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Clinical Paper

First use of Bedaquiline, Linezolid, and Pretomanid (BPaL) in a family cluster of multi-drug resistant (MDR) TB infection.

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Introduction

Rates of tuberculosis, also known as "consumption" or "the white death", were falling with the introduction of patient isolation, vaccination, and improved general public health in urban areas. However, it was only with the introduction of effective antituberculous therapy since 1946 that individual patients could expect cure. Unfortunately, drug-resistant TB has become a major public health problem, with an estimated 450 000 new cases per annum (2021).[1] Scientific advances in understanding the pathophysiology of TB and potential drug targets have resulted in novel treatment strategies.[2, 3]

Over the past decade, there have been major advances in the treatment of drug- resistant tuberculosis. Previous treatment regimens include a minimum of 18 months of medication, with drugs that have extensive side effect profiles. Prior to 2018, injectable medication was a cornerstone of treatment. Recent studies have shown that shorter all oral regimens are non-inferior to longer regimens and have fewer major adverse effects.[4] The updated World Health Organisation consolidated TB treatment guidelines now recommend shorter all oral regimens as first line where indicated.[5]

Here we present our experience of accessing and using Pretomanid in combination with Bedaquiline and Linezolid to successfully treat two patients with drug resistant tuberculosis.[6] To our knowledge, this is the first use of Pretomanid as part of a recognised regimen in the United Kingdom. Pretomanid has been licenced through the Orphan drug register since 2007, for the treatment of pulmonary extensively drug resistant, or treatment-intolerant or nonresponsive multidrug-resistant tuberculosis.[7] Pretomanid is a nitroimidazooxazine with activity against replicating and dormant mycobacteria through inhibition of mycolic acid biosynthesis and nitric oxide release, respectively.[8]

Recent randomised controlled trials (TB-PRACTECAL[9], Nix-TB[10], and ZeNix[11]) have shown high rates of treatment success with low rates of adverse events using Pretomanid in combination with Bedaquiline and Linezolid, with or without a fluoroquinolone compared to previous standard of care regimens.

TB PRACTECAL showed a treatment success rate of 89% in those receiving Bedaquiline, Pretomanid, Linezolid and Moxifloxacin, and 77% in those receiving Bedaquiline, Pretomanid and Linezolid, compared to 52% treatment success in the standard of care group.[9]

The NIX-TB Trial showed a treatment success rate of 90% with Bedaquiline, Pretomanid and Linezolid and the ZENIX trial had treatment success rates between 84-93% with different dosages of the same drugs.[10, 11]

The TB PRACTECAL trial has also demonstrated significantly lower incidence of adverse events related treatment with BPaL compared to the standard of care (19% vs 59%).[9] Lower levels of toxicity from treatment means monitoring requirements are less intense. Reduced adverse events, reduced monitoring and a shorter duration of treatment have a significant impact on the cost of delivering treatment. The cost of medications for Bedaquiline, Pretomanid and Linezolid for the 6 month treatment course was £39,505, compared to the standard of care which costs £46,089.

In light of this new evidence, and when constructing a regimen to manage our cases of pulmonary drug-resistant TB we were keen to treat our patients in line with WHO recommendations. We have experience using Bedaquiline, and Linezolid, but to our knowledge, Pretomanid has not been prescribed to any patients in the United Kingdom.

The WHO has not yet defined a minimum inhibitory concentration (MIC) for pretomanid. The sensitivity testing for our isolates was carried out at the Irish Mycobacterial Reference Laboratory using two provisional concentrations released in the 2023 EUCAST guidelines.[12] The WHO are making efforts to establish MIC values using epidemiological cut off values, clinical outcome data and PK-PD data.[13]

Cases

We had two cases who we thought would benefit from BPal regimens, both had close contact with a patient who had been diagnosed with extensive pulmonary tuberculosis with the following resistance profile: Resistant to Rifampicin, Isoniazid, Pyrazinamide, Streptomycin, and Levofloxacin. Susceptible to Bedaquiline, Delamanid, Clofazamine,

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Linezolid, Ethambutol, Prothionamide, and aminoglycosides. Of note, the index patient had received repeated courses of levofloxacin monotherapy for "lower respiratory tract infections" prior to TB diagnosis.

Patient A is a 90 year old female with medical history of ischaemic heart disease and cognitive impairment. She had an Interferon-Gamma Release Assay carried out due to the aforementioned contact, which was reactive. Chest x-ray suggested right basal consolidation, and she went on to have a CT of her chest, which showed: "Right hilar and right lower lobe intra-lobar lymphadenopathy. Impacted and dilated airways within the right lower lobe with some associated peripheral consolidation." She was non-productive and unable to provide a sputum sample. She progressed to have a bronchoscopy, which was smear negative, but PCR and culture positive with resistance detected to rifampicin, isoniazid, pyrazinamide, streptomycin and fluroquinolones. Whole Genome Sequencing had one Single Nucleotide Polymorphism difference from the index case, and on culture had the same susceptibility profile, apart from susceptibility to levofloxacin.

After discussion with the British Thoracic Society, drug resistant TB management service (BTS MDRTB), we elected to commence her on Bedaquiline, Pretomanid and Linezolid. It was ultimately decided we would not add levofloxacin to her regime.

She initially suffered from nausea as an inpatient which was managed with anti-emetics and improved with time. She did not miss any doses. Follow up CT chest at two months showed improvement. She did not have a repeat bronchoscopy due to increasing frailty but sputum samples were smear, PCR and culture negative. She was discharged home, with isolation and respiratory precautions, completing 6 months of treatment with no further adverse events. Blood monitoring, ECGs, peripheral neuropathy and Ishihara screens were normal throughout.

Patient B is a 59 year old female with no past medical history of note. She also had a reactive IGRA and therefore went onto have a CT of her chest which showed non-specific enlarged right hilar lymph nodes measuring up to 14 mm and a right lower lobe 5 mm pulmonary nodule. PET Scan showed a mildly avid right hilar lymph node, and biopsy of this via endobronchial ultrasound was smear negative, but PCR positive for TB with genotypic Rifampicin resistance detected. Given her close contact with the index case and Patient A, antibiotic resistances were inferred.

She was also commenced on Bedaquiline, Pretomanid and Linezolid, again after discussion with the BTS MDRTB. There was no growth after 12 weeks of mycobacterial culture.

She initially suffered from gastritis which settled with addition of omeprazole. She completed 6 months of treatment with no further adverse events. Blood monitoring, ECGs, peripheral neuropathy and Ishihara screens were normal throughout.

Discussion

BPaL has displayed superior outcome rates, fewer adverse events, reduced cost and has a shorter duration. Despite being licenced in the UK, Northern Ireland is the only nation of the UK that has been able to access Pretomanid due to commissioning policy in England, Scotland and Wales. We were able to access Pretomanid through a cost per case application to the Trust, presenting evidence of effectiveness, improved side effect profile and reduced cost compared to the standard of care regime. These cases provide further evidence that Pretomanid based regimens should be sought as a more effective and well-tolerated treatment where possible.

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