RESULTS

Subretinal injections were generally well tolerated and not associated with systemic toxicity. Most animals had mild to moderate conjunctival hyperemia, chemosis and subconjunctival hemorrhage immediately after surgery that generally resolved by postoperative Day 7. Two animals treated with the higher dose of AAV2tYF-PR1.7-CNGA3 and three of the efficacy control group animals treated with AAV-P2r1.7-CNGA3 had microscopic findings of outer retinal atrophy with or without inflammatory cells in the retina and choroid, that were procedural- and/or test article-related. All vector-treated eyes showed improved cone-mediated ERG responses with no change in rod-mediated ERG responses (Figure 1). Behavioral maze testing under photopic conditions showed significantly improved navigation times and reduced numbers of obstacle collisions in all vector-treated eyes compared to their contralateral control eyes or pre-dose results in the treated eyes (Figure 2). CNGA3 protein expression was detected by IHC in eyes treated with AAV2tYF-PR1.7-CNGA3 (Figure 3).

Figure 1. ERG responses in CNGA3-deficient sheep before treatment, and 6 and 12 weeks after treatment with an AAV vector expressing CNGA3. (A) Mean ± SD dark-adapted ERG b-wave amplitude (µV). (B) Mean ± SD light-adapted 30 Hz cone ERG cone amplitude (µV). (C) Mean ± SD light-adapted critical flicker fusion frequency (Hz).

Figure 2. Maze navigation test results in CNGA3-deficient sheep before treatment, and 6 and 12 weeks after treatment with an AAV vector expressing CNGA3. (A) Mean ± SD time in seconds taken to move through a maze containing two obstacles. (B) Mean ± SD number of collisions during navigation through the maze. Each animal received a 0.5 µL subretinal injection to the right eye. All results were evaluated both by the investigator and an independent masked observer.

CONCLUSIONS

Subretinal injection of AAV2tYF-PR1.7-CNGA3 in CNGA3-deficient sheep was well tolerated. The outer retinal atrophy and retinal and choroidal inflammation observed in two animals treated with AAV2tYF-PR1.7-CNGA3 could be procedure- and/or test article-related. ERG and behavioral testing showed that a single injection restored photopic vision in all vector-treated eyes. These results support the use of AAV2tYF-PR1.7-CNGA3 in clinical studies in patients with ACHM caused by CNGA3 mutations. A Phase I/II clinical trial evaluating AAV2tYF-PR1.7-CNGA3 is scheduled to begin in 2017.

REFERENCES