

New Treatment Regime for *Aspergillus* Mediated Infections

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Commentary

Aspergillus species such as *A. fumigatus*, *A. flavus* and *A. terreus* are among the leading opportunistic fungal infections in immunocompromised patients. They are the causative agent of pulmonary or invasive aspergillosis, or various allergic manifestations such as allergic bronchopulmonary aspergillosis (ABPA) [1]. The mortality rate is 60% to 85% in hematopoietic stem cell transplant patients and 22% in patients having solid organ transplant [2]. The emergence of drug resistance *Aspergillus* species possess a new threat to these individuals. Over the last few years, the use of azole fungicides in agriculture have been increased that lead to emergence of azole resistant *Aspergillus* species strains [3]. Chowdhary et al. reported the prevalence of triazole resistance environmental isolates of *A. fumigatus* (4.8% to 7%) over different years [4]. Thus the emergence of resistance *Aspergillus* species strains and drug toxicity to immunocompromised patients put forward a new challenging task to control *Aspergillus* infections. To overcome these challenges, adoptive T-cell immunotherapy can play an important role [5]. Recently, studies on T-helper cells have been carried out to protect patients from fungal infections. Studies in mouse and human suggested the importance of TH1 and TH17 cells in controlling invasive aspergillosis and T-helper subset showed promising regime to eliminate invasive *Aspergillus* infections [6]. Studies in patients demonstrated that the early release of IFN- γ suppress the activation of TH2 T-helper cells and increase the activity of TH1 cells. These TH1 cells showed the promising role in protection against aspergillosis [5]. Further, over the last few years, different methods have been developed for the proliferation or expanding of functionally active or fungal characterized T-helper cells. Along with this, now a day's more data is available on the use of donor derived T-cells (Virus specific T-cells) associated to viral infections in allogeneic stem cell transplantations, which suggest the negligible severe adverse effects in recipients [7]. However, only few studies have been reported on adoptive T-cell immunotherapy against fungal infections. Perruccio et al. demonstrated the adoptive T-cell immunotherapy in haploidentical stem cell patients having T-cell depleted graft. Study has been performed in patient having invasive aspergillosis and a promising result was observed. Ten recipients of haploidentical stem cell transplant having evidence of invasive aspergillosis received a single dose of $1 \times 10^5 - 1 \times 10^6$ donor derived anti-*Aspergillus* expanded T-cell clones. Within three weeks of infusion of anti-*Aspergillus* T-cells, CD4⁺ T-cells have detected in recipients and 9 of 10 recipients also clear the *Aspergillus* infection within 7.8 ± 3.4 weeks. Further, galactomannan level progressively declined below 1 ng/ml within the measured period of 6 to 12 week of infusion. Whereas in control individuals, who did not receive anti-*Aspergillus* T-cell clones, 6 of 13 patients succumbed to *Aspergillus* infection within 4.8 ± 1.2 weeks of diagnosis and galactomannan level was also observed to be elevated during the study period [8].

In addition, bioengineering of T-cells has opened another approach to treat fungal infections in immunocompromised patients. The pattern recognition receptor such as soluble (Pentraxin-3) and cell bound receptors (Dectin-1) play crucial role in recognition and elimination of fungal pathogens [9]. Thus, the engineering of cell bound receptors on T-cell eliminate the need of MHC representation of antigens and fast removal of pathogens. Kumaresan et al. engineered cytotoxic T-cells to combat *Aspergillus* infections. They link the innate immune cell receptor (Dectin-1) with T-cells to redirect their specificity for *Aspergillus* fungus. A chimeric antigen receptor (CAR) was developed to express it on T-cell. Dectin-1, a receptor present on innate immune cells (e.g., macrophages, neutrophils and dendritic cells) was selected, which recognize β -glucan present on fungal cell wall. Kumaresan et al. use the sleeping beauty (SB) transposon/transposase system to develop such cells. T-cells having these designated chimeric antigen receptors (D-CAR) have specificity for β -glucan and thus lead to damage of *Aspergillus* hyphae [2].

Thus, it is a promising avenue that adoptive T-cell immunotherapy and bioengineered T-cells with specific receptors that recognize fungal cell wall antigens, open a new way to treat *Aspergillus* associated infections or fungal infection. But efforts are required to develop new technologies for expanding fungal specific T-cell on large scale under good medical practice conditions. In addition, there is need of large scale clinical trials of fungal specific T-cell that not only contain effector T-cells (TH1 or TH17) but also contain memory T-cells to build up long term memory against pathogen in recipients. Whereas bioengineering of T-cells is a new emerging technology to combat fungal infection that also need to evaluate clinically on large scale, so that they can be used for treatment against fungal infections in future and potentially to combat the drug resistance and toxicity.

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