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Relief of neuropathic pain through epidermal growth factor receptor inhibition: a randomized proof-of-concept trial

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Conflict of interest and Funding

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Merck KGaA funded trial medication, placebo and a study grant. They also funded two external pain experts to review the protocol prior to study start. Merck KGaA was not involved in the collection, analysis or interpretation of data or in the writing of the report.
Abstract

Objective: Case reports and a case series have described relief of neuropathic pain (NP) after treatment with epidermal growth factor receptor inhibitors (EGFR-Is). These observations are supported by preclinical findings. The aim of this trial was to explore a potential clinical signal supporting the therapeutic efficacy of EGFR-Is in NP.

Methods: In a proof-of-concept trial using a randomized, double-blind, placebo-controlled design, fourteen patients with severe, chronic, therapy-resistant NP due to compressed peripheral nerve or complex regional pain syndrome were randomized to receive a single infusion of the EGFR-I cetuximab and placebo in cross-over design, followed by a single open-label cetuximab infusion.

Results: Mean reduction in daily average pain scores 3-7 days after single blinded cetuximab infusion was 1.73 points (90% CI = 0.80 – 2.66), conferring a 1.22 point greater reduction than placebo (90% CI = -0.10 – 2.54). Exploratory analyses suggested that pain reduction might be greater in the 14 days after treatment with blinded cetuximab than after placebo. The proportion of patients who reported ≥50% reduction in average pain 3-7 days after cetuximab was 36% (14% after placebo) and comparison of overall pain reduction suggests a trend in favor of cetuximab. Skin rash (grade 1-2) was the most frequent side-effect (12/14; 86%).

Conclusion: This small proof-of-concept evaluation of an EGFR-I against NP did not provide statistical evidence of efficacy. However, substantial reductions in pain were reported and confidence intervals do not rule out a clinically meaningful treatment effect. Evaluation of EGFR-I against NP therefore warrants further investigation.

Trial registry number: ClinicalTrials.gov: NCT02490436
Keywords: neuropathic pain, compressed nerve, failed back surgery syndrome, complex regional pain syndrome, epidermal growth factor receptor, cetuximab.

Introduction

Neuropathic pain (NP) results from damage to the somatosensory nervous system.\textsuperscript{1,2} It reflects a range of different and often poorly understood underlying pathophysiologies.\textsuperscript{3,4} Clinical features may be variable, but are often characterized by spontaneous continuous and/or lancinating pain, aberrant sensations and amplified pain responses.\textsuperscript{5} Chronic NP is associated with worse health outcomes than non-NP and is considered more difficult to treat with available medications, which frequently have unacceptable side effects.\textsuperscript{6-10} The prevalence of moderate to severe chronic NP is estimated to be 5%\textsuperscript{11} and rising,\textsuperscript{12} representing a critical unmet medical need.

NP due to compressed nerves (CN) and CRPS are particularly difficult to treat.\textsuperscript{13,14} CN can occur at numerous sites within the body as nerves can be compressed directly or indirectly by any number of pathological tissues or trauma. Post-operative scar tissue formation, as seen in failed back surgery syndrome (FBSS), is a frequent cause of CN. It is critical to differentiate irradiating NP from simultaneous local nociceptive back pain when studying the affected patients.\textsuperscript{15} CRPS has established diagnostic criteria (Budapest criteria).\textsuperscript{16} Those described criteria are used in this study. It is characterized by pain that is disproportionate to an inciting event. The pain has neuropathic features, including allodynia, hyperalgesia and spontaneous bursts of pain. In addition, vasomotor (color and temperature) and sudomotor (sweating, edema) skin changes, and eventually decreased motor function and trophic changes develop. CRPS most often starts in one limb, but may spread to other areas. The pathophysiology is not sufficiently understood, although it is thought to be caused by damage to or malfunction of the peripheral and central nervous systems.\textsuperscript{17}
The epidermal growth factor receptor (EGFR), a member of the HER (Human Epidermal Growth Factor Receptor) family, has been targeted by inhibitors (EGFR-Is) in the treatment of various cancers for over ten years. Following a serendipitous finding, there are now at least 18 published cases of clinical observations in which four different EGFR-Is appeared to result in markedly improved NP. Chronic pain has recently been associated with mutations in the EGFR and reduction of nocifensive behavior has been demonstrated in rodent models of NP after treatment with EGFR-Is. These findings point to the EGFR as a plausible target for the treatment of NP, warranting further investigation.

Widespread use in oncology of oral and intravenous EGFR-Is, including the monoclonal antibody cetuximab, has led to an understanding of the pharmacokinetics and toxicities of EGFR-Is. Skin reactions are the most common side-effects, with 8% and 22% moderate to severe skin toxicity reported in two-year trials of adjuvant EGFR-Is. This may be reduced by rigorous prophylactic and supportive treatments.

Proof-of-concept (POC) trials using a randomized, cross over design are recommended by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) to identify targets for pain disorders and explore phenomena such as magnitude, frequency and kinetics of analgesic effects. We have taken such an approach here to further explore the activity, including kinetics, of cetuximab in the treatment of NP.

In our published case series of clinical observations, patients with CN and CRPS reported pain relief within days after EGFR-I administration, before the appearance of skin-related side-effects. In order to increase the validity of blinding, these two specific NP entities presumed to respond rapidly, were the ones chosen for this trial.
The objective of this POC trial was to explore a placebo-controlled preliminary clinical signal of efficacy and the kinetics of treatment of NP with the EGFR-I cetuximab on an individual and group level.

Methods

Trial design

The study was carried out as an investigator-initiated POC trial using a randomized, placebo-controlled, single-dose, double-blind, cross-over design (Figure 1). Single-dose design was chosen in order to limit study duration, and cross-over of patients to reduce between-subject variability, thereby reducing the sample size requirement.

![Figure 1: Schematic of the trial design. BL = baseline (5 days; days -7 to -3 prior to each study infusion); PEW = predefined evaluation window (5 days; days 4 to 8 after each study infusion).](image)

Setting and Patients
The trial was conducted at the regional hospital in Kristiansand, Norway. Key eligibility criteria were age ≥ 18 years and definite NP (due to either CN or CRPS), confirmed by Special Interest Group on Neuropathic Pain guidelines in patients with CN and by “Budapest clinical diagnostic criteria” in patients with CRPS. NP had to be chronic, likely irreversible, and treatment-refractory, with a duration between six and 30 months. An independent neurologist made the diagnosis of NP. A pain specialist determined whether the pain was refractory to standard treatments. There could be no new or increased dose of analgesic during the four weeks prior to trial inclusion. Patients had to have PainDETECT questionnaire final score ≥ 13/38 with average pain intensity ≥ 6 (0-10 numeric rating scale [NRS]) over the last four weeks and a PainDETECT questionnaire pattern indicating that the NP was constantly present. Full eligibility criteria are available at ClinicalTrials.gov (NCT02490436).

**Interventions**

Catalent Pharma Solutions, UK provided cetuximab and placebo, which were equivalent in terms of fluidic properties and appearance. Cetuximab was administered at a dose of 400 mg/m². Standard supportive medications (corticosteroids, dextchlorpheniramine, paracetamol and tetracycline) were given to all patients in order to prevent allergic reactions and acneiform rash. Patients were permitted to continue with both their regular and rescue pain medications for the duration of the trial.

**Outcomes and assessments**

The objective of this POC trial was to investigate whether a clinically relevant signal supporting the efficacy of EGFR-inhibition in NP could be observed in individual patients and at a group level. In order to determine an appropriate sample size, a primary outcome that
EGF receptor inhibition for neuropathic pain

would have been applicable in a comparable hypothesis-testing trial was chosen. This primary outcome was defined as the difference in mean average daily NP, measured on a 0-10 patient-reported NRS for five days after treatment with cetuximab versus placebo, compared to the corresponding baseline.

The trial consisted of 3 periods (Figure 1):

- **Period 1:** Patient-reported pain assessments on days -7 to -3 leading up to the first blinded infusion established baseline pain levels. Patients received either one intravenous dose of cetuximab or matching placebo on day 1 of each period. Treatment was followed by a fourteen day period in which the primary outcome was assessed on days 4-8; the predefined evaluation window. This was followed by a fourteen day wash-out period and establishment of the second baseline (days -7 to -3 prior to period 2).
- **Period 2:** All patients crossed over to the alternate treatment, after which outcomes were assessed and a third baseline was established in a manner corresponding to period 1.
- **Period 3:** Twenty-eight days after the second blinded infusion, patients received one dose of open-label cetuximab. The trial ended after a further 30 days. Period 3 was intended to provide additional exploratory data and guide follow-up after the study.

Secondary and exploratory objectives included:

- Rates of 30% and 50% reductions in average and worst pain during the 5-day predefined evaluation window after each infusion.
- Exploration of area under the curve (AUC) analysis of average daily pain scores during the 14 days following each infusion.
- Daily worst and average pain daily throughout the trial.
• Assessment of patient-reported overall health satisfaction seven days after each infusion using a 1-7 NRS of a patient global impression of change where responses 3-7 defined improved health satisfaction.

• Daily use of pain medication.

• Assessment of pain and pain interference scores at baseline and during the 5-day predefined evaluation window after each infusion using the Brief Pain Inventory-Short Form.

• Exploration of effect differences between CN and CRPS.

• Safety according to Common Terminology Criteria for Adverse Events v. 4.0.

**Randomization and blinding**

Frontier Science Scotland (FSS), a non-profit academic foundation, managed randomization and blinding. A unique identification number was assigned to each patient and emailed to the trial nurse. Patients were randomly assigned (permutated block system), in a non-stratified, 1:1 ratio, to receive either cetuximab or placebo first. The randomization system emailed the treatment lot number to the pharmacist. Patients, investigators, nurses and pharmacists were blinded to treatments one and two.

**Statistics**

As the objective of a POC trial is to demonstrate the potential of a novel concept, sample sizes for POC trials may be pragmatic. For this trial, sample size was calculated based on identifying a difference of 2.5 points in pain reduction between cetuximab and placebo, 2 points being a conservative estimate of clinically meaningful change. The cut-off for significance level was set at 10% to avoid a falsely negative outcome at this early stage of
EGF receptor inhibition for neuropathic pain

development. Assuming 1.25 standard deviations, 90% power and 10% significance for a two-tailed test, the resultant sample size requirement was 14 patients.\textsuperscript{28,36}

Patients who were not fully evaluable for the primary outcome were replaced, as specified per protocol, in order to reach 14 evaluable patients. This modified intention to treat (m-ITT) population includes patients who have received both blinded study medications and for whom pain scores are available until at least 8 days following administration. Analyses were performed on the m-ITT population, using SAS version 9.3 and R version 3.2.2.

For the primary outcome, the effect of cetuximab compared to placebo was analyzed using a multivariable analysis of covariance model, with patients included as fixed effects and baseline scores for both periods as covariates, modelling the five day mean differences in pain from baseline as a function of treatment, period, patient, and baseline scores. It was assumed that the planned washout period would be sufficient so there was no testing for carryover effect. It was also assumed that there would be no missing data for the primary end-point and that the baseline measurement contained useful information not otherwise accounted for. Based on these assumptions patients were not included as random effects. P-values were included in the analysis; these should be interpreted with caution and are not included for formal hypothesis-testing for efficacy.

Percentage reductions in pain across treatments were compared using a Wilcoxon rank sum test, accounting for period.\textsuperscript{37} Sensitivity of the signal was assessed using a post-hoc AUC analysis of average pain scores in the 14 days following treatment, fitting a multivariable model with AUC as a function of treatment, period, and patient. For the AUC analysis there were some missing pain scores, all beyond the five-day predefined primary endpoint.
evaluation window. These missing values were assumed to be missing at random and the values imputed using multiple imputation (R package MICE).

**Trial and data management**

The trial was managed by three oncologists (CK, MC, SM). FSS contributed to protocol development, maintained the database, managed the Independent Data Monitoring Committee (IDMC) and performed periodic on-site monitoring and statistical analyses. The IDMC assessed validity and integrity of safety data. Merck KGaA funded trial medication, placebo and a study grant. The trial was registered at ClinicalTrials.gov (NCT02490436) and approved by the Norwegian Regional Committees for Medical and Health Research Ethics (REK # 2015/618) and the Norwegian Medicines Agency (EudraCTnr 2015-001195-21).

**Results**

Fifteen patients (eight with CN, seven with CRPS) were randomized between 12/2015 and 08/2016. One patient (CN-06) was removed from the trial due to an allergic reaction to cetuximab in treatment period one. The infusion was stopped after <3% of the scheduled dose. This patient was replaced and apart from Figure 2 and safety reporting, is not included in further results.
Figure 2: Participant flow diagram. #One patient (CN - 09) chose not to receive the open-label cetuximab due to lack of pain relief after both blinded treatments.

Baseline data are shown for the m-ITT population (Table 1).
Objective and primary outcome

Figure 3 shows individual pain scores for all 14 evaluable patients.

Figure 3. Individual pain scores. Baseline pain levels were established on days -7 to -3 prior to infusions of cetuximab and placebo. Infusions were administered on day 1 of each period. Primary outcome assessment took place on days 4-8 (highlighted by red rectangles in patients 01 and 02). Arrows (↓) indicate onset of skin changes. Patient CN - 09 chose not to receive the open-label cetuximab due to lack of pain relief after both blinded treatments. Patient
CRPS - 15 experienced dramatic pain recurrence during the placebo phase. As a result of this, for ethical reasons, open label cetuximab treatment was moved forward by 19 days. Patients CN - 04 and CRPS - 14 started taking oral EGFR-I (erlotinib) on days 21 and 16, respectively, after open label cetuximab.

Together, the 14 patients reported an adjusted mean reduction in daily average pain scores of 1.73 points (90% CI 0.80 – 2.66) during the 5-day predefined evaluation window after the blinded cetuximab infusion. This confers a 1.22 point (90% CI -0.10 – 2.54; p = 0.126) larger reduction than the 0.51 point (90% CI -0.41 – 1.44) reduction reported after the placebo infusion (Figure 4). This difference does not provide conclusive statistical evidence for the efficacy of the active treatment.

Due to protracted placebo-responses in period 1, two patients (CN - 03 and CRPS - 07) had baseline pain scores <4 prior to testing of cetuximab in period 2 (Figure 3).

**Figure 4**: Point estimates and 90% confidence intervals for pain reduction after cetuximab and placebo (n=14). * = Primary outcome measure. Both cetuximab and placebo are subtracted from their respective baseline scores, and adjusted for baseline and period. The AUC is not adjusted for baseline.
Secondary outcomes

Comparison of baseline scores with the mean daily average pain measured exclusively during the early 5-day predefined evaluation window yielded ≥ 50% pain reduction in 5/14 (36%) patients after blinded cetuximab and in 2/14 (14%) patients after placebo (Figure 5a).

Comparing overall percentage pain reduction for blinded cetuximab versus placebo suggests a trend in favor of cetuximab (Figure 5a; p=0.107).

The sensitivity of the signal was also assessed with an AUC analysis of average pain scores, suggesting greater pain reduction in the 14 days after treatment with blinded cetuximab than after treatment with placebo (Figure 4; p = 0.076).

Average pain scores for the three periods (Figure 5b) suggest a shorter duration of NP reduction after placebo compared to cetuximab. Separate displays for patients with CN and CRPS (Figure 5c and 5d) indicate that maximum response to blinded treatment appeared earlier for patients with CN (day 3) than for those with CRPS (day 14).
Figure 5: Average pain responses. One patient (CN - 09) chose not to receive open-label cetuximab due to lack of pain relief after both blinded treatments. One patient (CRPS - 15) had their open-label cetuximab infusion brought forward due to recurrence of extreme pain. Data sets from these two patients are therefore missing from the open-label cetuximab results (n=12). 5a: Percentage of patients reporting reduction in mean daily average pain scores during the 5-day predefined evaluation window after each treatment, by percent. 5b: Daily average pain scores before and after treatment with blinded and open-label cetuximab and placebo. 5c: Daily average pain scores before and after treatment with blinded and open-label cetuximab and placebo for seven (six in period 3) patients with compressed nerve (CN). 5d: Daily average pain scores before and after treatment with blinded and open-label cetuximab and placebo for seven patients with complex regional pain syndrome (CRPS).

Nine out of 14 (64%) patients reported improvement in overall health satisfaction after a single dose of blinded cetuximab, compared to 4/14 (29%) after placebo.
Use of pain medication remained stable during this short cross-over trial, with the exception of one patient (CRPS-15) who, after a marked analgesic response to blinded cetuximab (with subsequent reduction in opioid use), experienced severe pain recurrence during wash-out and placebo periods and therefore resumed pre-cetuximab high doses of opiates. This patient’s open-label cetuximab was brought forward (Figure 3). Of nine patients that used opioids at baseline (Table 1), one patient (CRPS-14) discontinued use.

Results of other predefined secondary outcomes including pain interference and functional scores consistently showed similar, possible beneficial trends after treatment with cetuximab (electronic supplement; eFigure 1).

**Safety**

The IDMC found the trial satisfactory with regard to conduct and safety. One patient was replaced due to an allergic reaction to cetuximab (Figure 2). Two grade 3 serious AEs (pain recurrence during wash-out and subsequent opioid overdose), neither of which was associated with cetuximab, occurred in one patient. Mild to moderate skin rash was the most frequent AE reported after blinded cetuximab. All AEs are listed in Table 2 and onset of skin changes after blinded cetuximab is indicated in Figure 3.
EGF receptor inhibition for neuropathic pain

Table 2: Adverse events (AE) (according to CTCAE v.4.0) among the 15 included patients in the 28 days after each infusion. TRAE = treatment-related adverse events. *Cetuximab infusion (in period 1) was stopped due to an allergic reaction after <3% of the scheduled cetuximab dose had been delivered. The patient is reported separately in the table because he did not receive enough cetuximab to develop further adverse events. #One patient (CN; 009) chose not to receive the open-label cetuximab due to lack of pain relief after both blinded treatments. She did not report AEs in period 3.

Discussion

This small POC trial is the first randomized, placebo-controlled clinical trial of an EGFR-I for NP. Its aim was to uncover a clinical signal of potential treatment effect and to inform on aspects such as kinetics, magnitude and duration of responses for future trial design.

The primary outcome, based on differences in average pain reduction during an early 5-day predefined evaluation window, comparing cetuximab and placebo, did not provide statistical evidence of efficacy. However, the 90% CI for the primary endpoint (Figure 4) and includes the possibility of a meaningful treatment effect.38

Based on this, the individual placebo-controlled responses, the secondary outcomes such as patient-satisfaction and the exploratory AUC calculations, we propose that there is an underlying clinical signal for the efficacy of cetuximab for treatment of NP. Although this
small trial did not provide statistical evidence for the efficacy of the primary outcome, it is important not to rule out atherapeutic potential at this early stage. CRPS and neuropathic back pain due to FBSS (present in five of the seven patients with CN) are NP entities that are particularly difficult to treat and for which novel therapeutic options with different pathophysiological approaches should therefore be actively pursued.\textsuperscript{13,14}

All trial participants had chronic, stable, severe and therapy-resistant NP. In light of this, achieving the maximum pain relief possible only 3-7 days after a single infusion of cetuximab was unrealistic. However, the early primary outcome evaluation window was necessary at this early stage of investigation, in order to reduce unblinding due to the earliest mild skin changes during the blinded cetuximab period (indicated by the black arrows in Figure 3). Capture of the clinical significance of NP relief could have been improved by evaluation over a longer period, as indicated by the exploratory 14-day AUC analysis. This analysis discounts the rigid timing of the trial’s primary outcome measurement (the predefined evaluation window), which in itself is not crucial for establishing a clinical signal of efficacy (Figure 3).

Lowest pain scores following cetuximab infusion were reported by individuals both before and after the predefined evaluation window (Figure 3). In fact, only one of the eight patients who reported improved total health satisfaction and chose to continue with oral EGFR-I after the trial reported maximal pain reduction within that window.

The proportion of patients who experienced at least 50% reduction in average pain during the early 5-day predefined evaluation window after only one blinded (36%) or second open-label (58%) infusion of cetuximab is promising when compared to results for placebo (14%).\textsuperscript{35}
Pain reduction was consistently greatest after the second (open label) infusion of cetuximab. While additive placebo-type responses to the active treatment may certainly have contributed to the greater reduction, it is also important to keep in mind that chronic pain may require longer treatment duration to reach maximum relief. One may speculate that repetitive dosing of cetuximab can lead to greater pain reduction, as observed in our previous case series\textsuperscript{22} and as demonstrated by the 2–4 fold larger NP reduction reported after 12 versus one week of treatment with pregabalin and gabapentin.\textsuperscript{39}

Uncovering the mechanism of EGFR-I induced NP relief appears important. The EGFR is expressed on peripheral nerves\textsuperscript{40} and it has been shown that members of the HER family of receptors, including the EGFR, are upregulated in the nervous system following nerve injury.\textsuperscript{41,42} Also, potential downstream pathways of the EGFR have been proposed as targets for treatment of NP.\textsuperscript{43} Furthermore, recent research in rodent NP models has demonstrated dose-dependence of EGFR-I induced NP relief.\textsuperscript{24}

The mild to moderate degree of cetuximab-related side-effects seen in this trial are consistent with those described in cancer patients.\textsuperscript{18,19} Importantly, EGFR-Is do not have the central nervous system side effects or addictive potential that complicate the drugs currently used to treat NP. This is particularly relevant in light of the ongoing opioid crisis in the US and Europe, increasing the demand for non-opioid pain management options.\textsuperscript{44}

EGFR-I related skin reactions tend to develop gradually, starting with dry skin, then eczema, and eventually acneiform rash. These changes typically peak at around six to eight weeks of treatment\textsuperscript{27} after which time the severity generally improves. In an adjuvant chemotherapy trial of 2686 presumably cancer-free patients, half received cetuximab. During the six months
of treatment, an excess of 10% of patients in the cetuximab arm discontinued treatment, indicating tolerability among the vast majority of patients in that population. Since then, vigilant clinical follow-up including routine use of prophylactic antibiotics, topical steroids and moisturizers has improved the management of EGFR-I related skin reactions. The short-term acceptability of EGFR-Is in the setting of severe NP is indicated by the trial patients’ positive responses to the health satisfaction assessment and by the fact that eight of 14 chose to take oral EGFR-Is upon study completion. Feasibility of using EGFR-Is in the setting of chronic NP presupposes studies with longer follow-up and prophylactic and supportive management of side-effects.

This trial has notable shortcomings and several lessons can be learned from it. It is clear that the small sample size precludes generalizability of findings, although it could be argued that including patients with different underlying pathophysiologies strengthens the potential signal of EGFR-I induced pain relief across NP conditions.

A cross-over study design has the advantage of reduced sample size requirement since each participant acts as their own control. However, this approach may have exacerbated challenges posed by pain recurrence, or lack thereof, during wash-out and placebo periods. The fixed timing of each period in this trial made drug testing invalid for two patients who exhibited insufficient recovery of pain scores prior to blinded cetuximab, following blinded placebo. Allowing trial schedule flexibility in order to re-establish pain scores could have prevented this problem. Additionally, cross-over design may have contributed to unblinding of the second infusion due to side-effects or lack thereof, during the first treatment period.

**Conclusion**
The objective of this trial was to investigate whether a clinically relevant signal supporting the efficacy of EGFR-inhibition in NP could be observed in individual patients and at a group level. At a group level this small POC trial failed to demonstrate superiority of cetuximab over placebo although the confidence intervals indicate that the data do not rule out a clinically meaningful treatment effect. Individual patient responses provide preliminary clinical signals indicating that the EGFR-I cetuximab may in fact be a treatment option for some patients with NP. The high response rate among treatment-resistant patients and the magnitude of pain relief seen in those patients who benefited are encouraging. Repetitive dosing and longer follow-up of larger, homogeneous samples of patients with sufficiently high pain scores at the time of testing of analgesic effect are now warranted in order to determine the benefit to side-effect ratio of this treatment.

Authors’ contributions

Study design/planning: C.K., M.C., A.B., V.P., F.D, S.M.

Study conduct: C.K., M.C., V.P., S.M.

Data analysis: C.K., M.C., A.B., M.F., B.L., R.M., S. FW., F.D., S.M

Writing paper: all authors.

Revising paper: all authors.

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EGF receptor inhibition for neuropathic pain
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EGF receptor inhibition for neuropathic pain


