Venn diagram for 5 representative stranis of C.glabrata

Cgl-J5
304
142
97
106
Cgl-J2   90 47   121
290   76   1027   Cgl-J9
37   113   395
37   88056   120
82 107   108 161
97   62
72   137 61 63
291 71 92 45 338
Cgl-J6   Cgl-J10
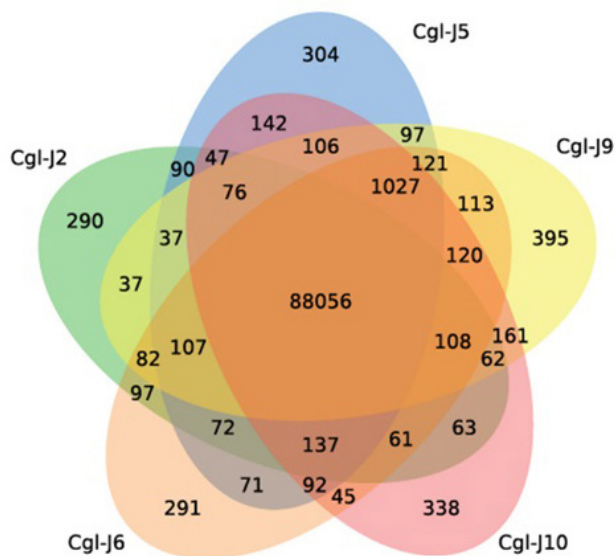
Conclusion. Mitochondrial dysfunction and SCVs may be under-recognized determinants of azole resistance in *CG*, if micro labs select single colonies from BCs for antifungal susceptibility testing, or in absence of prolonged incubation.

Disclosures. **Cornelius J. Clancy, MD**, **Merck** (Grant/Research Support) **Minh-Hong Nguyen, MD**, **Merck** (Grant/Research Support)

117. Trends in Four-class HIV Drug Resistance in Treatment-experienced Patients in the United States

Dusica Curanovic, PhD[1]; Johnny Lai, BS[1]; Christos J. Petropoulos, PhD[1]; Charles M. Walworth, MD[1]; [1]Monogram Biosciences, San Francisco, California

Session: O-24. New Developments in Infectious Diseases Diagnostics

Background. Despite the availability of potent antiretroviral therapy, only 56% of people living with HIV in the US were virally suppressed in 2018. Drug resistance can hinder suppression, especially among treatment-experienced patients, in whom the prevalence of 4-class drug resistance (4CR) is unknown.

Methods. Genotypic results of PhenoSense GT® *Plus* Integrase (Monogram Biosciences, South San Francisco, CA) obtained from Apr 2014 to Dec 2020 were used to assign susceptibility to nucleos(t)ide reverse transcriptase, non-nucleoside reverse transcriptase, integrase, and protease inhibitors (NRTIs, NNRTI, INIs, and PIs). Data were analyzed using summary statistics, 2 proportion Z test, one-way ANOVA and Tukey-Kramer; p < 0.05 was significant.

Results. Among 13,651 patients with 15,372 tests, median age was 43 years; most had HIV-1 subtype B infection (95.09%), followed by AG (1.32%).

Among 12,303 patients with only one test, 4CR prevalence was 1.55%. Among 1,348 patients with more than one test, 4CR was seen in 3.64% of patients, and in 4.60% if cumulative resistance reports were assembled for each patient. Patients with 4CR were significantly older than those with less resistance.

The incidence of 4CR fluctuated, with a decline from 2.61% of patients tested in 2014 to 1.38% in 2017, an increase to 2.36% in 2018, and a decline to 1.56% in 2020. Among patients with more than one test, 21.01% gained resistance to a drug in a new class over an average of 19.5 months.

Most new resistance each year was to NNRTIs, followed by NRTIs, INIs, and PIs. The incidence of PI resistance declined for PIs from 13.34% of patients tested in 2014 to 11.82% in 2020, but increased for INIs from 14.56% in 2014 to 16.49% in 2020. The regimen expected to be suppressive in the greatest proportion of patients was dolutegravir + darunavir/cobicistat (94.51%).

Conclusion. The prevalence of 4CR has declined over time, but remains clinically relevant, particularly in older patients who may struggle with adherence due to complex regimens, comorbidities and polypharmacy. New drug classes may benefit this group. The concurrent increase in INI and decline in PI resistance may reflect changes in prescribing practices. Drug resistance may be underestimated unless cumulative resistance is determined.

Disclosures. **Dusica Curanovic, PhD**, **Monogram Biosciences** (Employee) **Johnny Lai, BS**, **Monogram Biosciences** (Employee, Shareholder) **Christos J. Petropoulos, PhD**, **Monogram Biosciences** (Employee, Shareholder) **Charles M. Walworth, MD**, **Monogram Biosciences** (Employee, Shareholder)

118. Machine Learning Approaches to Predicting Treatment Outcomes for Carbapenem-Resistant Enterobacterales in a Region with High Prevalence of Non-Carbapenemase Producers

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Session: O-24. New Developments in Infectious Diseases Diagnostics

Background. Carbapenem-resistant Enterobacterales are a growing threat globally. Early detection of CRE is necessary for appropriate treatment and infection control measures. Many hospital labs can test for carbapenemase production; however, in some regions, including South Texas, the majority of CRE are non-carbapenemase producing (NCPE). This study had two interrelated aims to develop decision rules tailored to a region with high prevalence of NCPE to predict 1) antimicrobial resistance (AMR) from whole genome sequencing (WGS) data and 2) CRE treatment outcomes.

Methods. To better understand links between resistome, phenotypic AMR, and prediction of outcomes for CRE, we developed decision rules to build machine learning prediction models. We conducted WGS and antibiotic susceptibility testing (21 antibiotics) on CRE isolates from unique patients across 5 hospitals in the South Texas region between 2013 and 2020. Day 30 outcomes were based on desirability of outcome ranking (DOOR). The overall classification accuracies of the models are reported.

Results. Overall 146 CRE isolates were included, 97 were used to train each model, and 49 were used for validation. Among the *K. pneumoniae* and *E. coli* CRE isolates that were available with susceptibility data, the majority (62%) were NCPE. For the clinical recovery model (DOOR), the combination of admission ICU status, piperacillin-tazobactam (PT) MIC > 16, presence of *sul* gene, and polymyxin-sparring regimens associated with an overall accuracy of 95% for having a worse DOOR. Majority (60%) of patients were empirically treated with piperacillin-tazobactam; notably, less than 33% isolates had PT MIC ≤ 16. Interestingly, combined effects of isolates that did not harbor carbapenemases, blaOXA-1, blaCTX-M-15, blaCMY, or aac(6')ib-cr genes resulted in a decision rule with a 95.7% overall accuracy for susceptibility to PT (MIC < 16 ug/mL).

Conclusion. Herein, we used machine learning approaches to predict AMR and treatment-based outcomes linked with WGS data in a region with predominantly NCPE infections. Machine learning can obtain a model that can make repeatable predictions, further data can improve the accuracy and guide tailored clinical decision-making.

Disclosures. **Grace Lee, PharmD, PhD, BCPS**, **Merck Co.** (Grant/Research Support)**NIA/NIH** (Research Grant or Support)

119. A Humanized Antibody Targeting the CotH Invasins is Protective Against Murine Mucormycosis

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Session: O-25. New Findings in Medical Mycology

Background. Despite antifungal therapy and surgical debridement, overall mortality of invasive mucormycosis is >40%. Currently the world is witnessing an explosion in mucormycosis in India among COVID-19 patients with an official count of 28,252 cases as of 06/07/2021. Thus, novel therapeutic modalities are needed. We previously reported on a mouse monoclonal antibody (C2) targeting CotH invasins being protective against mucormycosis. Here, we humanized C2 MAb and assessed its efficacy *in vitro* and *in vivo*.

Methods. The C2 (IgG1) paratopes of the heavy chain and light chain were grafted on the most suitable human IgG1 with back mutations in the paratopes needed to restore binding of humanized clones to CotH3 (by biolayer interferometry using Gator). Clones were compared to C2 in their ability to prevent *Rhizopus delemar*-induced injury to A549 alveolar epithelial and primary human endothelial cells and for enhancing human neutrophil killing of the fungus *in vitro*. C2 and the humanized clones were also compared for their ability to protect neutropenic mice from mucormycosis induced by *R. delemar* or *Mucor cicrinelloides* with and without antifungal therapy.

Results. Three humanized clones showed 10-fold enhanced binding affinity to CotH3 protein (~5 nM for humanized *vs.* ~50 nM for C2). One humanized clone (VX01) doubled the ability of neutrophils to kill *R. delemar* and resulted in ~50% reduction in host cell damage. A single low dose of VX01 (30 µg) given 24 h post infection resulted in comparable survival of 60-70% in mice infected intratracheally

with either *R. delemar* or *M. cicrinelloides vs.* placebo mice (0% survival, *P* < 0.02). Importantly, VX01 acted synergistically in protecting mice when combined with liposomal amphotericin B or posaconazole in a severe model of mucormycosis with treatment starting 48 h post infection (~70% survival for combination *vs.* 0-20% survival for monotherapy and reduced lung fungal burden by 1.5 log, *P*< 0.001). GLP-tissue cross reactivity studies of VX01 showed favorable safety profiles.

Conclusion. VX01 shows enhanced binding to CotH3 protein and maintained the protective features of C2 MAb against murine mucormycosis. Clinical testing of combination therapy of VX01 + antifungals is warranted. VX01 is currently in manufacturing.

120. An open-label comparative trial of SUBA-itraconazole (SUBA) versus conventional itraconazole (c-itra) for treatment of proven and probable endemic mycoses (MSG-15): a pharmacokinetic (PK) and adverse Event (AE) analysis

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Session: O-25. New Findings in Medical Mycology

Background. C-itra is the drug of choice for treatment of most non-CNS, non-life-threatening forms of endemic mycoses (EM), including histoplasmosis, blastomycosis, coccidioidomycosis, sporotrichosis and talaromycosis. SUBA represents a new formulation of itraconazole that utilizes nanotechnology to improve bioavailability when administered orally. SUBA is formulated as nanoparticles allowing for absorption in the small bowel while not relying on gastric acidity for optimal absorption. MSG-15 is an open-label, comparative clinical trial comparing SUBA to c-itra for the treatment of EM. Herein we report the final PK and AE profiles of these two compounds.

Methods. Subjects with proven and probable EM were eligible this open-label comparative study. The protocol allowed up to 14 d of prior therapy with any antifungal for this episode of EM. Subjects were randomized to receive either SUBA 130 mg po bid or c-itra 200 mg po bid for up to 6 months. Follow up occurred at 7, 14, 28, 42, 84 and 180 d post-enrollment. PK samples were obtained at 7, 14, and 42 d. Clinical assessment, including symptom assessment, AEs, overall drug tolerance, and quality of life were assessed at each visit. We used descriptive statistics for this analysis.

Results. 89 subjects with EM entered the trial, including 43 on SUBA and 46 on c-itra. We measured PK serum levels of itra and hydroxyl-itra at days 7, 14, and 42 and these data are depicted in Figures 1-3. There were no significant differences in these levels, including combined itra/hydroxyl-itra levels, among the two study arms. AUC for itra and hydroxyl-itra were similar for both arms. AEs as assessed at each study evaluation were also quite similar among the two study arms. Overall, any AE occurred in 74% vs 85% of SUBA and c-itra recipients, respectively (NS). Drug-related AEs occurred in 35% vs 41% of SUBA and itra recipients, respectively (NS). Most common drug-related AEs included cardiovascular (edema and hypertension), nausea and loss of appetite.
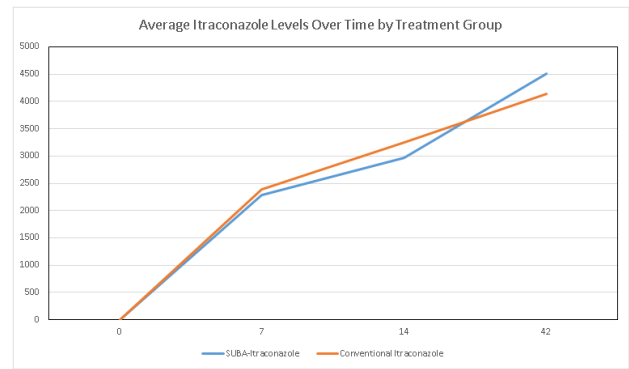
Mean Hydroxy-Itraconazole Concentration Over Time
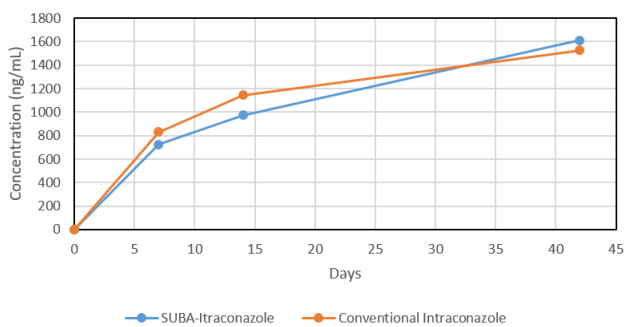
Mean Itraconazole Concentration Over Time
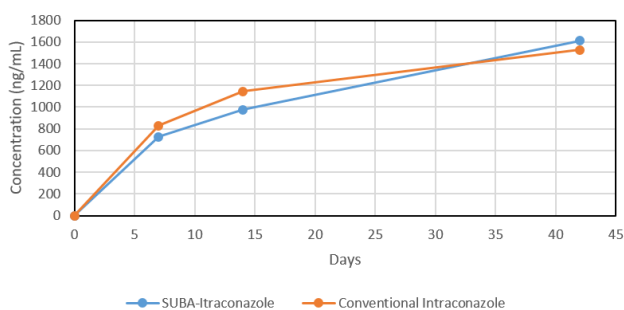
Combined Itraconazole and Hydroxy-itraconazole Concentration Over Time

Average Itraconazole Levels Over Time by Treatment Group

Conclusion. Compared to c-itra, SUBA demonstrates almost identical serum levels despite being dosed at roughly 60% standard dosing for c-itra (130 mg po bid vs 200 mg po bid). SUBA is slightly better tolerated than c-itra, although the specific AEs are similar.

121. Mucormycosis and COVID-19 in the United States: a Real-World Evidence Analysis of Risk Factors and Survival Among Patients with Mucormycosis, with and without COVID-19 Preceding the Infection

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Session: O-25. New Findings in Medical Mycology

Background. Mucormycosis has been associated with COVID-19 infections, notably in India, and known risk factors for mucormycosis such as diabetes mellitus have been studied in this context. This analysis aims to characterize patients in the US with mucormycosis, with and without COVID-19, by risk factor and mortality.

Methods. Data from the TriNetX Research Network representing over 66M de-identified patient-lives in the US was used to examine characteristics and outcomes among mucormycosis patients with and without preceding COVID-19 infection. Patients must have had a mucormycosis diagnosis recorded from 1/1/2020 to 6/8/2020. Patients were then identified as having either a COVID-19 diagnosis or positive SARS-CoV-2 RNA laboratory result (M+COV) or no COVID-19 diagnosis or positive RNA result (MnCOV) any time prior to through one day after the mucormycosis diagnosis. These cohorts were evaluated across characteristics recorded in the EMR within 1 year prior to and including the date of mucormycosis record. Mortality was evaluated with Kaplan-Meier statistics as survival until recorded death on or after mucormycosis diagnosis.

Results. Of 302 patients with mucormycosis from 1/1/2020-6/8/2021, 30 patients (10%) had M+COV, and 272 (90%) had MnCOV. Among the M+COV cohort, 22 patients (73%) had mucormycosis recorded within 2 weeks of COVID-19 infection. The M+COV and MnCOV cohorts had majority male sex (60,59%;p=0.93) and a similar prevalence of transplanted organs (40,28%;p=0.16), long-term drug therapy (60,54%;p=0.56), chronic kidney disease (43,31%;p=0.16), and glucocorticoid treatment (67,64%;p=0.76). The M+COV cohort had a greater prevalence of type II diabetes mellitus (67,35%;p< 0.01), acidosis (53,22%;p< 0.01), and posthemorrhagic anemia (43,14%;p< 0.01) than the MnCOV cohort. M+COV patients seem to progress to mortality more quickly than MnCOV patients (p=0.01, see Figure 1).

Figure 1. Survival until all-cause mortality after mucormycosis diagnosis, 0-180 days, among patients with (M+COV) and without (MnCOV) COVID-19 preceding the infection.
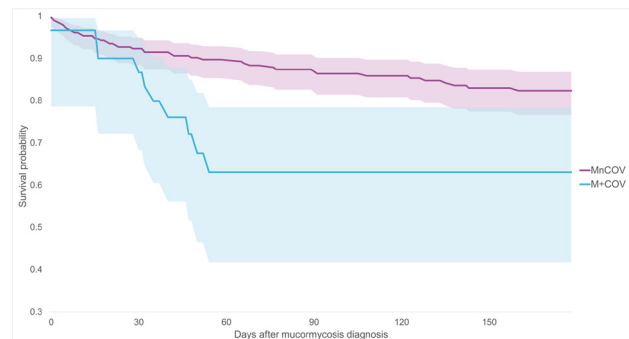
Conclusion. This study found that patients in the US with mucormycosis and current or previous COVID-19 infection have a greater prevalence of underlying conditions, including diabetes, and more rapid progression to mortality than those