Successful Intravenous Regional Block with Low-Dose Tumor Necrosis Factor-α Antibody Infliximab for Treatment of Complex Regional Pain Syndrome 1

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Cytokines, particularly tumor necrosis factor-α, may play an important role in the mediation of mechanical hyperalgesia and autonomic signs in complex regional pain syndrome 1. We performed an IV regional block with low-dose administration of the tumor necrosis factor-α antibody, infliximab, in a patient with typical clinical signs of complex regional pain syndrome 1 (moderate pain, edema, hyperhidrosis, elevated skin temperature compared with the contralateral side). A significant improvement of clinical variables was observed 24 h after infliximab treatment. Almost complete remission was reached within 8 wk, but sensory signs improved only after 6 mo. No adverse events were observed.
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Chronic complex regional pain syndrome (CRPS) is characterized by spontaneous pain that is often accompanied by somatosensory disturbances such as mechanical allodynia, and thermal or mechanical hyperalgesia. These alterations of evoked pain sensitivity are not restricted to a single peripheral nerve innervation territory, and are often disproportionate to the precipitating injury. Other clinical signs include edema, disturbed blood flow of the skin, and abnormal sudomotor activity in the affected limb. CRPS is a clinical diagnosis and can be excluded by the existence of other conditions or diseases (1–4).

Cytokines, particularly tumor necrosis factor (TNF)-α, seem to play an important role in the mediation of mechanical hyperalgesia in CRPS and other neuropathic pain syndromes (5). Huygen et al. (6) showed evidence of an inflammatory process in CRPS 1 by detecting increased levels of cytokines, such as interleukin 6 (IL-6) and TNF-α, in blister fluids of the involved limb of patients with CRPS 1, which may suggest a local inflammatory process. According to these findings, we concluded that IV regional block (IVRB) with low-dose administration of infliximab could be an appropriate and sufficient therapy for treating CRPS patients who do not respond to other symptomatic therapies, e.g., administration of systemic steroids or sympathetic blocks. Additionally, the local low-dose treatment with TNF-α antibodies could reduce treatment costs and minimize the risk of potential serious adverse events (mostly ordinary infections of the respiratory and urinary system, reactivation of tuberculosis and, uncommonly, heart failure or drug-induced lupus).

CASE REPORT

We present the case of a 62-yr-old woman who had suffered for 3 mo from CRPS 1 affecting the left hand. She developed a CRPS 1 after a left Colles' fracture. On removal of the cast, her left hand showed clinical signs of CRPS 1, including moderate pain at rest, edema, hyperhidrosis, and increased skin temperature compared with the right side. Range of motion of the wrist, the metacarpophalangeal joints and proximal interphalangeal joints was restricted, and fist closure was incomplete (Table 1, Fig. 2). Conventional treatment included intensive physical therapy twice a week, ibuprofen (1200 mg/d for 4 wk) and steroids (starting with 50 mg prednisolone and tapering over 4 wk). Two stellate ganglion blocks were performed. Her clinical variables, such as skin temperature changes, pain relief, and the occurrence of a Horner syndrome, were monitored. Skin temperature of the treated hand increased during this intervention to 35.0°C, indicating complete autonomic blockade (7). Horner syndrome occurred during both interventions. However, the blocks did not affect continuing pain intensity during the observation period. Therefore, we assumed her pain was independent from the sympathetic nervous system. After signing an informed consent, our patient was treated with 25 mg infliximab (Remicade®) dissolved in 40 mL sodium chloride 0.9% via IVRB, which is about one-tenth of the common systemic dose of TNF-α inhibition therapy for rheumatic diseases (3 mg/kg body weight, patient body weight 83 kg). Before this, tuberculosis screening and chest radiograph, as strictly required, were performed and remained without pathological findings. The procedure

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Table 1. Clinical Outcome Measures

Measures	Baseline	1 d after baseline	2 wk after baseline	4 wk after baseline	8 wk after baseline	24 wk after baseline
Continuing pain VAS (0–100)						
Affected hand	50	20	0	0	0	0
Contralateral hand	0	0	0	0	0	0
Temperature						
Affected hand	30.9	29.7	29.0	28.5	28.7	28.9
Contralateral hand	28.1	28.5	28.6	28.9	29.1	28.7
Hand grip strength						
Affected hand	0	0	0	0.2	0.3	0.5
Contralateral hand	0.7	0.8	0.8	0.8	0.8	0.8
ROM wrist						
Affected hand	30/0/20	40/0/25	45/0/30	45/0/30	50/0/40	60/0/50
Contralateral hand	70/0/60					

VAS = visual analog scale (in mm), 0 = no pain, 100 = intolerable pain. Temperature measured in degrees Celsius by laser temperature device; hand grip strength is measured by hand grip dynamometer (in kp/cm^2), ROM = range of motion, measured in degrees of flexion and extension.

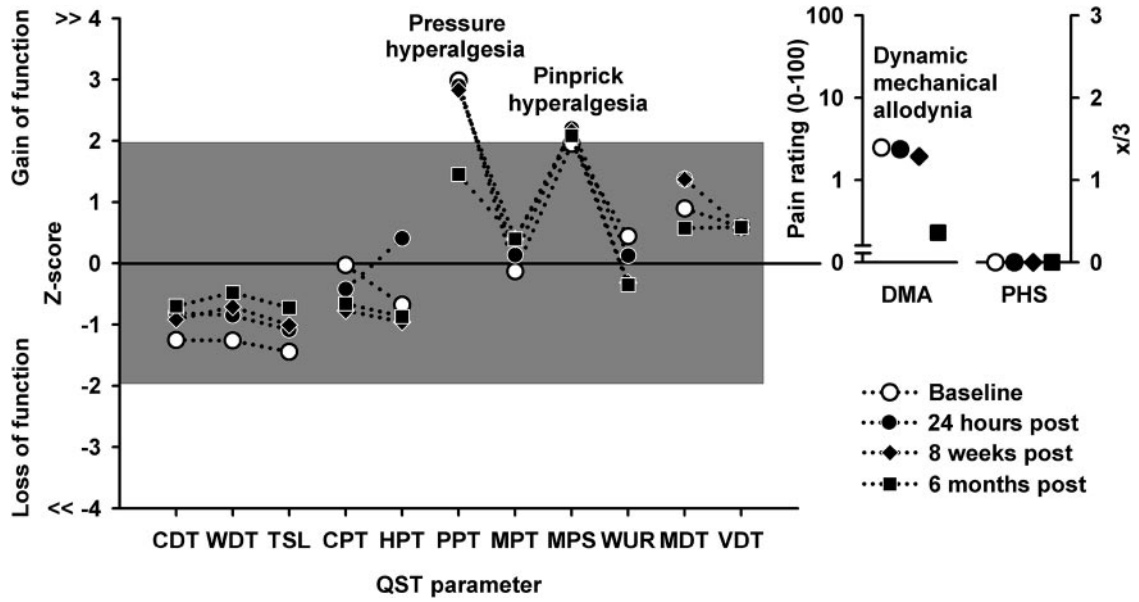

Figure 1. Quantitative sensory testing (QST) sensory profile in complex regional pain syndrome (CRPS) before and after treatment (*Z*-scores and raw data) The QST profile of the affected hand dorsum showed pressure hyperalgesia (PPT; pressure pain threshold). Additionally pinprick hyperalgesia (MPS; mechanical pain sensitivity) and dynamic mechanical allodynia (DMA) were observed. Six months after treatment pressure sensitivity as well as touch-evoked pain (DMA) were decreased, whereas the amount of pinprick hyperalgesia remained almost unchanged. Other QST parameters neither differed from reference data [Rolke et al., (8)] nor during the 6 mo follow up. CDT = cold detection threshold; WDT = warm detection threshold; TSL = thermal sensory limit; CPT = cold pain threshold; HPT = heat pain threshold; MPT = mechanical pain threshold; WUR = wind-up ratio; MDT = mechanical detection threshold; VDT = vibration detection threshold; PHS = paradoxical heat sensations.

was performed twice: first at baseline and a second time after 1 wk. Her clinical signs were monitored at baseline, 24 h after the first treatment, 2, 4, 8 wk and 6 mo after baseline. Normal serum levels of TNF-α, IL-6, and IL-8 and high-sensitive-C-reactive-protein (hs-CRP) were found before treatment both over the affected side (ipsilateral) and over the unaffected side (contralateral). Hs-CRP is an acute phase protein, which indicates systemic inflammation at an early stage.

Additionally, quantitative sensory testing (QST) was used to characterize the complete somatosensory phenotype. QST provides parameters for the detection of sensory loss (small and large fiber functions) as well as sensory gain (hyperalgesia, allodynia, hyperpathia). We used the QST protocol of the German Research Network on Neuropathic Pain that consists of seven tests measuring 13 parameters (8). The tests are grouped as follows: thermal detection thresholds for the perception of cold, warm, and paradoxical heat sensations; thermal pain thresholds for cold and hot stimuli; mechanical detection thresholds for touch and vibration; mechanical pain sensitivity including thresholds for pinprick and blunt pressure; a stimulus-response function for pinprick sensitivity and dynamic mechanical allodynia (DMA); and pain summation to repetitive pinprick stimuli. To compare our patient's QST sensory profile with control data, independent of the different units of measurement across QST parameters, the patient data were Z-transformed for each single parameter by using the following expression: *Z*-score = (X single patient − mean controls)/SD controls. This procedure results in a QST profile (Fig. 1) where all parameters are presented as standard normal distributions (zero mean, unit variance). For clarity of data presentation, we adjusted the algebraic sign of

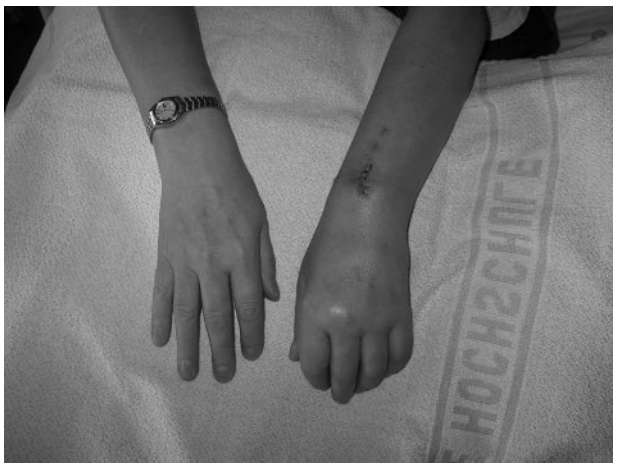

Figure 2. Affected left hand before treatment.

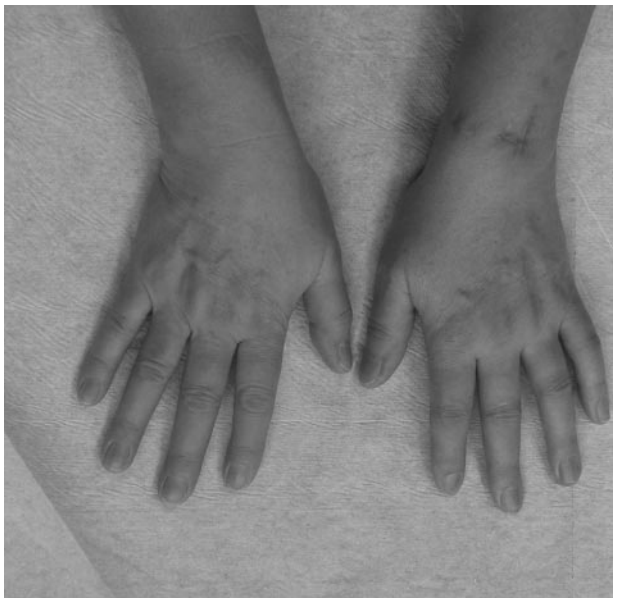

Figure 3. Affected left hand 6 mo after baseline.

Z-score values for each parameter, so that it reflected the patient's sensitivity for this parameter. *Z*-values above "0" indicate a gain of function when the patient is more sensitive to the tested stimuli compared with controls, whereas *Z*-scores below "0" indicate a loss of function referring to a lower sensitivity of the patient.

A substantial improvement of pain intensity, temperature difference, and range of motion of the wrist was already found in the first evaluation after 24 h and was almost complete after 8 wk and 6 mo (Table 1, Fig. 3). As depicted in Figure 1, baseline QST parameters showed signs of peripheral nociceptive sensitization (pressure hyperalgesia: pressure pain threshold), and central nociceptive sensitization (dynamic mechanical allodynia: DMA; pinprick hyperalgesia: MPS). During follow-up, the QST profile remained almost unchanged for the first 8 wk. Six months after treatment, the amount of peripheral sensitization (pressure hyperalgesia) as well as central sensitization (DMA) was reduced for these parameters. Interestingly, pinprick sensitivity remained unchanged, indicating that even after that long-term observation period, centrally mediated alterations of the nociceptive system were present (Fig. 1). No adverse events were observed.

DISCUSSION

It is a common belief that a multimodal treatment of CRPS should start as soon as possible (9). There are, however, a few controlled clinical studies supporting this view. Patients should usually receive physical therapy. Pain threshold is a good indicator for individual limits of exercise and should not be exceeded (3). Unequivocal positive randomized controlled trials for drug treatment are available for steroids (10) and bisphosphonates (11). There is further evidence for treatment with 50% dimethyl sulfoxide (12) and IVRB with lidocaine and bretylium or ketanserin (13). In a review of controlled clinical trials for peripheral neuropathic pain and CRPS, Kingery found no advantages of IVRB with guanethidine compared with placebo (14), albeit not >10 mg guanethidine was administered. Because of frequent treatment failures with all of these therapies, there is a further need for an efficient CRPS therapy.

Maihoefner et al. (5) found that soluble TNF-α receptor type I is significantly increased in CRPS 1 patients, in particular if there is mechanical hyperalgesia as in the present case. Because of the evidence that TNF-α is important in the pathophysiology of CRPS, Huygen et al. treated two patients with CRPS 1 using infliximab (3 mg/kg body weight) given systemically IV twice during a 4-wk observation period (15). Clinical and biochemical variables were measured just at the beginning and only once at the end of treatment. There was no long-term evaluation or treatment control beyond 4 wk. QST data were not provided. Concentrations of local TNF-α and IL-6 in suction blister fluid decreased significantly at the end of treatment, in particular in the ipsilateral affected extremity, but also marginally in the contralateral unaffected extremity. The patients showed a noticeable improvement of pain, temperature difference, and motor function, in particular one patient with a shorter period of CRPS 1. The motor function of the wrist and the range of motion of metacarpophalangeal joints improved about 50% and pain intensity (Visual Analog Scale) decreased about 25% after 4 wk.

Compared with those from Huygen et al., we collected data at different time-points (24 h, 2 and 8 wk, 6 mo after the end of treatment). Continuing pain intensity and skin temperature were already normalized after 2 wk. Range of motion and hand grip strength almost recovered after 24 wk. In addition, we used QST to characterize the complete somatosensory profile over the affected hand dorsum (Fig. 1) in the course of 6 mo. QST showed a pressure hyperalgesia, indicating the presence of peripheral sensitization of the nociceptive system. This finding is consistent with an inflammatory process interacting with peripheral nervous structures. Such a peripheral sensitization could be the origin of continuing nerval input to central nociceptive structures, resulting in a secondary central nociceptive sensitization. Corresponding to

this hypothesis, we observed pinprick hyperalgesia and DMA. These sensory signs reflect the presence of a central sensitization (16). Most interestingly, the initial rapid reduction of pain intensity and decreased motor function did not correspond to a fast reduction of pressure hyperalgesia or DMA. Normalization of the somatosensory system for these sensory plus signs was achieved much later during the 6 mo follow-up. Surprisingly, this normalization was incomplete, since pinprick hyperalgesia was still present after 6 mo, indicating continued central sensitization of other nociceptive pathways. There are similar observations in patients with restless legs syndrome, characterized by pinprick hyperalgesia. In these patients, motor signs immediately improved after L-Dopa treatment, whereas improvement of the sensory phenotype was delayed by 12 mo (17). Our cubital-venous blood analysis was in accordance with the findings of Schinkel et al. (18). IL-6, IL-8, TNF-α, and hs-CRP levels were not elevated compared with normal ranges, neither in the affected nor in the unaffected contralateral limb, pointing to the presence of a more localized inflammatory process. Thus, a local therapy (IVRB) might be appropriate. Compared with systemic IV administration, local low-dose treatment with TNF-α-antibodies may minimize the risk of potentially serious adverse events (mostly ordinary infections of the respiratory and urinary system, reactivation of tuberculosis and uncommonly heart failure or drug induced lupus) and reduce treatment costs (19,20).

In conclusion, IVRB infliximab administration was chosen for the present patient due to the following aspects: 1) No success with standard therapies, 2) CRPS 1 seems to be a local inflammatory process in the affected extremity, 3) reduced side effects, and 4) lower costs compared with systemic IV administration. Randomized, controlled, clinical trials seem promising and are urgently needed.

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