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CASE REPORT

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Lumacaftor/ivacaftor initiation in two liver transplantation patients under tacrolimus and antifungal azoles

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Key Clinical Message

We report the initiation of CFTR modulator lumacaftor/ivacaftor combination (LUM/IVA) in two adolescents with cystic fibrosis who were treated with antifungal azoles (AZO) and tacrolimus (TCS) for liver transplantation. Despite multiple drug-drug interactions, maintaining therapeutic TCS levels was achievable. During the following year, LUM/IVA was well tolerated, providing clinical benefits.

KEYWORDS

azoles, cystic fibrosis, ivacaftor, lumacaftor, tacrolimus

1 | INTRODUCTION

The use of the CFTR modulator lumacaftor/ivacaftor combination (LUM/IVA) is part of the pharmacopeia for cystic fibrosis (CF) patients. However, it is not recommended for patients receiving tacrolimus (TCS) for solid organ transplantation because of the drug-drug interaction.[1] As a cytochrome P450/3A4 (CYP3A4) inducer, LUM/IVA decreases blood levels of the molecules that are substrates of CYP3A4 such as TCS.[2]

As recently underlined in a review paper by Mitchell et al, CFTR modulators should sooner or later become available for a large proportion of patients, some of which will likely require solid organ transplantation.[3] Do patients receiving these medications should definitively be excluded from transplantation program is actually an open question.

To begin to answer this question, we report two cases of adolescents followed in different CF centers receiving TCS for liver transplantation (LT) in which LUM/IVA was initiated because of progressive respiratory status worsening.

2 | CASE 1

A 17-year-old male patient underwent a LT in March 2014. In the year preceding LT, *Aspergillus fumigatus* (AF) and *Scedosporium apiospermum* (SAp) were recovered in his sputum cultures. Because of a high risk of post-LT systemic scedosporiosis and/or invasive aspergillosis, he was put under voriconazole (VCZ). Before LT, his FEV_1 was 76%. LT was performed using a deceased liver donor and was uncomplicated. He initially received TCS and mycophenolate mofetil, the latter being withdrawn in September 2014 because of hematological toxicity. VCZ was stopped because the patient's respiratory condition was good and both AF and SAp were no longer recovered. Unfortunately, his respiratory status gradually worsened, with repeated low-volume hemoptysis and rapid lung function decline (at its nadir, FEV_1 was measured at 60%). SAp was again recovered and VCZ was resumed. FEV_1 stabilized at 60% but repeated low-volume hemoptysis still occurred. Therefore, 11 months after LT, it was decided to introduce LUM/

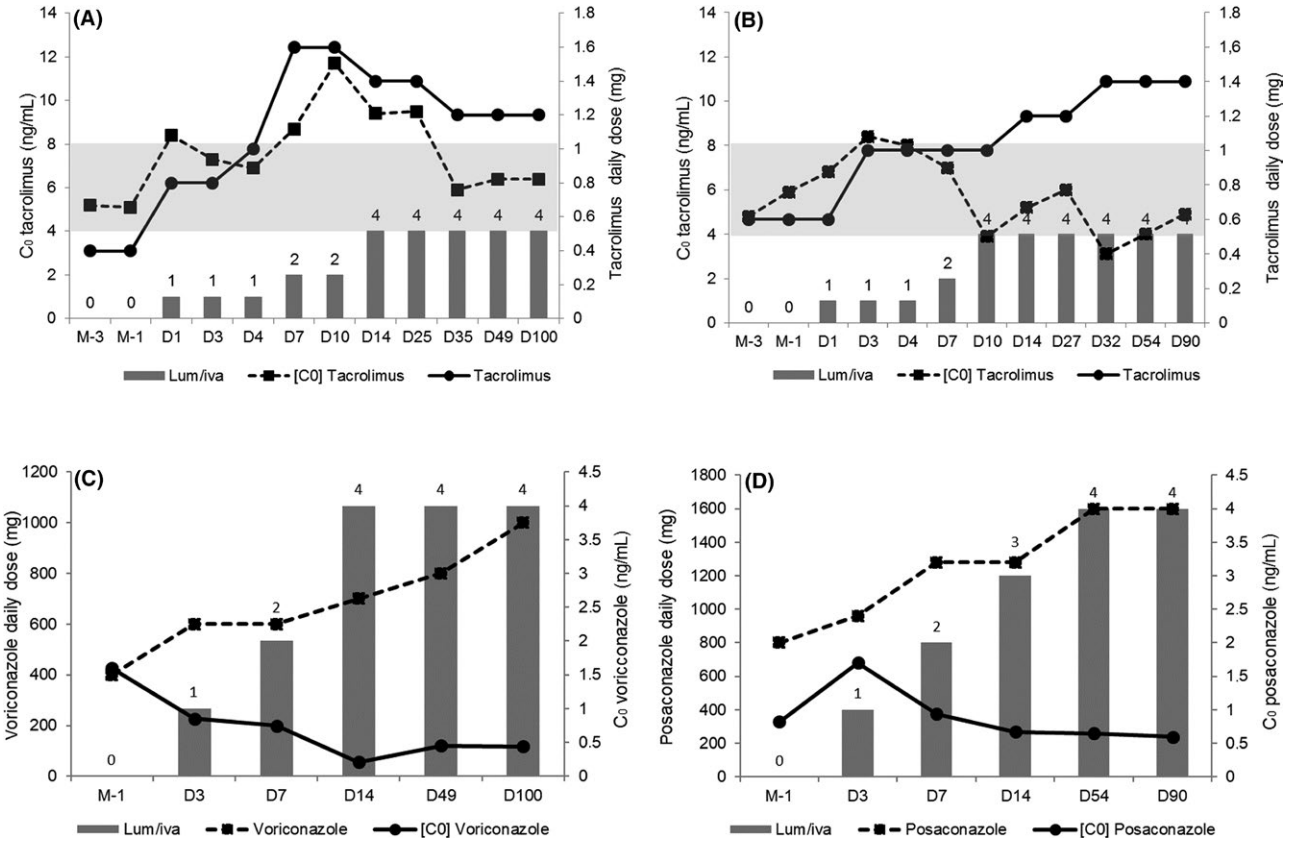

FIGURE 1 Residual concentrations ($[C_0]$) of tacrolimus over time in case 1 (A) and case 2 (B) after lumacaftor/ivacaftor (250 mg/200 mg) initiation. Gray bands on panels A and B represent tacrolimus therapeutic targets after the 1st year of liver transplantation ($[C_0]$ of tacrolimus between 4 and 8 ng/mL). Vertical gray bars on panels A and B represent the gradual increase in the number of LUM/IVA pills administrated daily. Although not indicated on panels A and B, the progressive increase of LUM/IVA pills included a step to three pills (between D10 and D14 in case 1; between D7 and D10 in case 2). Time points given on the x-axis of panels A and B do not exactly correspond to drug modification times or monitoring. These should be viewed as in between time points. Lower panels represent $[C_0]$ for voriconazole (C) and posaconazole (D)

IVA in this patient receiving TCS (0.6 mg/d) and VCZ (400 mg/d). LUM/IVA (200 mg/125 mg) was introduced during hospitalization. It was started at one pill a day for 5 days, then one pill twice a day until reaching the final dose (two pills twice a day) at day 14. There was no immediate adverse event. Progression of TCS residual concentrations (C_0) after LUM/IVA introduction is shown in Figure 1A. A relative increase of 130% of TCS was needed before reaching its therapeutic targets (4-8 ng/mL). LUM/IVA introduction was also responsible for a steeper VCZ C_0 decrease that remained below therapeutic targets despite a successive increase (Figure 1C). Liver function tests remained within normal ranges during the following year; clinical tolerance was good. A 13% absolute increase in FEV_1 was observed at M1 and M6, which decreased thereafter (Figure 2).

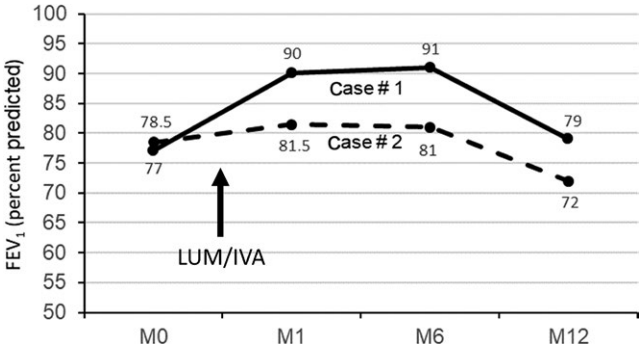

FIGURE 2 Patients FEV_1 progression during the year following LUM/IVA initiation (arrow). M0 reports FEV_1 value collected immediately before LUM/IVA initiation

3 | CASE 2

An 18-year-old female patient underwent a LT in January 2002. The LT was performed using a deceased liver donor. The clinical course was marked by an acute rejection in April 2002. The patient was chronically colonized by *Pseudomonas aeruginosa* with a mean need for two IVs a year, and she was also receiving posaconazole (PCZ) for a chronic AF airway colonization prior to LT. Because her respiratory status gradually deteriorated despite treatment, it was decided to introduce LUM/IVA (200 mg/125 mg) 15 years after LT (April 2017). Fifteen days before LUM/IVA initiation, the

daily TCS dose was progressively increased from 0.4 mg to 0.8 mg. Her FEV_1 was 78.5%. TCS was introduced during hospitalization. The patient received one pill a day of LUM/IVA for 6 days, then one pill twice a day for 4 days until the full daily dose was given at day 14. There were no short-term safety concerns. TCS C_0 decreased slightly after LUM/IVA introduction but then remained within therapeutic ranges (Figure 1B). The daily TCS dose was increased to 200% compared to the starting dose (Figure 1B). The drop in PCZ C_0 was steeper and remained below therapeutic targets despite a gradual increase (Figure 1D). Liver function tests remained within normal ranges; clinical tolerance was good. A moderate increase in FEV_1 was noted at M1 and M6, but did not continue beyond the 1st year (Figure 2).

4 | DISCUSSION

We report that introducing LUM/IVA in patients receiving TCS for LT was safe with a good tolerance both short- and mid-term and some clinical benefit. We also shown that despite multiple drug-drug interactions, it was possible to maintain achievable TCS blood levels in those patients.

LUM/IVA was introduced in two different ways by different CF teams (100% increase of the daily dose of TCS 2 weeks before the first dose of LUM/IVA in case # 2; no pre-LUM/IVA increase in case # 1). It seems that the "pre-LUM/IVA increase" approach used in case # 2 was the most appropriate to initially maintain TCS levels within therapeutic ranges. In these two patients, whose immunosuppression was relatively low and with lower therapeutic ranges of TCS, the 100% pre-LUM/IVA increase made it possible to maintain adequate TCS blood levels and avoided TCS under-dosing as seen in patient # 1 after the second step of the LUM/IVA increase. The half-life of tacrolimus varies greatly among healthy individuals and liver transplantation patients. After oral 0.3 mg/kg daily dose administration, steady-state concentrations of TCS are reached at day 3.[4] This means that a 100% pre-LUM/IVA increase of TCS between 3 and 6 days before LUM/IVA introduction would be warranted to avoid TCS dropping below therapeutic targets in LT patients in the late phase of their immunosuppression. A different approach would be needed at the earliest phase of LTs that require maintenance of higher TCS blood levels.

The need for antifungal azoles in our patients was a matter of added complexity. On one hand, antifungal azoles are inhibitors of CYP3A4, 2C9, and 2C19 and are responsible for an increase in TCS blood levels.[5] On the other hand, LUM/IVA is a strong inducer of CYP3A4 and therefore decreases blood levels of other CYP3A4 substrates such as VCZ and PCZ.[2] The LUM/IVA induction effect was much steeper on both VCZ and PCZ than on TCS. Finally, the concomitant use of azoles in our cases can be seen as beneficial because it likely participated in maintaining adequate TCS levels. However, whenever possible, we would advise withdrawing azoles before LUM/IVA initiation, or using azoles not metabolized through CYP3A4 such as itraconazole.[2]

In conclusion, based on these two cases, we found that the initiation of LUM/IVA in patients who have received transplants with CF immunosuppressed with TCS and also receiving azoles may be safe and well tolerated with clinical benefits.

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AUTHORS CONTRIBUTION

IC: collected the data and wrote the first draft of manuscript. NL-S: obtained patient consent and reviewed manuscript edits. PR: obtained patient consent and reviewed manuscript edits.

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REFERENCES

1. (CHMP) CfMPfHU. Assessment report. Orkambi. International non-property name: LUMACAFTOR/IVACAFTOR. Assessment report-EMA/667775/2015. 24 september 2015:1-103.
2. Jordan CL, Noah TL, Henry MM. Therapeutic challenges posed by critical drug-drug interactions in cystic fibrosis. *Pediatr Pulmonol*. 2016;51(S44):S61-S70.
3. Mitchell RM, Jones AM, Barry PJ. CFTR modulator therapy in patients with cystic fibrosis and an organ transplant. *Paediatr Respir Rev*. 2018;27:6-8.
4. (CHMP) CfMPfHU. Summary information on referral opinion pursuant to article 30 of council directive 2001/83/EC for Prograf and associated names. Assessment report-EMA/85997/2006. 10 April 2006.
5. Vanhove T, Bouwsma H, Hilbrands L, et al. Determinants of the magnitude of interaction between tacrolimus and voriconazole/posaconazole in solid organ recipients. *Am J Transplant*. 2017;17(9):2372-2380.

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