DR-TB STAT - November 2017 call

30 November 2017

Attendees: Vivian Cox (DR-TB STAT); Jennifer Furin (DR-TB STAT); Erica Lessem (TAG); Sharonann Lynch (MSF); Christophe Perrin (MSF); Khairunisa Suleiman; Hashim Khan Amirzadah (NTP, Afghanistan); Brenda Waning (StopTB); Gunta Dravniece (KNCV); Claire Albert (CHAI); Tiziana Masini (MPP); Nataliya Morozova (PIH)

Agenda:

1. Off-label use of new TB drugs; a review of the recent WHO guidance document on off-label use (Dr. Cathy Hewison, MSF)

Minutes: Nataliya Morozova

General Update – Jennifer Furin

I. It is the last call for 2017. Thanks everyone for ongoing participation with the DR-TB STAT team.
   - Exciting results of the year:
     - Increased access to the novel drugs and shorter regimen.
   - Confusing results of the year
     - Phase III clinical trial results, including the STREAM trial and DLM Phase III clinical trial presented at the Union Conference in Guadalajara.
   - It is time for the DR-TB community to continue open collaboration and talk about issues where we can provide optimal care to patients and optimal support to countries and programs

II. A statement issued by DR-TB STAT regarding the results of the Phase III clinical trials was circulated to the DR-TB STAT mailing list; any comments or feedback on the document is welcomed. It is also available on the DR-TB STAT website.

Off-label use of new TB drugs; a review of the recent WHO guidance document on off-label use

Introduction by Jennifer Furin: Dr. Cathy Hewison is TB Advisor with MSF who is involved in the implementation of the endTB project funded by Unitaid. Dr. Hewison has worked as a clinician and operational researcher, and a support person to programs working in the highest-burden settings of DR-TB in the world. Please see the presentation from Dr. Hewison circulated via email before the call.

- Expanded use of BDQ/DLM
  - It is not always off-label
  - How to use new TB drugs in an optimal way.
  - Clinicians make decisions based on patient treatment needs

- Includes:
  - > 24 weeks BDQ and DLM
  - Combination BDQ and DLM
  - BDQ and DLM in children and adolescents
  - BDQ in Pregnant women

- WHO best practice on expanded ("off-label") use of new TB drugs
  - It is to help countries to understand that we use drugs to optimize treatment
  - "Off label use" is legal and common for treatment of MDR-TB
  - "Off-label use" falls under the purview of national regulatory agencies
  - "Off-label use" is usually case by case
  - MDR-TB is an off-label disease, this term is used by WHO

- MSF and endTB experience
  - MSF experienced the use of new TB drugs earlier in 2013
  - At the early stage we used Medical Committee to help clinicians make decisions which patient needed which regimen
  - We followed WHO recommendations on sufficient number of effective drugs, which is #1 recommendation to treat patients as early as possible with enough drugs.

- More than 24 weeks of using BDQ or DLM
  - Our experience to use these drugs for compassionate use was great. The first patients were positive for a long time, then we treated them with a combination of Linezolid, BDQ, sometimes with Imipenem. We had fantastic results of a 6 months conversion rate.
  - Some patients became positive again after initially become negative. We tried to get more BDQ for the patient, but because of compassionate use rules, Janssen could not give us more BDQ and we had to stop and wait. The clinicians do not want to stop BDQ
  - Today BDQ is not officially off-label because the manufacturer registration with the European Medical Agency gives a possibility of more than 24 weeks of use in patients with XDR-TB.
  - More evidence is coming out about the safety and effectiveness of BDQ extension. A very good paper to read about it is from France –where patients received more than 6 months of BDQ: Guglielmetti L, Jaspard M, Le Dû D, et al. Long-term outcome and safety of prolonged bedaquiline treatment for multidrug-resistant tuberculosis. Eur Respir J 2017; 49: 1601799 [https://doi.org/ 10.1183/13993003.01799-2016].
  - DLM is off-label drug; however, the European Medical Agency gives a possibility of 24 weeks of use.

- Comments - Hashim Khan Amirzada (Afghanistan)
  - Now we have a 1,5-year-old patient. According to WHO, we cannot start DLM for patients who are under 6 years old.
    - Answer – Cathy Hewison – The use of DLM under 6-year-old requires a case-by-case approach. Within MSF there are approximately 10 patients under 6 years old on DLM. The decision has been made in conjunction with the International Committee and with specific pediatricians giving advice. We will be able to help you get advice on this case from endTB

medical committee and pediatricians we have contact with. It is a national regulatory authority problem. I think WHO is trying to make it clear that on a case-by-case basis, national regulatory authority can decide to use drug off label. The drug is not recommended by WHO for patients under 6. There is an ongoing clinical trial conducted by Otsuka between age 0 and 5 years old where they are looking at pharmacokinetics and dosing. Pediatricians who treat MDR-TB could give good advice. You also need to discuss with your regulatory authority on a case-by-case basis.

- Patients are given Amikacin or Capreomycin for two or three months, then the patient would lose his hearing. They do not have basic audiometry. They diagnosed the patient with GeneXpert, then started Amikacin and other drugs based on the Guidelines. We also have more XDR cases to treat with DLM who have side effects, like hearing loss.
  - Answer (Cathy Hewison) – the use of new TB drugs to replace TB drugs in patients who have adverse events is necessary and this is what has not been done enough with no sufficient audiometry testing. This is where you need to go to the regulatory authority. You can contact my MSF colleagues in Afghanistan to continue this discussion. A case-by-case basis to use new TB drugs is the responsibility of the national regulatory authority. NTP and MoH have responsibility to give enough effective drugs and take care of the patients avoiding any harm.

- endTB extended use of BDQ or DLM – it was presented at TB Symposium at the Union Conference in Mexico
  - 223 of 687 (32%) patients received more than 24 weeks of BDQ or DLM or both drugs.
  - There will be more patients on extended use of the new TB drugs. Based on the experience of the compassionate use, there is no sense to stop an effective and well tolerated drug
  - In endTB Medical Committee, we previously reviewed all cases for extended use. After reviewing 200 cases, we came up with broad guidelines (available on the endTB website. For most countries, they do not use their medical committee; it is a routine case-by-case assessment according to general pre-requisites and criteria. Basically, if they do not have enough effective drugs, they continue BDQ and DLM.

- DLM and BDQ Combination
  - The combination is not off-label, there is no evidence, no recommendation
  - It was possible with Otsuka compassionate use program
  - It has been done in clinical trials
  - There is an ongoing Drug-Drug Interaction study (DELIBERATE)
  - There are many patients with limited number of effective drugs and this is the reason why we use DLM and BDQ combination
  - If you don't have enough effective drugs, use both DLM and BDQ

- Evidence overview – endTB project
  - Evidence was presented at the endTB symposium at the 2017 Union Conference in Mexico
  - Good tolerability and effectiveness
  - None of concerns about QTc prolongation

- 46 patients ever received DLM and BDQ in combination

- For endTB resources, please visit www.endtb.org
  - Under "Resources" you can find endTB Guidelines

- Pediatric and adolescent use
  - There are few publications
  - More and more adolescents are getting BDQ and children over 6 years old getting DLM
  - MSF has about 10 children under 6 on treatment who get DLM
  - The major problem with pediatric MDR-TB is not enough diagnosing

- Pregnant women
  - We would not recommend DLM
  - We have treated pregnant women with BDQ
  - We try to avoid pregnancies but they happen, we have had about 11 pregnancies
  - We design a regimen which is least toxic but still effective
  - Breast feeding is not recommended
  - We will follow up on any children born from mothers on treatment, we are collecting the data

- Comments and Questions
  - If you have any questions to Dr. Hewison, please email them to Jennifer Furin at jenniferfurin@gmail.com
  - Use of Linezolid in children – Do you have an experience of using LNZ in children?
    - Jennifer Furin – I specialize in the care of children with DR-TB. LNZ has been used in children either with resistance or intolerance to the other SLD. We have fair amount of evidence on the safety of LNZ because the drug is used to treat other bacterial infections – resistant gram-positive infections, like Staphylococcus aureus. The problem with LNZ is that we are not sure about the optimal dosing, particularly that the drug is used longer. We are still learning and working on the optimal dosing strategy. A recent report issued by Anthony J. Garcia-Prats is very reassuring. The article is to be circulated to DR-TB STAT group. Children tend to tolerate LNZ much better that adults. We should be confident in using the drug in children while we are sorting out the optimal dosing.
  - Is there any evidence that use of DLM and BDQ in combination may increase QTc prolongation and lead to patient's death?
    - Cathy Hewison – We provide enhanced monitoring of patients, in some patients we do weekly monitoring for the first three months that allows us to detect any QTc prolongation. There were few patients with over 500 and none of them had to stop the combination. We should take into account Clofazimin – another QTc prolonged drug, and Moxifloxacin. The DLM Otsuka Phase III study showed that the QTc prolongation was only 5 mcs. The key is monitoring of your patients and checking electrolytes.
  - Is there a pediatric formulation for children under 5 years? - Hashim Khan Amirzadah (NTP, Afghanistan)
    - Jennifer Furin - There are new developments in terms of pediatric formulation and the Sentinel Project will follow up with you.

- Jennifer Furin –The WHO can make recommendations based on the populations that were included in the studies. Programs and clinicians need to make decisions for populations that may not be included in trials. The WHO issued a very important document in October, which gives countries the freedom to use drugs in ways that are not necessarily indicated in the WHO recommendations. The recommendations are never against the use of these drugs. If countries make decisions about use/extended use in these populations, they are well within the scope of what is allowed. These decisions should be done on a case-by-case bases and in conjunction with experts. Cathy Hewison and MSF tell us their experience of using the drugs. This is the way to learn from each other.

- DR-TB STAT statement on the safety of clinical trials of the STREAM trial and Otsuka 213 DLM study
  - The goal is to provide additional information about the results of the studies and how people in the field might interpret them
  - The results of the Phase III trials under program conditions were poor. Both trials were not powered to detect the difference that was expected.
  - **The STREAM trial** – the differences in outcomes were close to those reported in the public press – 78% in the shorter regimen arm compared to 81% in the longer control arm. Statistically, the study was not able to show non-inferiority of the shorter regimen. We cannot say that the shorter regimen is as good as the longer regimen. Countries may proceed with the shorter regimen because of the good reason. The rate of adverse events was similar between the two groups.
  - We need to carefully select the patients for the shorter regimen as it is recommended by the WHO. Patients with SL resistance are not the best candidates for the shorter regimen.
  - Not all patients may be willing to get a shorter regimen. We hope stage II will provide us with the statistical power to confirm that the shorter regimen is as good as the longer regimen.
  - **The Delamanid trial** - the study was not powered to look at overall outcomes. The sample size was chosen based on primary outcome – the differences in time to culture conversion. Compared to the placebo arm, there was a finding that DLM was associated with faster time to culture conversion in a primary analysis. The difference was not statistically significant. The *p* value was 0.056. The drug has some mycobacterial effectiveness. For patients treated with a conventional regimen, adding DLM to all those patients may not be a beneficial strategy. However, those with resistance or intolerance and are not able to be treated with a conventional regimen, DLM may be an important option.
  - **Experts to consult regarding the new drugs** – MSF, ERS WHO Concilium. For pediatric questions contact the Sentinel project at tbsentinelproject@gmail.com

We will resume DR-TB STAT calls in February 2018. Compliments of the season from DR-TB STAT!