

Clinical Care Scenario 1

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- Your program has decided to implement an operational research protocol for a 9-12 month regimen consisting of bedaquiline, linezolid, levofloxacin, clofazimine and pyrazinamide for the treatment of RR-TB. Persons are able to be started on this regimen if they are age 6 years or above, if they provide consent, and after undergoing baseline ECG testing and laboratory evaluations. You chose this regimen because it contains all Group A drugs, 1 of the Group B drugs that is a component of successful treatment shortening regimens (clofazimine) and PZA based on theoretical synergy with bedaquiline and levofloxacin. All of the drugs will be given the entire 9 to 12 months unless toxicity develops.

- You are contacted by one of the clinics participating in the OR protocol about a 16 year-old female patient who meets all other study criteria but who was found to have a hemoglobin of 8.1 g/dL (normal is 12.1 to 15.1 g/dL). They want to know if she is able to be started on the regimen as they are concerned about her low hemoglobin.

- What would you advise them? What additional information would you want to collect? If she is unable to be started on the all-oral shorter regimen, what would you recommend for her alternative treatment regimen?
- How would your advice change if the young woman were on the treatment regimen and developed a hemoglobin of 8.1 g/dL on Month 4 of treatment?

- It will be important to obtain additional information before making a decision about whether or not this young woman can be started on a regimen containing linezolid. Anemia can be a very common finding in persons with tuberculosis, and there are also other potential reasons for her hemoglobin to be low. She is a young female and should be asked about her menstrual periods and she should be tested for pregnancy. She should also be assessed for other possible co-morbidities that can be associated with anemia, including HIV, malaria, malnutrition, and iron deficiency. She should be asked about any recent trauma or signs of bleeding. Alcohol use can also lead to anemia and she should be asked about her use of alcohol in a supportive and non-judgmental fashion. Any medications she is currently taking that could be associated with anemia should also be assessed (i.e. AZT). A blood smear could be examined to try and assess red cell morphology, which could narrow down the differential diagnosis, but people with RR-TB may have a low hemoglobin for multiple reasons.

- Any identified factors that could lead to anemia should be addressed. However, it is important to remember that TB itself can cause anemia and the most effective way to address this anemia is through treatment of her RR-TB with an effective regimen. Linezolid is one of the most effective medications in the treatment of RR-TB and its use has been associated with improvements in treatment outcomes and sputum conversion in randomized controlled trials (although some of these were not placebo controlled but rather utilized a delayed start approach). It was also associated with improved outcomes and decreased mortality in a large individual patient data meta-analysis of almost 13,000 patients. Therefore, it should be given unless there is a compelling reason not to. Baseline low hemoglobin levels may actually correct with administration of linezolid.

- Some clinicians would suggest that a hemoglobin of 8.1 g/dL is an indication for hospitalization while work up is being done. Possible blood transfusion could be considered. Erythropoietin (a hormone that stimulates the production of red blood cells) might be considered, although this medication takes some time to work and also requires adequate stores of iron to be effective.
- It is important to mention that RR-TB treatment should be started as soon as possible. Fortunately, most of the work-up of baseline anemia relies on history and a basic blood test (i.e. a blood smear) and can be done the day the baseline results are received. Care should be taken to avoid delays in starting linezolid while assessing the anemia.