Targeted Approach to Immunosuppression with AAV Gene Therapy: Nonclinical Support for Clinical Approaches


Homology Medicines, Inc. Bedford, Massachusetts; *Plexision Pittsburgh, Pennsylvania

Introduction

Gene therapy using recombinant adeno-associated virus (AAV) vectors has been successfully in initial clinical studies for the treatment of a wide range of human diseases. However, clinical trials with AAV can develop a number of serious adverse events (AEs) that can lead to the loss of therapeutic transgene expression and formation of neutralizing antibodies; moreover, these AEs can lead to the loss of therapeutic transgene expression and formation of neutralizing antibodies, thereby hampering the potential for clinical development.

To combat the immune response to AAV gene therapy and gene editing, cotransduction has become more frequent over time in clinical trials, particularly with systemic AAV delivery. Given the broad mechanism of action of cotransduction, adverse effects can be expected across a range of indications. In addition, one of the most common manifestation of systemic AAV vector delivery is increased transgene expression by 2- to 10-fold when compared to a control group administered AAV/HSC17+PAH without immunosuppression.

Immunosuppressant Use in AAV Clinical Trials

- Over time, the use of immunosuppressants in AAV clinical trials has increased from 18% before 2007 to 45% in 2022, as shown in Figure 1.
- Cotransduction treatment regimens have been widely used to manage ALT/AST levels and immune responses in AAV-treated patients.
- Higher doses and longer courses of cotransduction have been associated with an increased likelihood of developing more severe side effects.
- More potent terminates cotransduction, and more specific T-cell and B-cell inhibitors (sirolimus, tacrolimus, rituximab) were also used.
- To improve the immunosuppression regimen while reducing adverse effects in patients, studies with more specific targeting have been introduced into AAV gene therapy. For example, maximal target of rapamycin (mTOR) inhibitor sirolimus targets mainly B cells and T cells, and calcium/calcium-sensitizer targets mainly T cells.

HMI-103 and HMI-203 Clinical Trial Designs

The results of the study supported the approach of a prophylactic combination of imlifidase and dexamethasone in conjunction with dosing in clinical trials. In the clinical trials, the pheEDIT+study arms included imlifidase to reduce humoral and cellular immune responses. The placebo arm showed reduced transgene expression and reduced adverse effects in patients compared to the treatment arms, as shown in Figure 1. The pheEDIT+ study arms included imlifidase to reduce humoral and cellular immune responses. The placebo arm showed reduced transgene expression and reduced adverse effects in patients compared to the treatment arms, as shown in Figure 1.

Assessment of a Targeted Immunosuppressant Regimen in Cynomolgus Monkeys

A 28-day study in cynomolgus monkeys with imlifidase and dexamethasone was performed to demonstrate the potential for clinical effectiveness of the targeted approach to immunosuppression in conjunction with clinical trials. The pheEDIT+ study arms included imlifidase to reduce humoral and cellular immune responses. The placebo arm showed reduced transgene expression and reduced adverse effects in patients compared to the treatment arms, as shown in Figure 1. The pheEDIT+ study arms included imlifidase to reduce humoral and cellular immune responses. The placebo arm showed reduced transgene expression and reduced adverse effects in patients compared to the treatment arms, as shown in Figure 1.