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1 **Efficacy of Lanadelumab in acquired angioedema with C1-inhibitor deficiency**

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11 **Author Contributions:**

12 **Aude Belbezier:** acquisition of data, analysis, interpretation of the data, drafting the  
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14 **Isabelle Boccon-Gibod:** acquisition of data, critical revision of manuscript for intellectual  
15 content, given final approval of the version to be published.

16 **Laurence Bouillet:** study concept and design of the study, critical revision of manuscript for  
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27 interpretation, and conduct of the research. Laurence Bouillet has full access to all data and  
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32 L. Bouillet received research grants, consulting fees and honoraria from Shire/Takeda France,  
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38 **The text is strictly limited to**

39 • less than 1000 words (please supply a word count)

40 • up to 9 references in the Journal's style

41 • 2 figures and/or table

42 • < 60 words for figure legend

43 **Clinical Implications**

44 Lanadelumab seems to be a safe and efficacious treatment in patients with acquired C1Inh  
45 deficiency angioedema based on a retrospective French cohort study.

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48 **Keywords:**

49 Acquired angioedema, lanadelumab, C1-Inh .

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76 **Clinical Communications:**

77 Acquired angioedema with C1-inhibitor deficiency (C1-Inh AAE) is a rare, life-threatening  
78 disease<sup>1</sup>. Like the C1-Inh hereditary angioedema (C1-Inh HAE), it is characterized, by  
79 transient recurrent subcutaneous and/or submucosal swelling episodes, which mainly affect  
80 the skin, gastrointestinal tract, and upper airways<sup>1</sup>. However, contrary to the hereditary form,  
81 C1-Inh AAE has a late onset (> 40-year-old), with no family history<sup>1</sup> and is often associated  
82 with B-cell lymphoid hemopathy or monoclonal gammopathy<sup>2</sup>. Some cases have also been  
83 associated with autoimmune conditions or cancer<sup>1</sup>. C1-Inh AAE is caused by an acquired  
84 deficit of C1-Inh (often under 50% of the reference value) secondary to the presence of anti-  
85 C1-Inh antibodies or consumption by tumoral cells<sup>3</sup>. Decreased levels of C4, CH50, and C1q  
86 are frequently associated<sup>1</sup>. Few treatments, either by direct or indirect bradykinin metabolism  
87 modulation, have been recommended for symptomatic C1-Inh AAE patients. The choice is  
88 dependent on the stage of disease with icatibant, a bradykinin 2 receptor antagonist, or C1-Inh  
89 replacement most often used as on demand therapy for acute attacks. Prophylactic treatment  
90 should be introduced if patients suffer from frequent (>3/month) or severe attacks. Treatment  
91 of associated conditions such as hemopathy can often help to cure the angioedema<sup>1</sup>. In  
92 addition to the above, other treatment options have also been shown to reduce the frequency  
93 and severity of recurrent attacks: Tranexamic acid (an antifibrinolytic agent) and Danazol (an  
94 attenuated androgen)<sup>4,5</sup>. Rituximab should also be considered if these therapies are ineffective,  
95 especially in the context of an underlying malignancy<sup>4</sup>. However, some patients remain  
96 symptomatic (25%) despite these therapies<sup>1</sup>. We investigated the efficacy of Lanadelumab, an  
97 anti-plasma kallikrein monoclonal antibody<sup>6</sup>, in a population of French patients with C1-Inh  
98 AAE. Since 2019, 3 patients were treated (2 females, 1 male). Informed consent was obtained  
99 from all patients. Clinical and biological characteristics of patients are presented in Table. The  
100 median age was 51 years (50.4-53.6). The median age of first symptom manifestation was 41  
101 years (range: 38-49) and the age of diagnosis was 46.8 years (40.7-49.3). One patient had a  
102 past medical history of a nodal marginal zone B cell lymphoma which was treated with  
103 Rituximab. All 3 patients suffered from severe attacks that affected the tongue (1), the  
104 posterior pharynx and/or larynx (2), the face (3), the lips (2), the abdominal region (3) and  
105 extremities (3). C1-Inh activity was low and anti-C1-Inh antibodies were detected in all  
106 patients. Danazol long term prophylaxis was used for all patients but was not effective.  
107 Tranexamic Acid (2 patients), recombinant C1-esterase inhibitor (1) and Rituximab (1) were  
108 also tested as prophylactic treatments without efficacy. Before Lanadelumab therapy  
109 initiation, the median number of AE attacks per year was 36 (range: 6-48). Lanadelumab was

110 injected subcutaneously at home for all patients with a dose of 300 mg once every 2 weeks  
111 for the first 6 months and then once every 3 weeks for Patient 3 and once every 4 weeks for  
112 Patient 2 (see Table). With this therapy, we noticed a meaningful improvement with no attack  
113 during follow up under therapy. Lanadelumab was given during a median period of 13.7  
114 months (range 10-19.3) with no severe or serious adverse events. One patient stopped the  
115 treatment and developed new attacks 4 months after halting treatment. After resuming  
116 treatment, the patient did not develop any further attacks. One patient experienced pruritus  
117 localized at the injection site and one developed asthenia 48 hours after injection. No long-  
118 term side effects were observed.

119 Lanadelumab is an effective treatment for C1-Inh HAE<sup>7,8</sup> with a reduction of 85% of attacks<sup>9</sup>.  
120 It was also associated with an improvement in HAE quality of life. Based on the phase 3  
121 controlled trial (HELP)<sup>7,8</sup>, this treatment has obtained FDA and European approval in  
122 refractory C1-Inh HAE. It offers the convenience of self-administered subcutaneous injections  
123 that are well tolerated with the most commonly occurring adverse events being injection site  
124 reactions. Some cases of hypersensitivity and increased PTT have been reported. Because of  
125 the pattern similarities between C1-Inh HAE and C1-Inh AAE and the ease of use of  
126 Lanadelumab, this therapy has been considered as a potential therapy for refractory C1-Inh  
127 AAE. The clinical characteristics of our patients with C1Inh-AAE are consistent with the  
128 previous studies<sup>1</sup>. The attacks were localized in abdominal, laryngeal, facial, peripheral, or in  
129 multi-location areas. C1-Inh neutralization secondary to anti-C1-Inh antibodies seems to be  
130 the main C1-Inh deficit underlying mechanism in these reports. In Patient 3, C1-Inh  
131 consumption was also likely due in part to the associated B cell lymphoma. In the current  
132 analysis, the treated attacks were often severe and frequent despite the use of recommended  
133 prophylaxis therapies and hemopathy treatment. Because of that, the CREAK (the French  
134 National Angioedema Reference Center) has decided to treat these patients with  
135 Lanadelumab. No new attacks were reported for patients under this treatment, except for in  
136 patients who stopped therapy. This underlines the great efficacy of this therapy but not  
137 following discontinuation. We observed few side effects of Lanadelumab which is also in line  
138 with other studies<sup>7,8</sup>. Patients were first administered a 300 mg Lanadelumab dose every 2  
139 weeks as recommended. Adjustments in doses were made based on symptom recurrence and  
140 patient compliance. No side-effects were found after dosing interval adjustments.

141 In conclusion, Lanadelumab seems to be a safe and efficacious treatment in patients with C1-  
142 Inh AAE.

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**Table Legend:** Characteristics of the 3 C1-Inh AAE patients treated with Lanadelumab . M : male; F: female; m : month, y : year; C1-Inh : C1 inhibitor; NA : not acquired

**Table : Characteristics of the 3 CA-Inh AAE patients treated with Lanadelumab**

	<b>Patient 1</b>	<b>Patient 2</b>	<b>Patient 3</b>
Sex/Age at onset (years)	M/49	F/41	F/38
Delay in diagnosis (m)	2	70	21
Age at the initiation of Lanadelumab	51	49	49
Associated disease	No	Hypothyroidism	Marginal zone B cell lymphoma
Attacks localization	Face, pharynx and larynx, abdomen, extremities	Face, abdomen, extremities	Face, pharynx and larynx,, abdomen, extremities, perineum
AE attacks in the previous year	36	48	6
Attack treatments	Icatibant,	Icatibant,	Icatibant,
Prophylactic therapy before Lanadelumab initiation	Tranexamic Acid, Danazol, Rituximab	Tranexamic Acid, Danazol, Recombinant C1-esterase inhibitor, Rituximab	Tranexamic Acid, anti-tumoral therapy
Functional C1-Inh, % ( reference value : >70%)	2	13	21
C1-Inh antigen, mg/L (reference value: >170mg/L)	157	NA	27
C1q antigen, % (reference value: >70% of a pool of normal plasma)	28		13
C4, mg/L (reference value: >93mg/L)	17	30	15
CH50, % (reference value: >70% of a pool of normal plasma)	3	NA	10
Anti-C1-Inh, UI (reference value : <100 U)	455	354	215
Anti-C1-Inh isotype	IgG	IgG	IgG, IgA, IgM
Number of attacks after Lanadelumab therapy	0	0	0
Frequence of Lanadelumab injection	once/2 weeks	once/4 weeks	once/3 weeks
Lanadelumab time of follow up (m)	19	10	14