INDIAN HEALTH SERVICE
National Pharmacy and Therapeutics Committee
Formulary Brief: ***Short Course Tuberculosis Treatment***
-April/May 2024-

Background:

The Indian Health Service (IHS) National Pharmacy and Therapeutics Committee (NPTC) provided a drug review of short-course tuberculosis (TB) treatment regimens. Medications currently listed on the IHS National Core Formulary (NCF) for the treatment of latent and active pulmonary tuberculosis include ethambutol, isoniazid, pyrazinamide, rifampin and rifapentine. Historically, regimens to treat TB were prolonged in order to eradicate the fastidious *Mycobacterium tuberculosis* bacteria. New drug development has led to changing recommendations regarding the duration and composition of TB treatment regimens. In 2021, the NPTC reviewed the treatment for latent TB infection (LTBI) at which time no changes were made to the NCF. This review examines data and guidelines with regards to active pulmonary TB treatments, specifically short-course treatments for drug sensitive (DS) and drug resistant (DR)-TB. Following clinical review and analysis, **no changes were made to the IHS NCF**.

Discussion:

In 1884, Dr. Robert Koch announced his discovery of the bacteria, *Mycobacterium tuberculosis*, responsible for the disease known then as consumption. At that time, TB was responsible for the death of 1 in every 7 people in the United States (U.S.) and Europe[1]. In the early 20th century, race was considered a risk factor for TB. In 1941, James Townsend, Director of Health at the U.S. Bureau of Indian Affairs, began to dispel this idea recognizing poverty, malnutrition and inadequate housing as risk factors.[2] In 2000, the Institute of Medicine called for "Ending Neglect" and fighting TB became the focus of many public health programs.[5] In 2019, the NPTC collaborated with federal partners to establish the first ever Strategic Initiative for Latent Tuberculosis, providing internal guidelines and agency recommendations for treatment of LTBI for the IHS. Review of this topic has been ongoing, both within and outside our agency. In 2020, the U.S. Centers for Disease Control and Prevention (CDC) updated the LTBI guidelines recommending "short-course (3- to 4-month) rifamycin-based treatment regimens are preferred over longer-course (6–9 month) isoniazid monotherapy for treatment of LTBI".[6] In 2022, the CDC recommended a 4-month short course regimen which included moxifloxacin for treatment of DS-TB[7] and the World Health Organization (WHO) released new guidelines for DR-TB[8].

Treatment of Drug-Susceptible Pulmonary TB: Prior to 1998, TB courses for DS-TB were typically 9 months of rifampin, isoniazid, pyrazinamide and ethambutol (RIPE) requiring multiple daily doses. These burdensome regimens led to poor adherence and adverse events (AEs) due to long durations of drug exposure. In 1998, rifapentine (a rifamycin drug with longer half-life and once-daily dosing) was approved and thereafter, duration of treatment decreased to 6 months and intermittent weekly dosing was shown to be effective. In the early 2010's, evidence emerged showing that increased exposure to drugs in the rifamycin class started to shift course duration further. Evidence also supported that fluoroquinolones, specifically moxifloxacin, accelerated sputum conversion when administered with rifampin but was not sufficient to shorten the course to 4-months. In 2021, Dorman et al. performed a phase 3, randomized clinical trial to determine if rifapentine- containing regimens with or without moxifloxacin could provide durable cure for DS-TB in 4 months compared to 6 months.[9] The trial was carried out in 13 countries with 2,516 participants over the age of 12 and a rate of 8% HIV-positivity in all arms. They demonstrated that rifapentine without moxifloxacin was inferior (14.2% vs. 9.6%; [95% CI, 1.2 to 7.7]). Rifapentine with moxifloxacin was non-inferior (11.6 vs. 9.6%; [95% CI -1.1 to 5.1]) and TB unfavorable outcomes (treatment failure or recurrence) occurred in 5.7% RIF-MOX vs. 3.1% of RIPE. Patients with HIV had similar outcomes, however patients with smear-positive or cavitary disease, as well as those with tobacco use or diabetes did not meet non-inferiority criteria for the short course regimens. Authors concluded that efficacy of the 4-month regimen containing rifapentine and moxifloxacin was non-inferior to that of the standard 6-month regimen and that grade 3 or higher AEs were similar in the rifapentine–moxifloxacin group and the control group. Feasibility of these regimens does rely on the availability of drug-susceptibility testing for fluoroquinolones and isoniazid and rapid molecular susceptibility testing for rifampin. Based on this primary study, the CDC changed its primary treatment recommendation to the 4-month daily regimen in patients with the exception of those with extra-pulmonary TB, breastfeeding and pregnant patients, patients with prolonged QT syndrome or concurrent use of a QT-prolonging agent, patients on medications that have clinically significant interactions with drugs in the regimens, and those who have known drug resistance to the drugs in the regimen[7]. The WHO also recommended the 4-month daily regimen in 2022.

The NPTC reviewed fluoroquinolone AEs in the past ("Urinary Tract Infections") and did not add any to the NCF in part due to the concerning level of AEs within this class. A meta-analysis of efficacy and safety of moxifloxacin in the treatment of multi-drug resistant (MDR) TB from 2020 supported that the addition of moxifloxacin to TB regimens increases the rate of treatment success without an increase in AEs[10]. Despite the rapid adoption of the Dorman data into the CDC and WHO guidelines, real world experience has not been as encouraging. Louie at al. published their experience from the San

Francisco Department of Public Health TB Prevention and Control that roughly 50% of participants prematurely discontinued the 4-month daily regimen due to AEs[11]. Based on challenges with real-life feasibility, expert recommendations from Dr. Jon Iralu, the IHS Chief Clinical Consultant for Infectious Disease, and concern for use of moxifloxacin for other indications which may increase risk of AEs, moxifloxacin (the only component of the 4-month daily regimen for DS-TB treatment not already on the NCF) was not added to the NCF.

Treatment of Drug-Resistant Pulmonary TB: Similar to DS-TB treatment, regimens for DR-TB and MDR-TB are evolving quickly. Similar advances with drug development and resistance testing have pushed courses to be simpler and shorter. Notably, regimens containing bedaquiline, pretomanid, linezolid, clofazimine and moxifloxacin have been added to current WHO guidelines. Nyang'wa et al. published an open label, randomized, controlled noninferiority trial entitled the TB-PRACTECAL trial. This study compared a 36-80 week standard care regimen (individually based on resistance patterns according to WHO 2019 recommendations for standard of care) vs. 24 weeks of oral bedaquiline, pretomanid, and linezolid (BPaL) vs. 24 weeks BPaL + clofazimine vs. 24 weeks of BPaL + moxifloxacin (BPaLM). Outcomes were based on the percentage of participants with composite unfavorable outcome of treatment failure, death, treatment discontinuation, disease recurrence, or loss to follow up. Of note, clofazamine is not available in the U.S. Results of this study demonstrated 11% of patients in the BPaLM group and 48% of those in the standard-care group had a primary-outcome event (risk difference, −37%, 96.6% CI: −53 to −22) and in the as-treated population, the incidence of AEs of grade 3 or higher or serious AEs was lower in the BPaLM group than in the standard-care group (19% vs. 59%). Non-inferiority was also met by the BPaLC group, however this has less efficacy when compared to the BPaLM group.[12] In light of this data, the WHO changed its recommendations for treatment of MDR-TB in 2022 after their own meta-analysis which showed that the BPaL regimen had higher efficacy than standard of care (RR 1.32, 95% CI: 1.19-1.39), a 600mg dose of linezolid for 26 weeks was found to have similar efficacy to a 1200mg dose but with fewer severe AEs, and success rates were higher in BPaLM (89%) versus BPaL (77%) with an absolute RR of 1.15 [95% CI: 0.95-1.38].[13]

Findings:

Tuberculosis is a disease that has long affected Native populations out of proportion to white populations in the U.S. In recent years, drug development has led to new treatment regimens for TB. Currently, the NCF includes ethambutol, isoniazid, pyrazinamide, rifampin and rifapentine - four drugs used to treat LTBI. This review evaluated new TB drugs including moxifloxacin, bedaquiline, pretomanid, linezolid, and clofazimine. Data demonstrates the safety and efficacy of these drugs for the treatment of DS- and DR-TB. At this time, no NCF additions were made due to the small size of the affected population and the need for specialty care in this disease state.

References:

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