BION-1301: a Novel fully Blocking APRIL Antibody for the Treatment of IgA Nephropathy

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INTRODUCTION

Mouse anti-human IgA serum and a humanized antibody targeting a proliferation Inducing Ligand (APRIL, TNFSF13): APRIL is a ligand for the receptors BCMA and TACI. APRIL serum levels are elevated in patients diagnosed with IgA Nephropathy (IgAN) and treatment with an anti-mouse APRIL antibody reduced serum IgA and proteinuria increase in an IgAN mouse model (Kim et al. PLOS One 2015). Altogether, these data suggest that the APRIL axis is important in IgA pathology and strongly support the development of Aduro’s anti-APRIL antibody, BION-1301, to treat IgAN Nephropathy (IgAN). BION-1301 is currently in a dose-escalation trial in Multiple Myeloma patients (NCT03048853).

Fig.1 BION-1301 Unique Epitope Mapped to Receptor Binding Sites

Mouse B-cell proliferation and IgA production in vitro and in vivo

Mouse B-cells were stimulated with human APRIL (200ng/mL), and IgA secretion was determined after 6 days of incubation. The mouse anti-APRIL antibody hAPRIL.01A (IgG1) or mouse IgG1 isotype-matched control. (A) Each sample was analyzed in triplicates. **P < 0.01, 1-way ANOVA, error bars = SD. (Guadagni et al. Blood 2015).

Fig.2 BION-1301 Blocks APRIL-Induced B-Cell Proliferation and IgA Production in vitro and in vivo

Fig.3 BION-1301 Single and Multiple Dose Studies in Non-Human Primates (NHP): No BION-1301 Related Toxicity

Single dose PK/PD study in NHP (A) BION-1301 was dosed as a single dose via IV injection to female cynomolgus monkeys. Animals in Groups 1-6 (0-5 mg/kg, n=4) were observed post-dose for 84 days, whereas those in Groups 7-8 (10-15 mg/kg, n=3) were observed post-dose for 42 days. (B) AUC0-t is the area under the concentration-time curve from time 0 to the time of last quantifiable concentration. (C)hAPRIL.01A reduced the number of IgA secreting plasma-blasts/cells. Exposure to BION-1301 induced a significantly reduced IgA levels vs baseline of -50% (10 mg/kg) and -65% (15 mg/kg) at the terminal necropsy.

Fig.5 BION1301: parental antibody hAPRIL.01A Inhibits APRIL-Dependent Human Plasma-Blast/Cell Survival and IgA Production

IN VITRO

Total and anti-TNP IgA level in single dose PK/PD study in NHP (A) Total IgA and anti-TNP IgA (A: Total IgA) specific immunoglobulin type A (IgA) levels were determined after a single intravenous dosing of BION-1301. Anti-TNP IgA was examined at the terminal necropsy after 4 weeks. (B) Anti-TNP IgA levels were undetectable in the TNP treated group. Circles represent the average IgA level among animals which reached a level above baseline (dashed line). (C) Circles represent the average IgG level among animals which reached a level above baseline (dashed line). (D) Summary of results in all NHP studies. **P < 0.01 vs Vehicle control.

CONCLUSION

We developed a novel fully humanized high-affinity anti-APRIL antibody BION-1301. Its efficacy was measured in preclinical and TACI binding site conferring full blocking capacity to BION-1301. This mouse anti-human parental antibody hAPRIL.01A inhibited APRIL-dependent B-cell proliferation and IgA production in vitro and in vivo. BION-1301 suppresses the T-cell independent (TI) B-cell response in NHP, confirming its suppressive activity in the TI mouse model. In human B-cell cultures, hAPRIL.01A reduced the number of IgA secreting plasma-blasts/cells. Exposure to BION-1301 induced a significantly reduced IgA levels vs baseline of -50% at 10 mg/kg and -65% at 15 mg/kg.

P values were calculated using the t-test and 2-way ANOVA. *P<0.05, **P<0.01, ***P<0.001. All animal experiments were conducted in accordance with the institutional guidelines of the responsible institutional ethics committee and the laws and guidelines of the European Union and USA. The data are presented as mean±SD. Presented at 2018 American Society of Nephrology, October 23-28, 2018, San Diego, CA.

No. of
Treated
Group
Treatment
No. of Animals
Low Dose (mg/kg)
High Dose (mg/kg)
1 Control 3 0
2 BION-1301 3 0.5
3 BION-1301 3 3
4 BION-1301 3 30
5 Control 3 0
6 BION-1301 and TNP Ficoll 3 3
7 BION-1301 and TNP Ficoll 3 30
8 BION-1301 and TNP Ficoll 3 30

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Fig.4 BION-1301 Single Dose Pharmacokinetics

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