Meeting Minutes

Meeting Information

Date: Tuesday, July 12th, 2016
Time: 09:00 - 14:30 EDT
Type: Meeting
Topic: Optimization of Oxazolidinones for Use in TB Drug Regimens

In-Person Attendees:

Melvin Spiegelman, WGND
Barbara Laughon, WGND
Zaid Tanvir, WGND
Christine Sizemore, NIAID
Richard Hafner, NIAID
Cathy Bansbach, BMGF
Jim Boyce, NIAID
Ray Chen, NIAID
George Drusano, Univ. of Florida
Ann Eakin, NIAID
Daniel Johnson, NIAID
Petros Karakousis, Johns Hopkins
Francisco Leyva, NIAID
Mamodikoe Makhene, NIAID
Kenneth Olivier, NHLBI
Charles Peloquin, Univ. of Florida
Philippe Prokocimer, Merck
Laura Via, NIAID
Mukadi YaDiul, USAID

Teleconference Attendees:

Veronique Dartois, Rutgers Univ.
Eric Nuermberger, Johns Hopkins
David Olsen, Merck
Katherine Young, Merck
Richard Tschirret-Guth, Merck
Bob Wallis, Aurum Institute

Decisions/Suggestions

- **Another workshop on optimizing oxazolidinones should be planned**
- **Invitations should be extended to a broader range of individuals including oxazolidinone chemists, pharma, and research groups working on new oxazolidinone analogs**
- **Confidentiality agreements should be required for attendees of the next workshop**
- **There should be a remote option for those abroad**
- **The meeting will be held at the NIH office in Rockville, MD**

Action Items

Action Item	Responsible Party
Plan another workshop including broader spectrum of oxazolidinone experts and key players.	Barbara & Zaid
Find a suitable date for the workshop for the majority	Zaid

Summary

Welcome and Introduction *Barbara Laughon*

- Goals for the Optimization of Oxazolidinone Workshop
  - Map the landscape of knowledge
  - Planning for a larger meeting in the fall
  - Identification of key individuals for participation in the larger meeting and of available data sets for presentation
- WGND as a Resource
  - The WGND provides an online resource via the updated pipeline and clinical trials database
  - Presentations from WGND meetings are available on the website
- Current Oxazolidinones on the Pipeline
  - The only clinical research on oxazolidinones are the NixTB study (linezolid), STREAM study, NExT trial (linezolid)
  - The reason for urgency in discussing oxazolidinones is to fill the pipeline with more regimens involving these compounds. Discussions on which ones should progress and what kind of dosing should be used need to be made.

Current Research Questions *Richard Hafner*

- Why do we like oxazolidinones?
  - These compounds have good evidence from various places that these compounds work.
  - They have powerful sterilizing activity and there is not a significant QT problem
  - Generally good bio-availability, solubility, and resistance profile
  - In terms of distribution, the CNS penetration is great and used in for MDR meningitis
- Research Questions
  - What is known about the pharmacokinetics and tuberculosis-specific pharmacodynamics of linezolid, sutezolid, and tedizolid?
  - What PK drivers need to be considered in optimizing dosing for efficacy (sterilization) and tolerability?
    - Sterilization, trough-driven or not, etc.
  - What are the mechanisms of mitochondrial and other toxicities and how can they be minimized?
    - The FDA has warned against using oxazolidinones with SSRI's and we need to investigate if this is a real threat
  - What guidance can be proposed for potential dose reductions when toxicity is encountered?
    - Dose-reduction and interruptions have been part of the treatment strategy and this drug can be interrupted for up to a week and still have efficacy – what can we learn from that?
    - Are the side-effects from the drug (primarily peripheral neuropathy) tolerable?
  - Are data available on CNS penetration, effectiveness for TB meningitis, and potential neurotoxicity?
    - Excellent CNS penetration – we need to learn more about this for TB.
  - What measures should be considered to reduce the probability of resistance developing?
    - We need more assays
  - What preclinical assays can be used to select new candidate oxazolidinones with reduced mitochondrial toxicity?
  - What key clinical studies should be undertaken to test optimization and compatibility with other TB drugs?
    - Optimizing dose duration and interruption to get a balance of dose safety and efficacy for best clinical outcomes
- Hopefully, we will have multiple drug regimens with these oxazolidinones for comparison in order to find the optimal one.
- As a class, oxazolidinones generate great interest and there are many people developing new compounds with less toxicity.

Experience with Linezolid in XDR TB *Ray Chen*

- A study was conducted in Korea on XDR TB. Findings were published twice in NEJM and once in EbioMedicine
- Phase 2a randomized, 2-arm study in Changwon and Seoul. Enrolled 2008-2011, treated for 2 years
  - Patients had to be on an unchanged failing regimen for previous 6 months
  - No placebo was used
    - A delayed dose of linezolid was used in place of placebo
    - For two months, the failing treatment was used.
  - 50 patients were screened, 40 randomized, 19 patients in the immediate arm and 20 in the delayed arm
  - 31/38 developed a clinically significant adverse event possibly/probably related to LZD

- Pharmacokinetics – 4 had treatment failure,
- Among 38 received LZD
  - 27 cx negative 1 year after end of treatment
  - 3 lost to follow-up
  - 8 withdrew, including 4 failures
- Additional adverse events stopped after stopping Linezolid
- Mitochondrial function measured by cytochrome C oxidase and citrate synthase (cytosolic ribosomal proteins)
  - The ratio of cytochrome C oxidase : citrate synthase would decrease with increased mitochondrial toxicity.
- Single nucleotide polymorphisms have been associated in the past – but none were found in this study.
- The time after starting linezolid to the first adverse event happening for a patient was similar between the two arms.
- When looking at the risk an adverse event, you have a 2-fold increase when using linezolid (consistent in both arms).

➢ Questions
- What hypothesis was being tested with the delay?
  - It is an offset treatment instead of using a placebo
- What would be done differently if this were done again?
  - The number of blood samples taken were limited by Korean law. If this trial were redone, it could be done in a different country.

TB Alliance Experience with Linezolid *Mel Spigelman*

➢ We have a preclinical program using mitochondrial activity as a marker for toxicity and activity in linezolid
➢ Dose-ranging Linezolid Study – 2-week trial looking at safety, tolerability, and bactericidal activity
- Question: How does the total dose curve look as the total dose goes up?
- As dose response curve climbs, there is greater bactericidal activity. As far as can be seen, there is no significant difference in dividing the dose into twice a day makes a difference.
- There is a statistically significant increase in bactericidal activity between the 300mg and 1200mg per day, but not between one dose the next.
- Next steps are to look at a higher dose every other day.
- We do want to push dose as high as reasonable.

➢ Clinical trial – Nix-TB XDR/MDR Trial (ongoing)
- MDR TB patients or treatment-intolerant MDR patients, ie. all else has failed
- Regimen: pretomanid (200mg), bedaquiline (200mg), linezolid (600mg) – 6 months of treatment.
- This is a curative intent trial
- If patients convert within 4 months, they get 6 months of therapy. if they did not convert by 4 months, they get 9 months of therapy.
- Following patients for 2 years after therapy concludes
- 38 patients were enrolled and assigned to NixTB
  - 47% are HIV infected
  - 30 with XDR-TB
  - 7 with MDR-TB (treatment non-responsive)
  - 1 with MDR TB (treatment intolerant)
  - 27 patients have completed 6 months of treatment
- Everyone's Sputum converts within 4 months, most within 2 months.
- No relapsing yet after 6 months of treatment
- 4 deaths (3-7 weeks on treatment) (two severe TB, upper GI bleeding, acute, multi-organ failure)
- Toxicity – 7 or 8 have tolerated the full dose with no side effects, others had dose reduction for linezolid, some have stopped linezolid.
- Clinical judgement is used to decide when a patient needs to reduce or stop treatment of linezolid. It is up to the clinicians to decide that the patient experiencing peripheral neuropathy is hazardous enough to merit change in therapy. <u>This means that the trial requires strong clinicians.</u>
- There is nothing thus far that is appearing in terms of toxicity that are not disease related or related to known toxicities of linezolid.

- Comments/Questions
  - Both efficacy and toxicity are hard to judge. The "n" is very small. One of the biggest issues in evaluation is kinetics influence on efficacy and toxicity. To get maximal benefit, with relatively small numbers of blodod samples you can use a study with stochastic design.
    - At the University of Liverpool has developed a quick assay to identify necrosis or apoptosis. This may be something used in future trials.
  - It's tough in man to look for a parameter that drives the PKPD relationships. We make the assumption that sterilization
    - REMox showed us that cell killing activity at 2-weeks was indicative of 8-weeks; however that is the only marker/indicator we have at this point.
  - One thing we are looking to do is reducing dose of linezolid and seeing if we lose any efficacy.
  - What if you start with a lower dose at first and give the higher dose at the end?
    - The clinical results that have tested these theories in other drugs have never proven that this is a better method.
  - If there is a data that shows that TB cell killings should be seen in 2 weeks in murine models and this is not seen in clinical trials, then we would hesitate to invest in that drug.
    - All known TB drugs used in show "bactericidal activity" within 2 weeks in man.
  - Clofazimine – showed sputum conversion at 3 months. (Bob has this study)
  - Richard Hafner – 14 day EBA is not good enough for dose determining. Clofazimine is an EBA outlier – it is not a determinant.
  - Mel – in rifampicin, studies have shown that the later determinants are not as indicative of the dose.

Tedizolid as a Candidate for Tuberculosis Therapy *Phillipe Prokocimer*

- Tedizolid was discovered by a Korean company in 2006.
  - Drug was licensed to Trius 2007-2013.
  - Bayer has the rights to Tedizolid, but Merck is responsible for the development of the drug.
  - Sivextro is only approved oxazolidinone beyond lenozolid.
  - Tedizolid has a comprehensive dossier already available.
- Tedizolid dose cannot exceed 200mg – above this we see immunosuppression.
- Must be equal or greater to the efficacy and safety of Zyvox
- Pharmacokinetics of Oxazolidinones
  - There is little accumulation of the drug over time.
  - Excreted 80% in feces, 20% in the urine, and 97% form is metabolites, 3% as active tedizolid
  - No inhibition or induction of CYP450 enzymes
  - Potential for inhibition of BCRP substrates
- High penetration into lung
- Low-intersubect variability – unlike linezolid. There is a narrow effect range for all patients who take tedizolid.
- Pharmacology
  - Two issues with linezolid assessed during Sivextro development
    - Off target; monoamine oxidase inhibition
      - Serotonin Syndrome and Linezolid
      - FDA Drug Safety Communication and subsequent labeling changes for Zyvox – Oct 2011
      - CNS Drugs have potential drug interactions
      - Two clinical studies were conducted to examine potential for interactions due to peripherally mediated MAO inhibition
      - Clinical studies demonstrated no change in pressor response of pseudoephedrine or increase sensitivity to tyramine
    - Mitochondrial Protein Synthesis Inhibition
      - Tedizolid 1/3 of its time is spent below the C-min
  - Tedizolid is more potent than Linezolid, has a similar efficacy at a lower dose, lower toxicity and less side effects. All of these studies have been done in animal models
- Questions
  - Monte Carlo simulation should be performed to see the distribution of patients.
  - What about pediatric infections?

        - There are PK studies that show no dose changes in children down to 12 years old. A study is on-going about below that.
    - What about CNS Infections?
        - Currently there is little to no data on penetration in the CNS

Sutezolid as a Candidate for Tuberculosis Therapy *Dan Johnson*

- Sutezolid Overview:
    - Metabolites contribute to antibiotic effect as well as mitochondrial toxicity.
- Sutezolid vs. linezolid
    - STZ more potent than LZD in WBA
    - STZ has a similar efficacy to rifampin in non-replicating bacteria in murine and in vitro models.
        - LZD has modest efficacy in murine models using these models.
    - Sutezolid had a better rate of relapse after 4 months of treatment

Bridging Pre-Clinical and Clinical Development of Novel TB Regimens: An Example Employing Linezolid *George Drusano*

- Bridging requires:
    - High rates of cure
    - Minimize resistance emergence
    - Minimize concentration-driven toxicities
- What do these require?
    - Relationship between exposure and toxicity
    - Relationship between exposure and kill
    - Relationship between exposure and resistance suppression
- Need to fit a high dimensional mathematical model to all the effect data and resistance suppression data simultaneously
- Performed predictive plots with r^2 above 0.9
- Linezolid efficacy and toxicity – to bridge from animal model to man a monte carlo simulation was performed
    - The effect shows that it is trough driven (consistent with Bob Wallis' data)
    - "Inverted U Plot" – linezolid resistant organisms
- Toxicity
    - The best marker is Cytochrome oxidase 4
    - Once a day vs. every other day - the toxicity goes down with every other day
- Sutezolid & Linezolid together are good against Acid-phase MTB
    - Parent compound and metabolite are highly signify antly synergistic for cell kill (but this does not suppress all resistance).
- PK – half-life is 4.3-6.2 hour range. AUC is 90-140 micrograms/mL
- Substantial penetration into epithelial lining fluid (ELF) for linezolid
- Questions
- Is toxicity driven by trough levels?
    - Cytochrome C oxidase is correlated with toxicity

In Vitro and Animal Model Comparative Data *Laura Via*

- Study with multiple oxazolidinones
    - Linezolid, sutezolid, tedazolid, radezolid,
- TED toxicity in the marmoset – two month study
    - Marmosets were infected and 46-52 days dwelling
    - Daily (or BID) PO dosing 1 month or 2 months
    - There was a large reduction in the surviving marmoset; however, the toxicity was too high.
- Response diversity – Linezolid does not start fast but there is reduction in disease over time. Radazolid, the disease gets worse, AZD & SUT improve.

- AZD and SUT accumulated in epithelial lining fluid like LIN while RAD and SUT-M1 were under represented
- Cramnick Mouse model was used.
- Questions
    - What is the rationale for establishing a new model?
        - The level of drug needed is significantly higher for rabbits.
        - Marmosets require very little amount of the drug. This allows for easier funding for multiple studies.
        - The rabbit has a sensitive gut, the marmoset has similar PK to the human model.

Research Experience at Rutgers *Veronique Dartois*

- Why do we measure concentrations in lesions?
    - Because there are bacilli that need to be killed both extra and intracellularly. We are interested to know if oxazolidinones are equally diffused into both areas.
- There are strikingly different diffusion of drugs into necrotic nodules
- Originally thought there would be hydrophobic drugs would be attracted to caseum.
- Linezolid has very good diffusion in both nodule and cavity.
- What do we not understand about Radezolid?
    - Activity of standard TB drugs in caseum
- Linezolid is not very active, it kills 1 log at best at high concentration
- There is something that we do not understand about how oxazolidinones actually work. Radazolid has no efficacy in mice and in marmosets.
- Questions-
    - What is the pH of the caseum ?
        - It's 7. The idea of caseum being acidic is a bit of myth. Established caseum is not at all acidic.
    - RAD was designed to bind differently to the ribosomes. Could this be the cause of the difference?
        - Possibly, but it's not the current hypothesis.

Experience with Oxazolidinones for Non-Tuberculosis Mycobacteria *Ken Olivier*

- Non-TB Mycobacteria affect different populations
- Retrospective study of Linezolid for NTM
    - 6 NTM treatment centers
    - 102 NTM patients (78% pulmonary)
    - 44% were M. Abscessus
    - Median Rx time 21 weeks
- Tedizolid – Of all the oxazolidinones, the MIC is most favorable is tedizolid for these sets of organisms.
- Tedizolid for NTM – long term safety
    - Retrospective study – 25 patients on tedizolid for >2 weeks for NTM
    - 20 had pulmonary disease, 5 disseminated
    - Median duration of 101 days
    - Most failed prior treatment, all were on multi-drug regimens.
    - Adverse effects – 44%
    - 3 patients with prior linezolid neuropathy did not experience worsening on tedizolid (or better)

Planning for Another Meeting Discussion

<u>Questions and Focus for Next Workshop</u>

George:

- There needs to be a consensus of what the goal is and what questions need (an attempt at) an answer defined.
- We need more participation from diverse backgrounds. Pharma, chemists that developed the drugs, etc
- How do you identify optimal regimens? When you have new drugs and when you have new regimens, what are the effects on each of those metabolic states?

Phillipe:

- We need to think regimen not drug
- We need to make sure we all agree on the questions? What are the questions we have for a discovery or clinical program. In the next workshop we should agree on how the program should be develop the program.

Barbara

- There should also be focus on investigating new oxazolidinones in discovery
- This should be both Discovery and Clinical focused

George:

- All participants should sign a non-disclosure agreement [all attendees agreed]

Phillipe:

- Focus on what are the best Oxazolidinone drugs

George

- What happens with what kind of mutation with what frequency and what change from the baseline MIC? Those are critical pieces of information to get to optimal oxazolidinone regimens.

Petros

- We need a database for M TB mutations and phenotypic response
- We have this for HIV

<u>Goal of the Next Workshop</u>

Barbara

- Working Group goal is to stimulate research and collaboration

Mel

- There is a fair amount of work going on in Oxazolidinone field
- The communication is sub-optimal in terms of the players in the field and knowing/have the benefit of knowing what others are doing in that field.
- This looks like it's a promising area especially since there are a finite number of classes of TB Drugs
- The first goal was to share information by people who are actively engaged in the oxazolidinone and to facilitate on-going communication.
- Second goal is to change research currently going on based on what others are doing.
- The next step would be – who in addition to who is here to be critical participants?

<u>Participant Invitation</u>

George:

- Barry Hafkin is working on a new molecule that's an oxazolidinone.

Jim Boyce

- There are more than 10 research groups working on new analogs – we should invite them.

George

- Identify the largest number of people that we can come up with.
- Allow them to invite others
- Invite them to put in questions that should be addressed/answered.

Jim

- Do we want people outside of TB working on Oxazolidinones? [All agree yes]
- Mitochondrial researchers? [All agree yes]

Ann

- The number of oxazolidinones that have synthesized are enormous. There are a lot of new assays that are being determined as critical.
- TB drug accelerator may have worked with the many other oxazolidinones.

Phillipe

- Safety should be a main driver
- There should be more conversation between discovery and clinical. So that clinical

Mel

- Who else should we proactively reach out to?
    - Laura – Helena Boshoff – designs assays
    - Eric Nuremberger

- Cliff Barry
- Barry Christworth
- Medicinal chemist from oxazolidinones
- David Olsen
- Kelly Dooley

Location

- Have it in a location where there is good IT support, because we would like remote participation
- Agreement on returning to NIH is unanimous.

Possible Dates

- September 13th
- November 15th
- December 14th or 15th