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Editorial

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Immunotherapy for Invasive Fungal Infections in Transplant Patients: Back to the Future?

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In the past decade, we have witnessed striking advances in the diagnosis and therapy of invasive fungal infections in immunocompromised patients. Similar to the quantum leap in HIV medicine about 15 years ago, this progress resulted from the synergy of new diagnostic assays (galactomannan antigen, beta-glucan, (pan-)fungal polymerase chain reaction), with new and better antifungal drugs such as azoles (voriconazole, posaconazole) and echinocandins (caspofungin, micafungin, anidulafungin) as well as testing of drug susceptibility and drug level monitoring. As a consequence, therapeutic, preemptive and prophylactic use of new antifungals has significantly reduced fungus-related morbidity and mortality in high-risk patients such as those after allogenic hematopoietic stem cell transplantation. Fortunately, this emerging bonanza is chaperoned by international expert consensus defining microbiological, radiological and clinical criteria for diagnosis as well as for treatment response (1). Meanwhile, these antifungal strategies have also invaded the management of other immunosuppressed populations including solid organ transplantation (SOT) patients. In the recent surveillance data of the TRANSNET covering 23 US transplant centers, kidney transplant recipients had the lowest 1-year cumulative incidence rates of invasive fungal infections of 1.5% as compared to lung (8.6%), liver (4.7%) or heart (3.4%) transplant recipients (2). No increase in invasive fungal infections had been recorded among kidney transplant recipients as yet (2), but there is, fueled by case reports, a growing impression that these formerly rare disseminated fungal infections are more frequently encountered in the current era. Besides transplant tourism, the increasing intensity and duration of immunosuppression in the recent decade is among the key suspects. Thus, alemtuzumab induction was significantly associated with an increased risk of disseminated fungal infections as compared to the use of basiliximab (3). Also, fungal infections were increased in rituximab-treated kidney transplants and an independent risk factor for death (4). Apparently, the improved antifungal arsenal can be failing, even when withdrawing immunosuppressive treatment and thereby risking loss of the renal allograft.

In this issue, Armstrong-James and colleagues report their experience of using exogenous interferon-γ as an adjuvant salvage therapy for life threatening disseminated fungal infections of seven carefully characterized kidney transplant patients. Six of the seven patients were suffering from invasive molds in multiple body sites. Interferon-γ was used 6 weeks after failure of a first and second line antifungal therapy including modern antifungals and favorable susceptibility profiles. The authors report a dramatic clinical and laboratory response to interferon-γ therapy within few weeks and, particularly impressive for the invasive mold infections, a relapse-free observation time ranging from 6 months to 3 years, even after stopping antifungal therapy.

Given the concern of triggering graft rejection, what were the effects on renal allograft function? Two patients could not be evaluated for this purpose as they were dialysis-dependent and off immunosuppression prior to interferon-γ therapy. In the remaining 5 patients, no short-term adverse effect of interferon-γ therapy was noted, except in one patient with already impaired graft function. Thus, for four patients including three with life-threatening invasive mold infections, interferon-γ therapy appeared to have little or no detrimental effect even on long-term allograft function.

Was antifungal therapy really failing and thereby calling for adjunct measures that potentially jeopardized allograft and patient survival? The objective evaluation of the course of an invasive fungal infection is difficult. Recent consensus recommendations attempt to capture these uncertainties by trying to set standards through defining treatment failure after a minimal treatment time of 4–6 weeks for invasive mold and *Candida* infections (1). It seems that these criteria were largely met in this case series. Moreover, outcome of interferon-γ treatment was assessed

after more than 12 weeks whenever possible, as recommended (1).

What were the characteristics of the affected kidney transplant patients who were failing antifungal therapy? We noted prior antirejection treatment in six patients, alemtuzumab induction in three, antibody-mediated rejection in three, rituximab treatment in two, double transplants in two and BKV nephropathy in one. Only one patient transplanted oversees, presented without significant immunological risk factors, but intractable recurrences despite prolonged antifungal treatments. Taken together, the factors are multiple, but clearly indicative of a compromising net state of immunosuppression.

Why was interferon-γ chosen? The specific rationale to use interferon-γ in non-neutropenic SOT patients stems from animal models indicating impaired phagocytosis due to a poor T-helper 1 response and interferon-γ expression, whereas T-helper 2 profiles of interleukin-4, -5 and -10 were increased. Clearly, interferon-γ is a key cytokine to tackle fungal, mycobacterial and other intracellular pathogens via activating phagocytosis and intracellular killing. In this study, interferon-γ was dosed similar to what is used for prophylaxis in chronic granulomatous disease, to stimulate a NADPH oxidase-independent pathway for controlling the conidial stage of *Aspergillus*. Recent data suggest that the lack of NADPH oxidase and/or an impaired tryptophan degradation by indolamine 2,3-dioxygenase may result in failure to restrict interleukin-17 expression from T helper-17 cells either directly or indirectly via insufficient regulatory T-cell activity. Interleukin-17 causes dysregulated inflammation via G-CSF, GM-CSF and TNF-α, but the neutrophils are paradoxically unable to control aspergillosis (5). Thus, supplementing aspergillus-specific T-helper 1-cells or possibly more simply interferon-γ may at least partially fill this functional gap.

Given the striking results of this case series, are the data sufficient to recommend interferon-γ to kidney transplant patients failing antifungal therapies? The uncontrolled nature of this small case series, does not permit definitive conclusions regarding risk and benefit. Also, the competing risk of acute rejection and graft loss call for criteria to identify patients with largest benefit of interferon-γ treatment. Complex cytokine profiles may be helpful to accomplish this task in the future. Thus, the study is tantalizing, but begs for the enrolment of such kidney transplant recipients and possibly other SOT patients into appropriately designed prospective studies.

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