4                 | 4 |
| 70 or more        | 5                 | 5 |

E=ethambutol, FDC=fixed dose combination, H=isoniazid, R=rifampicin, RNTCP=Revised National Tuberculosis Program, Z=pyrazinamide

The mean duration between initiation of treatment and onset of visual symptoms was 3.62 ± 2.52 months. The onset of toxic optic neuropathy was most commonly between 3 and 6 months of its usage [Table 3].

Statistical analysis
Demographic data was represented as mean (±standard deviation) or median (range). All tables for age, gender, diagnosis, and clinical information were drawn by using Microsoft Excel 2013 (Microsoft Corporation, Redmond, WA, USA).

Results
Hospital-based prevalence of EON was assessed. Of the 322,143 new patients presenting to a single tertiary eye care center in Hyderabad between January 2016 and December 2019, 156 patients (0.048%) were diagnosed with EON. The number of patients diagnosed as EON in our institute increased from 16 in 2016 (167/million new patients), 13 in 2017 (118/million new patients), 31 in 2018 (264/million new patients) to 96 in 2019 (774/million new patients).

Age and gender
The mean age of the patients was 50.1 ± 13.5 years, with the age range being 16–80 years. The decade-wise distribution of age in patients with EON is presented in Fig. 1. It indicates that majority of the patients’ age ranged between 41 and 50 years (27.5%) and 51 and 60 years (28.8%) years. Overall, there were 101 (64.7%) males and 55 (35.3%) females.

Eye affected
One hundred and fifty-five patients had bilateral involvement of their eyes and one had unilateral involvement. Eighty-two (52.6%) patients had pulmonary TB, 62 (39.7%) had extrapulmonary TB, and in 12, it was unknown.

Treatment of TB and its outcomes
Majority of the patients whose cause of TB was extrapulmonary used ethambutol drug for greater than 6 months. Most of the patients with pulmonary TB used ethambutol for ≤6 months [Table 2]. The mean duration between initiation of treatment and onset of visual symptoms was 3.62 ± 2.52 months. The onset of toxic optic neuropathy was most commonly between 3 and 6 months of its usage [Table 3].

Presenting visual acuity and onset of decreased vision
The most prevalent complaint of the patients while presenting for eye examination was a gradual decrease in vision in one
or both the eyes (seen in all patients). The onset of decreased vision was 6 months or less in 120 patients and more than 6 months in the other 24 patients [Table 3]. A total of 227 eyes (113 patients) had documented visual acuity at baseline. The mean presenting BCVA was $1.17 \pm 0.59$ logMAR (Snellen equivalent of 20/320). A total of 47 eyes had a documented follow-up (baseline BCVA $0.85 \pm 0.36$, out of which 33 eyes had an improvement or stable visual acuity, with the final BCVA after a mean follow-up of $5.6 \pm 4.1$ months being $0.59 \pm 0.43$ logMAR. The improvement in vision was statistically significant ($P = 0.003$). None of the baseline parameters significantly predicted the final visual outcome on regression analysis.

**Humphrey visual field testing and color vision**

Of total 156 patients, Humphrey visual field (HVF) testing was performed in 112 patients. A majority of these patients (34.8%) demonstrated an advanced generalized visual field depression. This was followed by a bitemporal (22.3%), central (20.5%), or centrocecal (12.5%) field defect [Table 4]. Similarly, a color vision defect was documented in 110 patients and the most common type of color vision abnormality was a total color blindness (73.6%). A partial color vision defect was seen in 22 patients.

**Discussion**

Our study summarizes the clinical and demographic profile of eyes affected with ethambutol toxicity based on electronic medical record–based data retrieval. We found a rising trend in the number of patients with ethambutol toxicity and a poor visual acuity gain even with stoppage of ethambutol and initiation of vitamin supplementation in eyes with documented follow-up.

Earlier studies have reported the prevalence of EON to be around 1%–2%. In a large epidemiologic study on EON, Chen et al., in 2015, reported on the prevalence of EON in 4803 patients diagnosed with TB over a 10-year period in southern Taiwan. They found the prevalence of EON to be 1.29%, with the average ethambutol dose used being 16 mg/kg/day in these patients. Lim et al. reported that mild visual impairment caused due to EON in the initial period may lead to bilateral hemianopia in later life. Ezer et al. reported in a meta-analysis that during the years 1965–2011, 22.5/1000 and 2.3/1000 TB patients were affected by any kind of visual impairment and blindness, respectively. In other recent studies, the prevalence of EON was reported to be 1.29% and 1.5% in Taiwan and Korean populations, respectively. In our tertiary care eye hospital in South India, we have seen an alarming increase in the trend of EON, with the number of patients diagnosed as EON increasing from 16 in 2016 (167/million new patients), 13 in 2017 (118/million new patients), 31 in 2018 (264/million new patients) to 90 in 2019 (774/million new patients).

The WHO treatment guidelines for Mycobacterium tuberculosis therapy initiation include an ethambutol starting dose of 15–20 mg/kg/day. If ethambutol is continued for longer, the dose should be reduced to 15 mg/kg. Therefore, with the current recommended dosages of ethambutol in the FDC, it is evident that the Indian population is being subjected to higher doses and for a longer duration of time. Patients in the weight band of 24–39 kg are taking two tablets [Table 5] or 550 mg of ethambutol every day for 6 months. Similarly, patients in the weight band of 40–54 kg are receiving a cumulative dose of 825 mg/day. So, any patient in that weight band is receiving between 20.7 (for a weight of 40 kg) and 15.3 mg (for a patient weighing 54 kg) per kg of body weight per day. The same holds true for the other two categories of weight bands where patients of weight between 55 and 69 kg are taking 1100 mg and anyone above 70 mg is consuming 1375 mg of ethambutol every day for 6 months (19.64 mg/kg body weight).

Severe visual impairment due to ethambutol has been reported after just 3 days of treatment, while the longest reported interval is over 12 months. The mean interval is in the range of 4–5 months. A similar interval of 3.62 ± 2.52 months was found in our study, with almost 52.2% of patients presenting within 3–6 months of starting anti-tubercular treatment (ATT). However, the onset may be sooner in patients with a concurrent renal disease due to impaired excretion leading to higher serum

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**Table 2: Regimen of ethambutol usage in TB patients**

| Types of TB      | Regimen of ethambutol usage | Regimen data not available | Grand total |
|------------------|-----------------------------|----------------------------|-------------|
|                  | ≤6 months | >6 months |                           |             |
| Extrapulmonary   | 33        | 27        | 2                         | 62          |
| Pulmonary        | 52        | 25        | 5                         | 82          |
| Grand total      | 85        | 52        | 7                         | 144*        |

TB=tuberculosis. *Twelve patients did not have information about type of TB.

**Table 3: Onset of optic neuropathy after using ethambutol drug in all patients**

| Types of TB      | ≤3 months | >3-6 months | >6-9 months | >9-12 months | Interval data not available | Grand total |
|------------------|-----------|-------------|-------------|--------------|-----------------------------|-------------|
| Extrapulmonary   | 32        | 21          | 5           | 1            | 3                           | 62          |
| Pulmonary        | 40        | 27          | 9           | 2            | 4                           | 82          |
| Grand total      | 72        | 48          | 14          | 3            | 7                           | 144*        |

TB=tuberculosis. *Twelve patients did not have information about type of TB.

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levels of the drug. Also, this reaction is proportional to the dose of ethambutol and is observed in 18% of patients receiving 35 mg/kg/day, in 5%-6% of patients receiving 25 mg/kg/day, and in <1% of patients receiving daily doses of 15 mg/kg. Toxicty usually presents with simultaneous bilateral involvement. However, if it presents unilaterally, the second eye eventually gets involved. A similar trend was seen in our group patients, with almost 99% of patients presenting with bilateral involvement. Patients with toxicity usually present with gradual onset decrease in vision and might often present with a central scotoma (most common), bitemporal defects, or peripheral field defects. Almost 95.2% of patients in our study presented with gradual onset of vision loss in our study. However, a majority of patients in our cohort presented with advanced visual field defect. This could indicate a delayed presentation to the clinic following development of toxicity. Although stoppage of ethambutol is recommended on identification of toxicity, only around 40% of patients recover with visual acuity better than 20/200. This was evident by the fact that a significant number of patients in our cohort also had a visual improvement.

The study has its own share of limitations of being a retrospective observational analysis. Second, we did not analyze other baseline systemic parameters like serum creatinine levels that could have had a role in disease prevalence. Third, the study only represents patients visiting a tertiary eye center and might not represent the true burden of the disease. Nonetheless, a rise in cases has been seen in our institute in recent years and it does raise concern regarding the FDC.

Around 1.9 million patients were initiated on first-line standard treatment in 2018 in India, and even a prevalence of 2%-4% means that annually, there will be 38,000 cases of EON. If patients are taking a higher dose for 6 months, then we believe that we are veering from the Scylla of TB and the Charybdis of EON. Larger population-based studies in India are, therefore, a need of the hour to identify the magnitude of this problem.

### Table 4: Pattern of visual field defects

| Type of visual field loss         | Number of patients |
|----------------------------------|--------------------|
| Advanced                         | 39                 |
| Bitemporal                       | 25                 |
| Central                          | 23                 |
| Centrococcal scotoma             | 14                 |
| Inferior altitudinal defect      | 1                  |
| Inferior arcuate                 | 1                  |
| Nonspecific scotoma              | 6                  |
| Superior quadrantanopia          | 1                  |
| No defect                        | 2                  |

### Table 5: Daily dose schedule of FDCs for adults as per the weight bands

| Weight bands (kg) | Cumulative dose in mg | Range of dose in mg/kg body weight |
|-------------------|-----------------------|-----------------------------------|
| 24-39             | 550                   | 22.9-14.10 mg/kg                   |
| 40-54             | 825                   | 20.63-15.3 mg/kg                   |
| 55-69             | 1100                  | 20-15.94 mg/kg                     |
| 70 or more        | 1375                  | 19.64 mg/kg                        |

FDC=fixed dose combination

### Conclusion

In conclusion, the study results demonstrate the increase in prevalence of EON cases in a hospital-based cohort in India and its rising trend after the change in regimen in the RNTCP of the Government of India and after its complete implementation in 2017 and highlight the need to reconsider the strategy of using the FDCs and revise the duration of ethambutol usage. An altered renal function and a past history of ethanol and tobacco consumption may also predispose to ocular toxicity. We, therefore, recommend including a pretreatment renal evaluation for all patients. Apart from that, any history of preexisting eye diseases and a pretreatment visual acuity should be made a part of patient records. There is also a need to incorporate patient education regarding EON.

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### Conflicts of interest

There are no conflicts of interest.

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