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TRANSPLANT AND ONCOLOGY (M ISON AND N THEODOROPOULOS, SECTION EDITORS)

The Swiss Transplant Cohort Study: Lessons from the First 6 Years

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Abstract Prospective cohort studies significantly contribute to answering specific research questions in a defined population. Since 2008, the Swiss Transplant Cohort Study (STCS) systematically enrolled >95 % of all transplant recipients in Switzerland, collecting predefined data at determined time points. Designed as an open cohort, the STCS has included >3900 patients to date, with a median follow-up of 2.96 years (IQR 1.44–4.73). This review highlights some relevant findings in the field of transplant-associated infections gained by the STCS so far. Three key general aspects have crystallized: (i) Well-run cohort studies are a powerful tool to conduct genetic studies, which are crucially dependent on a

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meticulously described phenotype. (ii) Long-term real-life observations are adding a distinct layer of information that cannot be obtained during randomized studies. (iii) The systemic collection of data, close interdisciplinary collaboration, and continuous analysis of some key outcome data such as infectious diseases endpoints can improve patient care.

Keywords Observational studies · Transplantation · Infectious diseases · Cohort studies · Genetic studies

Introduction

The infectious disease burden after transplantation is one of the most important factors impacting patient morbidity, mortality, and, ultimately, the success of a transplant program [1]. Challenges in the management and prevention of infectious complications in transplant recipients, as well as the consequences of infection in the patient and the allograft, are unique to this population. Knowledge of local epidemiology is key to guide the care of both the individual transplant recipient and the implementation of prevention strategies. Long-term consequences of some infections, such as cytomegalovirus (CMV) infection, have been postulated, but missing long-term data hampers determination of their role. A particular pattern of occurrence of infections after transplantation has been recognized and associated with the net state of immunosuppression. The impact of a refined monitoring of immunosuppression and improved prevention of infections on this timeline is unclear. Increasingly, the role of host factors such as genetic polymorphisms is intensely explored, but a meaningful analysis is directly linked to the number of patients under observation as well as the quality of outcome data available.

The Swiss Transplant Cohort Study (STCS) was founded with the purpose to establish a tool to tackle some of these questions. Currently, over 60 research projects embedded in the STCS are active, from purely epidemiological analyses to translational studies, as well as randomized trials (http://www.stcs.ch/research/scientific-projects/). All topics relevant to transplantation are covered. This review concentrates on the published results concerning post-transplant infectious complications and focuses on the potential of such a cohort. STCS results on other aspects related to transplantation will not be discussed [2–5].

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The Features of the STCS

The STCS (www.stcs.ch) prospectively enrolls all transplant recipients from the six Swiss transplant centers. A modular concept collects general data such as transplant infectious endpoints and psychosocial variables, by dedicated teams. The type of data collected is tailored to the transplanted organ. Variables are predefined and assembled prospectively (Table 1). All involved patients provide an informed consent for the extensive data collection, as well as the sampling of biological material. By law, a minimal data set is obtained for each recipient. Since its start in 2008, enrollment has been >95 %, with currently 4150 (March, 25th, 2015) solid-organ recipients in the database. Since 2011, patients after allogeneic stem cell transplantation have been enrolled as well. The STCS is designed as an open cohort with regular follow-ups performed every year [6, 7]. Funding is provided by the Swiss National Science Foundation, the Swiss University Hospitals, and the five Swiss transplant centers (Basel, Bern, Geneva, Lausanne, St. Gallen, Zürich).

The studies described below have been performed in the context of the STCS.

Epidemiological Studies

The impact of enterococcal colonization and infection on recipients was studied in 1234 solid-organ transplant (SOT) recipients [8•]. Two-hundred fifty-five (20.7 %) patients with *Enterococci* were documented, 185 (47.2 %) with an infection, and 205 (52.3 %) with colonization. Only two isolates were vancomycin-resistant, reflecting the still favorable antimicrobial resistance situation in Switzerland. A shift toward *Enterococcus faecium* was noted, with the latter being responsible for about half of the infections by *Enterococci*. An important finding was that whereas enterococcal colonization was frequent in SOT recipients, progression from colonization to infection was rare (4/205; 2 %), supporting the restrained use of antibiotics for colonized patients.

The role of a positive serology for CMV on the incidence of biopsy-proven graft rejection or graft loss was analyzed in 1414 SOT recipients, including heart (n=97), kidney (n=917), liver (n=237), and lung (n=163) recipients [9]. A positive CMV donor or recipient serological constellation (IgG) predicted a higher incidence of graft rejection after liver

Table 1 Variables collected for assessment of infectious diseases events in the Swiss Transplant Cohort Study

Type of infectious event
• Viral
• Bacterial
• Fungal
• Parasite
• Pathogen unknown
Site of infection
• Site not identified
• Bacteremia/fungemia/viremia
• Bone and joints
• Central nervous system
• Eye
• Gastrointestinal
• Heart
• Liver
• Mucocutaneous
• Prosthetic infections
• Respiratory tract
• Urinary tract
• Catheter-related infection
• Surgical site infection
• Other
Clinical type
• Probable disease
• Possible disease
• Proven disease
• Colonization
• Asymptomatic replication
• Viral syndrome
• Fever during neutropenia
Potential donor-related infection?
• Yes
• No
• Unknown
Infection that required hospitalization?
• Yes
• No
• Unknown
Reduction of immunosuppression?
• Yes
• No
• Unknown

Specific pathogens are chosen from a comprehensive list. Resistance pattern is collected for *Enterococcus* spp, *Staphylococcus aureus* (MRSA), and Gram negative (MDR, ESBL). Type of therapy is indicated (antifungal, antiviral, antibacterial)

and lung transplantation. CMV replication in all SOT recipients was associated with an increased risk for biopsy-proven graft rejection within 4 weeks after detection. Valganciclovir prophylaxis delayed but did not prevent graft loss.

The best prevention strategy against CMV in SOT recipients remains an intensely discussed topic. In particular, the effect on non-CMV endpoints such as rejection or long-term graft function remains unclear. The long-term design of the STCS is well suited to shed some light on this issue. One thousand two hundred thirty-nine SOT recipients (all organs) were included in this analysis, in which prophylaxis was compared with a preemptive approach. The main result showed that the use of a prophylactic approach was associated with improved graft-failure-free survival after a median of 1.05 years of follow-up (hazard ratio 1.63 for the preemptive approach [95 % CI 1.01–2.64], $p=0.044$). This was not due to the incidence of CMV disease, as both strategies prevented this complication very efficiently, but potentially to the occurrence of asymptomatic CMV replication early after transplant. The limitations and benefits of a prospective cohort need to be taken into account when putting these results in a perspective. While not based on a randomized design, the almost complete inclusion of all transplanted patients depicts real life scenarios very precisely [10•].

Studies Using Biological Samples

Patients enrolled in the STCS are regularly sampled during the first year at 0, 6, and 12 months after transplantation. Plasma, DNA, and viable cells are available for studies. The strength of the STCS lies in a very precise description of multiple phenotypes with prospective collection of pertinent endpoints. This allows for careful patient selection and the ability to correlate findings generated in the laboratory with clinical relevant outcomes. This may form the basis for well-founded translational hypotheses.

Translational and Genetic Studies

Association of activating killer cell immunoglobulin-like receptor (KIR) genes with protection from CMV has been postulated after organ transplantation. This STCS study correlated KIR genotype and CMV serostatus at the time of transplantation with rates of CMV viremia in a total of 517 (heart ($n=57$), kidney ($n=223$), liver ($n=165$), or lung ($n=72$)) allograft recipients. In CMV-seropositive organ transplant recipients treated with intense immunosuppression (i.e., depleting protocols), KIR-activating haplotypes were associated with protection against CMV viremia. These data indicate an important role for KIR and natural killer (NK) cells in the control of CMV replication [11•].

Two genetic studies elucidated the role of polymorphisms of immune mediators. The first explored the role of IFNL3

and IFNL4, the genes encoding interferon λ3 and interferon λ4, on the incidence of CMV infection after transplantation. A polymorphism involved in the clearance of hepatitis C virus infection was investigated in 840 SOT recipients, of whom 44 % received antiviral prophylaxis. Homozygosity for the minor (−G/−G) allele was associated with a higher incidence of CMV replication in patients followed by a preemptive approach, in contrast to those under prophylaxis. This association remained valid in multivariate competing risk regression analysis [12].

The second study looking at interleukin-1 beta and β-defensin-1 polymorphisms among 1101 SOT recipients showed that single-nucleotide polymorphisms of the encoding genes were associated with mold colonization and proven/probable mold infections. A potential mechanism was proposed by showing a reduced secretion of IL-1 β and TNF-α upon stimulation with *Aspergillus* in peripheral blood mononuclear cells harboring two copies of the rare allele [13••].

Non-Scientific Benefits

Less well studied and more difficult to prove are potential non-scientific benefits of a systematic collection of outcome variables in cohort studies. The impact on routine clinical care in the STCS setting can be seen on many levels including the multidisciplinary collaboration required to decide on definitions and the auditing process that compels each center to revise its own protocols. If needed, a national consensus can be reached, as demonstrated by the recently published Swiss guidelines on vaccination of SOT recipients reflecting local custom [14]. The possibility to compare incidence rates for any infection between centers should not be used to discredit, but rather to detect uncommon patterns enabling a rapid response if necessary. The regular exchange in the Transplant Infectious Disease group fosters trust, allowing discussion of difficult cases with a low threshold, ultimately resulting in a benefit for the patients—as does the often challenging questions about potential infectious disease risk of possible donors. All centers receive a center-specific report with relevant outcome information, which can be used for internal quality control.

Challenges and Limitations

The STCS is a high-maintenance cohort. The data set collected is extensive and needs regular auditing to ensure a continuously high quality. The workload can also be substantial for clinicians and requires ongoing motivation and support. For many specific research questions, the cohort can flag patients of interest, but an additional chart review is often necessary. Sampling is not associated with specific events. Despite these challenges, the benefits are many, resulting in a high acceptance and support in all centers.

Conclusions

A well-designed high-quality prospective cohort study can be a powerful scientific tool for carefully chosen research questions. The limitations of the cohort design need be acknowledged, but it is crucial to realize that randomized trials have their shortfalls as well. The two concepts should not be played off against each other, but rather seen as complementary. Recent large trials have indeed merged the two designs, the concept of "the randomized registry trial" as recently discussed, a very promising trend [15, 16]. The STCS has already been successful in producing relevant published results concerning genetic or immunological markers and their relation to clinical endpoints. A new field of research may be seen exploring the non-scientific benefits of cohort studies resulting in improved patient care.

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Compliance with Ethics Guidelines

Conflict of Interest Alexia Cusini, Katia Boggian, Nicolas Mueller, David Nadal, Maja Weisser, Nina Khanna, Pascal Meylan, Oriol Manuel, Adrian Egli, Matthias Hoffmann, Hans H. Hirsch, Christian Garzoni, Christian van Delden, and Christoph Berger have no relevant disclosures to report. Pierre-Yves Bochud received a grant from Mérieux and lecture payment from MSD, Ademtech, and Janssen and travel accommodations/meeting expenses from MSD.

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