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Impact of Atacicept on Hematuria in IgA Nephropathy: Post-Hoc Analysis of The Phase 2b ORIGIN Study

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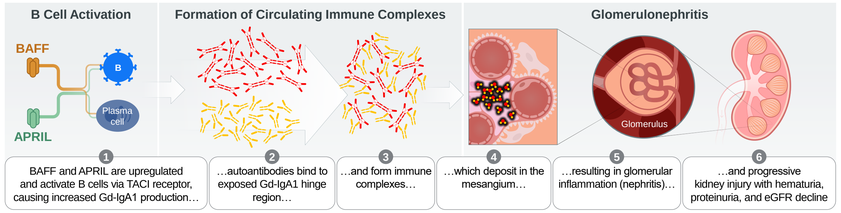
Introduction

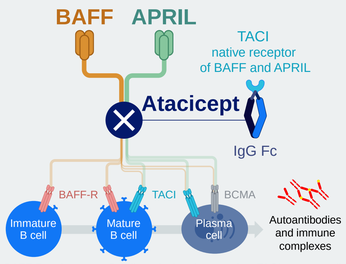
IgAN Pathogenesis



APRIL = A PRoliferation-Inducing Ligand; BAFF = B-cell Activating Factor; eGFR = estimated glomerular filtration rate; Gd-IgA1 = galactose-deficient immunoglobulin A1; IgAN = immunoglobulin A nephropathy; TACI = transmembrane activator and calcium-modulator and cyclophilin ligand interactor.

- IgAN is the most common primary glomerulonephritis and a significant contributor to end-stage kidney disease worldwide[1,2]
- Microscopic hematuria is a common clinical manifestation of IgAN, observed in 70–100% of patients,[3] and may be caused by the glomerular inflammation associated with IgAN pathogenesis[4]
- Recent data show that patients with IgAN and persistent hematuria have a greater decline in kidney function than those with minimal or no hematuria, while hematuria resolution has been associated with less decline in kidney function[3,5]
- Both persistent proteinuria and persistent hematuria have been shown to be independent risk factors for progression of kidney failure, with greater risk of progression in patients with both factors[3,5]
- It is therefore important to determine the effect of B cell modulators such as atacicept on hematuria

Atacicept: BAFF & APRIL Dual Inhibitor With Disease-Modifying Potential



- Fully humanized TACI-Fc fusion protein, at home weekly subcutaneous self administration
- Low nanomolar potency vs BAFF (Kd 1.45 nM) and APRIL (Kd 0.672 nM)[6]; $t_{1/2}$ = 35 days[7]
- Reduces overstimulation of B cells and plasma cells[8] and autoantibody production[9]
- Dual inhibition more potent than either alone,[10] may translate to more sustained B cell modulation
- Well-characterized safety profile with exposure in >1500 patients across different indications[11]

BAFF-R — immature B cell survival and maturation; TACI — responsible for T cell independent antibody responses, B cell regulation, class-switch recombination; BCMA — plasma cell survival. Fc = fragment crystallizable region.

- The ORIGIN Phase 2b randomized, double-blind, placebo-controlled trial of atacicept in IgAN met the primary endpoint and showed statistically significant Gd-IgA1 reduction, proteinuria reduction, and eGFR stabilization at 36 weeks compared to placebo[12]

Objective

- To evaluate changes in hematuria grade over 36 weeks with atacicept 150 mg vs placebo

Methods

- Hematuria was evaluated at baseline and weeks 2, 4, 12, 24, and 36 via urine dipstick at a centralized lab, and hematuria levels were graded negative/trace, 1+, 2+, or 3+

Hematuria grade	Negative/trace	1+	2+	3+
Urine blood, mg/dL	≤0.03	0.06 – 0.1	0.2 – 0.5	≥1

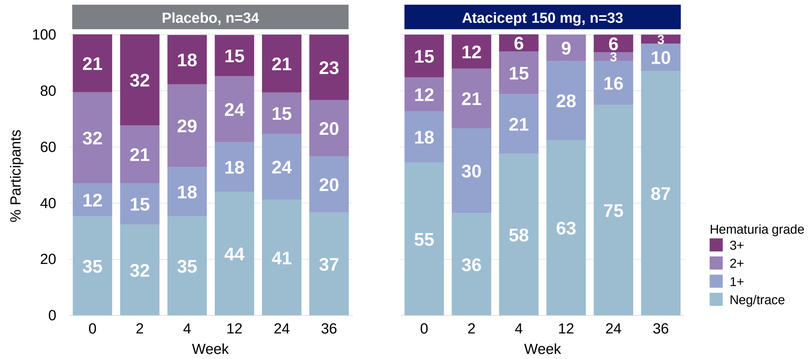
- In a post-hoc analysis, participants with hematuria grade of 1+ or higher at baseline were evaluated for improvement (defined as a decrease by ≥1 grade) or resolution (defined as decrease to negative/trace)
- Fisher exact test was used to compare proportions between treatment groups

Results

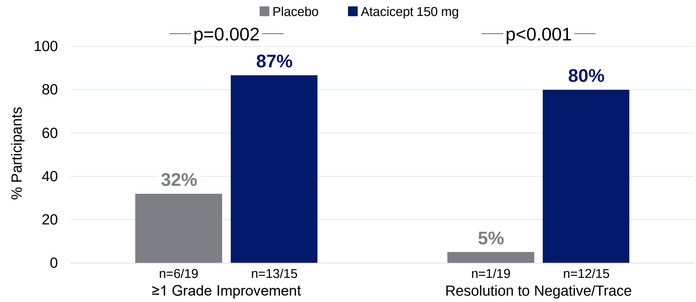
Baseline Characteristics by Hematuria Status

	Hematuria Negative/Trace		Hematuria 1+ or Higher	
Mean ± SD or n (%)	Placebo n=12	Atacicept 150 mg n=18	Placebo n=22	Atacicept 150 mg n=15
Age, years	41 ± 11	40 ± 12	37 ± 14	35 ± 10
Male sex	7 (58)	11 (61)	12 (55)	11 (73)
Race				
White	8 (67)	10 (56)	18 (82)	7 (47)
Asian	4 (33)	8 (44)	4 (18)	8 (53)
Other	0	0	0	0
eGFR, mL/min/1.73 m^2	55 ± 31	58 ± 27	72 ± 31	54 ± 16
UPCR by 24h urine, g/g	1.5 ± 0.7	1.6 ± 1.0	1.6 ± 0.9	1.9 ± 1.0
Time from biopsy, years	1.5 ± 1.8	4.2 ± 3.7	2.4 ± 2.7	2.2 ± 2.9

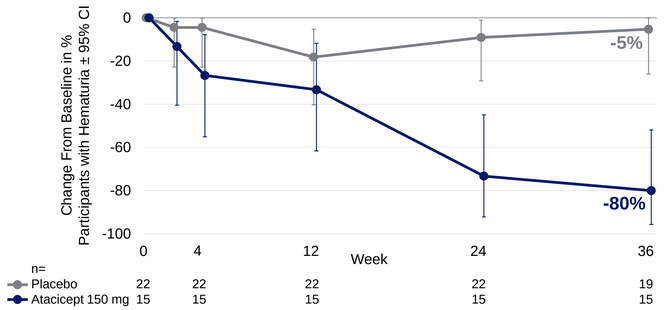
Shifts to Lower Hematuria Grades Through Week 36



Hematuria Improvement and Resolution at Week 36



Reduction in % Participants with Hematuria Through Week 36



Conclusions

- In this post-hoc analysis of the ORIGIN Phase 2b clinical trial, atacicept treatment led to hematuria resolution at 36 weeks in a significantly greater percentage of participants as compared with placebo
- Participants receiving atacicept 150 mg had rapid and sustained reductions in the degree of hematuria over 36 weeks, with improvements seen as early as 4 weeks
- These results add to the growing body of evidence supporting atacicept as a potential disease-modifying treatment for IgAN
- Atacicept 150 mg is currently being evaluated in a global Phase 3 randomized controlled trial

References: **1.** Lai KN, et al. Nat Rev Dis Primers 2016;2:16001; **2.** Schena P, Nistor I. Semin Nephrol 2018;38:435-42; **3.** Coppo R, Fervenza FC. J Am Soc Nephrol 2017;28:2831-34; **4.** Zand L, et al. Clin Kidney J 2023;16(suppl 2):ii19-27; **5.** Sevillano AM, et al. J Am Soc Nephrol 2017;28:3089-99; **6.** Vera data on file; **7.** Willen D, et al. Eur J Drug Metab Pharmacokinet 2020;45:27-40; **8.** Hiepe F, et al. Nat Rev Rheumatol 2011;3:170-178; **9.** Gordon C, et al. Arthritis Rheumatol 2017;69:122-30; **10.** Haselmayer P, et al. Eur J Immunol 2017;47:1075-1085; **11.** Gordon C, et al. Rheumatol Adv Pract 2019;0:1-12 and Vera data on file; **12.** Lafayette R, et al. Kidney Int 2024:S0085-2538(24)00236-9.

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