Interleukin-2: A Potential Treatment Option for Postherpetic Neuralgia?

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Postherpetic neuralgia is a chronic pain syndrome that is often difficult to treat and can lead to a disabling disease if it is resistant to therapy. Presented here is the case of a 46-year-old patient with human immunodeficiency virus infection and chronic, treatment-resistant neuralgia. Postherpetic pain resolved after treatment with 1 cycle of subcutaneous recombinant interleukin-2.

IL-2 is a pleiotropic cytokine approved for the treatment of metastatic renal cell cancer and metastatic melanoma. It is predominantly produced by activated CD4+ T lymphocytes and acts on a variety of target cells, such as T and B lymphocytes, macrophages, monocytes, and natural killer cells. As a potent immunomodulator, IL-2 is capable of increasing circulating levels of CD4+ T lymphocytes, and its potential clinical use in treating HIV-positive patients is currently being investigated in large clinical trials [1]. Data suggest that IL-2 plays a role as a neuroregulatory molecule in the CNS [2]. Furthermore, analgesic effects and the structural relatedness of IL-2 to opioid peptides have been demonstrated [3].

Postherpetic neuralgia (PHN) is a chronic pain syndrome and one of the most common complications of herpes zoster. Risk factors are immunosuppressive diseases or treatments, cancer, and old age. Prompt use of antiviral therapy appears to reduce the overall incidence of PHN [4]. The pain can be severe and disabling, resulting in a poor quality of life through disrupted sleep, decreased functioning, and depression [4].

PHN potentially has multiple distinct underlying pain mechanisms. The pain can result from injury of the peripheral nerves, damage of dorsal root ganglia (e.g., hemorrhagic necrosis, neuronal loss, and demyelination), and altered CNS signal processing [5]. Following injury, the peripheral neurons discharge spontaneously and have lowered activation thresholds. Axonal regrowth produces nerve sprouts that are prone to unprovoked discharge and are hypersensitive to mechanical stimuli. The dorsal horn shows hyperexcitability that, in turn, leads to exaggerated responses in the CNS [6]. Autopsy of patients with PHN reveals atrophy of the dorsal horn, and this is not found in patients with herpes zoster who do not have PHN [6].

The treatment of PHN includes multiple agents with divergent mechanisms of action [7, 8]. These include tricyclic antidepressants (e.g., amitriptyline and nortriptyline), anticonvulsants (e.g., gabapentin), opioids, topical analgesics (e.g., lidocaine), topical capsaicin (cream), and ketamine (N-methyl-D-aspartate antagonists). Transcutaneous electrical nerve stimulation and paravertebral nerve blocks may also be effective. Even though an array of therapeutic options exists, PHN remains difficult to treat. Patients may suffer debilitating symptoms, including inadequate pain relief, despite undergoing different treatment options. Searching for new treatment alternatives is, therefore, important. IL-2 is an agent with immunomodulatory effects and a potential antinociceptive and, as such, may play a role as a treatment alternative.

An example of this is the case of a 46-year-old HIV-positive patient with chronic, treatment-resistant neuralgia. After an episode of herpes zoster in 2003, the patient suffered from severe neuralgic pain that did not respond to oral opioids, tricyclic antidepressants, anticonvulsants, paravertebral nerve blocks, intravenous lidocaine infusions, and intravenous ketamine infusions. Despite this intensive treatment, pain control was never achieved. After receiving 1 cycle of 7.5 miU recombinant IL-2 (Proleukin [Chiron]) subcutaneously 2 times per day for 5 consecutive days within a clinical HIV trial, postherpetic pain resolved and has not reappeared during 3 years of follow-up to date. The treatment with recombinant IL-2 potentially induced cessation of the neuralgic pain in this HIV-positive patient.

Case report. A 46-year-old white man who had received a diagnosis of HIV infection in August 1998 presented to our clinic (Charité University Hospital Berlin, Berlin, Germany) in July 2002. At that time, the patient’s CD4+ cell count was 262 cells/μL with a viral load of 121,824 copies/mL. His past medical history was unremarkable, especially for opportunistic infections, and antiretroviral therapy had thus far been deferred. In August 2002, the patient developed thoracic herpes zoster affecting dermatome Th5 and was treated with acyclovir (800 mg 5 times per day).
for 10 days. During the acute episode of herpes zoster, the patient required oral opioids for pain control (tramadol 200 mg twice per day). The rash resolved within 2–3 weeks, but the pain persisted, and the addition of gabapentin for pain control did not prevent development of PHN. The permanent pain did not respond to tricyclic antidepressants, carbamazepine, paravertebral nerve blocks, intravenous lidocaine infusions, or intravenous ketamine infusion. In March 2003, the patient was still experiencing disabling, intractable PHN.

Antiretroviral therapy with zidovudine and lamivudine (Combivir [GlaxoSmithKline]), tenofovir (Viread [Gilead]), and lopinavir-ritonavir (Kaletra [Abbott]) was initiated in September 2002, because the patient’s CD4+ cell count had decreased to 138 cells/µL and his viral load had increased to 328,208 copies/mL. By January 2003, sustained virologic response was achieved (viral load, <50 copies/mL). In March 2003, the patient entered a clinical phase III trial of subcutaneous recombinant IL-2 (Proleukin [Chiron]). The patient’s CD4+ cell count at study entry was 312 cells/µL. Treatment consisted of subcutaneous injections of 7.5 mIU of IL-2 twice daily for 5 consecutive days with ongoing antiretroviral therapy. The patient experienced moderate constitutional adverse effects of World Health Organization grade II, which were managed symptomatically.

Immediately after the first cycle of IL-2, the patient reported that PHN had resolved. There was no relapse during the treatment-free intervals, and to date, no relapse has been reported.

The patient’s CD4+ cell count increased to 596 cells/µL 4 weeks after the first cycle of IL-2. Currently, the patient has completed 5 cycles of IL-2. At present, his CD4+ cell count is 877 cells/µL, and his viral load is <50 copies/mL.

**Discussion.** In this case, the resolution of chronic, treatment-resistant PHN coincided with the application of recombinant IL-2. Striking, during 3 years of follow-up, no recurrence of pain has been observed.

Cytokines are involved in the generation of pain by direct receptor-mediated actions on afferent nerve fibers, as well as effects involving other mediators. In preclinical studies, proinflammatory cytokines have been shown to play a key role in the propagation of persistent pain states [9]. On the basis of these findings, the potency of IL-2 for the treatment of pain was investigated in different preclinical models. In a preclinical trial, intrathecally administered adenovirus-IL-2 exhibited antinociceptive effects in models both for basal nociceptive response and for chronic neuropathic pain [10]. IL-2 has been described as stimulating the hypothalamic axis, activating the hypothalamus, and inducing the release of corticotropin via nitricoxidergic neurons [11]. Recombinant IL-2 also induced antinociception in morphine-insensitive rats, which was mediated via µ-opoid receptors and the IL-2 receptor (i.e., constitutively expressed in dorsal root ganglion neurons) [12]. Thus, IL-2 may also relieve morphine-insensitive pain. Neuroleptic agents that have shown to be effective in the treatment of PHN have been described as inducing an increase of IL-2 in human whole-blood assays [13].

In conclusion, taking into consideration the documented antinociceptive effector mechanisms of IL-2, the preclinical evidence, and this clinical observation, the existing clinical data regarding IL-2 treatment (e.g., data from the large, randomized Evaluation of Subcutaneous Proleukin in a Randomized International Trial [ESPRIT] study [1]) should be analyzed for the potential role of this immunoregulatory cytokine in the control of neuropathic pain.

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