HIV and solid organ transplantation: The Swiss experience

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Highly active antiretroviral therapy (HAART) has changed the natural course of HIV disease. In a majority of patients, complete suppression of viral replication and immunological recovery can be accomplished. Despite these achievements, persons with HIV infection are at a significant risk for end-stage organ disease. One third of them are co-infected with hepatitis C (HCV) and/or hepatitis B virus (HBV). Additional causes are related to direct or indirect effects of HIV itself (eg HIV-associated nephropathy). Solid organ transplantation (SOT) is often the only therapeutic option remaining, although HIV infection was considered a contraindication before the advent of HAART. However, in recent years, a considerable number of HIV-infected patients has undergone SOT with encouraging results [1]. In 2001, out of 18,014 US medicare solid organ recipients, 175 were HIV-positive. With a median follow-up of 42 months, no significant difference between HIV-negative and HIV-positive recipients was found in this retrospective analysis for a number of variables such as graft survival,

death-censored graft survival, death with functioning organ or mortality [2].

Ragni et al. published the first results of experience with liver transplantation and HIV. The results were comparable to the non-HIV population, with the subgroup of HCV-positive recipients showing a poorer outcome [3]. Despite these results, a survey performed in 2004 among 619 surgeons (all members of the American Society of Transplant Surgeons) showed that 70% would accept a HBV or HCV-positive recipient, but only 36% would accept a HIV-positive patient, even if his HIV infection was controlled [4]. This number dropped to 6% when patients with AIDS were included. Thus, SOT in HIV-patients is not yet uniformly accepted. The question of availability of SOT in patients with a HBV/HCV and HIV coinfection is all the more important, as disease progression is accelerated when compared to patients infected only by HCV or HBV [5].

Interactions between antiretroviral drugs and immunosuppression have emerged as a major challenge in HIV-infected patients after SOT. In addition Stock et al. reported on a possible increase in the number of rejection episodes after kidney transplantation in HIV-infected patients [6].

We assessed the current status of SOT in HIV-infected patients in Switzerland. With the use of a structured questionnaire, clinical course, side effects and drug interactions were recorded for all HIV-positive solid organ recipients. We included all HIV-positive patients who had received a solid organ so far in Switzerland. All patients participated in the Swiss HIV Cohort Study. The goal of this investigation was to identify specific problems associated with SOT and HIV, and to present our Swiss experience to a broader medical audience. We wish to contribute to the discussion about the inclusion of HIV-infected persons in transplant programs, and to enhance awareness of this new therapeutic modality. The course and outcome of eight HIV-positive patients transplanted in Switzerland is described.

Clinical course and cause of end-stage organ disease (table 1). Five patients received a cadaveric liver (two for cirrhosis due to HCV, one for cirrhosis due to HBV, one for fulminant hepatitis due to HBV reactivation, and one for HBV/HCV co-infection with hepatocellular carcinoma), and three received a cadaveric kidney/pancreas and kidney (one for end-stage renal failure due to diabetes, one for terminal kidney disease of unknown aetiology, one for HIV-associated nephropathy). Median follow-up was 19 months (range 7–61). The immunosuppressive regimen is detailed in table 1. Patient #1 died with liver failure after HCV recurrence. Patient #4 died with liver failure due to chronic rejection of the graft and renal insufficiency after unilateral nephrectomy for renal carcinoma and immunosuppressive drug toxicity. Of the six patients alive, three liver and two kidney recip-

ient had a good graft function at the time of analysis. In one patient, the graft failed due to chronic rejection resulting in dialysis. Four patients have had rejection episodes.

Course of HIV-infection. One previously reported patient was a long-term non progressor showing stable CD4 cell counts without antiretroviral therapy [7]. One patient had been diagnosed with a *Pneumocystis jiroveci* (*carinii*) pneumonia earlier. With the exception of the long-term non progressor all had experienced nadir CD4 cell counts <200/μl prior to transplantation. At the time of transplantation, three of these patients had counts above 200 cells/μl, and four had counts below. In two of these patients, it is likely that the concomitant liver cirrhosis prevented a further immunological recovery despite full viral suppression. In the two remaining patients, transplantation had been performed not knowing the HIV status in one case, in the other, only the last value before transplantation was below 200 cells/μl, while all the earlier CD4 cell counts had been above 200 cells/μl. Importantly, in all of the 7 HIV-infected patients under therapy, HIV replication remained suppressed, and none developed HIV-related complications.

Drug interactions and side-effects. In six patients (#1, 4–8), drug interactions and side effects necessitated a modification of HAART. In patient #1, ritonavir-induced inhibition of CYP3A4 activity led to very high levels of tacrolimus, and ritonavir was replaced by ritonavir-boosted lopinavir. A combined effect of mycophenolate mofetil and zidovudine was responsible for severe anaemia in patient #4. Mycophenolate mofetil was stopped, and stavudine given instead of zidovudine. Later, stavudine was replaced by tenofovir; this change was made for better control of hepatitis B, as tenofovir has excellent activity against HBV. Patient #5 experienced renal toxicity probably related to cyclosporine A, and modification of his tenofovir dose was necessary. In patient #6, ritonavir-boosted lopinavir replaced efavirenz at the time of transplantation, because of concerns of insufficient viral control by efavirenz. As in patient #1, this led to very high tacrolimus levels and a difficult adjustment of therapy. Patient #7 showed low levels of cyclosporine A despite good adherence. An interaction with ritonavir-boosted lopinavir is unlikely because the low levels persisted after changing to ritonavir-boosted atazanavir. This change of therapy was provoked by a massive dyslipidaemia with cholesterol levels of 20,1 mmol/l, which was most likely a combined and potentiated effect of both cyclosporine A and ritonavir-boosted lopinavir, two drugs known to increase lipid levels. Finally, in patient #8, two relevant interactions were observed. The concomitant use of atazanavir and omeprazole, a proton pump blocker, led to undetectable blood levels of atazanavir despite regular intake. Omperazole had been started at time of transplantation as part "routine" pre-

vention of gastrointestinal ulceration without informing the physician in charge of the anti-HIV treatment. Despite boosting of atazanavir with ritonavir and increase of the dose, reliable levels of atazanavir were only achieved after discontinuation of omeprazole. The second observation concerned the interaction between ritonavir-boosted atazanavir with tacrolimus, which necessitated a progressive lowering of the tacrolimus dose from an average of 6 mg/day to 0.14 mg/day.

In the Western hemisphere, better control of HIV infection has led to immunological recovery in many patients, and to a greatly decreased HIV-related mortality and morbidity. Concomitant health-related issues have emerged as new challenges in this population. 30% of HIV-infected individuals have a co-infection with HBV or HCV. The course of HBV and HCV infection is accelerated in patients with HIV infection. Additional potential causes of end-stage organ disease are side effects of drugs, or HIV-related direct or indirect effects (eg HIV nephropathy). For these patients, solid organ transplantation is often the only therapeutic option remaining. Despite an increasing number of reports showing a comparable outcome between HIV and non-HIV-infected solid organ recipients, this therapeutic modality is still used very reluctantly.

To date, only eight HIV-positive individuals have had a solid organ transplantation in Switzerland. Since the routine recording of liver failure-associated deaths in the HIV cohort in 1999, a total of 76 patients with liver-associated death have been reported (10 patients/year). (personal communication, B. Ledergerber). The number of transplanted patients is therefore small, even if we consider that a high proportion of the HIV-infected patients are not easy to manage, and not considered good candidates for transplantation, eg due to ongoing injection drug use. On the other hand, many of these patients have proved that they are able to adhere to therapy, as measured by continuous viral suppression, which is an absolute prerequisite for success of transplantation. These patients are likely to succeed after SOT.

Of the eight patients, one died due to relapse of HCV. Unfortunately, the outcome after liver transplantation for HCV is not foreseeable and sometimes disappointing in both the HIV- and non-HIV-infected recipients. Relapse of HCV-infection is universal, and in almost all recipients, treatment for HCV needs to be restarted. That must be considered before transplantation, and taken into account when evaluating a potential

Table 1

Cause of end-stage organ disease, and transplant-related complications.

Patient #	cause of end-stage disease	type of transplant	immuno-suppression	rejection episodes	graft function	death	opportunistic infections	F/up time months	comments
1	HCV	cadaveric liver	prednison, tacrolimus	no	failure	death due to graft failure: recurrent HCV	none	9	interaction ritonavir tacrolimus underestimated; HCV relapse
2	HCV	cadaveric liver	cyclosporin A	week 1 after tpl.	good	alive	none	19	HCV relapse
3	diabetes mellitus	cadaveric pancreas/ kidney	cyclosporin A, MMF	chronic rejection (kidney)	pancreas: ok; kidney: back on dialysis, waiting for ReTpl	alive	none	61	long-term non progressor (case published in: Am J Transplant 2003;3:631–3)
4	HBV reactivation	cadaveric liver	tacrolimus changed to sirolimus because of chronic rejection; MMF stopped for anemia	chronic rejection	failure	death due to graft and renal failure	CMV infection, genital HSV 2 reactivation	42	no relapse with HBV treatment; renal carcinoma → nephrectomy → dialysis; transplantation was performed not knowing HIV status
5	HBV and HCV, cirrhosis and hepatocellular carcinoma	cadaveric liver, donor HBSAg +	cyclosporin A stopped for renal failure, switched to sirolimus; MMF stopped when ribavirin + Peg. INF were started	none	good, treatment of HCV (relapse), and HBV with 3TC, tenofovir	alive	none	38	haemophilia cured with the transplantation; HCV relapse
6	HBV cirrhosis	cadaveric liver	tacrolismus (0.5 mg once a week)	none	good, treatment for HBV with tenofovir; 3TC	alive	none	20	osteoporosis, tremor, hypertension
7	end-stage renal disease of unknown aetiology	cadaveric kidney	cyclosporin A, prednison, MMF	one probable	good	alive	none	19	dyslipidaemia (max. cholesterol: 20.1 mmol/l), low cyclosporin levels
8	HIV-associated nephropathy	cadaveric kidney	tacrolimus, prednison, MMF	none	good	alive	none	7	progressive lowering of tacrolimus dose (6 mg/day to 0.14 mg/day), eventually, replaced by cylosporin A because of hair loss

HBV: Hepatitis B virus; HCV: Hepatitis C virus; MMF: Mycophenolate mofetil; Peg. INF: Pegylated interferon gamma; Tpl: Transplantation

recipient. However, the overall outcome has been very similar between HIV- and non-HIV-infected recipients of a kidney or liver. A recent retrospective study comparing the kidney transplantation experience in HIV-positive patients in the US with 114 deceased donors and 64 living donors showed a comparable graft and patient outcome when compared to the HIV-negative population.

All eight patients were able to successfully control their HIV-infection. For many transplantation teams, an uncontrolled HIV-infection is considered an exclusion criteria. If an HIV patient is not able to tolerate an antiretroviral therapy due to liver insufficiency, or has CD4 counts below 200 cells/µl, transplantation should still be considered if the HIV-infection is potentially controllable (ie no multi-resistance of HIV and valid antiretroviral options) and CD4 cells are above 100 cells/µl. Detailed inclusion and exclusion criteria have been published [8].

Complications recorded included rejection, drug interactions and recurrence of underlying disease. While most of these complications are well known in HIV-negative solid organ transplantation, the drug interactions are challenging and require a close interdisciplinary collaboration. Careful monitoring of these potential problems is crucial to assure a successful outcome. Availability of drug levels in a timely manner is mandatory. One important point to mention is the potent interaction between HIV protease inhibitors and immunosuppressive agents, in particular the calcineurin inhibitors cyclosporine A and tacrolimus. HIV protease inhibitors are potent inhibitors of the cytochrom P3A4 system and calcineurin inhibitors are substrates of this system. Frequent monitoring of blood levels of these drugs is mandatory, especially when new drugs are introduced. The use of the non-nucleoside inhibitor efavirenz, although an inductor of cytochrome P450 3A4, seems easier to manage together with calcineurin inhibitors as shown in three of our patients (table 1). Drug interactions should be anticipated and changes of HAART made preferentially before transplantation. Potentially, they could be usefully exploited, even in HIV-negative patients, to attain more stable levels of tacrolimus and cyclosporine A, and to diminish costs.

The relatively high incidence of rejection in our small series has to be confirmed in larger studies. However, a higher incidence of rejection in HIV-positive recipients has recently been reported in the literature [6].

The use of non-ideal organs is a matter of controversy. One of our patients (#5) received a cadaveric liver from a HBs antigen positive donor, with a good result. HAART, which includes drugs that are also efficacious against hepatitis B virus, may have contributed to the good result.

In summary, our favourable experience and the current data suggests that in selected patients, SOT is a potential therapeutic option. Patients with a stable or treatable HIV infection should no longer be a priori excluded from solid organ transplantation based on their HIV status. A close collaboration between the different teams is mandatory.

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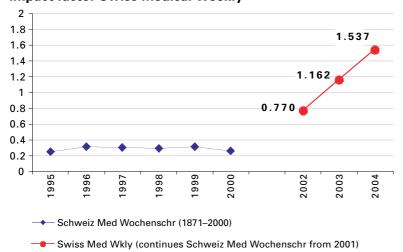
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