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Penetration of Ibrexafungerp (formerly SCY-078) versus Micafungin at the Site of Infection in an Intra-abdominal Candidiasis Mouse Model

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ABSTRACT

Background: Ibrexafungerp (IBX), formerly SCY-078), is a novel, orally bioavailable, semisynthetic triterpenoid glucan synthase inhibitor in clinical development for treating multiple fungal infections, including invasive candidiasis. Promising data have been obtained for IBX from both *in vitro* and *in vivo* studies and in human clinical trials. Yet, little is known about drug penetration at the site of infection for intra-abdominal candidiasis (IAC), one of the most common types of invasive candidiasis associated with high mortality. Using matrix-assisted laser desorption/ionization mass spectrometry imaging (MALDI-MSI) and standard analytical techniques, we investigated tissue distribution and lesion penetration of IBX in a clinically relevant IAC mouse model.

Methods: Female 6-8 week old CD1 mice were infected intraperitoneally (IP) with $1x10^7$ CFU of *C. albicans* SC5314 in sterile stool matrix. A single oral dose of IBX (30mg/kg) or a single IP dose of micafungin (MFG, 5mg/kg) was administered to mice on day 3 post-inoculation. Mice were sacrificed at pre dose, and 1, 3, 6, 24, and 30 h post-dose. Blood was collected for serum drug concentration measurement. Liver and kidneys were collected for MALDI-MSI. Laser capture microdissection (LCM)-directed liquid chromatography coupled tandem mass spectrometry (LC-MS/MS) was performed to quantify drug levels within different tissue sub compartments. In the repeated dose experiment, mice were treated with 2 days of IBX (15 mg/kg, BID) or MFG (5 mg/kg, QD), and drug accumulation was analyzed at 24, 48, and 72 h post the last dose.

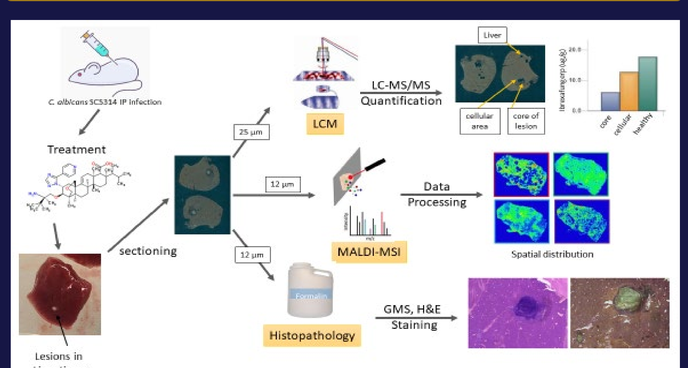
Results: IBX quickly distributed into tissues after a single dose and efficiently accumulated within lesions. Drug concentrations of IBX within the necrotic center of liver abscesses were 35.9 and 10.2 µg/g at 24 and 30 h post-dose, respectively, almost 100-fold higher than the serum concentrations at corresponding time points. Robust and long-lasting lesion penetration of IBX was observed after two days of treatment, with 21.0 and 9.0 µg/g of IBX retained within necrotic core at 48 and 72 h post the last dose. In comparison, MFG within lesions was 0.96 µg/g at 48h and completely undetectable at 72h after two days therapy.

Conclusions: IBX penetrates into intra-abdominal abscesses highly efficiently. It holds promise as a potential therapeutic option for IAC patients.

INTRODUCTION

Intra-abdominal candidiasis (IAC) is a prominent invasive fungal infection associated with high mortality[1]. Echinocandins are recommended as first-line agents; however, their clinical effectiveness is highly variable, with known potential for breakthrough resistance. Ibrexafungerp (IBX) is a novel, orally bioavailable, semisynthetic triterpenoid glucan synthase inhibitor in clinical development for treating multiple severe fungal infections, including invasive candidiasis. Promising data have been obtained for IBX from both in vitro and in vivo studies. Yet, little is known about drug penetration at the infected tissue sites. This study was aimed to evaluate the penetration of IBX at the site of infection in *a* clinically relevant IAC mouse model due to *C. albicans*.

MATERIALS AND METHODS[2]



RESULTS

Figure 1 30mg/kg IBX (PO), serum

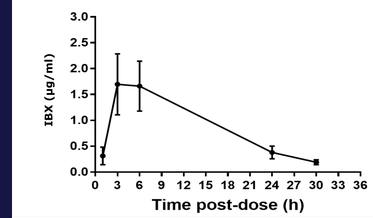


Figure 1 (top) : **IBX serum drug concentration-time curve following a single oral dose at 30mg/kg.**

Figure 2 (right) : IBX distribution in infected liver tissues.
Ion maps of IBX in representative liver tissues collected at 1, 3, 6, 24, 30h after a single oral dose of IBX at 30mg/kg. GMS and H&E staining of adjacent sections are shown below each set of ion maps. The signal intensity bar gradually increases from blue (no signal) to red (maximum signal).

Figure 2 SINGLE-DOSE

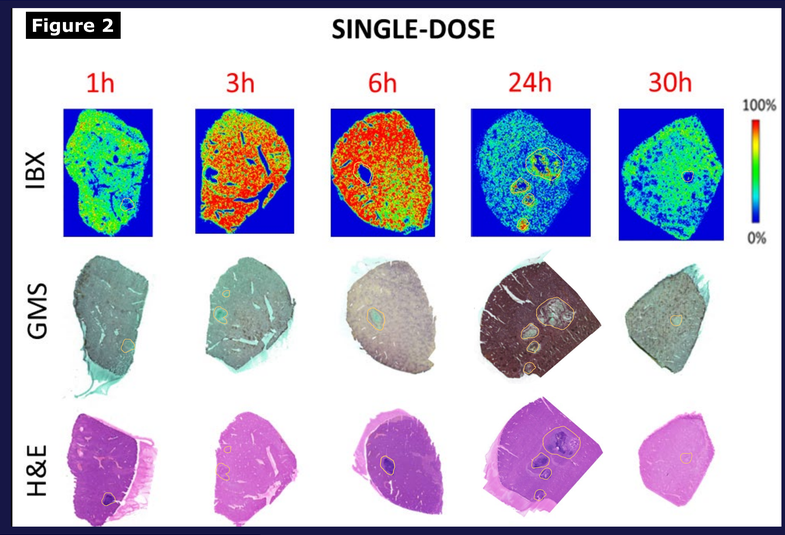


Figure 3 30 mg/kg IBX, liver

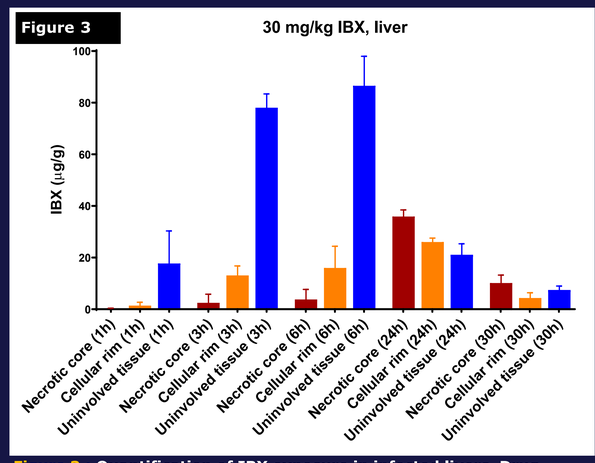


Figure 3 : Quantification of IBX exposure in infected livers. Drug concentrations in lesions (necrotic core, cellular rim) and uninvolved tissues dissected from liver sections collected at 1, 3, 6, 24, and 30h after a single oral dose of Ibrexafungerp (IBX) at 30mg/kg.

Figure 4 5 mg/kg Micafungin

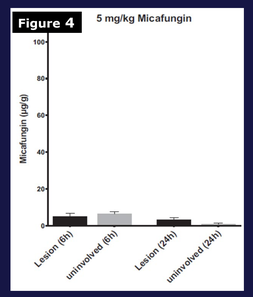


Figure 5 Serum drug concentration two days Tx of IBX vs. MFG

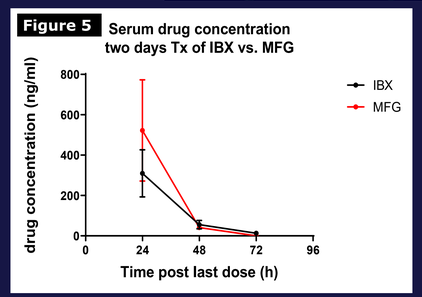


Figure 4 (upper left) : MFG concentrations in liver lesions and surrounding uninvolved tissues collected at 6 and 24h post single dose treatment at 5mg/kg.

Figure 5 (upper right) : Serum drug concentration-time curves at 24, 48, and 72 h after the last dose of two days treatment of IBX (PO) at 15mg/kg b.i.d. or MFG (IP) at 5mg/kg q.d.

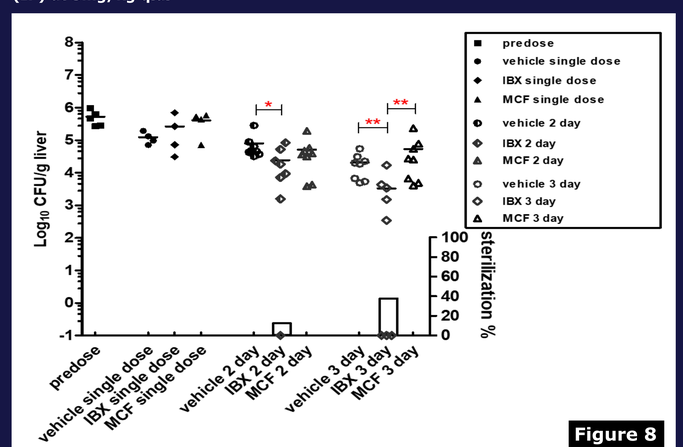


Figure 8

Figure 8 : Liver burden comparison at pre-dose, single-dose treatment, 2 and 3 days treatment with IBX at 15mg/kg BID, MCF at 5mg/kg QD, and vehicle control.
*** *P*< 0.05; ** *P*<0.005**

Figure 6 STEADY-STATE

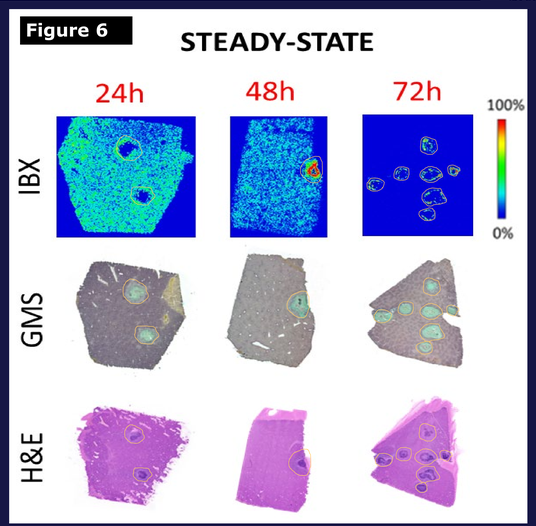


Figure 6 : Drug penetration after multiple doses of IBX. Ion maps of IBX in representative liver tissues collected at 24, 48, 72h after the last dose of two days treatment of IBX at 15 mg/kg, b.i.d. GMS and H&E staining of adjacent sections are shown below each set of ion maps. The signal intensity bar gradually increases from blue (no signal) to red (maximum signal).

Figure 7 2 days Tx of Micafungin vs. 2 days Tx of IBX

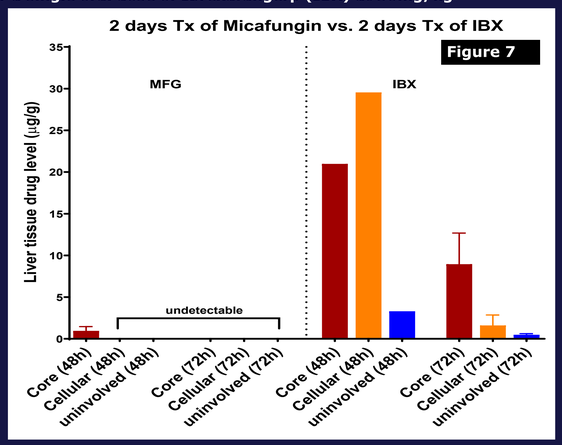


Figure 7 : Drug accumulation comparison in infected liver compartments between repeated doses of MFG and IBX. Drug concentration was measured in lesions (necrotic core, cellular rim) and uninvolved areas dissected from liver sections collected at 48 and 72h after the last dose of two days treatment of MFG (IP) at 5mg/kg q.d. or IBX (PO) at 15mg/kg b.i.d.

CONCLUSIONS

- ✓ **IBX penetrates into and accumulates within intra-abdominal abscesses highly efficiently, resulting in superior antifungal efficacy compared to micafungin.**
- ✓ **It holds promise as a potential therapeutic option for IAC patients.**

REFERENCES

1. Vergidis P, Clancy CJ, Shields RK, Park SY, Wildfeuer BN, Simmons RL, Nguyen MH. 2016. Intra-Abdominal Candidiasis: The Importance of Early Source Control and Antifungal Treatment. PLoS One 11:e0153247.
2. Zhao, Y., Prideaux, B., Nagasaki, Y., Lee, M., Chen, P., Blanc, L., Ho, H., Clancy, C., Nguyen, M., Dartois, V. and Perlin, D. (2017). Unraveling Drug Penetration of Echinocandin Antifungals at the Site of Infection in an Intra-Abdominal Abscess Model. *Open Forum Infectious Diseases*, 4(suppl_1), pp.S479-S479.

ACKNOWLEDGEMENTS

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