Lanadelumab for the prevention of hereditary angioedema attacks

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To the Editor,

Title: Lanadelumab for the prevention of hereditary angioedema attacks: A real-world UK audit.

Lanadelumab is a recombinant human anti-kallikrein monoclonal antibody indicated for long-term prophylaxis in hereditary angioedema (HAE). Following clinical trials (1, 2), lanadelumab has been commissioned in the UK for HAE patients aged ≥12 years who are having 2 or more significant attacks per week over 8 weeks, despite oral preventive therapy, including attenuated androgens or antifibrinolytics, unless contraindicated or not tolerated, or where patients would otherwise be considered for long-term prophylactic C1-inhibitor concentrate (3-5). Dosing can be extended from 2 to 4 weeks provided adequate symptom control (3). There is a growing cohort of UK patients receiving lanadelumab not adequately represented in published trials. Moreover, UK commissioning criteria require greater baseline attack frequency than seen in trials. We therefore collected attack, treatment and prophylaxis data prior to and after commencing lanadelumab in the first national UK lanadelumab audit.

Demographics

Sixteen centres returned data on 62 patients (Table 1). Most had type 1 HAE and 56 (90.3%) received prior prophylaxis, predominantly C1-inhibitor concentrate, with 1-6-month follow-up at baseline. Six patients commenced lanadelumab without prior prophylaxis, 5 due to historical poor efficacy or unacceptable side effects.

Dosing regimens

Of 60 patients with data, half reduced their dosing frequency to 3-weekly or less. Of 28 patients on ≥4-weekly dosing, it took a mean of 15.2±12.1 weeks to achieve this.

Efficacy

Mixed-effects model analyses showed statistically significant reductions in total and severe monthly attacks at all time points *vs.* baseline ($P<0.0001$, Figure 1A & 1B). For total attacks at 6 and 12 months this equalled

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87.7% and 93.5% reductions, respectively (0.89±1.96 and 0.47±1.02 attacks, *vs.* baseline monthly mean attacks of 7.23±7.19), and 92.2% and 94.1% reductions in severe attacks at 6 and 12 months, respectively (0.35±1.37 and 0.26±0.73 attacks, vs. 4.44±4.08 at baseline). This was true even for those on prior C1-inhibitor prophylaxis (83.6% and 91.4% reductions in total and 87.5% and 89.8% for severe attacks at 6 and 12 months (n=27, 11), respectively). Severe attacks were defined as unable to perform activities of daily living or potential airway involvement.

Breakthrough attack severity varied, but the proportion of severe attacks was reduced at 1 and 6 months (34.67±44.79% and 23.08±38.81%, respectively, vs. 60.74±35.58% at baseline; $P<0.05$). Attacks requiring C1-inhibitor were reduced with an 85.7% reduction at 6 months and 97.2% reduction at 12 months ($P<0.001$, Figure 1C), as was icatibant use (94.7% and 93.7% reductions at 6 and 12 months, respectively; $P<0.01$, Figure 1D). There was a reduction of 95.2% (n=45) and 100% (n=19) in acute attacks requiring two doses of C1-inhibitor at 6 and 12 months, respectively ($P<0.01$ for 12 months).

Treatment failure and adverse effects

Three of 54 patients (5.6%) failed to show a ≥50% fall in total attacks at 3 months despite 2-weekly dosing, and 4 of 44 patients (9.09%) failed to show the same response at 6 months. All aside from 1 previously received regular C1-inhibitor alone or with oral prophylaxis. A similar pattern was observed for severe attacks with only 1 patient failing to show a ≥50% fall at 3 and 6 months. Two patients returned to C1-inhibitor prophylaxis. One adverse event was reported (injection site pain, Table 1).

This real-world data demonstrates that lanadelumab is effective in patients with severe HAE, despite prior prophylaxis, including those previously on prophylactic C1-inhibitor, and possibly with greater control. Longer-term real-world studies are required to assess whether factors including anti-drug autoantibodies, previously described (1), could reduce long-term efficacy, but this data provides assurance for lanadelumab efficacy and supports lanadelumab as a first-line treatment. Consistent with others (6), this study also shows dosing can be reduced whist preserving efficacy, improving cost-effectiveness.

Tables and Figures

	Value	Percentage (if applicable)
Total number of patients	62	
Female	45	72.6%
Male	17	27.4%
Mean age	40.6±16.4 years	
Mean age female	43.2±15.8 years	
Mean age male	33.7±16.2 years	
Patients with data for up to 6 months	46	74.2
Patients with data for up to 12 months	19	30.6
Diagnoses		
Type I HAE	61	98.4
Type II HAE	1	1.6
Patients on prophylactic treatment prior to lanadelumab	56	90.3%
		Percentage of those on prophylaxis
C1-inhibitor concentrate	*32*	*57.1%*
Modified androgen	*8*	*14.3%*
Tranexamic acid	*4*	*7.1%*
Modified androgen and tranexamic acid	*4*	*7.1%*
Modified androgen and C1-inhibitor concentrate	*3*	*5.4%*
Berotralstat	*2*	*3.6%*

Modified androgen, tranexamic acid and C1-inhibitor concentrate	*1*	*1.8%*
Progestogen, tranexamic acid and C1-inhibitor	*1*	*1.8%*
Progestogen	*1*	*1.8%*
Dosing frequency on data submission (n=60)		*% of those with data*
2-weekly	29	48.3%
2.5-weekly	1	1.7%
3-weekly	2	3.3%
4-weekly	27	45.0%
5-weekly	1	1.7%
Reported adverse effects (n=51)		*% of those with data*
None	*50*	*98*
Injection site pain	*1*	*2*

Table 1: Patient demographics, prior long-term prophylaxis, dosing frequency on data submission, and reported adverse effects.

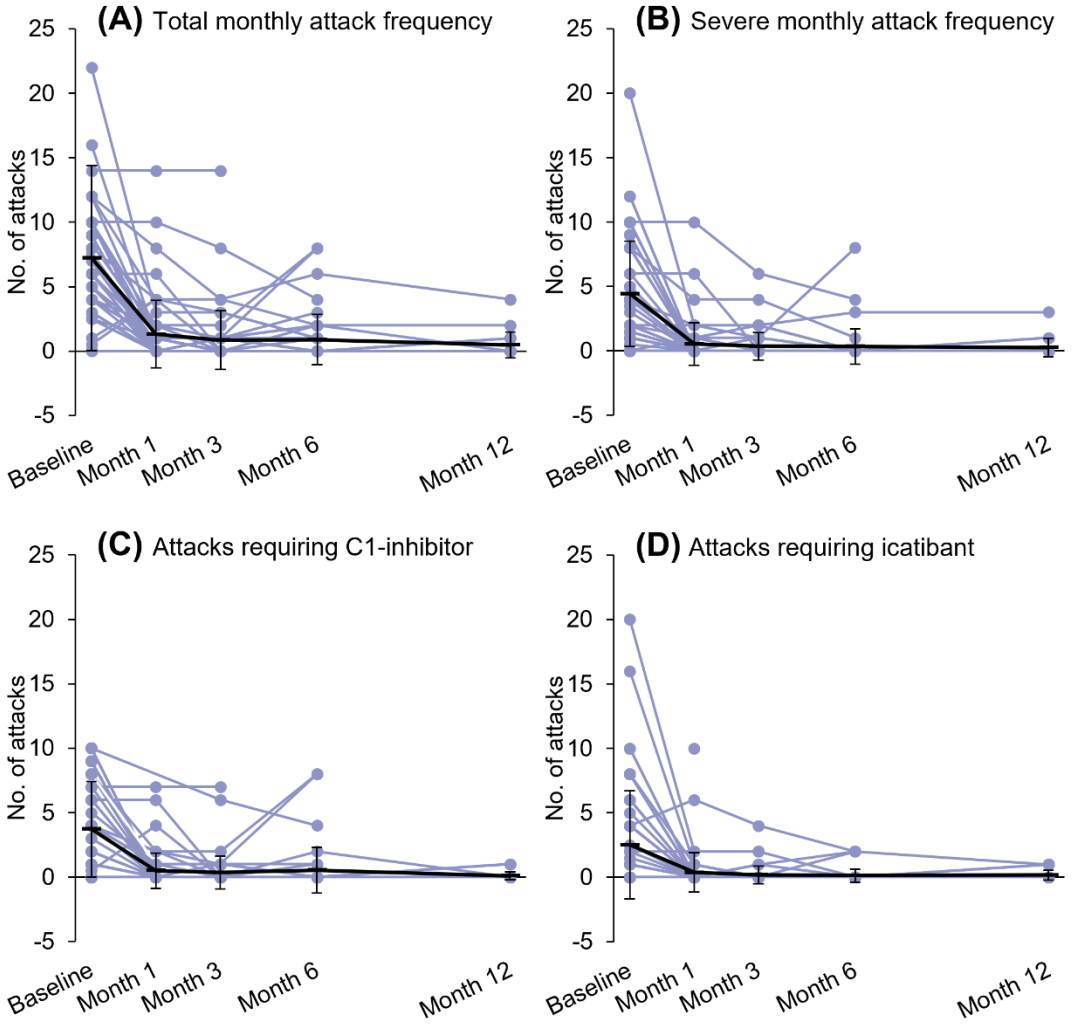

Figure 1_ Dorr et al.

Figure 1. HAE attack frequency at baseline and during lanadelumab treatment recorded as total (A), severe (B), and attacks requiring rescue treatment with C1-inhibitor concentrate (C) and icatibant (D). Black lines denote mean±SD. *P<0.001 vs. baseline, †P<0.01. For total attacks n=62, 59, 56, 46 & 19 for baseline and months 1, 3, 6 and 12, respectively. For severe attacks n=54, 58, 55, 46, & 19 for the same time points. For attacks requiring C1-inhibitor n=60, 57, 55, 45 & 19. For attacks requiring icatibant n=60, 59, 55, 45, & 19.

References

1. Banerji A, Riedl MA, Bernstein JA, et al. Effect of Lanadelumab Compared With Placebo on Prevention of Hereditary Angioedema Attacks: A Randomized Clinical Trial. *JAMA*. 2018;320(20):2108-2121.

2. Banerji A, Bernstein JA, Johnston DT, et al. Long-term prevention of hereditary angioedema attacks with lanadelumab: The HELP OLE Study. *Allergy*. 2022;77(3):979-990.

3. The National Institute for Health and Care Excellence. Lanadelumab for preventing recurrent attacks of hereditary angioedema Technology appraisal guidance [TA606] 2019. Accessed March 29 2022. https://www.nice.org.uk/guidance/ta606

4. Northern Ireland Formulary, HSCNI 2019. Accessed March 29 2022 https://niformulary.hscni.net/managed-entry/managed-entry-decisions/

5. Scottish Medicines Consortium SMC2206 2019. Accessed March 29 2022. https://www.scottishmedicines.org.uk/media/4947/lanadelumab-takhzyro-final-november-2019-for-website.pdf

6. Buttgereit T, Vera C, Weller K, et al. Lanadelumab Efficacy, Safety, and Injection Interval Extension in HAE: A Real-Life Study. *J Allergy Clin Immunol Pract*. 2021;9(10):3744-3751.

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Conflict of interest statement

AD – Has received honoraria and support for attending scientific meetings from Takeda.

CC – No conflicts to declare.

TC – No conflicts to declare.

JD – Has received honoraria from BioCryst, CSL Behring, Pharming, Takeda (previously Shire) for advisory board and speaking services. JD has also received reasonable expenses to attend meetings and conferences from CSL Behring, and Takeda (previously Shire).

MD – Has received support for attending scientific meetings from CSL and Takeda.

TE – Has received educational support, speaker fees and/or advisory board fees from: Allergy Therapeutics, CSL, Novartis, Takeda, Thermo Fisher, Viatris.

TG – Is the past Chair of NHS England Clinical Reference Group for immunology and allergy and has received honoraria from BioCryst, CSL Behring, Octapharma, Pharming, Takeda (previously Shire) for advisory board and speaking services. Has also received reasonable expenses to attend meetings and conferences from BioCryst, CSL Behring, Pharming, Takeda (previously Shire).

MG – No conflicts to declare.

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Author contribution statement

All authors contributed to the acquisition of data and manuscript revision and have given final approval for the published version. AD, PY and SK were additionally responsible for the conception and design of the study. AD was additionally responsible for data analysis, interpretation and initial drafting of the manuscript.

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Online Supplementary Repository

Patient questionnaire (S1).