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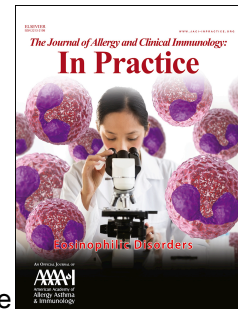
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Lanadelumab efficacy, safety, and injection interval extension in HAE - a real life study

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Conflict of Interest Statement:

All authors declare that there are no conflicts of interest to declare.

Abstract

Background:

Lanadelumab has been available in Germany for the prophylactic treatment of hereditary angioedema (HAE) since February 2019.

Objective:

To investigate real-life treatment outcome of lanadelumab and gain practical experience in adapting the therapy to individual patients.

Methods:

The study included 34 patients. In 24 patients with HAE and four patients with angioedema due to acquired C1-inhibitor deficiency, the previous treatment was switched to lanadelumab. In six patients with HAE, lanadelumab from the open-label HELP study was continued in regular care. During the transition, patients were monitored using the angioedema control test (AECT) and the angioedema quality of life questionnaire (AE-QoL). At the time at which patients became symptom-free, the dosage interval was increased gradually (+3 days).

Results:

On average, the AECT values improved from 7.5 (poorly controlled disease) to 14.9 (well-controlled disease), and all patients showed adequate disease control. All treated patients, except one outlier, scored AE-QoL values representing only a slight reduction in quality of life (mean 14 points). At the time point of data collection, nine patients used an average fixed injection interval of 30 days. Twenty-two patients were symptom-free from the beginning of the treatment phase and intended to extend their injection interval from 30 to 32.5 days (median). We recommended reducing the initial dosing interval from 24 to 21 days (median) to three patients due to intermediately occurring symptoms.

Conclusions:

Gradual extension of injection intervals of lanadelumab presented in this study can minimize the burden of therapy without losing efficacy.

Keywords: individualized treatment; hereditary angioedema; lanadelumab; quality of life

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Abbreviations

Acquired Angioedema (AAE)
Angioedema Center of Reference and Excellence (ACARE)
Angioedema control test (AECT)
Angioedema Quality of Life (AE-QoL)
C1 inhibitor (C1-INH)
Hereditary Angioedema (HAE)
Minimal clinically important difference (MCID)
Open-label extension (OLE)
Patient-Reported Outcome Measures (PROMs)
Quality of life (QoL)
Roll-overs (RO)
Hereditary angioedema (HAE)

Highlights Box

1. What is already known about this topic?

Recently, the monoclonal antibody against kallikrein lanadelumab was approved for the prophylaxis of hereditary angioedema (HAE) attacks. It showed very good efficacy in clinical trials. In patients who are attack-free, dose reductions can be considered.

2. What does this article add to our knowledge?

Outside of clinical trials, lanadelumab was safe and effective in larger cohorts of patients with HAE and acquired C1-INH deficiency. Moreover, our protocol for extending injection intervals improved disease control and quality of life.

3. How does this study impact current management guidelines?

The presented approach for the extension of injection intervals of lanadelumab should be considered early on since it can minimize the burden of therapy without losing efficacy.

Introduction

Hereditary angioedema due C1 inhibitor (C1-INH) deficiency (HAE-C1-INH) is a rare autosomal dominant inherited disease with a minimal prevalence of 1 in 67,000 (1, 2). The underlying mutations in the SERPING1 gene lead to an absolute (HAE-C1-INH type 1) or functional (HAE-C1-INH type 2) deficiency of the C1-INH, which controls the release of bradykinin in the contact system. The excess of bradykinin triggers attack-like swellings (angioedema) of the skin and/or mucous membranes. Depending on the swellings' location, they can lead to functional impairment and can be disfiguring, painful or life-threatening. Patients with HAE have significantly impaired quality of life (3, 4). HAE attacks usually occur spontaneously, however, triggering factors such as infections, mechanical trauma, surgery, physical exertion, stress, puberty or the use of estrogen-containing contraceptives can provoke attacks in many patients (5).

In acquired angioedema caused by C1-INH deficiency (AAE-C1-INH), inactivation or increased consumption of C1-INH leads to the deficiency and thus to an imbalance in the kinin system (6). AAE-C1-INH is frequently associated with lymphoproliferative diseases (7).

There are two therapeutic strategies for treating HAE-C1-INH: on-demand and long term prophylactic treatment (1). For on-demand treatment, the bradykinin receptor 2 antagonist icatibant and an intravenous substitution of C1-INH are available. In the U.S., subcutaneous administration of the kallikrein antagonist ecallantide is an additional option. For long term prophylaxis, substitution of C1-INH is available since 2019, and prophylactic C1-INH can be applied intravenously and subcutaneously (8). In 2018, the monoclonal antibody lanadelumab was approved for the prophylactic treatment of HAE-C1-INH in patients aged 12 years and older. It has been available in Europe since February 2019. All of these therapies are off-label for the treatment of patients with AAE-C1-INH.

Lanadelumab is specifically directed against plasma kallikrein. The HELP study showed superior efficacy of lanadelumab 300 mg dosed every two weeks subcutaneously as compared to placebo for the prophylaxis of HAE attacks. Yet, the effectiveness and tolerability of lanadelumab remain unknown in larger cohorts of patients with HAE-C1-INH and AAE-C1-INH in daily clinical practice. It also remains unclear how the injection intervals' extension, as recommended in the product information, can be implemented in clinical practice, when the patient is free of attacks.

Here, we report our experience on the efficacy of lanadelumab and its impact on disease control and quality of life in patients with HAE-C1-INH and AAE-C1-INH from our

Angioedema Center of Reference and Excellence (ACARE) (9) at Charité. Also, we present our approach for extending injection intervals of lanadelumab.

Methods

Patients

The patient cohort comprised of 34 patients, 21 female and 13 male, diagnosed with recurrent angioedema due to C1-INH deficiency and treated with lanadelumab as long-term prophylaxis. Thirty patients had HAE-C1-INH (median age 44 years, range 19–78 years, standard deviation [SD] 16.3) and four had AAE-C1-INH (median age 64 years, range 60–69 years, SD 4.05). Before switching to lanadelumab, ten patients used long-term prophylaxis with C1-INH intravenously (on average five breakthrough attacks per month), eleven patients administered C1-INH prophylaxis subcutaneously (on average four breakthrough attacks per month), and one patient received prophylactic tranexamic acid orally (six breakthrough attacks per month). Six patients had used only on-demand treatment (with icatibant, on average six attacks per month). All these patients either showed inadequately controlled disease, had an impaired disease-specific quality of life and/or reported a high burden of prior treatment. A further six patients were roll-overs (RO) from the open-label extension (OLE) HELP Study (OLE-RO). Lanadelumab treatment (or continuation of lanadelumab treatment in OLE-RO) was initiated in all patients between February 4 2019 and April 1 2020. The medical history was obtained by a standardized questionnaire and complemented by available patient files and swelling calendars.

Treatment and procedure for extension of injection intervals

The decision to switch from prior on-demand treatment to prophylactic treatment with lanadelumab was made by the treating physician and the patient and considered disease activity, impaired disease-specific quality of life (AE-QoL), inadequately controlled disease (measured with the angioedema control test, AECT), and patient's preferences. Patients receiving long-term prophylaxis (C1-INH intravenous/subcutaneous or tranexamic acid) were considered to have an ongoing indication for prophylactic treatment. The switch to prophylaxis with lanadelumab was made if there was a prospect of further improvement in disease control and/or quality of life. Moreover, patients under prior long-term prophylaxis that have experienced significant difficulties in self-administrations of C1-INH (e.g. problems with venous puncture due to scarring of veins or impaired vision, time and organizational effort) were offered the switch to lanadelumab. The goal of the change in treatment was to achieve complete control (AECT = 16 points), absence of signs and symptoms (0 attacks) and normalization of daily life (AE-QoL $\leq$ 24). In OLE-RO patients, the indication for long-

term prophylaxis was assumed to persist, and continuation was suggested by the treating physician.

The switch to lanadelumab took place after providing patients with information about the potential risks and expected benefits in the context of regular care during a consultation in the following pattern (Figure 1): The first injection always took place (with one exception due to COVID-19 restrictions) in the presence of the consulting and prescribing physician after detailed information as a self-injection. The overlap with any previous existing long-term prophylaxis was over a maximum of three days. The second injection was administered by the patients themselves 14 days later. A follow-up visit in person was scheduled after four weeks shortly before the third injection. During this visit, tolerability and efficiency of lanadelumab treatment were evaluated. If no symptoms were observed or reported (the first two days after the first injection were not taken into account), we recommended extending the next injection interval by three days each (with injections scheduled after 17, 20, 23 days, etc.). Whilst the interval was increased, patients were closely monitored. In the event of an attack or prodromal signs, patients treated themselves with C1-INH or icatibant, and the next injection interval was shortened to the penultimate interval that had provided freedom from signs and symptoms (but not less than 14 days).

Patients who experienced an attack during the first four weeks of lanadelumab treatment were advised to continue at 14-day intervals. If those patients were symptom-free over a period of at least two months, they were offered an extension of the interval according to the above mentioned scheme with a lower interval increase (one to two days).

The OLE-RO patients completed the trial between 22 July, 2019 and 20 September, 2019, and have been symptom-free for months or years. Prior to the first injection after the end of the trial, these patients were asked to extend the injection interval by three days.

Patient-Reported Outcome Measures (PROMs)

All patients completed the AECT and the Angioedema Quality of Life (AE-QoL) questionnaire. The AECT is a validated, retrospective tool that comprises four questions and estimates patients' disease control over recurrent angioedema symptoms in the previous four or 12 weeks (10). The evaluation is based on a cumulative score, whereby the cut-off value of 10 points separates those with insufficiently controlled disease (minimum 0 points) from those with well-controlled disease (maximum 16 points) (11). The minimal clinically important difference (MCID) of the AECT is not yet known.

The AE-QoL is a validated questionnaire to assess patients' quality of life with recurrent angioedema (12, 13). It contains 17 questions and encompasses functioning, fatigue/mood, fears/shame and nutrition. AE-QoL total values of 0-23, 24 to 38, and ≥ 39

define patients with "no effect", "small effect", and "moderate to large effect" of recurrent angioedema on their quality of life, respectively (14). The MCID of the AE-QoL is 6 points (13).

Statistical data analysis

The current study is a retrospective observational study, and thus no sample size was calculated for subsequent analysis. A paired two-tailed T-test was performed to compare the AECT scores of the same participant before and after a change in therapy. It was assumed that a significant increase in the AECT score per patient before and after a change in treatment would represent an improvement in disease control. Also, an exploration of individual injection intervals was conducted to monitor dose interval adjustments more accurately. The AE-QoL mean value of each sub-domain was determined, and it was assessed in which domain patients showed the most significant changes.

Results

Lanadelumab injection intervals can be extended in most patients

Patients were treated for a median period of 29.9 weeks with lanadelumab (range 3.3–65.3 weeks, not including results from OLE-RO). At the time of analysis, nine patients used a fixed injection interval with a median of 30 days (range 21–90 days). Of these nine patients, eight (89%) achieved injection intervals of 28 days or longer. Most patients (22 of 34), at the time of analysis, were still in the process of extending their treatment intervals (Figure 2), from, on average, 30 days (median, range 14–48 days) to 32.5 days (median, range 17–50 days), and 14 of these 22 patients (64%) had injection intervals of 28 days or longer.

Very few patients need to shorten their lanadelumab treatment intervals

Of 34 patients, three patients had shortened their injection interval or were in the process of doing so, on average from 24 to 21 days (median). Eight patients had more than one attack during the interval prolongation, two of whom were patients with AAE-C1-INH (Figure 3).

Three months is the longest lanadelumab treatment interval

One patient (Patient 34, Figure 2) deviated from the recommended treatment regimen and waited for attacks to recur after the first injection. On April 10 2019, he administered 300 mg lanadelumab and remained symptom-free until August 4 2019, when one to two attacks per week started to occur again. He administered lanadelumab on August 13 2019 and has since used 90-day treatment intervals, only one abdominal attack (as of September 1 2020), which was treated intravenously with C1-INH.

As of 28 October 2020, one other patient (patient 33, Figure 2) used 90-day injection intervals. She received the first dose of lanadelumab on May 17 2019 and increased the interval by 3 days as planned. On May 19 2020, she reported the next targeted injection

interval of 50 days (Figure 2). Yet, the patient had missed one injection and delayed the next dose, which resulted in an injection interval of 113 days. This patient was also advised not to exceed an interval of 90 days. To date (October 28 2020) she is completely free of symptoms and her last attack occurred on May 12 2019.

Less than 10% of patients discontinue lanadelumab treatment

One patient, with AAE-C1-INH and monoclonal gammopathies of unknown significance (MGUS), had well-controlled disease with lanadelumab. However, other complaints (undiagnosed febrile attacks, fatigue and loss of performance) remained, and the patient stopped lanadelumab and switched to on-demand icatibant. Another patient, an adolescent with HAE-C1-INH and severe psychological impairment and somatization, discontinued twice per month treatment with lanadelumab after several months because of 1–2 breakthrough attacks per month. After switching to C1-INH subcutaneously (Berinert®) 2x/week, she continued to report at least one attack per month despite sufficient substitution of C1-INH. In a third patient, lanadelumab treatment was changed to prophylactic treatment with intravenous C1-INH because she wanted to get pregnant.

Lanadelumab treatment significantly improves disease control in patients with HAE-C1-INH and AAE-C1-INH

The average AECT score in patients on lanadelumab treatment (n=34) was 14.8, and 22 of 34 patients, including two patients with AAE-C1-INH, had complete control, i.e. the maximum AECT score of 16. Among the 25 patients with available AECT scores before and after switching to lanadelumab, the score changed significantly from a mean of 7.5 to 14.9 ($p<0.001$), with 18 patients achieving the maximum score of 16 points (Figure 4). The improvements in AECT were independent of whether patients had previously received prophylactic (mean 7.5 [range 1-15] to 14.7 [range 10-16]) or on-demand treatment (mean 7.4 [range 3-13] to 15 [range 13-16]). This difference between groups (on-demand versus prophylactic treatment) was not statistically significant. Six patients were controlled satisfactory with their prior C1-INH prophylaxis (AECT mean 12.2, range 10-15). Nevertheless, these patients were switched to lanadelumab as the burden of the prior treatment was high in these patients and disease control was not complete (AECT <16). Five out of these six patients scored 16 points in the AECT after the switch.

Lanadelumab treatment significantly improves quality of life in patients with HAE-C1-INH and AAE-C1-INH

The AE-QoL was assessed in 33 patients treated with lanadelumab and averaged 14 points; 25 patients achieved values < 24. In 24 patients, AE-QoL was measured before and during treatment with lanadelumab and decreased significantly from 45.8 to 13.8 to a mean change score of 32 (95% CI 22.6-41.4, $p<0.001$). Within the individual domains, we observed an average decrease of 42.4 (95% CI 30-54.9, $p<0.001$) in "functioning", 23 (95% CI 4.8-13, $p<0.001$) in "fatigue/mood", 30.6 (95% CI 6-18, $p<0.001$) in "fears/shame", and 22.73 (95% CI 7.9 - 37.6, $p=0.004$) in the domain "nutrition" (Figure 5). Only one patient had a reduction to the restriction of quality of life below the MCID of 6 points (Figure 6). This patient had been treated with lanadelumab for 9.3 weeks at the time of the survey and had been completely symptom-free during this time. The slight improvement in quality of life contradicted the questionnaire, in which the patient stated: "We are doing better than ever in our lives".

Patients who switched from on-demand treatment to lanadelumab showed virtually the same baseline AE-QoL total values as patients with previous prophylactic treatment (AE-QoL total 46 vs 45.7, $p=0.73$), however, lower impairment of QoL after treatment with lanadelumab (AE-QoL total 9.6 vs 14.8, $p=0.71$). This difference between the groups was not statistically significant.

The majority of patients experience no or mild to moderate side effects

Safety data was documented from all patients. Twenty four patients did not experience side effects of lanadelumab (answered "no" to: "Do you suspect or are you certain that lanadelumab / Takhzyro[®] is causing side effects?"). Four patients described an unpleasant feeling or pain during the injection procedure. An additional three patients reported redness, wheals and itching (once also away from the injection site) and two patients described hematomas at the injection site. One patient reported local urticaria skin reactions and was recommended to pre-medicate with a 2nd generation non-sedating antihistamine before injection; thereafter, the skin reactions were almost completely controlled. Dizziness and "possibly" headache after the injection were mentioned once each. Fourteen patients found handling the vial and the enclosed needles impractical and 23 patients would have welcomed the introduction of a pre-filled syringe (available since October 2020).

Discussion

The treatment goals of HAE, including freedom from attacks, complete control over disease activity, and unimpaired quality of life, can be achieved using long-term prophylaxis. With the sole use of on-demand medication, these goals are unattainable.

We observed a significant increase in disease control among our patients with C1-INH deficiency after switching to the long-term lanadelumab prophylaxis, regardless of previous prophylactic or on-demand treatment. All patients reached the AECT range of "well-controlled disease" in the injection interval extension and two thirds (65%) of patients reached the maximum possible value (16 points). Furthermore, we were able to show that long-term prophylaxis with lanadelumab led to a significant improvement in quality of life in routine clinical practice. Thus, AE-QoL improved beyond the MCID of 6 points in all except one patient. The most significant changes occurred in the "functioning" domain, with a mean reduction of more than 42 points.

In accordance with our results, Hahn *et al.* recently reported high efficacy and tolerability of lanadelumab in daily clinical practice: their prospective analysis showed a significant reduction in disease activity as well as an improvement in quality of life among 12 patients with HAE over a 6-month period (15). In Hahn *et al.*'s population, most patients (9/12) were using on-demand treatment before switching to lanadelumab prophylaxis. Interestingly, the mean AE-QoL values of these patients before switching to lanadelumab was much higher than in our population: ~68 vs 45.7 (data from Hahn *et al.* extracted from the graph). Under treatment with lanadelumab, Hahn's previous on-demand patients showed AE-QoL values very similar to ours: ~11 vs 9.6 (data from Hahn *et al.* extracted from the graph). Consequently, Hahn's reported AE-QoL improvements turn out to be slightly higher than ours, regardless of whether they are compared to the previous on-demand or the overall population. The extent of improvement of the individual domains is very similar in both reports: the domain "functioning" showed the greatest improvement, followed by "fears/shame" and "fatigue/mood" and lastly, "nutrition". Similarly, a recently published report by Lumry *et al.* shows that the domain "functioning" improves most of all domains (16). In our study, AE-QoL baseline values were very close to the baseline values observed in the placebo-controlled trial reported by Lumry *et al.* of between 42.8 and 48.8 (45.8 for our results). The improvement under lanadelumab, however, was markedly greater in our population (AE-QoL total: Lumry -21.3 with 300 mg every 2 weeks; -32 for our results). We assume that in contrast to our uncontrolled real-life conditions, Lumry's patient evaluations of AE-QoL could have been influenced by the possibility of being administered placebo, even when the majority of patients at the day of assessment were symptom-free for many weeks or even months.

In our study, we used the AE-QoL to assess patients for their QoL impairment. Other PROMs for QoL assessment in patients with HAE include the Hereditary Angioedema QoL questionnaire (HAE-QoL). The HAE-QoL is a disease-specific questionnaire for patients with HAE-C1-INH that captures relevant issues including treatment difficulties, physical functioning and health, disease-related stigma, emotional role and social functioning, concern about offspring, perceived control over illness, and mental health (17). The HAE-QoL, in a recent study, was used to show that QoL, in patients with HAE, can improve as a result of a systematic management program (18). We used the AE-QoL, rather than the HAE-QoL, for three reasons. First, the HAE-QoL – unlike the AE-QoL – is not developed for AAE-C1-INH, and our study includes several patients with AAE-C1-INH. Second, the recall period of the HAE-QoL (six months) is much longer than that of the AE-QoL (four weeks), which could have been impractical for investigation of QoL during the investigation of interval extension. Finally, the minimal clinically important difference (MCID) of the HAE-QoL remains to be determined, whereas the MCID of the AE-QoL is known.

Most side effects reported by the patients are already known from published literature (19) and occurred less frequently in our real-life population. Approximately half the patients in the phase 3 study complained of pain, erythema, and/or bruising at the site of injection. In our cohort, only nine patients (26%) reported local site reactions. In contrast to Banerji's study cohort (19), our patients administered the drug by self-injection in the abdominal area, which we believe is the reason for the observed reduction of injection site reactions. We made an observation with icatibant: physician-administered drug was frequently considered painful; once self-administration became the rule, this local side effect was only reported occasionally. At no point was discontinuation of the treatment during the study considered due to side effects.

We report on the following limitations of this study: In nine patients, the comparative values before treatment with lanadelumab were missing. Particularly in those patients from OLE-RO, that were included at a time when the AECT was not available. This is similar to some AE-QoL data, of which no more values could be collected or found in ten patients.

According to the product information of the E.U. (20), "the recommended starting dose is 300 mg lanadelumab every two weeks. In patients who are stably attack-free on treatment, a dose reduction of 300 mg lanadelumab every four weeks may be considered, especially in patients with low body weight". In addition, the U.S. product information states that an extension of the interval should only be considered after six months without symptoms (21). Based on our own observations, we have established the treatment regimen described above with an early, but continuous and slow extension of the interval by three days at a

time. This approach results in patients experiencing at least one HAE attack until a fixed individual injection interval is defined. The occurrence of breakthrough attacks beyond a 14-day interval immediately leads to the shortening of future intervals in order to maintain the therapeutic goal of freedom from attacks. The gradual extension of injection intervals in individuals who were symptom-free was highly appreciated by our patient population as the burden of treatment itself was individualized and reduced to a minimum. Furthermore, we were able to show that the majority of the examined patients achieved freedom from symptoms with injection intervals of 28 days or longer (median of 30 days). Future studies should answer the question, why individual patients achieve significantly longer intervals. By contrast, we observed early on that some patients had difficulties in calculating the proposed interval extension. Consequently, all patients were given a tabular injection plan after verbal explanation, which contained the exact proposed injection dates as well as instructions in case of a breakthrough attack: immediate therapy of the attack with the known on-demand medication, reduction of the injection interval to the penultimate interval, which provided freedom from symptoms (but no less than 14 days). If an attack occurs unexpectedly after a fixed interval has been reached, we recommended shortening the interval and adapted it to the individual patient. In addition, we observed that some patients "missed" the scheduled injection dates when reaching a regular injection interval. We interpret the missing of injection appointments as a change in patients' disease perception. The previous experience of HAE as a limitation to life changed if patients adapted well to long-term treatment. Therefore, we provided our patients with a list of upcoming injection intervals and asked them to enter these time-points in their calendar or in their smartphone. An additional problematic behavior is the handling of the still recommended on-demand medication. We observed that patients who are free of complaint for a substantial period of time tend to neglect to carry their on-demand medication. In order to counteract this behavior, we asked our patients at each visit if they were carrying their emergency medication and could state the expiry date. If we suspected non-compliance, we informed the patient about possible complications. The question of the necessity of short-term prophylaxis before medical interventions under therapy with lanadelumab has been raised since the introduction of the medication, but there is still no satisfactory answer to this question. Due to the excellent symptom control of lanadelumab, we have decided to forego mandatory short-term prophylaxis in the 14 days after the last lanadelumab administration. We generally emphasize the provision of effective on-demand medication. Currently, the patients' feedback has been positive, and there has been no swelling due to medical intervention. However, the number of observed individual cases is too small to derive general recommendations.

The introduction of lanadelumab as long-term prophylaxis has closed a significant gap in the care of patients with recurrent angioedema due to C1-INH deficiency. Lanadelumab is an extremely effective, well-tolerated and highly appreciated long-term prophylaxis for HAE attacks. In our observational study, we showed that individualized treatment regimens for interval prolongation can minimize the burden of therapy without losing efficacy.

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Contributions

M Magerl designed the study. T Buttgereit, M Maurer, R Krüger, V Wahn, EM Grekowitz, K Weller, C Vera, S Aykanat and A Gutsche collected, analysed and/or interpreted data. T Buttgereit, M Magerl, M Maurer, C Vera and A Gutsche prepared the main manuscript text. All authors contributed to writing or reviewing the manuscript and final approval.

Figure 1: Individualized injection regimen of lanadelumab

Figure 2: Previous injection interval and targeted injection interval (n=34 patients)

Figure 3: Total Number of angioedema attacks of each patient (n=28) within a given period of time (in weeks) since switch to long-term prophylaxis with lanadelumab (including extension of injection intervals). Patients from HELP-OLE were not included in the evaluation. Blue dots: patients with hereditary angioedema, blue dots with red circles: patients with acquired angioedema

Figure 4: Angioedema control test (AECT) values before and after change to lanadelumab (n=25 patients)

Figure 5: Results of the subdomains of the angioedema quality of life questionnaire (AE-QoL) before and after treatment with lanadelumab (n=24 patients)

Figure 6: Individual reduction in the restriction of angioedema quality of life (AE-QoL, n=24 patients). Red line: Minimal clinically important difference (MCID)

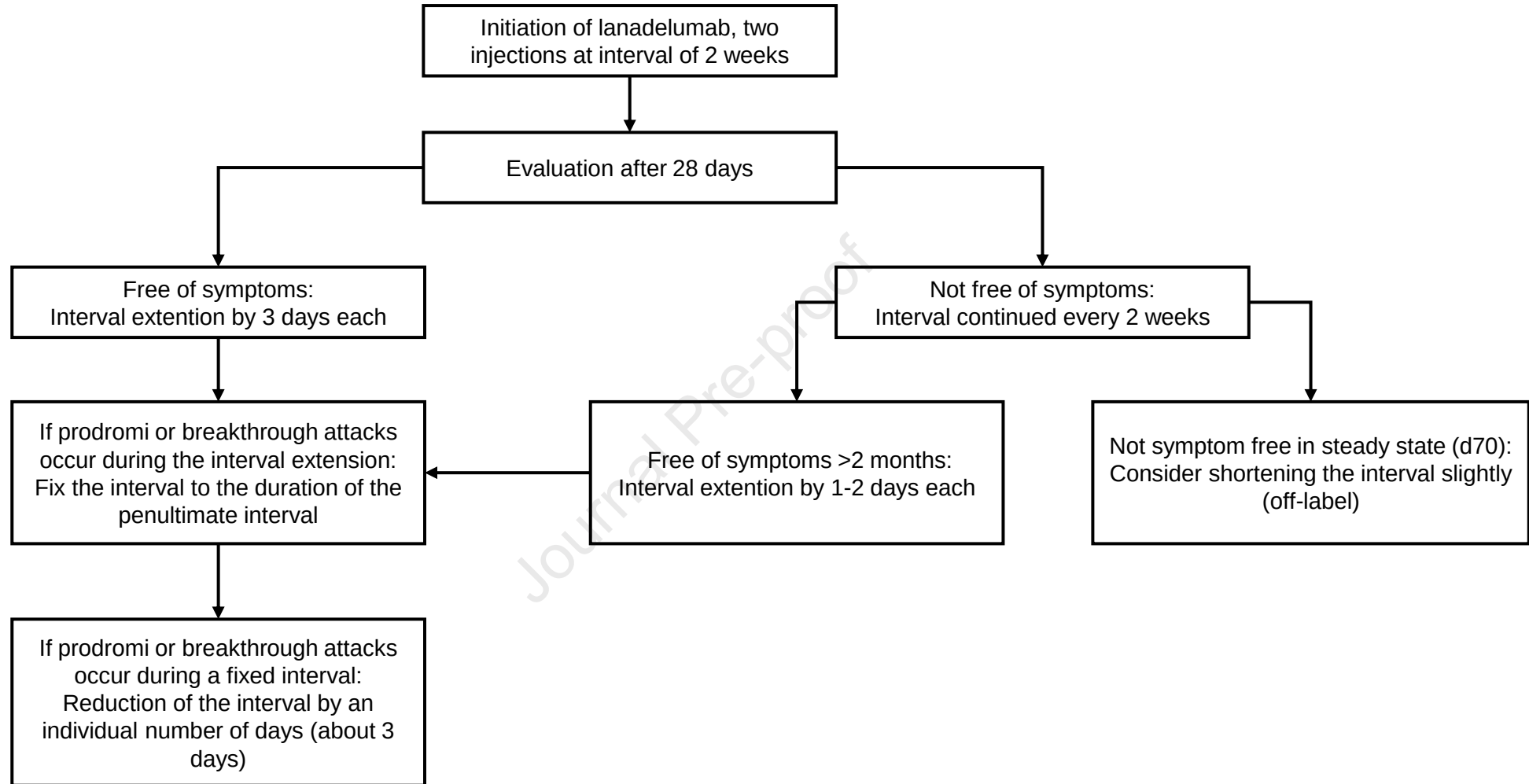
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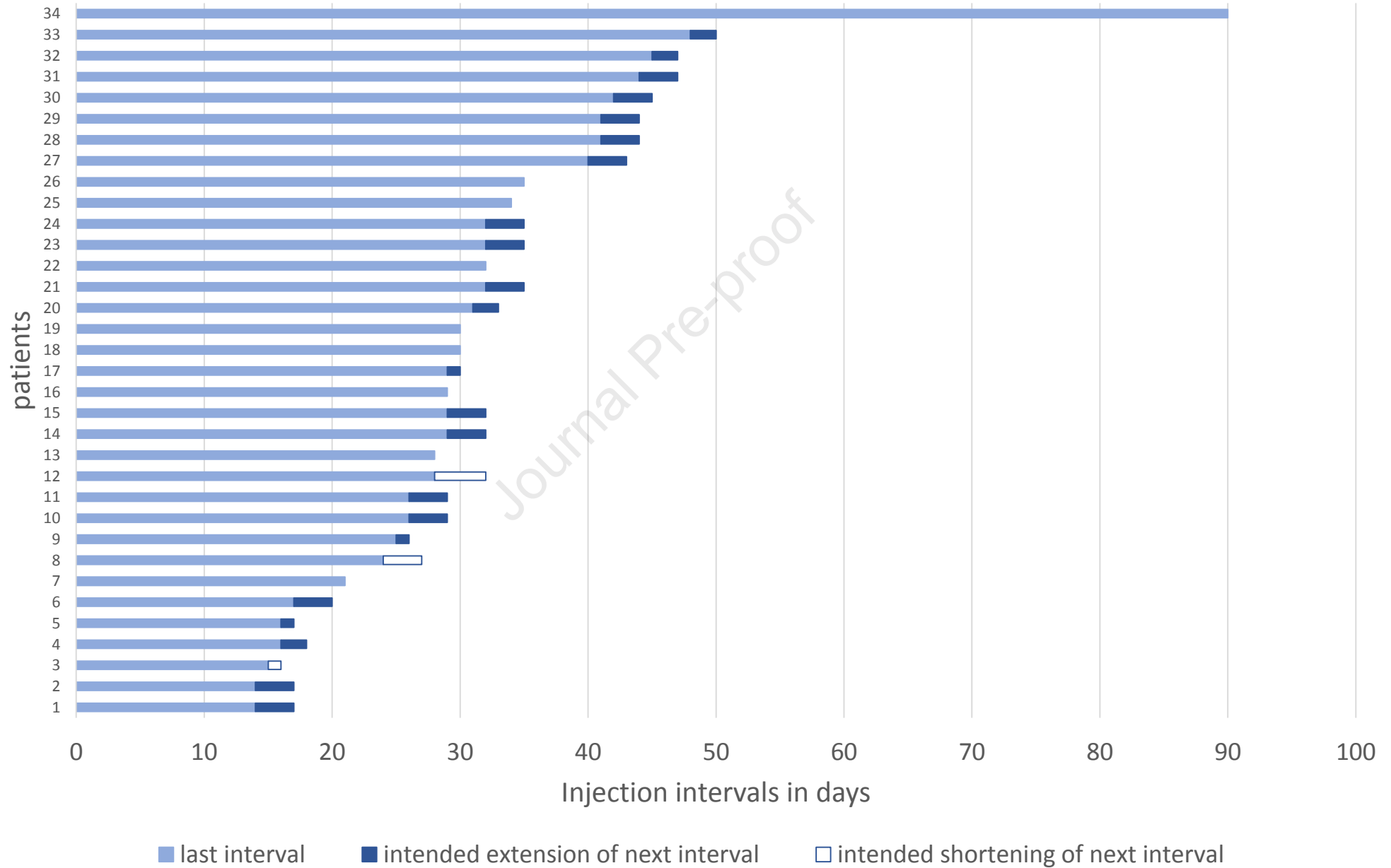
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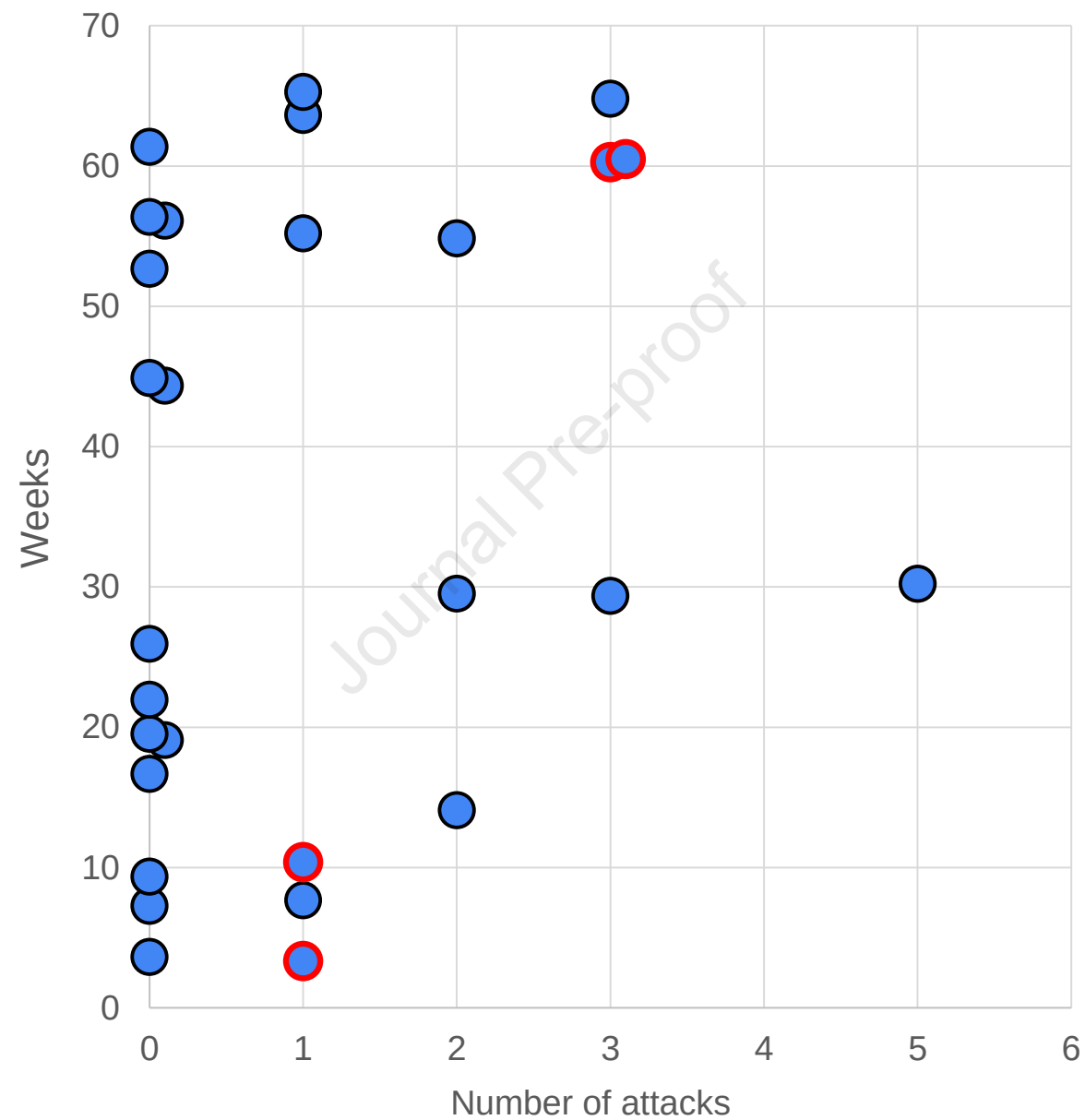
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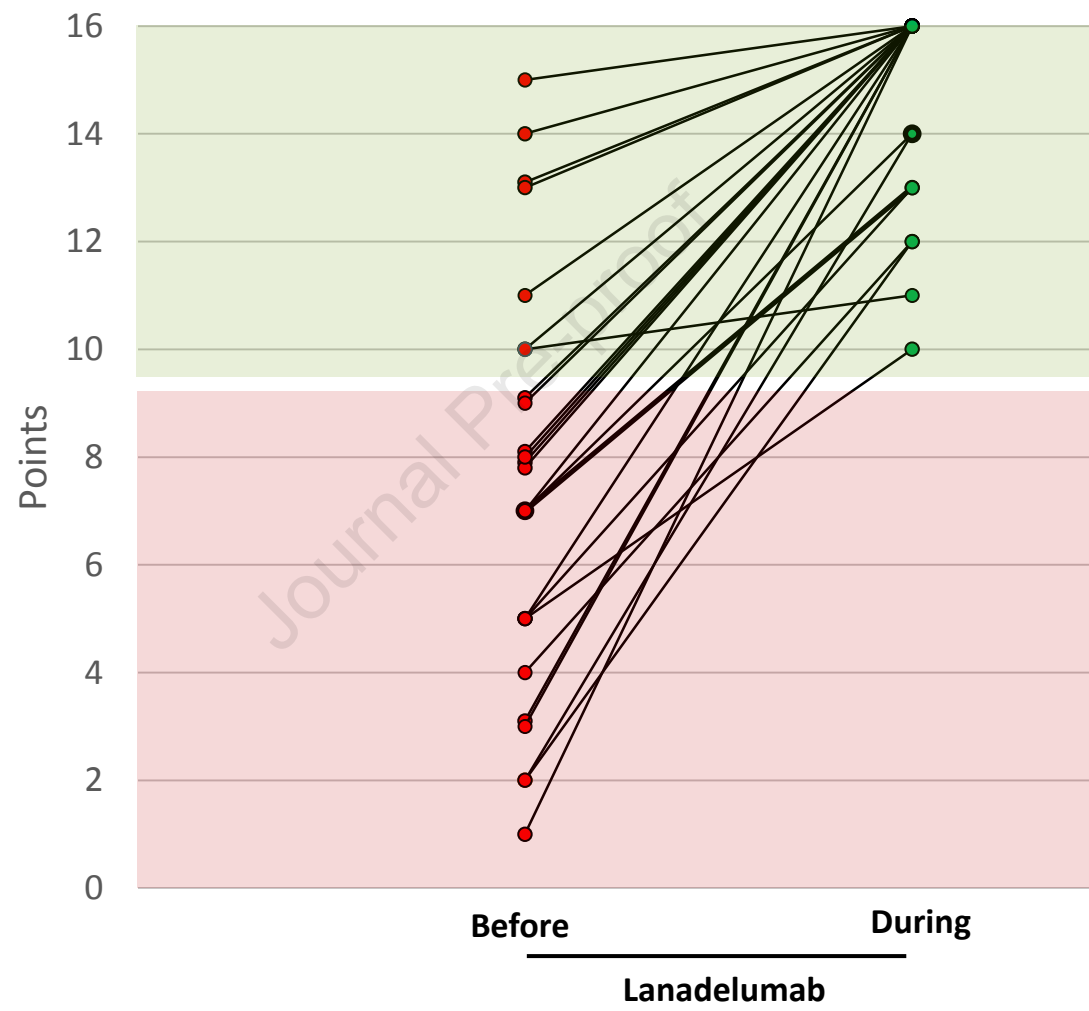
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Injection intervals of lanadelumab



Number of attacks since switch to lanadelumab



AE-QoL before and during treatment with lanadelumbab

