Iptacopan concentration below 0.6uM fails to inhibit C3bBb-mediated activation of C3

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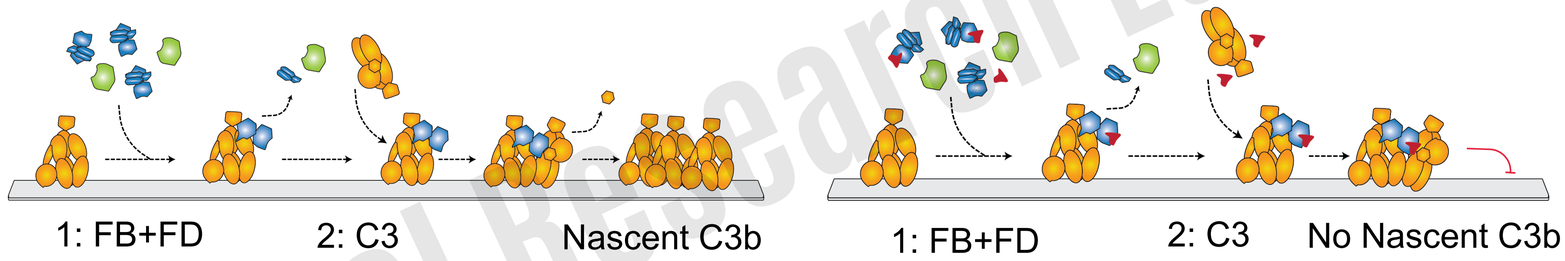
Background

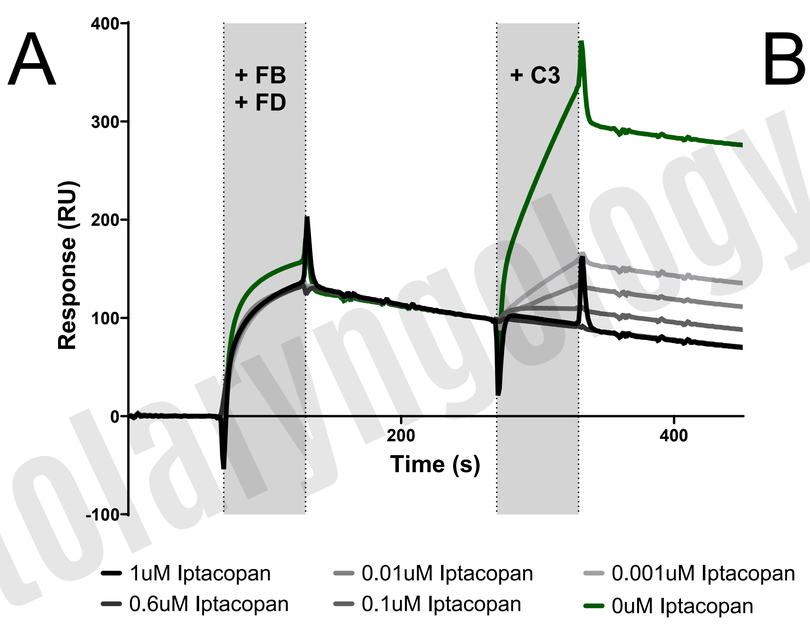
Iptacopan is a factor B (FB) inhibitor approved by the U.S. Food and Drug Administration and the European Medicines Agency in early 2025 for use in C3 glomerulopathy. There are anecdotal reports that some patients respond poorly to treatment. Given iptacopan's short half-life, we hypothesize that a poor response may be explained by iptacopan PK/PD. Published evidence for FB inhibition shows that iptacopan blocks fluid-phase CVFBb activity with an IC50 of ~0.01uM and maximal efficacy by ~1uM.[1] We titrated iptacopan to measure its potency for inhibiting surface-bound native convertase (C3bBb) and for blocking nascent C3b deposition by SPR.

Methods

C3b was amine-coupled to a CM5 chip to 1200-1400 RUs. Conditions were tested via two injections: **1)** FB (40ug/mL)+FD (2ug/mL) to build the convertase, then **2)** C3 (1uM) to measure nascent C3b opsonization. Injections and running buffer contained iptacopan doses from 1uM to 0.001uM and 0uM. Bb was tested at 40ug/mL and patient-purified Nephritic factor (Nef) positive polyclonal IgG was tested at 350ug/mL.



Results



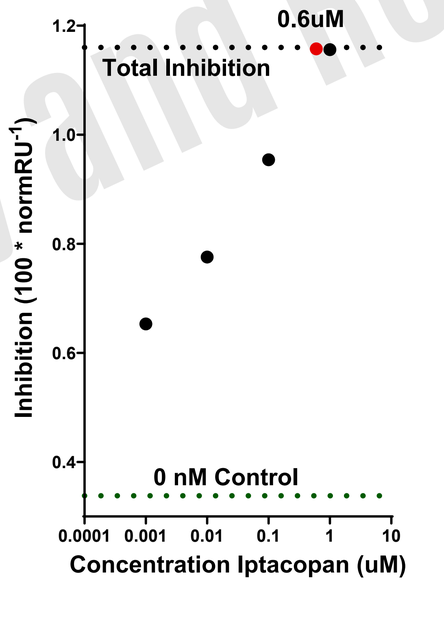
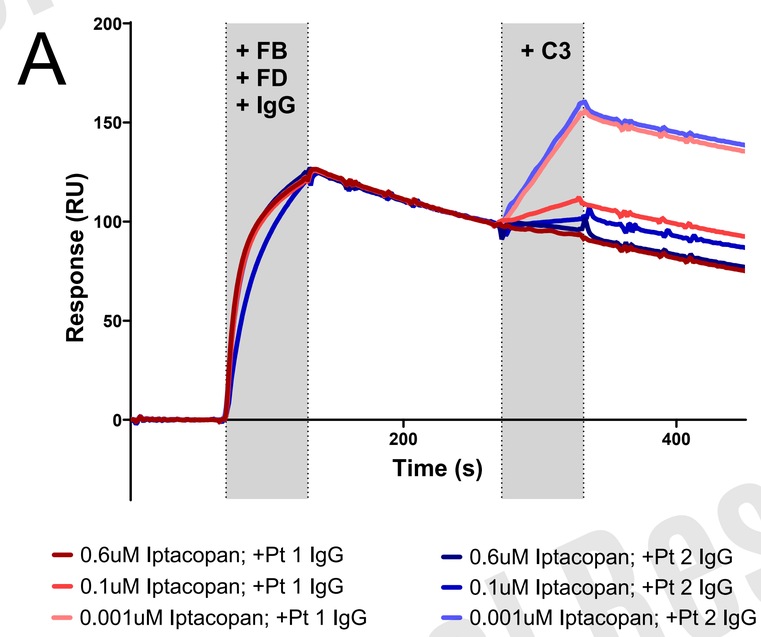


Figure 1. Iptacopan Titration below 0.6uM shows C3b deposition. A) Sensorgram results for titrated concentrations of iptacopan. B) Dose-response of iptacopan-mediated inhibition of C3b deposition.



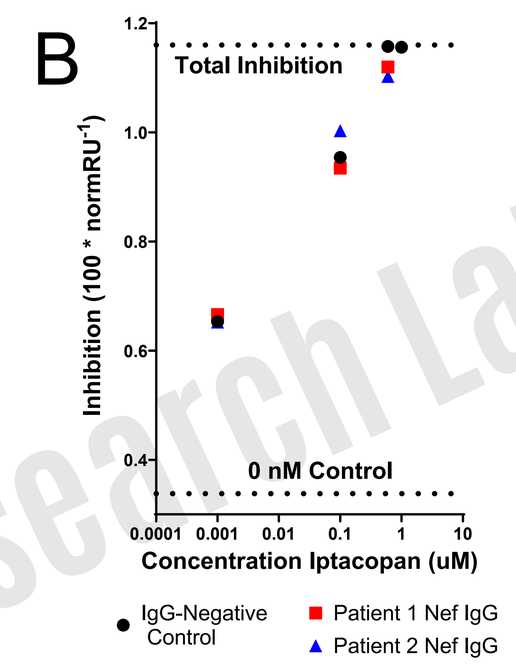


Figure 2. Nephritic Factors show minimal rescue of C3b deposition. A) Sensorgram results for nephritic factor-supplemented iptacopan titration. B) Dose-response of iptacopan-mediated inhibition of C3b deposition.

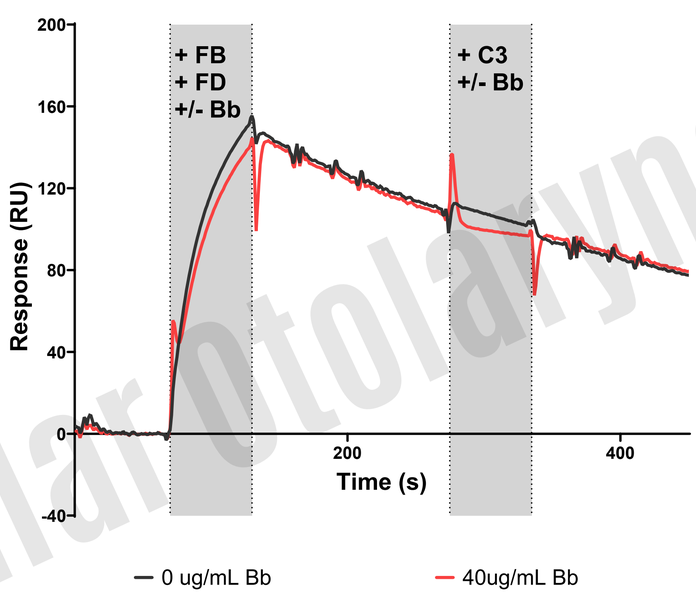


Figure 3. Bb has minimal impact on C3 activation. Both cycles tested at 1uM iptacopan.

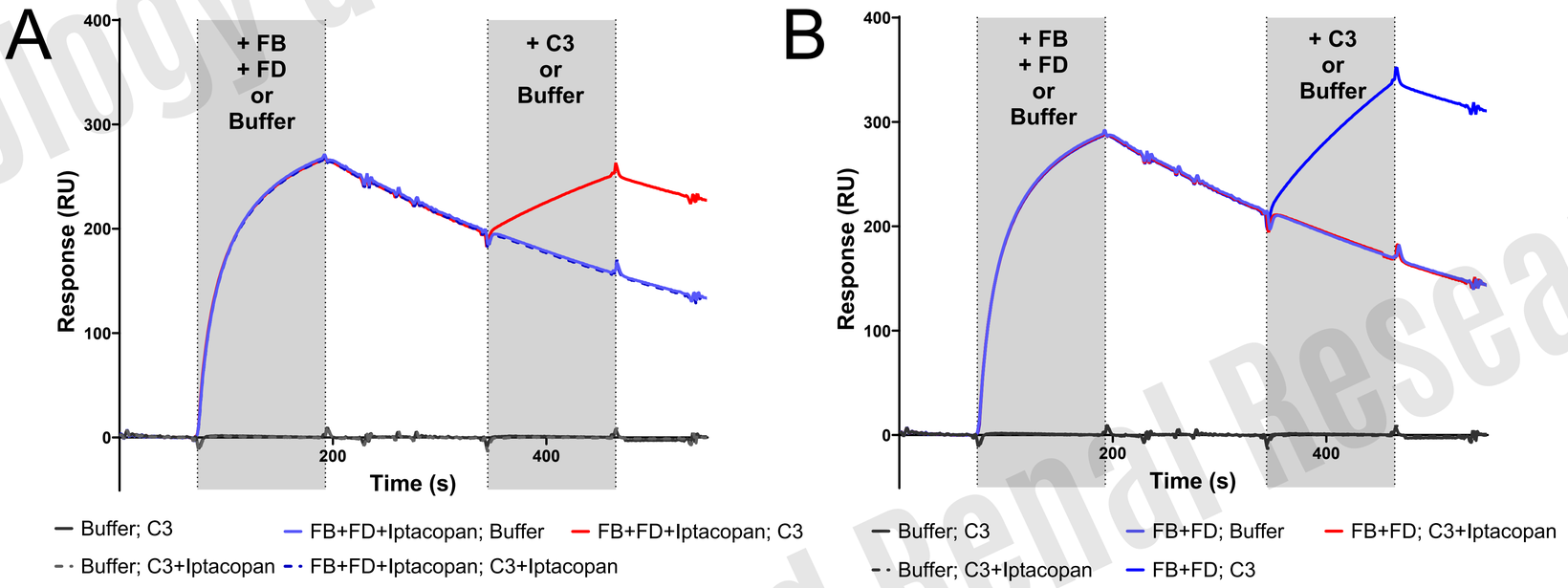


Figure 4. Real-time dose of iptacopan determines the efficiency of blockade. A) Iptacopan dissociates quickly and allows C3 activation. B) Iptacopan associates rapidly to achieve C3bBb inhibition.

Discussion

Patient compliance is required for optimal iptacopan pharmacokinetics: it has a reported mean half-life of 12.3 hours and reaches a concentration of ~0.6uM between 24-48 hours after dosing.[2] Our results demonstrate that below this critical concentration, iptacopan does not stop C3b opsonization. Furthermore, iptacopan's kinetics suggest that drug concentration rapidly influences FB inhibition in real-time. Thus, it is essential that patients maintain the twice-daily dosing for total AP blockage. This is especially important for patients with complement-driven GN and unique complement dysregulation. Although published data[3] show supratherapeutic doses of iptacopan are well tolerated, our results with Bb and Nephritic factors do not necessarily indicate that dose adjustment would be helpful in patients with a suboptimal response to standard iptacopan dosing. Rather these patients may have additional mechanisms of complement dysregulation, such as classical or lectin pathway dysfunction.

Acknowledgements

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References

1. PMID 30926668 2. PMID 37308298 3. PMID 41085230