Adjunctive Immune Therapy for Fungal Infections

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Fungal infections in immunocompromised patients can pose difficult problems in clinical management, because the available antifungal chemotherapy is often unable to eradicate the infection in these people. Hence, the use of immune modulating therapy to augment impaired host immune responses—and thus enhance the efficacy of antifungal drugs—is a reasonable approach to improve the prognosis of fungal infections. Advances in biotechnology have produced a variety of biological response modifiers with the potential to serve as adjunctive immune therapy for the treatment of fungal infections, including cytokines, monoclonal antibodies, and cell growth factors. In recent years, immune-modulating therapies have been studied in an effort to define their potential use for the treatment of fungal infections. Much of the available information on the use of this approach is encouraging and invites further investigation—with the caveats that the information is mostly anecdotal and that immune-modulating therapy occasionally has produced adverse effects.

The prevalence of fungal infections increased dramatically in the late 20th century as a result of multiple factors, including the AIDS epidemic, the widespread use of intravascular catheters and broad-spectrum antibiotics that alter host flora, advances in surgery and organ transplantation, and the development of antineoplastic therapies that produce leukopenia and immune suppression. Currently, the great majority of life-threatening invasive fungal infections occur in severely immunosuppressed people. These infections are often difficult to eradicate with the available antifungal chemotherapeutic agents and, as a result, they constitute some of the most intractable clinical problems doctors face today. The increasing prevalence of fungal infections, the availability of only a few antifungal drugs, and the relative inefficacy of these drugs in severely immunosuppressed patients underscore the urgent need for new approaches to antifungal therapy.

The paucity of fungal infections in people with intact immune function is strong evidence that normal immunity mediates effective resistance to this class of microorganisms. Consequently, the clinical disease caused by fungal pathogens is often a function of immunological deficits found in the host. The defects that predispose people to fungal infections vary for different fungal pathogens and include breakdown of integument, neutropenia, and impairments in cell-mediated immunity [1, 2]. Defects in barrier immunity, such as the presence of an intravascular catheter or other breaches in the integument, alterations to the resident microbial flora due to antimicrobial therapy, or both, are associated with an increased risk of infection with *Candida* species. Neutropenia is a risk factor for candidiasis, aspergillosis, and infections with the Zygomycetes, such as infections with *Mucor, Rhizopus, Absidia,* and *Rhizomucor* species [3]. Defects in cell-mediated immunity predispose to cryptococcosis, aspergillosis, coccidiomycosis, histoplasmosis, and penicilliosis, as well as mucosal candidiasis.

The pathogenic fungi exhibit diverse virulence strategies and many manifest a capacity for latency, which contributes to an increased risk of invasive fungal disease for patients who are immunosuppressed. *Aspergillus* species elaborate powerful hydrolytic enzymes that destroy tissue (reviewed in [4]). In contrast, *Cryptococcus neoformans* often elicits little or no inflammatory response; however, its capsular polysaccharide mediates a variety of deleterious immunological effects (reviewed in [5]). Differences among the fungi in their pathogenetic mechanisms and clinical manifestations underscore the importance of understanding the nature of host-fungus interactions in the design of immunotherapy.
RATIONALE FOR THE USE OF IMMUNOTHERAPY TO TREAT FUNGAL INFECTIONS

Antifungal therapy is often ineffective in the setting of immune suppression. Hence, immunotherapy is a rational approach to the treatment of fungal infections because it is intended to enhance immune function. Immune therapy can be either replacement or reconstitution therapy, which is intended to correct the underlying immunological defects that predispose people to fungal disease, or augmentative therapy, which is intended to enhance immune function against the pathogen. For example, transfusion of leukocytes (for patients with neutropenia) is a form of replacement immunotherapy, whereas the administration of growth factors and specific immunoglobulin are augmentation therapies. However, the distinction between augmentative and replacement therapy is not always clear-cut.

Immune therapy can also be either nonspecific or specific. Cytokines, growth factors, and leukocytes can enhance host defense against a variety of pathogens and are examples of nonspecific immunotherapy. In contrast, the administration of antibody is specific immunotherapy that, similar to antimicrobial therapy, is directed at the pathogen itself. An important consideration in the design of immunotherapy for fungal infections is whether or not the immunological defect that predisposes the host to disease can be reversed. Nevertheless, the redundancy in the immune system allows certain immune functions to compensate for the immune deficit even if the primary defect is irreversible. For example, antibodies to *Candida albicans* and *Candida neoformans* protect mice with neutropenia and healthy mice, respectively, against infection with these pathogenic fungi, although antibodies are not thought to contribute to natural resistance to these pathogens [6–9].

REPLACEMENT IMMUNE THERAPIES

**Leukocyte transfusions.** The association of neutropenia with severe fungal infections in the 1960s suggested that leukocyte replacement might be a logical approach to reduce vulnerability to mycotic infection. However, interest in leukocyte transfusion declined in the 1970s because of marginal efficacy, low neutrophil harvests, the development of new antimicrobial agents, and association with toxic reactions and alloimmunization (reviewed in [10, 11]). However, in recent years, there has been a renewed interest in the use of leukocyte transfusions spawned by technological advances in leukocyte cell collection and the problems posed by intractable infections with fungi and antibiotic-resistant microorganisms in neutropenic patients. Because the success of leukocyte transfusion is linked to the number of polymorphonuclear leukocytes (PMNL) that are transfused [12], the finding that administration of granulocyte colony-stimulating factors (G-CSFs) to leukocyte donors increases the yield of PMNL [12] has raised new hope for the success of leukocyte transfusion therapy [10, 13]. Moreover, there is also evidence that leukocytes from donors treated with G-CSF have better antimicrobial function [14, 15].

A few case reports suggest that administration of G-CSF–primed leukocytes can be beneficial for patients with *Aspergillus* [16] and *Candida tropicalis* [17] infections. A phase 1/2 trial of leukocyte transfusion has used cells from donors primed with G-CSF and prednisolone to treat patients with severe neutropenia and bacterial or fungal infections [18]. This study reported that toxicity was low (12%) and that fungal infection was cleared in 5 of 13 patients. Notably, infections were cleared in 5 of 9 patients with aspergillosis. Another phase 1/2 study of leukocyte transfusions from G-CSF–treated donors to 20 patients who had undergone stem cell transplantation found that transfused PMNL migrated to peripheral tissues and demonstrated microbiological resolution of candidemia in 4 of 7 transfusion recipients [19]. However, this study also found that only 1 patient with candidemia was alive 30 days after the diagnosis of infection, which suggests that despite a possible antifungal effect of donor-primed PMNL, the therapy did not significantly affect outcome.

The utility of leukocyte transfusion for treating invasive fungal infections in cases of profound neutropenia has not been established. In some studies, poor response rates and the inefficacy of combined leukocyte and antifungal therapy have been attributed to patient heterogeneity, insufficient numbers of PMNL, or both [13, 15]. Consistent with the view that neutrophil antifungal activity is most important early in infection, there is some indication that patients with more recent infection respond better to this treatment modality [20]. Moreover, neutrophils provide the predominant host defense against invasive and disseminated candidal infections, whereas cell-mediated immunity predominates against mucosal candidiasis [21]. For aspergillosis, mononuclear cells may be more important in the initial control of disease [22]. Therefore, despite the apparently nonspecific nature of leukocyte replacement therapy, the efficacy of this treatment modality against fungal infections is likely to be pathogen specific, disease specific, or both.

Lethal pulmonary reactions can follow leukocyte infusion in patients receiving amphotericin B therapy, as a consequence of increased obstruction of capillaries by PMNL [23] or PMNL aggregation [24]. However, another study reported no toxicity from the combination of administration of amphotericin B and transfusion of leukocytes and suggested that combination therapy was safe [25] but recommended that the infusions be separated by 4–6 h [10].

In aggregate, the available data suggest that leukocyte transfusions are less effective against fungal infections than against
bacterial infections [10]. Nonetheless, some successes have been reported in individual or small groups of patients with fungal infections in uncontrolled studies [15], and there is anecdotal evidence that leukocyte transfusions are useful for the treatment of certain fungal infections in patients with neutropenia [17, 26–28]. Thus, despite the technological improvements associated with the use of G-CSF–mobilized PMNL, which permit the recovery of nearly $10^{10}$ PMNL per donor, many questions regarding the timing of leukocyte transfusions, the selection of patients, the efficacy of the intervention, and the indications for therapy remain unanswered [10, 29].

**Other agents.** Dinitrochlorobenzene sensitizes for delayed cutaneous hypersensitivity and has been administered to 1 patient who had a cutaneous *C. immitis* nasol nasal lesion that was refractory to treatment with amphotericin B [30]. Chloroquine is an antimalaria drug that has antifungal properties as a result of its ability to enhance macrophage effector function against fungal cells [31, 32]. Chloroquine can limit the availability of iron inside the macrophages and promote killing of *Histoplasma capsulatum* [32]. In the case of *Cryptococcus neoformans*, chloroquine inhibits intracellular growth by raising the phagosomal pH [31]. Chloroquine is effective in animal models against both *H. capsulatum* [32] and *C. neoformans* [31, 33].

**NONSPECIFIC AUGMENTATIVE IMMUNE THERAPIES**

**Colony-stimulating factors (CSFs).** CSFs regulate leukocyte maturation from bone marrow progenitor cells. Three types of recombinant human CSFs are available: G-CSF, granulocyte-macrophage CSF (GM-CSF), and macrophage CSF (M-CSF; for reviews, see [37, 38]).

G-CSF promotes the proliferation and differentiation of neutrophil progenitor cells and increases the number of peripheral blood neutrophils, including band forms (reviewed in [37, 38]). In patients with neutropenia, susceptibility to fungal infections is proportional to the duration and degree of neutropenia [39]. G-CSF is useful to promote bone-marrow recovery in patients with neutropenia and for the treatment of chronic neutropenia, myelodysplastic syndrome, and aplastic anemia [37]. In comparison to GM-CSF and M-CSF, G-CSF produces anti-inflammatory rather than proinflammatory factors and is thought to protect against endotoxin-mediated damage [40]. In addition, G-CSF can induce dendritic cells with a Th2 cellular response profile [41] and, accordingly, may downregulate the proinflammatory response and have a more favorable benefit-to-toxicity ratio against infections for which neutrophils are the predominant antifungal effector cell. The effect of growth factors on effector cells varies depending on the pathogen and the immunomodulator. For example, G-CSF augmented PMNL-mediated damage of *Fusarium solani*, and GM-CSF augmented the fungicidal activity of PMNL and peripheral blood mononuclear cells against *Fusarium* and *Candida*, but not against *Aspergillus* [42]. However, IFN-γ appears to be a better mediator of hypal and pseudohyphal damage than are the CSFs [42]. Neutrophils from patients treated with G-CSF demonstrate enhanced in vitro activity against *Aspergillus fumigatus*, *Candida albicans*, and *Rhizopus arrhizus*, possibly as a consequence of an enhanced respiratory burst [43]. PMNL from HIV-infected patients who have received G-CSF have been shown to have enhanced activity against *C. neoformans* and *C. albicans* as a result of augmented superoxide anion production [44].

Clinical experience with use of the CSFs to treat fungal infections is limited, although there is growing anecdotal evidence that they may alter the course of established fungal infection, when used as adjuncts to antifungal therapy. Although much of the data regarding the use of G-CSF comes from case reports of patients with neutropenia, a double-blind, randomized, placebo-controlled comparison of treatment with fluconazole alone or fluconazole and G-CSF in patients without neutropenia revealed a trend toward resolution of disseminated candidiasis that was associated with an increase in and the magnitude of the leukocyte count [40]. A number of reports suggest that G-CSF may be useful as adjunctive therapy for certain fungal infections in combination with amphotericin B; these include reports of 5 children with aspergillosis [45], patients with fungemia in the setting of hematologic malignancy [46], a patient with disseminated zygomycosis [47], and 4 patients with refractory mucormycosis [48]. A study of 29 patients with deep-seated fungal infections following chemotherapy or bone marrow transplantation reported that combined therapy with amphotericin B and G-CSF was associated with an improved response rate and greater cost-effectiveness [49]. Unlike G-CSF, GM-CSF promotes the differentiation and proliferation of mononuclear cells, as well as neutrophils [20]. Although it is biologically similar to G-CSF, GM-CSF acts on progenitor cells capable of differentiating into both granulocyte and monocyte lineages. Consequently, it can increase the numbers of neutrophils, eosinophils, and monocytes. The effect of GM-CSF on neutrophil number may be due to its relatively long half-life (reviewed in [38]). GM-CSF is used clinically to promote bone marrow recovery after chemotherapy for solid tumors, engraftment of bone marrow cells and treatment of graft failure, myelodysplastic syndromes, and aplastic anemia. GM-CSF also primes macrophages to release mediators of inflammation [20] that can overcome dexamethasone-mediated suppression of the antifungal activity of monocytes against *Aspergillus* [50].

GM-CSF may be effective in the prevention of fungal infec-
tions in patients with neutropenia associated with chemotherapy and/or bone marrow transplantation. A retrospective analysis of 145 patients who had undergone chemotherapy with or without autologous bone marrow transplantation and who received therapy with either G-CSF, GM-CSF, G-CSF and GM-CSF, or no CSF found that the greatest reduction of the risk of systemic fungal infection was associated with GM-CSF therapy [51]. Similarly, a prospective, randomized, placebo-controlled study of 124 patients who received either GM-CSF or placebo after induction therapy for the treatment of acute myelogenous leukemia reported that the fungal infection-related mortality was reduced relative to the placebo control group [52]. GM-CSF therapy was associated with a clinical response when administered with amphotericin B to a small number of patients with established fungal infections, including patients with refractory Aspergillus infection [53], 3 patients with AIDS and oropharyngeal candidiasis [54], and 1 patient with systemic infection with Blastoschizomyces capitatus [55].

GM-CSF therapy has been associated with toxicity that may reflect its ability to increase proinflammatory mediators. In one study in which GM-CSF was administered to 8 patients with systemic fungal infections and severe neutropenia [56], 4 patients were cured, 2 had a partial response, and 2 failed to respond to therapy [56]. Unfortunately, 3 patients developed a capillary leak syndrome, suggesting that the dosage of GM-CSF was excessive [56].

There has also been the theoretical concern that GM-CSF therapy could hinder PMNL migration to sites of infection. However, a study of the migration of radiolabeled WBCs in a patient with fungal infection who was being treated with GM-CSF and pentoxifylline revealed that the leukocytes did localize to the site of infection [57]. Another potential complication of GM-CSF therapy stems from its activity in stimulating recovery of leukocyte function. A 10-year-old girl who received GM-CSF and amphotericin B for pulmonary aspergillosis developed massive fatal hemoptysis [58]. Resolution of neutropenia has been associated with cavitation and hemoptysis in patients with pulmonary aspergillosis, and these complications may become more frequent with the increased use of growth factors to reverse neutropenia [58]. Immune reconstitution disease has been observed after recovery from neutropenia in patients with aspergillosis and hepatosplenic candidiasis [59]. Hence, the inflammatory consequences of immune reconstitution raise some concerns regarding the use of immunotherapy.

M-CSF promotes the differentiation, proliferation, and activation of monocytes and macrophages [60]. Synergy was reported between M-CSF and amphotericin B and between amphotericin B and IL-4 antagonists in mice with disseminated candidiasis, whereas fluconazole and IL-12 were synergistic in mice with primary Candida infections [1]. These observations suggest that immunotherapy differentially regulates enhancement of cellular responses by modulating the activity of the effector cells against the relevant pathogen. Augmented effector cell function may be disease- and tissue-specific. Studies have shown that M-CSF enhanced the antifungal activity of mononuclear cells in a murine model of disseminated Trichosporon asahii infection through the induction of TNF-α [61], but it enhanced the fungicidal and phagocytic activities of splenocytes only—rather than Kupffer cells or pulmonary alveolar macrophages—in a rabbit model of disseminated candidiasis [62]. Moreover, studies of the immunomodulatory activity of M-CSF in mice have revealed complex effects, including some that are detrimental [63]. Hence, in patients with certain fungal infections, the stimulation of Th1 cellular responses may induce too much inflammation to exert a beneficial effect in the absence of a counterregulatory mechanism.

M-CSF was used as an adjunct to antifungal therapy in patients with bone marrow transplants and established fungal infections [64, 65]. In one phase 1 study of 24 patients treated with M-CSF, 6 (25%) patients had their infections resolve, 12 (50%) were considered not assessable for purposes of judging the efficacy of the intervention, and 6 (25%) did not respond to therapy [64]. Comparison of the long-term survival of bone marrow transplant recipients treated with M-CSF and antifungal therapy and that of historical control subjects revealed significantly prolonged survival among those receiving adjunctive therapy [65]. However, the benefits of M-CSF therapy in this study were largely limited to patients with Candida infections [65].

IFN-γ. IFN-γ is a potent activator of macrophage function [66] that can enhance the antifungal activity of murine macrophages against a number of fungal pathogens both in vitro and in vivo [67]. The efficacy of IFN-γ against human fungal infections has not been extensively studied, with the exception of a major study that showed its ability to prevent infection in patients with chronic granulomatous disease [68, 69]. However, there is anecdotal evidence suggesting that IFN-γ can be useful adjunctive therapy for the treatment of certain unusual fungal infections [70, 71]. Synergy between IFN-γ and antifungal agents against Candida species, Aspergillus fumigatus, C. neoformans, Paracoccidioides brasiliensis, and Blastomyces dermatitides has been demonstrated in vitro by use of macrophages [20] and in vivo for experimental cryptococcosis [72].

IL-12 and enhancement of Th1-mediated immunity. The rationale for the use of IL-12 as therapy for fungal infections is that Th1 type cellular responses [2] are essential for protection against fungal pathogens, including C. neoformans, Candida species, Aspergillus species, and Histoplasma capsulatum. IL-12 production is strongly correlated with the development of Th1 immunity against Candida albicans, and studies of experimental murine candidiasis suggest that it exerts a beneficial effect in the setting of neutropenia. However, IL-12 can be
detrimental in animals that do not have neutropenia because it can induce an excessive inflammatory response [2]. The inhibition of Th2 type cellular responses by IL-12 can enhance host defense against candidiasis, although IL-12 has also been found to induce IL-10, which in turn can worsen mucosal disease in mice [73]. IL-12 can enhance fluconazole efficacy against Candida infections in mice with neutropenia [1] and has activity alone in experimental murine cryptococcosis [74, 75], histoplasmosis [76], early in the course of aspergillosis [2], and in coccidioidomycosis [77].

A small study of the use of IL-12 immunotherapy in patients with autologous bone marrow transplants reported that 2 of 12 patients developed fatal fungal infections, one with Aspergillus and the other with Mucor [78]. This rate for severe fungal infection is significantly higher than expected for this procedure, which raises the possibility that IL-12 administration may have unintended deleterious effects on immune function [78]. In view of the potentially deleterious effects of IL-12–mediated inflammatory responses, particularly in the setting of chronic Candida infections, more data are needed to understand the mechanism and efficacy of IL-12–mediated immunomodulation.

PATHOGEN-SPECIFIC IMMUNE THERAPY

Therapeutic vaccine for Pythium insidiosum infection. P. insidiosum is a relatively common pathogen in horses and occasionally causes disease in humans. Vaccines composed of either whole P. insidiosum cells or concentrated soluble antigens have been used for the therapy of this infection in horses and presumably mediate their effects by eliciting strong inflammatory responses that control the infection [79]. Such a vaccine was used in a 14-year-old Thai boy with P. insidiosum arteritis who was reported to have recovered [80].

Transfer factor. The biological basis for the antifungal activity of transfer factor is controversial, but there are several literature reports claiming that transfer factor therapy has efficacy against a variety of refractory fungal infections [81, 82]. Administration of transfer factor to patients with chronic candidiasis increased reactivity to candidal antigens and was associated with clinical improvement [83]. Transfer factor and amphotericin B were used to treat coccidioidomycosis in 3 patients, 2 of whom showed clinical improvement [84].

Fungal antigens. Allergic fungal sinusitis is associated with asthma, nasal polyps, and the production of “allergic mucin,” a viscous secretion that contains degenerating eosinophils and Charcot-Leyden crystals [85, 86]. The mucin is frequently infected with a variety of fungal organisms, including those belonging to Aspergillus, Bipolaris, Curvularia, Alternaria, and Cladosporium species [87, 88]. The pathogenesis of this disease involves an inappropriately strong response to common fungal antigens. Immunotherapy for fungal sinusitis involves the injection of fungal antigens to which the person is sensitized [88] and was found to be beneficial in a prospective study [86].

Saccharomyces cerevisiae glucan administration was reported to be a useful adjunct to antifungal therapy in the treatment of paracoccidiomycosis [89]. A study of glucan administration to 18 patients subdivided into groups with either serious manifestations of disseminated disease or lesser disseminated disease revealed statistically significant clinical improvement in both groups, but a greater degree of improvement in those with serious disease.

Intravenous immunoglobulin (IVIG). In theory, IVIG therapy could be useful against fungal infections if the antibodies found in normal serum samples are active against pathogenic fungi. Nonetheless, although serum antibodies may promote natural resistance to infection, they may not necessarily ameliorate established or chronic infections. Hence, , and their efficacy against some fungi may be dependent on intact cellular immunity [90–92]. The potential efficacy of serum antibodies against fungi was suggested by the modest prolongation of survival of mice with experimental Candida infection that were treated with human IVIG in combination with amphotericin B [93]. In humans, IVIG therapy was associated with a significant reduction in the incidence of fungal infections in liver transplant recipients receiving anticytomegalovirus prophylaxis [94]. However, IVIG therapy was not associated with a significant reduction in patients who had undergone bone marrow transplantation, who had a 9% incidence of fungal infections, compared with a 6% incidence among control subjects, when receiving IVIG [95]. A single dose of IVIG given to healthy soldiers as prophylaxis against hepatitis A reduced the incidence of fungal infection of the skin [96], which suggests that serum antibodies can prevent certain fungal infections in the setting of normal immunity. However, oral administration of bovine antibodies to C. albicans to bone marrow transplant recipients reduced Candida colonization in 7 of 10 patients [96], which suggests that pathogen-specific antibodies can be effective in patients with immune defects.

Monoclonal antibodies and antibody engineering. Advances in the technology used to produce therapeutic mouse and human antibodies have renewed interest in the potential of antibody therapy against infectious diseases [97–99]. For both C. albicans and C. neoformans, several protective monoclonal antibodies have been described [7, 8, 100–103]. A Blastomyces dermatitidis adhesin can elicit antibody- and cell-mediated immune responses that mediate protection against pulmonary blastomycosis [104], although mouse monoclonal antibodies to this antigen did not alter the course of infection in mice and sometimes enhanced disease [104]. The failure of certain antibodies to mediate protection may be a function of many variables. For example, antibody efficacy against C. neoformans is a function of antibody isotype, idiotype, specificity,
inoculum, and antibody dose [92, 103, 105, 106]. Recently, antibody excess was reported to result in prozonelike effects that abrogated the protective efficacy of passive therapy [106]. This phenomenon may be responsible for the failure of certain antibody reagents and vaccines to treat or protect against other fungal infections.

Historically, antibody preparations containing specific antibody to C. neoformans have been used to treat several patients with cryptococcosis (reviewed in [107]). Antibody therapy was well tolerated and cleared serum antigen, but the sample size was insufficient to make any conclusions about therapeutic efficacy [107]. A murine monoclonal antibody to C. neoformans capsular polysaccharide is currently in clinical evaluation for therapy of cryptococcosis [108]. A similar antibody has been shown to enhance the antifungal activity of fluconazole and amphotericin B [109–111]. For patients with cryptococcosis, antibody therapy is envisioned as an adjunct to antifungal therapy.

Antibody therapy is also under development for C. albicans infection. In the early 1990s, it was shown that patients who died of disseminated candidiasis did not manifest an antibody response to the candidal heat shock protein (hsp) 90 [112]. This finding led to studies that demonstrated that human serum antibodies and a mouse monoclonal antibody to hsp90 were protective against candidiasis in mice [113]. A human recombinant antibody to an hsp90 linear epitope mediates protection against invasive murine candidiasis [114]. Antibodies to C. albicans polysaccharides have also been shown to be protective in murine models of infection [102, 115, 116]. Another approach to antibody therapy has been to engineer antibodies with dual functions, or bispecific antibodies. A bispecific antibody that binds both the Fcε receptor (CD89) and C. albicans has been shown to enhance neutrophil-mediated antifungal activity in G-CSF–primed cells [117, 118].

SUMMARY, CONCLUSION, AND FUTURE PROSPECTS

The clinical experience with immunotherapy for invasive fungal infections is largely limited to anecdotal case reports and small studies. Nevertheless, the outcomes noted with this treatment modality are encouraging, and call for controlled trials to evaluate the efficacy of immunotherapy with and without concomitant antifungal therapy. However, this may be difficult to accomplish because of the relative rarity and sporadic nature of certain types of fungal infections. In addition, the many immune defects that predispose to fungal infections, the biological differences among pathogenic fungi, and the variable responses to immune modulators are likely to complicate the design of clinical studies, and large sample sizes will likely be required for valid conclusions. Nevertheless, in view of the intractable nature of most invasive fungal infections, the promise of certain immunotherapeutic agents underscores the need for interdisciplinary research to establish parameters for their use, and presents a major challenge to clinicians and scientists: namely, to translate immunotherapeutic agents from the bench to the bedside.

References


