Poster# PS2257

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Efficacy of Ianalumab in a Mouse Model of Autoimmune Hemolytic Anemia (AIHA)

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KEY FINDINGS & CONCLUSIONS

- In the Playfair-Marshall Clarke mouse model of AIHA, the anti-BAFF-R monoclonal antibody ianalumab (100 mg/kg; i.p.; weekly) led to B-cell depletion in both blood and spleen as well as a reduction in the levels of circulating anti-RBC autoantibodies which both correlated with the ianalumab plasma concentration.
- In addition, ianalumab reduced the frequency of splenic marginal zone B cells and corrected the imbalance between splenic Teff and protective Foxp3+ Treg.
- These data suggest that ianalumab may be effective in reducing anti-RBC autoantibodies in wAIHA. The observed restoration of Teff/Treg balance by ianalumab also highlights its immunomodulatory potential in inducing durable responses.
- Ongoing phase 3 studies in wAIHA (NCT05648968, in first-line (1L) and second-line (2L) primary ITP (NCT05653349 and NCT05653219, respectively), and in additional autoimmune indications will provide further evidence on the efficacy and safety of ianalumab in larger patient populations.

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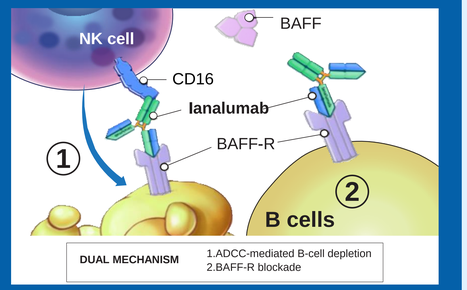
INTRODUCTION

- Warm autoimmune hemolytic anemia (wAIHA) is caused by premature destruction of the patient's own red blood cells (RBC) by autoantibodies reactive at 37°C and can be life-threatening.[1]
- To date, approved therapies for the treatment of wAIHA are very limited.
- Ianalumab, a glycoengineered (afucosylated), fully human IgG1 monoclonal antibody directed against the B-cell–activating factor receptor (BAFF-R), depletes B cells through enhanced antibody-dependent cellular cytotoxicity (ADCC) with concurrent blockade of BAFF:BAFF-R–mediated signals (**Figure 1**).[2]

Figure 1. Ianalumab's dual mechanism of action

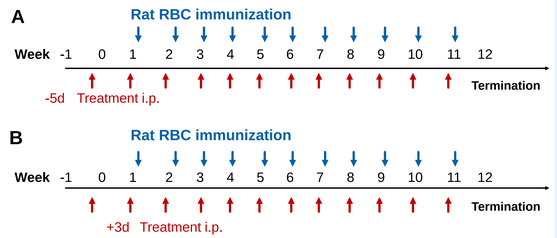


ADCC, antibody-dependent cellular cytotoxicity; BAFF, B-cell–activating factor; BAFF-R, BAFF receptor; CD16; cluster of differentiation 16; NK cell, natural killer cell.

METHODS

- To determine its efficacy in the inhibition of autoantibodies in wAIHA, ianalumab was studied in a Playfair-Marshall Clarke autoimmune hemolytic anemia (AIHA) mouse model which involves a repeated immunization protocol against rat RBC, resulting in the induction of anti-mouse RBC autoantibodies and development of anemia.[3]
- In this model, a 11-week-long immunization protocol (2×10^8 cells leuko-reduced rat RBC injected per mouse on a weekly basis) was used to induce AIHA.
- C57BL/6 (B6) mice were dosed with ianalumab (100 mg/kg; intraperitoneally (i.p.); weekly) from either 5 days prior to (n=15) or 3 days post (n=15) first rat RBC immunization. Control mouse groups included rat RBC-immunized B6 mice dosed with phosphate-buffered saline (PBS) (n=24 mice), non-diseased B6 mice dosed with ianalumab (n=6 mice) or PBS (n=6 mice), and unmanipulated B6 mice (n=6) (**Figure 2**).

Figure 2. Mouse AIHA model study design



Prophylactic (A) and therapeutic (B) treatments with ianalumab in the Playfair-Marshall Clarke AIHA mouse model. Blue arrows indicate the time points of the injection of leuko-reduced rat RBC; red arrows indicate the time points of ianalumab injection. AIHA, autoimmune hemolytic anemia; i.p., intraperitoneally; RBC, red blood cell.

RESULTS

Ianalumab significantly depletes B cells

- Results from two separate studies were pooled and analyzed. Mean circulating B-cell counts in the blood were significantly reduced within the first 3 weeks of weekly dosing with ianalumab ($p<0.0001$; **Figure 3**), while no effect was observed on non-B lineage cell populations.

B-cell depletion correlates with ianalumab exposure

- The degree of B-cell depletion in both blood and spleen of mice correlated with ianalumab plasma concentration ($p<0.005$) as well as a reduction in the levels of circulating anti-RBC autoantibodies (p=0.005, **Figure 4**).

B-cell depletion correlates with the presence of anti-drug antibodies

- Moreover, low ianalumab plasma concentration was associated with the presence of anti-drug antibodies (ADA), consistent with the immune response in mice exposed to human antibodies **(Figure 5**).

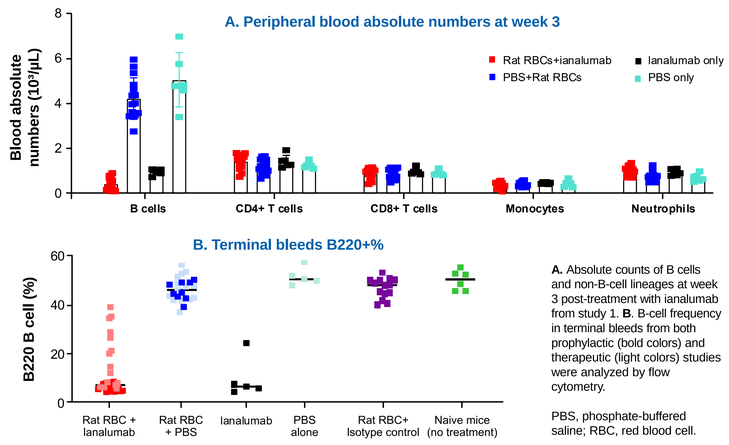
Ianalumab reduces splenic marginal zone B cells

- Within the splenic B compartment, the frequency of marginal zone (CD21/35+IgM+) B-cell subset, implicated in autoreactive B-cell responses, was significantly reduced in ianalumab-treated rat RBC-immunized mice relative to PBS-treated rat RBC-immunized mice ($p<0.0001$) (**Figure 6**).

Ianalumab corrects the imbalance between effector and regulatory T cells

- Additionally, in the spleen, ianalumab treatment corrected the imbalance between CD4+CD44^{high} effector T cells (Teff) and protective CD4+Foxp3+ regulatory T cells (Treg) ($p<0.0001$) in rat RBC-immunized mice, reversing the Teff/Treg ratio skewed toward Teff (which favors autoimmunity as seen in PBS-treated rat RBC-immunized mice) to levels comparable to those in unmanipulated mice or non-disease mice treated with ianalumab or PBS (**Figure 7**).

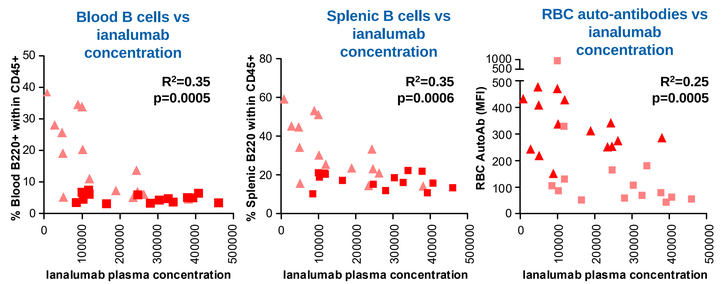
Figure 3. B-cell depletion induced by ianalumab in blood



A. Absolute counts of B cells and non-B-cell lineages at week 3 post-treatment with ianalumab from study 1. **B.** B-cell frequency in terminal bleeds from both prophylactic (bold colors) and therapeutic (light colors) studies were analyzed by flow cytometry.

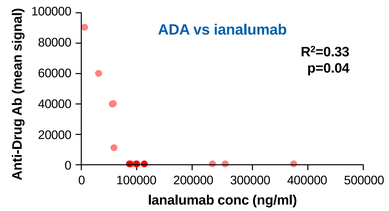
PBS, phosphate-buffered saline; RBC, red blood cell.

Figure 4. Correlation between ianalumab plasma levels and the degree of B-cell depletion and reduction in anti-RBC auto-antibodies



Correlative analysis of B cells in peripheral blood, spleen and plasma anti-RBC auto-antibody levels with ianalumab plasma concentration in AIHA induced mice treated with ianalumab in prophylactic (bold red) and therapeutic (light red) studies.
AIHA, autoimmune hemolytic anemia; CD, cluster of differentiation; RBC, red blood cell.

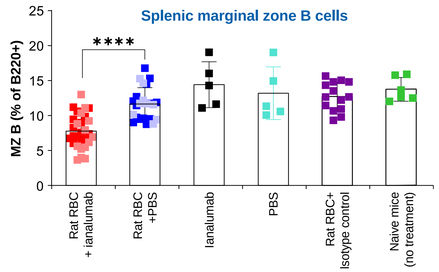
Figure 5. Correlation of ADA with ianalumab concentration in blood



Anti-ianalumab antibodies in mouse plasma were measured by electrochemiluminescence using biotin-labeled ianalumab for capture and sulfo tag-labeled ianalumab for detection. Correlative analysis of ADA with ianalumab plasma concentration in AIHA-induced mice treated with ianalumab in prophylactic (dark red) and therapeutic (light red) studies.

ADA, anti-drug antibodies; AIHA, autoimmune hemolytic anemia

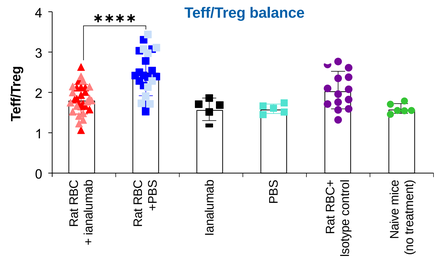
Figure 6. Reduction of splenic marginal B cells



Frequency of MZ B cells within splenic B (B220⁺) cells were analyzed by flow cytometry in both prophylactic (bold colors) and therapeutic (light colors) studies.

MZ, marginal zone; PBS, phosphate-buffered saline; RBC, red blood cell..

Figure 7. Ianalumab corrected the Teff vs Treg imbalance



Ratio of splenic effector T cells (Teff: CD4⁺CD44⁺) to T regulatory cells (Tregs:CD4⁺Foxp3⁺) in prophylactic (bold colors) and therapeutic (light colors) studies.

PBS, phosphate-buffered saline; RBC, red blood cells; Teff, effector T cells; Treg, regulatory T cells.

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Disclosures

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