Recombinant Human Granulocyte-Macrophage Colony-Stimulating Factor (rhu GM-CSF) as Adjuvant Therapy for Invasive Fungal Diseases

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Background. Sargramostim (yeast-derived, glycosylated recombinant human granulocyte-macrophage colony-stimulating factor [rhu GM-CSF]) augments innate and adaptive immune responses and accelerates hematopoietic recovery of chemotherapy-induced neutropenia. However, considerably less is known about its efficacy as adjunctive immunotherapy against invasive fungal diseases (IFDs).

Methods. The clinical courses of 15 patients with pediatric malignancies and IFDs treated adjunctively with sargramostim at a single institution were analyzed in a retrospective cohort review. Further, a systematic review of published reports of rhu GM-CSF for IFDs was also conducted.

Results. Among 65 cases, 15 were newly described pediatric patients and 50 were previously published cases of IFDs treated with rhu GM-CSF. Among the newly reported pediatric patients, IFDs were caused by Candida spp., Trichosporon spp., and molds (Aspergillus spp., Rhizopus spp., Lichtheimia spp., and Scedosporium spp). Twelve (80%) were neutropenic at baseline, and 12 (80%) were refractory to antifungal therapy. Among 12 evaluable patients, the overall response rate was 92% (8 [67%] complete responses, 3 [25%] partial responses, and 1 [8%] stable). Treatment is ongoing in the remaining 3 patients. Among 50 published cases (15 Candida spp., 13 Mucorales, 11 Aspergillus spp., 11 other organisms), 20 (40%) had baseline neutropenia and 36 (72%) were refractory to standard therapy before rhu GM-CSF administration. Consistent with responses in the newly reported patients, the overall response rate in the literature review was 82% (40 [80%] complete responses, 1 [2%] partial response, and 9 [18%] no response).

Conclusions. Sargramostim may be a potential adjunctive immunomodulator for selected patients with hematological malignancies and refractory IFDs.
Granulocyte-macrophage colony-stimulating factor (GM-CSF) is an immunomodulatory cytokine produced by circulating and tissue-resident immune cells, as well as endothelial and alveolar epithelial cells. GM-CSF modulates multiple biological functions regulating hematopoiesis and immunomodulation [1–4]. This spectrum of biological activities, termed "cytokine pleiotropy," and the ability of GM-CSF to link innate and adaptive immunity through effects on dendritic cell and T-lymphocyte function, highlight the central role of this cytokine in regulating the immune response.

GM-CSF also plays a central role in response to infection, including activation of macrophages, monocytes, and neutrophils [5]. GM-CSF augments phagocytosis, nonoxidative pathogen killing, and clearance by macrophages and peripheral blood monocytes, while also upregulating oxidative metabolism and microbicidal activity of neutrophils and signaling emergency hematopoiesis elicited by infection [6].

Sargramostim (yeast-derived, glycosylated recombinant human [rhu] GM-CSF) has been in clinical use in the United States for nearly 3 decades and is the only approved rhu GM-CSF. While sargramostim is used as a traditional hematopoietic growth factor, it is also utilized as adjunctive therapy for serious invasive fungal diseases. Although not commercially available, other rhu GM-CSF products include molgramostim (bacteria-derived) and regramostim (Chinese hamster ovary cell–derived), which differ in glycosylation profile and clinical toxicity compared with sargramostim. Molgramostim was approved by the European Medicines Agency but subsequently withdrawn from clinical use. Regramostim was never approved by a regulatory authority.

To our knowledge, there has been no systematic review of rhu GM-CSF for the treatment of invasive fungal diseases (IFDs). We therefore reviewed all available literature for rhu GM-CSF as adjuvant immunomodulatory therapy of IFDs in pediatric and adult patients. We also report 15 new cases of rhu GM-CSF used in the management of life-threatening mycoses in pediatric oncology patients in a retrospective cohort analysis.

**METHODS**

**Definitions**

*Neutropenia:* ANC <500 neutrophils/µL.

*Invasive fungal disease (IFD):* defined by European Organization for Research and Treatment of Cancer/Mycoses Study Group Education and Research Consortium (EORTC/MSG-ERC) criteria [7].

*Refractory to antifungal therapy:* lack of response to 7 or more days of antifungal therapy.

*Adjunctive therapy:* use of rhu GM-CSF in combination with antimicrobial therapy for treatment of IFDs.
Response to therapy:

Complete response: resolution of all signs, symptoms, and laboratory, microbiological, and diagnostic imaging evidence of IFD.

Partial response: resolution of most signs and symptoms, improvement of attributable laboratory abnormalities, resolution of microbiological findings, and ≥50% reduction of diagnostic imaging evidence of IFD.

Stable: resolution of most signs and symptoms and improvement of attributable laboratory abnormalities, resolution of microbiological findings, and <50% reduction of diagnostic imaging evidence of IFD.

Progression: worsening of signs, symptoms, laboratory, microbiological, and diagnostic imaging evidence of IFD.

Success: complete or partial response to therapy.

Failure: stable or progression of IFD despite therapy.
### Table 1. Original Cases of Sargramostim (Rhu GM-CSF) for Treatment of Pediatric Fungal Diseases

| Age and Sex | Underlying Disease | State | Infection Details | Neutropenic at Start of Rhu GM-CSF? | Treatment Refractory Before Rhu GM-CSF? | Rhu GM-CSF Treatment | Concomitant Therapy | Reason for Sargramostim Use | Clinical Course/Outcome |
|-------------|-------------------|-------|------------------|-------------------------------------|----------------------------------------|----------------------|----------------------|--------------------------|------------------------|
| 1 yo M      | T-cell ALL        |       | Disseminated mucormycosis | Yes | Yes | Sargramostim 250 µg/m²/dose daily with topical GM-CSF | LAmB, caspofungin | Development of fungal cellulitis of L arm, R leg, and R forearm | • Patient developed disseminated disease with pulmonary involvement and multiple cutaneous lesions requiring serial surgical debridements, hyperbaric oxygen therapy, wound vac placement, systemic sargramostim, topical dressings soaked with sargramostim solution, and eventual split-thickness skin grafts to defects. • Clinically doing well and in remission almost 12 y later. |
| 4 yo M      | Medulloblastoma   |       | Hematogenous meningoencephalitis (Candida albicans) | No | Yes | Sargramostim 100 µg/m²/dose q4 mo, Flucytosine, caspofungin, LAmB | Medulloblastoma resection complicated by posterior fossa syndrome, prolonged fever, and refractory Candida meningoencephalitis | Infection stabilized and sargramostim was discontinued following partial response. • Continues on lifelong suppressive antifungal therapy with fluconazole. • Survived infection but neurologically devastated requiring tracheostomy, ventilator, and G-tube. • Remains in remission almost 9 y later. |
| 8 yo F      | B-cell ALL        |       | Disseminated Candida albicans | Yes | Yes | Sargramostim 250 µg/m²/dose q4 mo when ANC <500, 100 µg/m²/dose q4 mo when ANC >500 x27 mo, Fluconazole, flucytosine, LAmB, micafungin | Candida esophagitis at ALL diagnosis, with prolonged fever and neutropenia; development of endocarditis, cutaneous and muscular lesions, nodular pneumonia, and splenic and renal microabscesses while on antifungal therapy; infection progressed from acute to chronic disseminated candidiasis, which required cardiothoracic surgery for fungal endocarditis | Complete modified maintenance chemotherapy along with antifungal therapy and sargramostim, with eventual hospital discharge and remission from ALL. • Complete resolution of infection. • Remained in remission for 2 y but had relapse of ALL and died of C. krusei sepsis and multiorgan failure following re-induction chemotherapy. |
| 10 yo F     | Relapsed B-cell ALL |       | Disseminated Candida parapsilosis | Yes | No | Sargramostim 250 µg/m²/dose q4 mo when ANC <500, 100 µg/m²/dose q4 mo when ANC >500 x4 mo, Fluconazole, micafungin, voriconazole, LAmB | Fungemia during prolonged period of fever and neutropenia with associated micronodular cutaneous lesions | Sargramostim continued throughout the period of neutropenia and until resolution of cutaneous lesions and fungemia. • Remains in remission 4 y later. |
| Age and Sex | Underlying Disease | Infection Details | Neutropenic at Start of Rhu GM-CSF? | Treatment Refractory Before Rhu GM-CSF? | Rhu GM-CSF Treatment | Concomitant Therapy | Reason for Sargramostim Use | Clinical Course/Outcome |
|-------------|--------------------|------------------|-------------------------------|----------------------------------|----------------------|-------------------|----------------------|-----------------------------|
| 1 yo M      | AML                | Disseminated *Candida parapsilosis* | Yes                           | Yes                              | Sargramostim 250 µg/m²/dose daily when ANC <500, 100 µg/m²/dose TIW when ANC >500 (held if WBC >50 or ANC >20K) x8 mo | Isavuconazole, LAmB, fluconazole, micafungin | *Candida parapsilosis fungemia, endocarditis, and possible left-sided multilobar fungal pneumonia during neutropenia; developed multiple pulmonary nodules in right lung while receiving antifungal therapy with isavuconazole during prolonged neutropenia; received G-CSF before sargramostim therapy* | • Added sargramostim to antifungal therapy for breakthrough fungemia.  
• Fungemia resolved and pulmonary nodules resolved with residual scarring.  
• Sargramostim continued for 1 mo following completion of chemotherapy.  
• Remains in remission 3 y later. |
| 15 yo M     | AML                | Disseminated *Candida lusitaniae* | Yes                           | Yes                              | Sargramostim 250 µg/m²/d at when ANC <500, 100 µg/m²/dose TIW when ANC >500 x7 mo | Voriconazole, micafungin, LAmB | *Prolonged fever, neutropenia, and fungemia while on micafungin prophylaxis; micronodular cutaneous and nodular pulmonary lesions present; received G-CSF before sargramostim therapy* | • Treated initially with sargramostim and LAmB (changed to voriconazole once susceptibility known).  
• Decreased size of pulmonary lesions on serial chest CT.  
• Able to proceed with HSCT for relapsed AML while on sargramostim plus antifungal therapy for disseminated candidiasis.  
• Most recent chest CT showed small (1-2-mm) residual pulmonary nodules.  
• AML relapse and death after transplant ~2 y later. |
| 10 yo M     | Relapsed B-cell ALL | Disseminated *Candida lusitaniae* | Yes                           | Yes                              | Sargramostim 250 µg/m²/d at when ANC <500, 100 µg/m²/dose TIW when ANC >500 x13 mo | Micafungin, LAmB | *Prolonged fever and neutropenia; development of new nodules in lung, liver, spleen, kidneys, and brain while receiving micafungin treatment* | • Treated with LAmB and sargramostim.  
• Lung wedge biopsy revealed granulomatous inflammation with fungal forms consistent with *Candida* species.  
• Continued chemotherapy with radiographic resolution of all lesions.  
• Achieved remission from relapsed ALL.  
• Remains in remission 4 y later. |
| Age and Sex | Underlying Disease State | Infection Details | Neutropenic at Start of Rhu GM-CSF? | Treatment Refractory Before Rhu GM-CSF? | Rhu GM-CSF Treatment | Concomitant Therapy | Reason for Sargramostim Use | Clinical Course/Outcome |
|-------------|--------------------------|------------------|------------------------------------|----------------------------------------|----------------------|---------------------|--------------------------|--------------------------|
| 16 yo M     | AML                      | Disseminated Candida species | Yes                               | Yes                                    | Sargramostim 250 µg/m²/d when ANC <500, 100 µg/m²/dose TIW when ANC >500 | 500 x5 mo           | Isavuconazole, micafungin, LAmB, ABLC | Prolonged fever and neutropenia, nodular cutaneous lesions with nodular pulmonary pneumonia, and progression of nodular pulmonary lesions on isavuconazole | Changed to LAmB and added sargramostim, with improvement in pulmonary lesions but developed renal insufficiency; due to severe acute infusion reaction to LAmB, changed to ABLC and continued on sargramostim. |
| 14 yo F     | AML                      | Fungal pneumonia (Trichosporon faecale) | Yes                               | No                                     | Sargramostim 250 µg/m²/d when ANC <500, 100 µg/m²/dose TIW when ANC >500 | 500 x12 mo          | Micafungin, isavuconazole, posaconazole | Nodular pulmonary lesions caused by Trichosporon faecale during prolonged period of fever and neutropenia while receiving micafungin prophylaxis; wedge resection performed | Completed chemotherapy with concurrent antifungal therapy and sargramostim. |
| 3 yo M      | B-cell ALL               | Fungal rhinosinusitis and pneumonia (Aspergillus fumigatus, Aspergillus flavus, Rhizopus species) | No                                | Yes                                    | Sargramostim 100 µg/m²/dose TIW x3 mo | Micafungin, LAmB, voriconazole, posaconazole, HBOOT | Patient developed fungal rhinosinusitis (clinical and radiographic evidence) with fever while on therapy for acute invasive Aspergillus pneumonia; Rhizopus and Aspergillus flavus identified on endoscopic sinus debridement | Underwent serial sinus debridements and started sargramostim to augment host response. |
| 15 yo F     | B-cell ALL               | Scedosporiosis (Scedosporium apiospermum/boydii) | Yes                               | Yes                                    | Sargramostim 250 µg/m²/d when ANC <500, 100 µg/m²/dose TIW when ANC >500 | 500 x25 mo, then x6 mo (31 mo total) | Voriconazole, micafungin, posaconazole, isavuconazole, LAmB | Pulmonary nodules observed on CXR following period of fever and neutropenia; progression of pulmonary lesions despite antifungal therapy; lung wedge biopsy culture grew Scedosporium apiospermum/boydii | Following sargramostim therapy, lesions of pulmonary scedosporiosis are stabilized, enabling completion of a course of leukemia therapy. |

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| Age and Sex | Underlying Disease State | Infection Details | Neutropenic at Start of Rhu GM-CSF? | Treatment Refractory Before Rhu GM-CSF? | Rhu GM-CSF Treatment | Concomitant Therapy | Reason for Sargramostim Use | Clinical Course/Outcome |
|-------------|--------------------------|------------------|-------------------------------------|----------------------------------------|----------------------|---------------------|------------------------|--------------------------|
| 16 yo M     | Chemotherapy-related myelodysplasia | Pulmonary aspergillosis and hepatic trichosporonosis (Aspergillus fumigatus, Trichosporon asahii) | Yes | Yes | Sargramostim 250 µg/m² dose daily when ANC < 500, 100 µg/m² dose TIW when ANC > 500 x 3 mo | Micafungin, LAmB, isavuconazole, posaconazole | Developed hepatic lesions and pneumonia during prolonged episode of fever and neutropenia | • Developed invasive pulmonary aspergillosis and hepatic trichosporonosis, for which he received combination antifungal therapy. While awaiting surgical intervention, he developed Stenotrophomonas endocarditis, was not able to undergo surgery, and died from overwhelming bacterial sepsis due to Stenotrophomonas maltophilia. |
| 20 yo M     | T-cell ALL | Pulmonary and CNS aspergillosis (Aspergillus species) | Yes | Yes | Sargramostim 250 µg/m² dose daily when ANC < 500, 100 µg/m² dose TIW when ANC > 500 x 1 y (treatment ongoing) | Voriconazole, micafungin, isavuconazole | Developed nodular fungal pneumonia and multiple ring-enhancing lesions in brain, eventually developing basilar artery thrombosis, presumably due to Aspergillus causing expressive aphasia and right-sided weakness | • Required emergent thrombectomy via interventional radiology and intense physical therapy for rehabilitation. Histopathology of thrombus demonstrated hyphal elements that were morphologically consistent with Aspergillus species; however, cultures did not grow. On serial imaging, CNS lesions have gradually improved following addition of sargramostim. • Treatment is ongoing 17 mo later. |
| 4 yo M      | B-cell ALL | Sino-orbital-cerebral and pulmonary mucormycosis (Lichtheimia corymbifera) | No | Yes | Sargramostim 250 µg/m² dose daily when ANC < 500, 100 µg/m² dose TIW when ANC > 500 x 6 mo (treatment ongoing) | LAmB, isavuconazole, micafungin, posaconazole | Developed invasive sino-orbital-cerebral and pulmonary mucormycosis | • Required combination antifungal therapy, sargramostim, and serial debridement of sinuses and periorbital tissues, resection of infected portion of frontal lobe, and hyperbaric oxygen therapy. Underwent staged nose, face, and skull base reconstruction with skin grafting. • Responding; treatment is ongoing 9 mo later. |
| Age and Sex | Underlying Disease State | Infection Details | Neutropenic at Start of Rhu GM-CSF? | Treatment Refractory Before Rhu GM-CSF? | Rhu GM-CSF Treatment | Concomitant Therapy | Reason for Sargramostim Use | Clinical Course/Outcome |
|-------------|--------------------------|-------------------|--------------------------------------|----------------------------------------|-----------------------|---------------------|-------------------------|--------------------------|
| 14 yo M     | B-cell ALL               | Pulmonary and hepato-splenic mucormycosis (Rhizopus arrhizus) | Yes                                  | Yes                                    | Sargramostim 250µg/m²/dose daily when ANC < 500, 100 µg/m²/dose TIW when ANC > 500 x 3 mo (treatment ongoing) | Fluconazole, liposomal amphotericin B, isavuconazole | Persistent hepatic lesions despite antifungal therapy | Developed multiple ring-enhancing lesions in liver and spleen. Initially thought to be disseminated candidiasis and treated with fluconazole based on urine culture positive for Candida parapsilosis. However, 1 lesion persisted, which returned positive for Rhizopus arrhizus by PCR on biopsy. | 

Fluconazole was discontinued, and isavuconazole was initiated with minimal decrease in size of the hepatic lesions. With addition of sargramostim, the lesions are decreasing in size. 

Responding; treatment is ongoing 12 mo later.

Abbreviations: ABLC, amphotericin B lipid complex; ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; ANC, absolute neutrophil count; BIW, twice a week; CXR, chest x-ray; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; HBOT, hyperbaric oxygen therapy; HSCT, hematopoietic stem cell transplantation; IFD, invasive fungal disease; LAmB, liposomal amphotericin B; MDRO, multidrug-resistant organism; PCR, polymerase chain reaction; rhu, recombinant human; TIW, 3 times per week.

*Partial response to sargramostim thought to be related to persistent indwelling ventriculoperitoneal shunt.*
Follow-up: time elapsed from completion of antifungal therapy to last clinical visit.

New Cases of IFDs Treated With Rhu GM-CSF
Original cases where rhu GM-CSF (sargramostim) was used in refractory IFDs were identified in a retrospective cohort analysis from the inpatient Pediatric Infectious Diseases Consultation Service, which has monitored all pediatric oncology patients with suspected and confirmed IFDs at a single institution (Miller Children’s and Women’s Hospital, Long Beach, CA, USA) from 2009 through 2022. Data collected included demographic features, type of infection, antimicrobial therapy, use of rhu GM-CSF, and outcome.

Published Cases
A comprehensive literature search of the PubMed and Embase electronic databases was performed (Figure 1). Search terms consisted of “granulocyte-macrophage colony-stimulating factor” OR “GM-CSF” OR “recombinant granulocyte-macrophage colony-stimulating factor” OR “sargramostim” OR “molgramostim” OR “regramostim” AND “fungal infection” OR “mycosis” AND “case report” to identify case reports published in the English language between January 1, 1990, and March 1, 2022, that evaluated use of rhu GM-CSF as adjunctive therapy in patients with IFDs. Additional studies identified on review of pertinent literature were also included. All cases in which the pathogen, treatment, and efficacy could be fully assessed were included; cases were excluded if no infectious organism was identified. Cases involving rhu GM-CSF for treatment of bacterial, viral, or parasitic infections were excluded.

RESULTS
New Case Studies of Sargramostim for IFD
Tables 1 and 2 detail and summarize, respectively, 15 contemporary, original cases of sargramostim as adjunctive therapy in the treatment of IFDs, including those caused by Candida spp., Aspergillus spp., Rhizopus sp., Lichtheimia sp., Scedosporium spp., and Trichosporon spp., in pediatric patients (1–20 years of age). A majority (80%) were neutropenic at baseline, and 12 patients (80%) were considered refractory to prior therapy. Sargramostim was administered adjunctively, with standard antifungal therapy and surgical debridement where appropriate, at a dosage of 250 µg/m² daily if the ANC was <500 cells/µL, then reduced to immunomodulatory dosing of 100 µg/m²/thrice weekly when the ANC exceeded 500 cells/µL.

Among the 15 patients, 12 completed treatment and were evaluable for response; 3 patients were still receiving therapy at the time of publication. Among the 12 evaluable patients, 8 (67%) achieved a complete response (resolution of infection), 3 (25%) attained a partial response, and 1 (8%) had a stable response. The remaining 3 patients who are continuing to receive antifungal and adjunctive sargramostim therapy are responding favorably, with continued improvement of signs, symptoms, and laboratory and imaging evidence of IFD. Importantly, with the addition of sargramostim, 11 patients were able to successfully complete scheduled chemotherapy, and 3 were able to restart chemotherapy. In 1 patient treated for 7 months with chemotherapy plus sargramostim, 1 additional month of sargramostim was administered after completion of chemotherapy and infection resolution to enhance further immune recovery and response.

Among the 3 patients still undergoing therapy, 1 with invasive aspergillosis had complete resolution of intracranial and pulmonary lesions but continues on antifungal therapy with sargramostim until completion of maintenance chemotherapy given the high risk of recurrence. One with sino-orbital-cerebral pulmonary mucormycosis continues on antifungal therapy and immunomodulatory dosing of sargramostim (100 µg/m²/thrice weekly) while undergoing staged surgical reconstruction of the face and continuing on modified maintenance chemotherapy with blinatumomab. Repeat cultures from serial debridesments have been negative, and pulmonary lesions continue to decrease in size on serial imaging. One with pulmonary and hepatosplenic mucormycosis remains on antifungal therapy and immunomodulatory dosing of sargramostim while on maintenance chemotherapy with demonstrated gradual decrease in size of the hepatic lesions on serial imaging.

In these new cases, treatment-related adverse events were infrequent with sargramostim. Three (20%) of 15 patients experienced bone pain, including 1 with bruising from local injection and 1 with fever. There also were no cases of fluid shifts leading to third-spacing. No new safety concerns were identified, and no one discontinued sargramostim therapy due to adverse events.

Published Cases of Rhu GM-CSF for Treatment of IFDs
Published case reports on the use of rhu GM-CSF in IFDs are detailed and summarized in Tables 3 and 4, respectively [8–45]. Among the 50 cases of IFDs, 15 were caused by Candida spp., 13 by Mucorales, 11 by Aspergillus spp., and 11 by less common organisms. Twenty (40%) had baseline neutropenia, and 36 (72%) were considered to be refractory to standard therapy before rhu GM-CSF administration. Complete response was reported in 40 (80%) patients and partial response in 1 (2%) patient, with 9 (18%) patients classified as failure to respond.

DISCUSSION
This systematic review is, to our knowledge, the largest reported series of patients treated adjunctively with rhu GM-CSF for
IFDs. This report includes 15 newly described pediatric patients who were treated adjunctively with sargramostim for IFDs in the setting of hematologic malignancies. Patients with IFDs were treated both in neutropenic and non-neutropenic states. This paper also reviewed 50 previously published cases of IFDs that were adjunctively managed with rhu GM-CSF. The outcome measures of 50 previously published cases mirrored those of the 15 prospectively managed pediatric patients presented in this report. Overall (complete and partial) response rates for the newly reported pediatric oncology patients and cases from the systematic literature review were similar: 92% and 82%, respectively. These favorable outcomes may be related both to the hematopoietic properties of rhu GM-CSF and to its broad immunomodulatory effects on innate host defenses against fungi. These results support consideration of adjunctive treatment with sargramostim for IFDs in pediatric and adult patients with hematologic malignancies and other immunocompromised conditions, given the limited treatment options for refractory mycoses.

While there are no randomized controlled clinical trials of GM-CSF for treatment of refractory IFDs in immunocompromised patients, there is a critical need for new strategies to augment host response in this patient population. Given the limited options available to such patients, the supportive pre-clinical laboratory data, the impact on significantly preventing infections in GM-CSF-treated patients, and the successes reported in individual cases with documented IFDs, the careful use of GM-CSF in this patient population seems tenable.

In addressing toxicity, one needs to distinguish between the yeast-derived, glycosylated form of GM-CSF (sargramostim) and the bacteria-derived nonglycosylated form of GM-CSF (molgramostim). Although comparative studies have not been conducted, the nonglycosylated form of GM-CSF appears to be associated with greater systemic toxicity in clinical trials [47]. By comparison, sargramostim has consistently shown a favorable safety profile. Beveridge et al., in 137 patients receiving sargramostim or filgrastim, showed no significant differences in the incidence or severity of systemic adverse events, with the exception of a slightly higher incidence of grade I fever (<38.1°C) [48]. Rowe and colleagues, in a randomized, placebo-controlled phase 3 study, compared the toxicity of induction chemotherapy with daunorubicin and cytarabine with sargramostim vs placebo and found that the overall treatment toxicity was reduced in the sargramostim arm (P = .049) [49, 50].

As pediatric patients are often considered to be therapeutic orphans in the development of new immunomodulatory strategies, we consider that treatment of this carefully monitored cohort of patients is an important advance that may inspire further studies in children and adults. The patients with hematological malignancies at Miller Children’s and Women’s Hospital Long Beach are managed in a seamless, well-organized system of supportive care through a multidisciplinary team, including Infectious Diseases and Hematology/Oncology.

Among the 15 new pediatric oncology cases of IFD reported here, 7 had disseminated candidiasis, 6 of which were refractory to initial antifungal therapy. GM-CSF upregulates the oxidative metabolism of neutrophils and increases microbicidal activity against Candida spp. in vitro, as well as augments nonoxidative killing by monocytes and macrophages [6, 51–53]. Sargramostim, in the 6 neutropenic patients with invasive candidiasis, was initially administered to induce hematopoiesis, then continued after neutropenia resolution to augment innate host response. Favorable outcomes among these pediatric cases are consistent with those described in individual case reports [8].

Among 50 previously published cases of IFDs adjunctively managed with rhu GM-CSF, 3 patients had disseminated candidiasis. Of these 3, 2 had chronic disseminated candidiasis that complicated neutropenia and necessitated extended courses of antifungal therapy (range, 2 months to 1.5 years) [8, 9]. Chronic disseminated candidiasis reflects a Th1/Th2 dysimmunoregulation. Upon recovery from neutropenia in disseminated candidiasis, an ineffective inflammatory response modulated by Th2 cytokines results in fever and progressive lesions in the liver, spleen, and other tissues [54, 55]. In these
| Author and Year (Location) | Age (Location) | Sex | Underlying Disease State | Infection Details | Neutropenic at Start of Rhu GM-CSF? | Treatment-Refractory Before Rhu GM-CSF? | Rhu GM-CSF Treatment | Concomitant Therapy | Clinical Course/Outcome |
|---------------------------|----------------|-----|--------------------------|------------------|------------------------------------|----------------------------------------|----------------------|--------------------|------------------------|
| Dignani 2005 (Arkansas)   | 14 yo F        | AML | Chronic disseminated fungal infection (Candida) | No               | Yes (11 mo prior fluconazole)     | Sargramostim 250 µg/ m² TIW x1 mo      | IFN-γ      |                    | Complete resolution of liver lesions after 2 mo of sargramostim; free of infection at 3-y follow-up. |
| Dignani 2005 (Arkansas)   | 28 yo M        | AML | Disseminated fungal infection (Candida) | No               | Yes (prior AMB followed by ABLC plus fluconazole x2 mo) | Sargramostim 250 µg/ m² TIW x3 mo      | IFN, fluconazole |                    | Complete response using rhu GM-CSF plus fluconazole. |
| Rókusz 2001 (Hungary)     | 29 yo F        | AML | Chronic disseminated fungal infection (Candida) | Yes              | Yes                                | Molgramostim 150 µg/d, then 50 µg/d, then 50 µg/wk (total of 18 mo) | Fluconazole |                    | Complete response using rhu GM-CSF plus fluconazole. |
| Gavino 2016 (Canada)      | 38 yo M        | CARD9 deficiency | Relapsing intracranial infection (C. albicans) | No               | Yes (prior fluconazole x3 mo) | Sargramostim 500 µg/d x9 + mo          | Fluconazole |                    | Ongoing headaches, worsening neurologic deficits, and abnormal CSF parameters, which improved with adjunctive sargramostim. Complete resolution of infection. |
| Gavino 2014 (Canada)      | 41 yo M        | CARD9 deficiency | Relapsing meningoencephalitis (C. albicans) | No               | No (prior “appropriate antifungal therapy”) | Sargramostim 500 µg/d, then 250 µg/d (for 18 mo at time of publication) | Voriconazole |                    | Relapsing infection over 11-y period despite appropriate antifungal therapy. Complete response and clinical remission with adjunctive sargramostim (18-mo follow-up). Attempts to decrease sargramostim to QOD led to recurrence; reduction of sargramostim to 250 µg daily was tolerated, with sustained improvement of CSF parameters. |
| Drummond 2018 (Maryland)  | 10 yo F        | CARD9 deficiency | Meningoencephalitis (Candida) | Yes              | Yes (prior LAmB, 5-flucytosine, voriconazole, then voriconazole and 5-flucytosine followed by high-dose fluconazole) | Sargramostim 200 µg x15 mo | None         | Lack of apparent clinical and microbiological response to sargramostim (2.5-y follow-up). |
Table 3. Continued

| Author and Year (Location) | Age and Sex | Underlying Disease State | Infection Details | Neutropenic at Start of Rhu GM-CSF? | Treatment-Refractory Before Rhu GM-CSF? | Rhu GM-CSF Treatment* | Concomitant Therapy | Clinical Course/Outcome |
|----------------------------|-------------|--------------------------|-------------------|-------------------------------------|-----------------------------------------|------------------------|-----------------------|------------------------|
| Dierdorf 1997 (Switzerland) | 22 yo F     | AML                     | Bilateral pneumonia (C. albicans) | Yes (prior amphotericin B, fluconazole) | Yes                                     | Molgramostim 400 µg/d x 15 d | Amphotericin B, fluconazole | • Rhu GM-CSF improved hematological recovery; complete response, with pneumonia resolved within 2 wk. |
| Poynton 1998 (United Kingdom) | 45 yo M    | AML secondary to MDS     | Hepatosplenic infection (Candida) | No                                  | Yes                                     | Rhu GM-CSF 3 µg/kg/d x 4 wk | IFN-γ, LAmB           | • Partial response to rhu GM-CSF plus LAmB; condition improved with addition of IFN-γ, but no resolution of infection until on IFN-γ monotherapy. • Died 2 mo later from leukemia relapse, but no signs of fungal infection. |
| Poynton 1998 (United Kingdom) | 21 yo F    | AML                     | Hepatosplenic infection (C. albicans) | Yes (prior therapy with G-CSF, LAmB) | Yes                                     | Rhu GM-CSF 3–5 µg/kg/d x 6 wk | LAmB                 | • Prior therapy with G-CSF and LAmB, with limited benefit. • Partial response to rhu GM-CSF; resolution of infection with addition of IFN-γ, which was subsequently continued as monotherapy. • No recurrence of fungal infection over subsequent 2 y. |
| Montgomery 1991 (Washington) | 25 yo M    | HD                      | Invasive cutaneous fungal infection (C. albicans) | Yes (prior amphotericin B) | Yes                                     | Sargramostim 250 µg/m²/d x 21 d | Amphotericin B, pentoxifylline | • Marked relief in pain and erythema within several days of initiating therapy; complete response with resolution of fever and IFD after 3 wk. |
| Vasquez 1998 (Michigan) | NR          | AIDS                    | Oropharyngeal candidiasis (C. albicans) | No                                  | Yes (prior fluconazole, clotrimazole, itraconazole, amphotericin B) | Sargramostim 150–300 µg/d x 14 d | Fluconazole           | • At 2-wk follow-up, clinical improvement and resolution of infection. |
| Vasquez 1998 (Michigan) | NR          | AIDS                    | Oropharyngeal candidiasis (C. albicans) | No                                  | Yes (prior fluconazole, clotrimazole, itraconazole, amphotericin B) | Sargramostim 150–300 µg/d x 14 d | Fluconazole           | • At 2-wk follow-up, clinical improvement and resolution of infection. |
| Vasquez 1998 (Michigan) | NR          | AIDS                    | Oropharyngeal candidiasis (C. albicans, C. glabrata) | No                                  | Yes (prior fluconazole, itraconazole, amphotericin B) | Sargramostim 150–300 µg/d x 14 d | Fluconazole, amphotericin B | • At 2-wk follow-up, clinical improvement and resolution of infection. |
| Martino 1990 (Italy) | 40 yo M     | ANLL                    | Candida endocarditis (C. parapsilosis) | Yes (prior fluconazole) | Yes                                     | Molgramostim 3–6 µg/kg/d x 1 mo | Fluconazole           | • At 1-mo follow-up, progressive disappearance of echocardiographic abnormalities. • Patient died 40 d after discontinuation of antifungal treatment due to P. aeruginosa sepsis complicating hemorrhagic cystitis. |
| Author and Year (Location) | Age and Sex | Underlying Disease State | Infection Details | Neutropenic at Start of Rhu GM-CSF? | Treatment-Refractory Before Rhu GM-CSF? | Rhu GM-CSF Treatment | Concomitant Therapy | Clinical Course/Outcome |
|---------------------------|-------------|--------------------------|------------------|-----------------------------------|----------------------------------------|----------------------|---------------------|----------------------|
| Rosti 1990 (Italy) [18]   | 28 yo M     | CML                      | Sepsis (C. tropicalis) | Yes                               | No                                      | Rhu GM-CSF 7 µg/kg/d LAmB x18 d |                      | • Authors attributed rhu GM-CSF therapy and large doses of LAmB to accelerated hematological recovery and complete resolution of infection at 8-mo follow-up. |
| Dignani 2005 (Arkansas) [8] | 22 yo M    | ALL                      | Disseminated fungal infection (Trichosporon beigelii*) | No                               | Yes (prior ABLC, fluconazole, 5-fluorocytosine, AMB ocular) | Sargramostim 500 µg/ d x6 wk | LAmB              | • Response observed with first 30 d of therapy, with defervescence and resolution of fever, endophthalmitis, hypercalcemia, and pulmonary lesions. • At 1-y follow-up, complete resolution of infection. |
| Pagano 1996 (Italy) [19]  | 57 yo F     | AML                      | Disseminated fungal infection (Blastoschizomyces capitatus) | NR                               | Yes (prior amphotericin B) | Molgramostim 300 µg/2x4 wk then 150 µg BIV x16 wk | Amphotericin B, flucytosine |                    | • Marked reduction of abdominal, pulmonary, and neurological abscesses after 4 wk of rhu GM-CSF. • At 10-mo follow-up, complete resolution of infection. |
| Chen 2017 (California) [20] | 16 yo M    | Germinoma of pituitary and pineal gland | Ventriculitis/abscess (Aspergillus fumigatus) | No                               | Yes (prior voriconazole, caspofungin) | Sargramostim 100 µg/m²/dose TW x1 6 mo (approximate total duration) | Voriconazole, caspofungin, amphotericin B |                    | • Due to progression of infection on conventional therapy within first mo, adaptive pharmacotherapy with voriconazole plus sargramostim was instituted. • At 2-y follow-up, clinical improvement and decreased CSF (1→3)-β-D-glucan levels. |
| Lujber 2003 (United Arab Emirates) [21] | 25 yo F | Immunocompetent host | Invasive rhinosinusitis with endocranial and orbital extension (A. fumigatus) | No                               | No                                      | Molgramostim 300 µg daily in week 2, 400 µg daily in week 3, 400 µg QOD in weeks 4-7, 400 µg BMV in weeks 8-11 | Rifampion, LAmB, dexamethasone, acetazolamide, IFN-γ, flucytosine |                    | • Combination of rhu GM-CSF, IFN-γ, and LAmB dose escalation helped to resolve extensive invasive fungal rhinosinusitis with cerebral and orbital involvement. • At 3-y follow-up, complete resolution of infection. |
| Ellis 2002 (United Arab Emirates) [22] | 25 yo F | Immunocompetent host | Sino-orbital infection (A. flavus) | No                               | No                                      | Rhu GM-CSF 200 µg TW x73 d | Rifampion, LAmB, dexamethasone, acetazolamide, IFN-γ, flucytosine | • Addition of IFN-γ to rhu GM-CSF and LAmB appeared to halt and reverse clinical deterioration; at 1-y follow-up, complete resolution of infection. |
| Author and Year (Location) | Age and Sex | Underlying Disease State | Infection Details | Neutropenic at Start of Rhu GM-CSF? | Treatment-Refractory Before Rhu GM-CSF? | Rhu GM-CSF Treatment* | Concomitant Therapy | Clinical Course/Outcome |
|---------------------------|-------------|--------------------------|-------------------|------------------------------------|----------------------------------------|-----------------------|----------------------|------------------------|
| Boots 1999 (Australia) [23] | 35 yo F | Immunocompetent patient postinfluenza | Tracheobronchitis (A. niger) | No | Yes (prior amphotericin B, flucytosine, itraconazole followed by LAmB) | Molgramostim 400 µg/d x2 wk | IFN-γ, LAmB, continuous nebulized adrenaline, nebulized budesonide | • Gradual patient improvement noted.  
  • At 3-y follow-up, complete resolution of infection. |
| Bandera 2008 (Italy) [24] | 67 yo M | Cystic-bronchiectatic pulmonary dystrophy | Disseminated invasive fungal pulmonary infection (A. fumigatus) | No | Yes (prior LAmB) | Molgramostim 300 µg daily x2 mo | IFN-γ, LAmB | • Rapid and complete resolution of fever and cough, with clearing of pleural fluid, after addition of rhu GM-CSF and IFN-γ; with 5 y of follow-up. |
| Bandera 2008 (Italy) [24] | 69 yo F | Pulmonary tuberculosis | Disseminated invasive fungal pulmonary infection (A. fumigatus) | No | Yes (prior itraconazole, amphotericin B) | Molgramostim 300 µg daily x48 d | IFN-γ, itraconazole | • Improvement in clinical condition after 2 wk of rhu GM-CSF and IFN-γ.  
  • Complete resolution of infection, with 4 y of follow-up. |
| Trachana 2001 (Greece) [25] | 13 yo M | Common variable immunodeficiency following pulmonary candidiasis | Hepatitis (A. terreus) | Yes | Yes (prior fluconazole, LAmB) | Rhu GM-CSF 5 µg/kg/d LAmB, itraconazole | • No remarkable changes seen in number and size of fungal lesions.  
  • By 2-y follow-up, patient had recovered from infection.  
  • IFN-γ and rhu GM-CSF added due to persistent sepsis; clinical improvement noted within 2 wk, with eventual complete response, with 6 y of follow-up. |
| Bandera 2008 (Italy) [24] | 32 yo M | HIV | Invasive fungal pulmonary infection (A. fumigatus) | Yes | Yes (prior itraconazole, amphotericin B followed by LAmB) | Molgramostim 300 µg/d x2 mo | IFN-γ, LAmB, antiviral HIV therapy | • "Dramatic" clinical and radiological improvement occurred after addition of rhu GM-CSF, complete resolution of infection by 4-mo follow-up. |
| Gari-Bai 1992 (Germany) [26] | 67 yo M | Felty’s syndrome and chronic obstructive lung disease | Recurrent pneumonia (Aspergillus) and infected wound (P. aeruginosa) | Yes | Yes (prior cefotaxim, tobramycin, flucloxacilline) | Molgramostim 6.25 µg/kg/d x6 d, then 3.125 µg/kg/d x5 d | NR | • Patient continued to deteriorate despite rhu GM-CSF and other intensive therapy.  
  • Died from widespread pneumonia with invasive aspergillosis. |
| Abu Jawdeh 2000 (Lebanon) [27] | 5 yo M | Primary defect in monocyte killing | Vertebral fungal infection (Aspergillus) | No | Yes (prior amphotericin B, flucytosine) | Rhu GM-CSF 10 µg/kg every other day x2 mo followed by every third day x2 mo | Amphotericin B (on alternating days with GM-CSF) | • Rhu GM-CSF immediately started with voriconazole upon fungal identification.  
  • Clinical improvement over 2–3 wk of treatment, allowing hospital discharge. |
| Author and Year (Location) | Age and Sex | Underlying Disease State | Infection Details | Neutropenic at Start of Rhu GM-CSF? | Treatment-Refractory Before Rhu GM-CSF? | Rhu GM-CSF Treatment* | Concomitant Therapy | Clinical Course/Outcome |
|---------------------------|-------------|--------------------------|------------------|----------------------------------|--------------------------------------|-----------------------|---------------------|-----------------------|
| Ma 2001 (Australia) [29]  | 77 yo M     | Hairy cell leukemia      | Disseminated pulmonary fungal infection (Rhizomucor pusillus) | Yes (prior G-CSF, cefepine followed by meropenem and AMB, then LAmB) | Yes | Rhu GM-CSF 400 µg/d, titrated based on ANC 1 x 10^9/L (400 µg/d–400 µg twice weekly) x7 mo | Meropenem, amphotericin B/LAmB | Persistent infection and neutropenia despite antifungal therapy. | Significant improvement in chest CT scan after 1 mo of treatment with LAmB and rhu GM-CSF. | With 13-mo follow-up, eventual resolution of lung infiltrate. |
| Chandine 2015 (Tennessee) [30] | 15 yo F | Astrocytoma | Cerebral fungal infection (Rhizopus oryzae) | No | No | Sargramostim 100 µg/ m2/d x54 d | Dexamethasone, micafungin, posaconazole | Abscess was effectively treated with posaconazole, micafungin, and sargramostim followed by posaconazole alone; remained stable for 19 mo. |
| Humphrey 2020 (Pittsburgh) [31] | 55 yo M | ALL | Disseminated cutaneous fungal infection (Mucor) following long-term voriconazole for fungal pneumonia | No | No | Sargramostim (dose/schedule NR) | Amphotericin B, caspofungin, isavuconazole, tacrolimus and methylprednisolone for GvHD | Case complicated by internal carotid artery and cavernous sinus thromboses. | Patient received high-dose corticosteroids for asthma just before IFD. | No clear response to rhu GM-CSF. | Authors stated that patient was youngest to survive rhinocerebral mucormycosis with carotid artery occlusion. |
| Simmons 2005 (Colorado) [32] | 8 yo F | Diabetes mellitus type 1, asthma | Rhinocerebral fungal infection (Mucor) | No | No | Rhu GM-CSF thrice weekly (dose/duration NR) | IFN-γ, LAmB, HBOT | Case complicated by internal carotid artery and cavernous sinus thromboses. | Patient received high-dose corticosteroids for asthma just before IFD. | No clear response to rhu GM-CSF. | Authors stated that patient was youngest to survive rhinocerebral mucormycosis with carotid artery occlusion. |
| Abzug 2004 (Colorado) [33] | 7 yo F | Diabetes mellitus type 1, reactive airway disease | Sinusitis and orbital cellulitis (Mucor) | No | Yes (prior LAmB, voriconazole, vancomycin, ceftiraxone, metronidazole) | Sargramostim 100 µg/ m2 daily x8-wk | IFN-γ, HBOT, LAmB, posaconazole, vancomycin, ceftiraxone, metronidazole and insulin drip, heparin | Sargramostim added due to continued decline on antifungal therapy; clinical improvement seen, with negative fungal cultures. | With 11 mo of follow-up, complete resolution of infection. |
| Mastroianni 2004 (Italy) [46] | 68 yo M | Immunocompetent host | Paranasal sinus fungal infection (Mucor) | No | No | Molgramostim 150 µg/ d twice weekly x12 wk | LAmB | First case report of invasive mucormycosis successfully treated with rhu GM-CSF plus LAmB in immunocompetent patient without a known underlying condition; remains well after 24 mo. |
| Author and Year (Location) | Age and Sex | Underlying Disease State | Infection Details | Neutropenic at Start of Rhu GM-CSF? | Treatment-Refractory Before Rhu GM-CSF? | Rhu GM-CSF Treatment* | Concomitant Therapy | Clinical Course/Outcome |
|---------------------------|-------------|--------------------------|------------------|-------------------------------------|----------------------------------------|----------------------|---------------------|----------------------|
| Garcia-Diaz 2001 (Louisiana/Texas) [35] | 51 yo F | Diabetes mellitus and asthmatic bronchitis | Rhinocerebral fungal infection (Rhizopus) | No | Yes (prior amphotericin B) | Sargramostim 4500 µg Amphotericin B SC (total dose) over 19 d | • Clinical improvement and resolution of infection after sargramostim addition; healthy at 4-y follow-up. |
| Garcia-Diaz 2001 (Louisiana/Texas) [35] | 65 yo M | Diabetes mellitus type 2 and asthmatic bronchitis | Maxillary osteomyelitis and rhinocerebral fungal infection (Mucor) | No | Yes (prior amphotericin B) | Sargramostim 245 µg/d x1 mo ABLC | • Patient with chronic sinusitis and increasing maxillary pain. • Clinical improvement with addition of sargramostim and extensive debridement; healthy at 3-y follow-up. |
| Garcia-Diaz 2001 (Louisiana/Texas) [35] | 52 yo F | Insulin-dependent type 1 diabetes mellitus in ketoacidosis | Rhinocerebral fungal infection (Mucor) | No | Yes (prior amphotericin B) | Sargramostim 250 µg/d x5 mo ABLC | Sargramostim and ABLC therapy allowed for cure of infection, with no recurrence after 2 y of follow-up. |
| Mackenzie 2002 (Louisiana) [36] | 50 yo F | Polycystic kidney disease | Pulmonary fungal infection (Mucor) | No | No | Rhu GM-CSF 5 µg/kg/d LAmB (duration NR) | Complete resolution of infection. • Authors suggested rhu GM-CSF may have a role in life-threatening infections requiring immediate host immune response. |
| Mir 2000 (United Kingdom) [37] | 53 yo F | NHL | Gastrointestinal infection (Mucor) | Yes | No | Rhu GM-CSF (dose/duration NR) LAmB, CHOP chemotherapy, surgical debridement, itraconazole | Authors noted use of rhu GM-CSF over G-CSF due to better fungicidal activity. • Mucor bowel infiltrate successfully treated with rhu GM-CSF and LAmB; healthy at 2-y follow-up. |
| Haque 2019 (Florida) [38] | 49 yo M | Liver transplant | Surgical site mucormycosis (Rhizopus) | No | Yes (prior fluconazole) | Rhu GM-CSF x11 d (dose NR) Amphotericin B, micafungin, posaconazole | No effect on infection; subsequent worsening hypoxia, metabolic acidosis, with bradycardic arrest and death. |
| Mlechkin 2001 (Australia) [39] | 52 yo F | MM | Fungal sinusitis (Rhizopus) | No | Yes (prior LAmB) | Rhu GM-CSF 400 µg/d SC x10 d LAmB, liposomal nystatin, HBOT | Effect on infection unclear. • Fungal stains negative following rhu GM-CSF therapy, but new MRSA infection and patient remained symptomatic. • Rhu GM-CSF therapy complicated by local skin reactions and fevers. |
| Author and Year (Location) | Age and Sex | Underlying Disease State | Infection Details | Neutropenic at Start of Rhu GM-CSF? | Treatment-Refractory Before Rhu GM-CSF? | Rhu GM-CSF Treatment | Concomitant Therapy | Clinical Course/Outcome |
|----------------------------|-------------|--------------------------|------------------|------------------------------------|----------------------------------------|----------------------|----------------------|------------------------|
| Spielberger 1993 (Illinois) [40] | 53 yo M | AML | Disseminated cutaneous fungal lesions, bloodstream infection, and pulmonary infiltrate (Fusarium) | Yes | Yes (prior amphotericin B) | Rhu GM-CSF 5 µg/kg/d x15 d | Amphotericin B, fluocytosine, granulocyte transfusions | • Patient’s condition improved within 2 d, and number of skin lesions progressively decreased, with complete response. • Leukemia relapsed several mo later, with Klebsiella pneumonia sepsis and death. |
| Lewis 2008 (Texas) [41] | 40 yo M | ALL | Sinusitis, preseptal cellulitis, and skin nodules (Fusarium species and Mycobacterium abscesses) | Yes | Yes (prior posaconazole, then ABLC followed by LAmB) | Sargramostim x13 d (dose NR) | Granulocyte transfusion, G-CSF, IFN-γ1b, voriconazole, micafungin, clarithromycin, doxycycline | • Infection resolved with antifungal dose escalation and immune augmentation. • Patient received both G-CSF and sargramostim on hospital days 13–26. |
| Goldman 2016 (New York) [42] | 77 yo M | Immunocompromised due to immunosuppressive (corticosteroid) therapy | Disseminated cutaneous fungal infection (Scedosporium apiospermum) | No | No | Rhu GM-CSF 250 µg/d (duration NR) | Voriconazole, micafungin | • Marked complete clinical response observed with rhu GM-CSF and micafungin in voriconazole-resistant infection, with no further metastatic nodules observed. • Remained stable until presenting on day 256 with sepsis secondary to pneumonia; death. |
| Abzug 2004 (Colorado) [33] | 10 yo M | HIV | Otomastoiditis (Scedosporium apiospermum) | No | Yes (prior AMB,itraconazole, then miconazole) | Sargramostim dose escalation to 10 µg/kg/d IV (duration NR) | IFN-γ,itraconazole, amphotericin B, HIV antiretroviral therapy | • G-CSF for chronic neutropenia changed to sargramostim for monocyte/macrophage activation. • G-CSF resumed after sargramostim to maintain target ANC. • Response unclear. |
| Erker 2018 (Wisconsin) [43] | 15 yo M | ALL (B cell) | Invasive sinopulmonary fungal infection (Conidiobolus coronatus) | Yes | Yes (prior voriconazole, micafungin) | Sargramostim 250 µg/m²/d, then 100 µg/m² TIW for maintenance; increased to 250 µg/m² when neutropenic | Granulocyte transfusions, HBOT, LAmB, anidulafungin, terbinafine | • Improvement and complete response with sargramostim added to granulocyte transfusions, HBOT, and antifungal therapy. • Sargramostim continued TIW as maintenance for IFD; remained free of infection at 10-mo follow-up. |
| Author and Year (Location) | Age and Sex | Underlying Disease State | Infection Details | Neutropenic at Start of Rhu GM-CSF? | Treatment-Refractory Before Rhu GM-CSF? | Rhu GM-CSF Treatment* | Concomitant Therapy | Clinical Course/Outcome |
|---------------------------|-------------|--------------------------|------------------|----------------------------------|----------------------------------|----------------------|-------------------|------------------|
| Miniero 1997 (Italy) [44] | 12 yo F ALL | | Cryptococcal meningitis | Yes | No | Rhu GM-CSF 5 µg/kg/d | Amphotericin B, fluconazole | No response to infection; patient died after 70 d. | Authors noted that the severely impaired phagocytic cell function caused by high-dose corticosteroids and use of antilymphocyte globulin likely contributed to treatment failure. |
| Manfredi 1997 (Italy) [45] | 7 yo NR AIDS | | Cryptococcal meningoencephalitis | Yes | Yes (prior fluconazole) | Molgramostim 1 µg/kg/d SC x14 d | LAmB | Remission of infection, with no recurrence with 3 mo of follow-up. |
| Dierdorf 1997 (Switzerland) [13] | 49 yo F | Kidney transplantation | Bilateral interstitial pneumonia (P. jiroveci and CMV) | Yes | Yes (prior nystatin) | Molgramostim 300 µg/d x2 d, then 150 µg/d x 5 d | None | Investigators assessed patient response to rhu GM-CSF as “good to very good.” |
| Dierdorf 1997 (Switzerland) [13] | 50 yo F AML | | Dual pneumonia infection (Pneumocystis pneumonia suspected, S. aureus) | Yes | Yes (prior amphotericin B) | Molgramostim 400 µg/d x4 d | None | Rapid, complete response to rhu GM-CSF observed. |

Abbreviations: ABLC, amphotericin B lipid complex; AMB, amphotericin B deoxycholate; ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; ANC, absolute neutrophil count; ANNL, acute nonlymphoid leukemia; APL, acute promyelocytic leukemia; BCG, Bacillus Calmette-Guérin; BIW, twice a week; CGD, chronic granulomatous disease; CLL, chronic lymphocytic leukemia; CML, chronic myelogenous leukemia; CMV, cytomegalovirus; CSF, cerebrospinal fluid; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; GvHD, graft-vs-host disease; HBOT, hyperbaric oxygen therapy; HSCT, hematopoietic stem cell transplantation; IFD, invasive fungal disease; IFN-γ, interferon gamma; LAmB, liposomal amphotericin B; MDS, myelodysplastic syndrome; MM, multiple myeloma; MRSA, methicillin-resistant Staphylococcus aureus; NR, not reported; PAP, pulmonary alveolar proteinosis; QOD, every other day; TIW, 3 times a week.

*All GM-CSF dosing details specified as reported in original publications. Cases in which the type of GM-CSF was not indicated are listed in table as “GM-CSF.”

GM-CSF dose listed in original publication as 5 mg/kg/d; changed here to indicate presumed actual dose.

GM-CSF dose listed in original publication as 100 µg/m²/d; changed here to indicate presumed actual dose.
settings, rhu GM-CSF upregulates the microbicidal activity of monocytes, macrophages, and neutrophils, which may contribute to favorable responses in cases unresponsive to antifungal therapy alone. As this disease has been proposed to be a form of immune reconstitution syndrome [4, 56], use of rhu GM-CSF may also serve as an immunomodulator that may regulate an aberrant host response.

Sargramostim also was used in 6 of the newly described pediatric patients as adjunctive treatment of invasive disease caused by Aspergillus spp., Rhizopus spp., and Scedosporium apiospermum/boydii, as well as another patient with sino-orbital-cerebral disease caused by Lichtheimia corymbifera. All patients demonstrated reduction or stabilization of disease following initiation of sargramostim. These findings are consistent with the known in vitro activity of GM-CSF-mediated augmentation of lyphal damage by neutrophils against Aspergillus spp. [57], Mucorales [53, 58], and Scedosporium [59] spp., as well as the favorable responses observed in individual cases [20–24, 27–30, 33, 35–37, 46]. Moreover, the favorable outcomes observed in patients with invasive aspergillosis in this study are also compatible with those of Kasahara et al. who reported that administration of recombinant GM-CSF enhanced neutrophil NADPH oxidase response, augmented conidicidal activity, and reduced residual fungal burden in lung tissue in a murine model of pulmonary aspergillosis [60].

A beneficial effect of rhu GM-CSF on invasive mold diseases caused by aspergillosis, mucormycosis, and fusariosis may be related both to upregulation of functional innate host response and hematopoietic growth properties that hasten recovery from neutropenia [4, 61]. Recovery from neutropenia is essential for successful treatment of IFDs in neutropenic hosts [62]. At the same time, GM-CSF may also upregulate or protect innate host responses in non-neutropenic oncology patients receiving immunosuppressive therapies, such as in those with refractory IFDs and acute lymphoblastic leukemia who are receiving maintenance chemotherapy. Little is known, however, about the role of GM-CSF in nononcology patients receiving immunosuppressive therapies.

Of 49 published cases with reported baseline neutropenia data, 20 (40.8%) patients had neutropenia before antifungal treatment. Of these, fungal infections resolved in 17 (85%) patients following the addition of rhu GM-CSF to standard antifungal therapy. Similarly, 5 patients with non-neutropenic rhinocerebral mucormycosis were treated with rhu GM-CSF, 3 of whom had failed to respond to prior antifungal therapy. These infections resolved in 4 patients, and no recurrence was observed over a follow-up period of 2 to 4 years [33, 35, 46].

Among the newly described pediatric patients, 1 patient with acute myeloid leukemia developed pulmonary trichosporonosis while receiving prophylactic micafungin. This patient received sargramostim during neutropenia and throughout subsequent cycles of chemotherapy in conjunction with isavuconazole or posaconazole until complete resolution of all pulmonary nodules. A second patient had hepatic trichosporonosis during persistently profound neutropenia caused by chemotherapy-related myelodysplasia. Although the hepatic lesion remained stable, the molecular signal from the metagenomic assay decreased from 31 molecules/mL to below the threshold level of detection. Previous in vitro studies demonstrated that GM-CSF augments neutrophil and monocyte microbicidal and phagocytic activity, respectively, against Trichosporon asahii [63, 64]. This antifungal activity may be related to reversal of the immunosuppressive effects of Trichosporon glucuronylxylomannan [65, 66].

In addition to the effects of augmenting innate and adaptive host responses, sargramostim may also protect against infections by enhancing mucosal barrier immunity. In support of this concept, GM-CSF knockout mice demonstrated enhanced susceptibility to P. jirovecii and group B Streptococcus pneumonia, impaired alveolar macrophage function, reduced pulmonary clearance of surfactant proteins and lipids in the alveolar space, and lymphoid hyperplasia surrounding airways and lung vasculature [62, 67–69]. Conversely, enhanced
pulmonary expression of GM-CSF confers protection against postinfluenza tracheobronchial bacterial superinfection and *P. jirovecii* pneumonia [62, 70].

Response to pulmonary infection may also be regulated by the pleiotropic effects of GM-CSF on macrophage mitochondrial function that underlie cellular proliferation and differentiation. Lack of GM-CSF signaling impairs amino acid biosynthesis, glycolysis, and the pentose phosphate pathway, suggesting the importance of GM-CSF in facilitating mitochondrial pathways crucial to macrophage differentiation and proliferation [66–71]. Macrophage efferocytosis and mitochondrial bioenergetics may also play a role in immune responses to infections [71, 72]. GM-CSF also regulates alveolar macrophage population size via STAT5 phosphorylation [73].

Several small clinical studies indicate that inhaled delivery of rhu GM-CSF may be effective in improving pulmonary host defenses and clinical outcomes for several acute respiratory diseases [68–78]. Ongoing trials are further evaluating sargramostim in patients with COVID-19 and in those with sepsis [74–76].

Further supporting a respiratory mucosal protective role of rhu GM-CSF, a phase 2 trial evaluating sargramostim plus ipilimumab vs ipilimumab alone for metastatic melanoma showed a protective effect of sargramostim on pulmonary and gastrointestinal toxicity [77]. Such a protective effect on respiratory epithelia might also be beneficial in early IFD [79, 80]. Based upon its pleiotropic effects on the phagocytic and respiratory epithelia in augmenting pulmonary and systemic innate host defenses, additional clinical studies of sargramostim should be considered for patients at risk for progression of IFD.

Based on our direct experience and previously published cases, some guidance can be made regarding the dosage, timing of initiation, and duration of sargramostim for treatment of IFDs. In the new cases presented here, patients with baseline neutropenia initially received sargramostim at a dosage of 250 µg/m²/d to promote recovery from neutropenia and were transitioned to a dosage of 100 µg/m² 3 times weekly when the ANC exceeded 500 cells/µL. In contrast, those without baseline neutropenia were initiated on a lower initial dosage of 100 µg/m² 3 times weekly. The initial sargramostim dose was therefore adjusted to each patient’s hematologic profile in order to avoid a supraphysiological neutrophilic response in those without neutropenia. In the published case studies of rhu GM-CSF, dosing varied widely. Most patients were treated with a dosage of 250 to 300 µg/m²/d, with dose and frequency often reduced during the maintenance phase. In most of the new cases, sargramostim was added to existing antifungal therapy, and the combination regimen was continued until resolution of infection. This approach also was used in the majority of published cases, although some patients with treatment-resistant infections were treated successfully with rhu GM-CSF alone or in combination with interferon-γ [8]. For our new cases presented, duration of sargramostim therapy ranged from 4 to 124 weeks, facilitating stabilization or resolution of infection and allowing completion of chemotherapy or hematopoietic cell transplantation in most patients.

As reduction or elimination of concomitant immunosuppressive therapies is a cornerstone of successful treatment of IFDs, immunosuppressive corticosteroid therapy was discontinued or not administered where possible, in conjunction with modified doses of maintenance chemotherapy. GM-CSF also reduces the immunosuppressive effects of corticosteroids on pulmonary alveolar macrophages and elutriated human monocytes by preserving pro-inflammatory and Th1 cytokine responses to *Aspergillus* conidia, increasing IκB degradation, and enhancing NF-κB translocation to allow macrophage-mediated release of pro-inflammatory molecules and augmentation of innate host response to invasive aspergillosis [78–82].

In assessing the risk/benefit ratio of sargramostim in the treatment of refractory IFDs, several considerations bear note. There exists a clear potential for augmenting host response when other therapeutic options are ineffective. As sargramostim is well tolerated with minimal fever, flu-like symptoms, or bone pain in some patients, the therapeutic benefits appear to outweigh minimal risks. When considering the administration of sargramostim for earlier treatment of IFDs before they become refractory, the same analysis applies but warrants further investigation.

There are several limitations to this study. The published cases presented varied widely in dose and duration of rhu GM-CSF, use of concomitant antifungal agents, causes of IFDs, and types of comorbidities. More favorably responding cases treated with rhu GM-CSF may have been published, reflecting selection bias. Yet the overall response rate of 82% in published cases was similar to that of 92% in the newly reported cases. Also, conclusions about the efficacy of rhu GM-CSF for specific pathogens may be hindered due to the limited case numbers for some pathogens. While a fungal pathogen was identified in most cases, these laboratory diagnoses may not always be accurate. Finally, increased use of newer antifungal agents, as well as emergence of more resistant infections, complicates determination of the efficacy of rhu GM-CSF, particularly when comparing more recent results with older studies. Continued investigations of the immunoregulatory effect mechanisms of sargramostim will help to elucidate further the immunology underlying its benefit and allow for more rapid evaluation of the effects of rhu GM-CSF against specific pathogens.

Based on these data, several potential pathways exist for further evaluation of sargramostim as an adjunct to antifungal therapy. A classical approach would involve the design of a prospective clinical trial to enroll pediatric oncology patients with refractory IFDs. Given the challenges of completing such a study of uncommon fungal diseases, alternative approaches for demonstrating substantial improvements over available therapies for these serious life-threatening infections could be...
considered, including innovative designs with easily interpreted end points and well-defined case controls from registries, contemporaneous cases, and literature reviews.

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