Novel use of Ritonavir boosting to achieve therapeutic itraconazole levels in disseminated Histoplasmosis

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Background

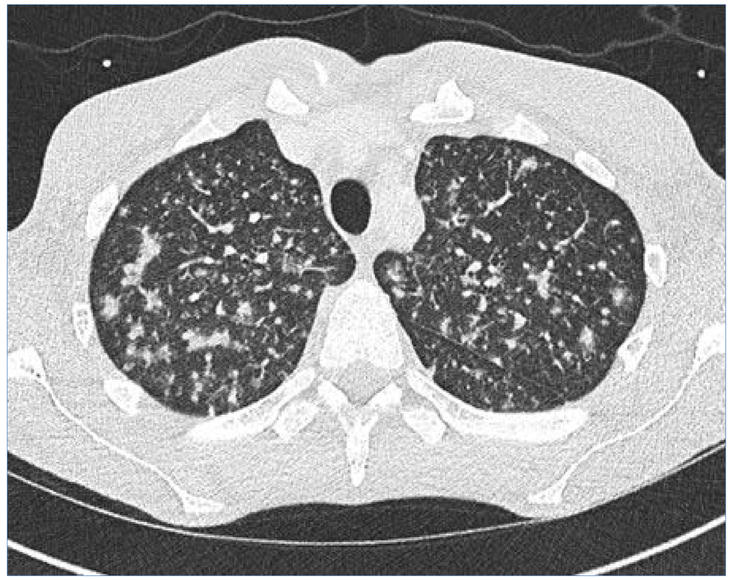
Itraconazole (ITZ) is a poorly soluble antifungal drug with variable pharmacokinetics. Serum levels vary between patients and over time, due to absorption issues and drug-drug interactions. Itraconazole suspension has more predictable absorption than capsules, but is poorly tolerated. Newer formulations dispersing drug in polymer aim to improve bioavailability, but are costly and not widely available. Standard therapy for histoplasmosis is induction with liposomal amphotericin B (LAmB) followed by 12+ months of itraconazole therapy with target pre-dose levels of 1-2 mg/L. Adverse events increase when levels are ≥ 4 mg/L.

Clinical Presentation

A 33yo male presented with weight loss, fever and dyspnoea, having returned to the UK from Central America, where he had been involved in a coastal building project. His background included a diagnosis of Crohn's disease, with a prior 60cm small bowel resection. He had been stable on long-term adalimumab and azathioprine until symptoms began a few months before presentation. On admission, there was acute kidney injury, severe hypercalcaemia and pancytopaenia. Imaging demonstrated innumerable pulmonary nodules (Fig. 1), splenomegaly, and bowel thickening.

Empiric anti-tuberculous and antifungal therapy with liposomal amphotericin B (LAmB) was commenced, pending confirmation of diagnosis, and immunosuppressants were discontinued. On day 9 of admission disseminated histoplasmosis was confirmed on urinary antigen testing (MiraVista Diagnostics, Indianapolis, USA) with a level above the measurable limit, as well as ultimately being cultured from blood after 16 days incubation followed by 3 days of subculture onto Sabouraud agar. Anti-TB therapy was discontinued.

Figure 1. CT thorax



Admission CT thorax demonstrated innumerable miliary lung nodules and enlarged mediastinal and hilar lymph nodes measuring up to 1.4 cm.

His course was complicated 3 months after presentation by significant bowel inflammation and obstruction, ultimately requiring subtotal colectomy and end-ileostomy. Histology of resected colonic tissue demonstrated numerous yeast forms and marked inflammation, potentially consistent with an immune reconstitution inflammatory syndrome. Since surgery, he has had a high output stoma, with rapid transit time and reduced absorption, requiring total parenteral nutrition as an inpatient and IV fluid and electrolyte replacement for several months following discharge.

Antifungal Therapy

Itraconazole is the azole of choice for the treatment of histoplasmosis with a much lower rate of relapse than fluconazole. Isavuconazole has been used in too few patients with histoplasmosis to be recommended. Oral posaconazole and voriconazole have been reported to be effective in a small number of patients with AIDS or other immunosuppressive conditions and may be reasonable alternatives for patients who are moderately ill and intolerant of itraconazole or for those with *Histoplasma* meningitis [1]. The patient's issues with pre-existing short bowel and further resection were a significant challenge for all oral medicines, including alternate azoles.

Serum trough itraconazole levels were sent to the UK Health Security Agency Mycology Reference Laboratory. Despite itraconazole dose titration to 300mg TDS, levels were generally < 0.5 mg/L and maximum serum itraconazole level achieved was 0.64 mg/L during the first 4 months of therapy [Fig. 2]. LAmB was continued during this time, despite some renal and electrolyte derangement. The patient had been trained to self-administer LAmB intravenously via a Hickmann line, as part of planning for outpatient parenteral antimicrobial therapy (OPAT) for the entirety of treatment.

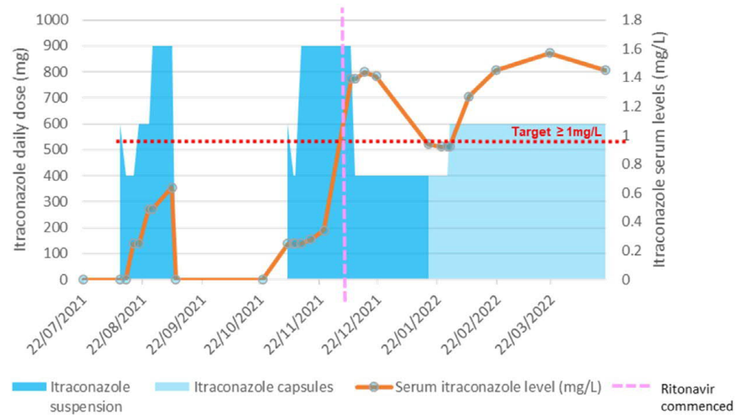
Effect of Ritonavir

On day 117 of antifungal therapy, ritonavir (RTV) 100mg once daily was added to itraconazole suspension 300mg TDS. Four days after this, itraconazole level was 1.39 mg/L (from 0.34 mg/L). ITZ dose was reduced and target concentration was maintained even after a switch from itraconazole suspension to capsules [Fig. 2].

Ritonavir and itraconazole are both inhibitors of cytochrome P450 3A4 (CYP3A4), with ritonavir more potent, resulting in considerable drug–drug interactions. Itraconazole is also a substrate of CYP3A4. Ritonavir dosed as a pharmacokinetic enhancer is expected to increase the plasma concentrations of itraconazole. Experience with co-administration of ritonavir-boosed HIV protease inhibitors results in increased plasma itraconazole levels due to this enzyme inhibition. This has led to the practice of reducing itraconazole doses for patients on protease inhibitor-based antiretrovirals. Until now, there was no data on using ritonavir as a pharmacological booster for itraconazole in patients without HIV and concomitant protease inhibitor.

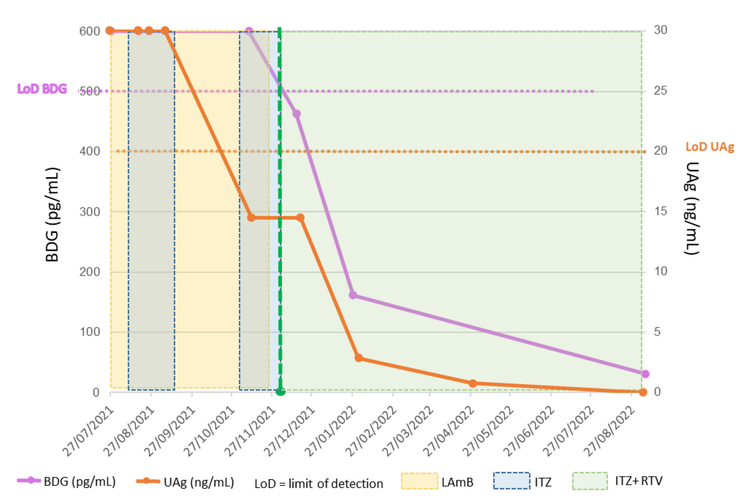
A response in fungal markers (serum beta-D-glucan and urine *Histoplasma* antigen) became most evident after RTV introduction when itraconazole levels were finally therapeutic [Fig. 3]. The patient is now day 400+ of therapy and due to complete soon.

Figure 2. Itraconazole dosing and levels pre- and post-ritonavir



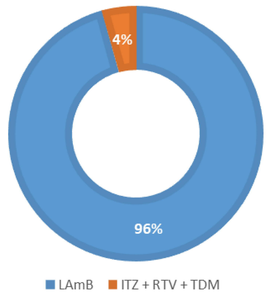
Total daily itraconazole (ITZ) dose in milligrams (suspension followed by capsules) was mapped over time. LAmB alone was used in the period surrounding the colorectal surgery. Serum ITZ levels dramatically increased 2 days after the introduction of ritonavir 100mg once daily and remained above target trough even after switching to itraconazole capsules.

Figure 3. Fungal biomarker (serum B-D-glucan) and quantitative *Histoplasma* urinary Ag) response to antifungal therapy



The response of serum beta-D-glucan and quantitative urinary Histoplasma *antigen EIA (Miravista Diagnostics) is represented alongside concurrent antifungal therapy. Of note, the first four urinary Histoplasma Ag levels were reported as above the limit of detection (> 20 ng/mL) and are represented here as an arbitrary value of 30 ng/mL. Similarly, initial serum beta-D-glucan values were above the limit of detection (>500 pg/mL) and are represented as an arbitrary value of 600 pg/mL. Cut-off for positivity with this assay is >80 pg/mL.*

Figure 4. Relative costs of antifungal strategies



To date, more than 12 months of therapy has been delivered. The first 4 months used liposomal amphotericin B (LAmB) alongside escalating doses of itraconazole suspension, without achieving target levels. The latter 8+ months of therapy has combined itraconazole capsules with ritonavir and consistently achieved stable target trough concentrations, as well as demonstrating fungal biomarker response. This switch allowed avoidance of long-term LAmB, and delivered an estimated cost saving for the last 8 months of over £140,000.

LAmB = liposomal amphotericin B; ITZ = itraconazole; RTV = ritonavir; TDM = therapeutic drug monitoring

Conclusion

Itraconazole pharmacokinetics is variable and unpredictable. To date, strategies to improve this have focused on improving absorption. We demonstrate for the first time that inhibiting itraconazole metabolism is an effective way to enhance itraconazole levels. Use of ritonavir alone to boost itraconazole levels has not previously been described. It avoids the longer-term complications of intravenous access, including infection and thrombosis, as well as potential adverse renal and other effects of liposomal amphotericin B. It is a less onerous regimen for patients. In addition, the last 8 months of therapy with RTV-boosted itraconazole, including the measurement of serum ITZ levels, accounted for only 4% of the cost of 12 months of treatment [Fig. 4]. Careful addition of ritonavir may offer a reliable and cost-effective method of boosting itraconazole levels where other drug:drug interactions do not preclude its use.

References

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