SIRTURO® (bedaquiline)
Activity of SIRTURO Against Nontuberculous *Mycobacterium* Species

SUMMARY

- SIRTURO is not indicated to treat infections due to *Mycobacterium* species other than as part of combination therapy in adults and pediatric patients (≥5 years and weighing at least 15 kg) with pulmonary tuberculosis (TB) due to *Mycobacterium tuberculosis* resistant to at least rifampin and isoniazid.[1]
- A retrospective study showed that in 10 patients with refractory *Mycobacterium abscessus* (*M. abscessus*) and *Mycobacterium avium* (*M.* avium) complex (MAC) lung disease, symptomatic improvement was seen in 9 patients with SIRTURO treatment. Six patients reported nausea that was considered related to SIRTURO.[2]
- A case report described 2 patients with human immunodeficiency virus (HIV) treated with SIRTURO, as part of combination therapy for nontuberculous mycobacteria infection due to *M. abscessus* and *M. avium.*[3]
- In a study of *M. avium* infections in mice, the activity of SIRTURO monotherapy was bacteriostatic. After 3 months of combination treatment with clarithromycin, amikacin, and SIRTURO, bactericidal activity was seen. However, the activity of combination therapy with clarithromycin, amikacin, and SIRTURO was not better than amikacin alone.[4]
- Combination treatment of SIRTURO with clofazimine was more effective than either drug used alone or other agents in reducing bacterial burden of *M. abscessus* in the lung, spleen, and liver in mice.[5]
- In an in vivo study, SIRTURO demonstrated bactericidal against *Mycobacterium leprae* (*M. leprae)* at varying doses and different dosing frequencies.[6]
- The SIRTURO minimum inhibitory concentration (MIC) range against 29 clinical isolates of *Mycobacterium ulcerans (M. ulcerans)* was ≤0.015-0.12 µg/mL.[7]
- Case reports on other species of nontuberculous *Mycobacterium* are available.[8,9]

CLINICAL DATA

Philley et al (2015)[2] described the results of patients that were treated with SIRTURO for refractory *M. abscessus* and MAC lung disease (N=10).

Study Design/Methods

- The study was a retrospective analysis of patients from the University of Texas Health Science Center.
- SIRTURO was administered as 400 mg once daily (QD) for 2 weeks followed by 200 mg 3 times a week for 22 weeks.
- Patients with MAC received the combination of azithromycin, ethambutol, streptomycin or amikacin, and rifabutin depending on macrolide-susceptibility.
- Patients with *M. abscessus* infections were treated with amikacin, cefoxitin, imipenem or tigecycline, and/or linezolid according to susceptibility results.

Results

Efficacy

- Symptomatic improvement was seen in 9 of the 10 patients at 2 months of treatment. Symptomatic improvement included less sputum production and cough, improved energy level, and/or weight gain or weight stabilization.

- Radiographic improvement was seen in 4 patients at 6 months of treatment. Stable or unchanged radiographic results were seen in 2 patients while worsening results were seen in 4 patients.
- At 6 months, 6 patients showed improvement in semi quantitative sputum culture scores. No patient achieved sustained sputum conversion to acid-fast bacilli culture negative.

Safety

- Six patients reported nausea that was considered related to SIRTURO.
- There were no significantly prolonged corrected QT intervals (QTc). The mean change in the QTc interval was 4.6 milliseconds (ms; month 1), 6.5 ms (month 3), and 2.4 ms (month 6).
- There were no cardiac-related adverse events (AEs), significant changes to laboratory values, or SIRTURO discontinuations due to AEs.

CASE REPORT

Gil et al (2021)[3] described a case report of 2 patients with HIV treated with SIRTURO, as part of combination therapy for disseminated nontuberculous mycobacteria infection.

The first patient was a 54-year-old male who had colonic perforation secondary to rectal trauma. Two months after having a Hartmann's procedure, the patient developed symptoms of fever, breathlessness, and purulent exudate at the abdominal wound site. The patient's HIV viral load was undetectable (CD4 count >900 cells/µL).

The wound exudate tested positive for *M. abscessus* and blood cultures were negative for mycobacteria. Susceptibility tested revealed extensive drug resistance and MIC estimations for SIRTURO showed in vitro susceptibility (MIC ≤0.0625 mg/L).

- Treatment with SIRTURO 400 mg per day was initiated for 2 weeks followed by 200 mg 3 times a week. As SIRTURO was well-tolerated by the patient, treatment continued for a year with a brief interruption due to a delay in compassionate use reapproval.
- The patient was also treated with intravenous amikacin (1g/day), which was later discontinued due to AEs, azithromycin, clofazimine, imipenem, tigecycline (later replaced by linezolid), and moxifloxacin.
- Pulmonary and hepatic lesions were seen intermittently but were culture negative and considered to represent immune-mediated lesions.
- Thirty-six months after treatment, a fluorodeoxyglucose-positron emission tomography/computed tomography scan showed ongoing, but greatly reduced fluorodeoxyglucose avidity in all areas.
- The patient continued maintenance therapy with clofazimine and azithromycin.

The second patient was a 30-year-old male who was diagnosed with advanced HIV infection (CD4 count 10 cells/µL; viral load >1 million copies/mL) a month prior to presenting to the hospital with pyrexia, pancytopenia, and lymphadenopathy. Antiretroviral therapy was started 10 days prior to hospital admission. Cultures were positive for *M. avium* in the lymph node, peripheral blood and sputum. The patient began treatment with azithromycin, rifabutin, and ciprofloxacin.

The patient was transferred to another hospital but returned 6 months later due to abdominal pain. Return cultures of blood, bone marrow, and lymph node were positive for *M. avium*. Treatment was augmented with amikacin, ethambutol, meropenem, clofazimine. There were many treatment modifications made due to AEs and extensive in vitro resistance.

Repeat blood cultures were positive for *M. avium*. Treatment with SIRTURO was initiated at month 13 with similar dosing as noted in the above case. Tedizolid was also started and rifabutin was discontinued. The patient reported no AEs and fevers resolved. Treatment with SIRTURO continued for 18 months, and the patient was successfully immune reconstituted.

IN VIVO STUDIES

Mycobacterium avium

Lounis et al (2009)[4] evaluated the efficacy of SIRTURO in *M. avium* infections in mice.

Study Design/Methods

- Female mice were infected intraperitoneally with 2.3 x 10^7 colony forming units (CFU) of *M. avium* 101.
- In the early infection model, mice received treatment starting the day after infection, and included a negative control, a positive control (clarithromycin) and 2 test groups (SIRTURO or clarithromycin + SIRTURO).
- In the late infection model, mice remained untreated for 1 month; followed by 4 months of treatment with
  - Clarithromycin
  - Amikacin
  - SIRTURO alone
  - Clarithromycin + amikacin
  - Clarithromycin + SIRTURO
  - Amikacin + SIRTURO
  - Clarithromycin + amikacin + SIRTURO
- In both infection models, SIRTURO was administered at a dose of 25 mg/kg orally.
- Efficacy was assessed by CFU counts.

Results

Early Infection Model

- The CFU counts in untreated mice increased from 6.53±0.56 $\log_{10}$ at day 0 to 8.0±0.9 $\log_{10}$ after 1 month (P=0.02).
- Monotherapy with SIRTURO decreased CFU counts by 2.56 $\log_{10}$ compared to late controls (P=0.002).
- The activity of the combination therapy of SIRTURO and clarithromycin did not improve the activity of the individual compounds.
- All regimens were considered bacteriostatic.

Late Infection Model

- The results from the late infection model are shown in Table: CFU of M. avium During 4 Months of Treatment.

CFU of *M. avium* Infection During 4 Months of Treatment[4]

Group	Mean $\log_{10}$ CFU count				
	Day 0	Month 1	Month 2	Month 3	Month 4
Controls	8.0±0.09	7.4±1.7	9.4±0.2	7.9±0.7	8.9±0.3
Amikacin	-	7.2±0.6	6.7±0.6	5.9±1.1	3.5±0.3

SIRTURO	-	7.7±0.6	6.5±0.8	6.5±0.6	6.6±0.2
Clarithromycin + SIRTURO	-	7.7±0.2	6.3±0.8	6.3±0.4	5.1±1.7
Amikacin + SIRTURO	-	7.1±1.2	6.4±0.5	6.2±0.6	4.8±0.7
Clarithromycin + amikacin + SIRTURO	-	6.1±2.0	6.4±0.7	5.4±0.8	4.5±0.5
Abbreviations: CFU, colony forming units.					

- After 1 month of treatment, none of the treatment arms showed activity.
- All regimens achieved bacteriostatic activity after 2 months of treatment.
- After months 3 of treatment, the combination of clarithromycin, amikacin, and SIRTURO demonstrated bactericidal activity (P=0.001) and persisted through month 4. However, the activity of combination therapy with clarithromycin, amikacin, and SIRTURO was not better than amikacin alone.
- The activity of SIRTURO monotherapy remained bacteriostatic.

Mycobacterium abscessus

Obregón-Henao et al (2015)[5] assessed the antimycobacterial activity of SIRTURO and SIRTURO-clofazimine combination against *M. abscessus*-infected mice.

Study Design/Methods

- Two experiments were run with gamma interferon knockout (GKO) mice first and then severe combined immunodeficiency (SCID) mice to confirm results.
- Mice were intravenously infected with 1 x 10^6 CFU of *M. abscessus* 103.
- Starting on day 2 of infection, the mice were treated via gastric lavage with either clarithromycin, clofazimine, SIRTURO, clofazimine-SIRTURO combination, or control (saline) for nine consecutive days, with termination of the drug at day 10.
    - For the clofazimine-SIRTURO group, each drug was given separately by six hours to avoid interference.
    - Ciprofloxacin (oral) and amikacin (SQ) treatment arms were also included in the study using GKO mice.
- Groups of mice were euthanized on days 1, 5, and 15 after infection in the GKO experiment, and on days 1 and 15 after infection in the SCID experiment.

Results

GKO Mice

- SIRTURO significantly reduced bacterial burdens compared to the control group in the liver (P<0.001) and spleen (P<0.001) at both 4 days of treatment and after eight days of treatment. Also, significantly reduced bacterial burden in the lung (P<0.01) after eight days compared to control.
    - SIRTURO compared to clarithromycin, ciprofloxacin, and amikacin was significantly better in reducing bacterial burden in the lung (P<0.05), spleen (P<0.001), and liver (P<0.001) after eight days of treatment.
- Combination therapy of SIRTURO and clofazimine significantly reduced burden at 4 days of treatment in the lung (P<0.05), spleen (P<0.001), and liver (P<0.001) as well as after eight days of treatment in the lung (P<0.001), spleen (P<0.001), and liver (P<0.001) against untreated control.
    - Combination therapy was significantly better against all other therapies (P<0.05).

SCID Mice

- Eight days of SIRTURO treatment yielded a significant reduction in bacterial burden in the lung ($P<0.05$), spleen ($P<0.05$), and liver ($P<0.01$) compared to control.
- Combination therapy with SIRTURO and clofazimine for eight days also significantly reduced bacterial burden in the lung ($P<0.05$), spleen ($P<0.05$), and liver ($P<0.05$) compared to all treatments and control.

Mycobacterium leprae

Gelber et al (2009)[6] evaluated the activity of SIRTURO against *M. leprae* in mice.

Study Design/Methods

- Mice were infected with 5000 *M. leprae* organisms and treated orally with SIRTURO from day 60 to day 150 with various dosing schedules.
- The study population was divided into the following groups and received the following treatment for 3 months:
  - Control mice (untreated)
  - SIRTURO 5 times weekly: 1 mg/kg - 25 mg/kg
  - SIRTURO once weekly: 25 mg/kg - 100 mg/kg
  - SIRTURO once monthly: 25 mg/kg - 120 mg/kg
- *M. leprae* organisms were quantified at day 152 (completion of therapy), 3 months later (day 238), and some groups were followed-up at days 302-363.

Results

- *M. leprae* growth ($\geq 10^5$ organisms) was confirmed on day 152 in all control mice and the levels increased to $>10^6$ organisms on days 228 and 338.
- SIRTURO demonstrated bactericidal activity against *M. leprae*.
  - Growth was not seen in the mice treated with any of the SIRTURO dosing schedules on days 152 or 228. The levels decreased to $\leq 10^4$ SIRTURO. The bactericidal activity of SIRTURO (levels decreased to $\leq 10^4$) was also seen on days 302 and 363 in several groups treated with once weekly and once monthly schedules.

Mycobacterium ulcerans

Ji et al (2006)[7] evaluated the activities of SIRTURO against *M. ulcerans in vivo*.

Study Design/Methods

- Other antimicrobials that were evaluated included moxifloxacin, PA-824, linezolid, rifampin, streptomycin, and amikacin.
- For the in vivo experiment, mice were inoculated with a suspension containing 2.3×10^3 CFU *M. ulcerans* CU001.
- Mice were randomized into 12 groups and immediately began treatment monotherapy or combination therapy with the antimicrobial agents.
- SIRTURO was administered 5 times per week at a dose of 25 mg/kg for a total duration of 8 weeks.
- Efficacy was based on the survival rate and the mean number of CFUs.
- Regimens were considered bactericidal if the mean number of CFU per footpad in the mice was significantly lower than the pretreatment level.

Results

In Vitro Experiment

- The SIRTURO MIC range against the 29 clinical isolates of *M. ulcerans* was ≤0.015-0.12 µg/mL.
- The minimum inhibitory concentration required to inhibit the growth of 50% of organisms (MIC_{50}) was 0.03 µg/mL.
- The minimum inhibitory concentration required to inhibit the growth of 90% of organisms (MIC_{90}) was 0.06 µg/mL.

LITERATURE SEARCH

A literature search of MEDLINE®, EMBASE®, BIOSIS Previews®, and Derwent Drug File (and/or other resources, including internal/external databases) pertaining to this topic was conducted on 30 May 2023. Studies containing in vitro data were excluded.

REFERENCES

1. SIRTURO (bedaquiline) [Prescribing Information]. Titusville, NJ: Janssen Therapeutics, Division of Janssen Products, LP;https://imedicalknowledge.veevavault.com/ui/approved_viewer?token=7994-50129896-ad56-408e-a5f4-ad02663cb042.

2. Philley JV, Wallace RJ, Benwill JL, et al. Preliminary results of bedaquiline as salvage therapy for patients with nontuberculous mycobacterial lung disease. *Chest*. 2015;148(2):499-506.

3. Gil E, Sweeney N, Barrett V, et al. Bedaquiline as treatment for disseminated nontuberculous mycobacteria infection in 2 patients co-infected with HIV. *Emerg Infect Dis*. 2021;27(3):944-948.

4. Lounis N, Gevers T, Van den Berg J, et al. ATP synthase inhibition of mycobacterium avium is not bactericidal. *Antimicrob Agents Ch*. 2009;53(11):4927-4929.

5. Obregón-Henao A, Arnett KA, Henao-Tamayo M, et al. Susceptibility of mycobacterium abscessus to antimycobacterial drugs in preclinical models. *Antimicrob Agents Chemother*. 2015;59(11):6904-6912.

6. Gelber R, Andries K, Paredes RMD, et al. The Diarylquinoline R207910 Is Bactericidal against Mycobacterium leprae in Mice at Low Dose and Administered Intermittently. *Antimicrob Agents Ch*. 2009;53(9):3989-3991.

7. Ji B, Lefrançois S, Robert J, et al. In Vitro and In Vivo Activities of Rifampin, Streptomycin, Amikacin, Moxifloxacin, R207910, Linezolid, and PA-824 against Mycobacterium ulcerans. *Antimicrob Agents Chemother*. 2006;50(6):1921-1926.

8. Ruiz M, Okada M, Hara H, et al. Successful treatment of disseminated Mycobacterium abscessus in a pediatric patient with leukemia [abstract]. *Pediatric Blood and Cancer*. 2022;69 (Suppl 2):S165-S166.

9. Dadhwal R, Ali M, Howard L, et al. Successfully treated multidrug-resistant Mycobacterium simiae [abstract]. *Chest*. 2021;160 (Suppl 4):A290.