Mast Cells: A New Target in the Treatment of Complex Regional Pain Syndrome?

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Abstract: There is convincing evidence that inflammation plays a pivotal role in the pathophysiology of complex regional pain syndrome (CRPS). Besides inflammation, central sensitization is also an important phenomenon. Mast cells are known to be involved in the inflammatory process of CRPS and also play a role (at least partially) in the process of central sensitization. In the development of a more mechanism-based treatment, influencing the activity of mast cells might be important in the treatment of CRPS. We describe the rationale for using medication that counteracts the effects of mast cells in the treatment of CRPS.

Key Words: complex regional pain syndromes, mast cells, treatment, cytokines, pathophysiology

INTRODUCTION

Complex regional pain syndrome (CRPS) is a painful and disabling complication after surgery or physical trauma, but spontaneous development is also described. A careful clinical evaluation of signs and symptoms remains the cornerstone of CRPS diagnosis. The general acceptance of the IASP diagnostic criteria for diagnosing CRPS has contributed to improved clinical communication and the ability to generalize research findings.1

The estimated overall incidence rate of CRPS is 26.2 per 100,000 person years.2 Females are affected at least 3 times more often than males. The upper extremity is affected more frequently than the lower extremity, and a fracture is the most common precipitating event (44%). Severe CRPS outcome is rare, but a majority of patients still suffer from persistent impairments two or more years postonset.3

It is reasonable to assume that different mechanisms are involved in a complex network of interactions, resulting in the painful and impairing disorder of CRPS.4 There is evidence that inflammation is one of the mechanisms that play a role in the pathophysiology of CRPS. The contribution of inflammation is also underlined by the successful reports from studies on treatment with immunomodulating agents, recently reviewed.5

The use of immunomodulating medication may counteract the ongoing inflammation; early use may be an important step in preventing sensitization. Therefore, such treatment may play an important role in recovery of the disabled hand or foot. However, it is unknown whether (apart from the immunomodulating medication) other drugs might also counteract the inflammation. Based on empirical findings on the role of mast cells in the pathophysiology of inflammation in CRPS,6 we describe the rationale for the use of medication targeting mast cell activity.
PATHOPHYSIOLOGY OF CRPS

Complex regional pain syndrome often displays the classic aspects of inflammation.\(^7\) Inflammation contributing to CRPS can arise from 2 sources.\(^8\) First, classic inflammatory mechanisms can contribute through actions of immune cells (such as lymphocytes and mast cells), which, after tissue trauma, secrete proinflammatory cytokines including interleukin-1β, interleukin -2, interleukin -6, and tumor necrosis factor (TNF)-α. Secondly, neurogenic inflammation may also occur, mediated by release of proinflammatory cytokines and neuropeptides directly from nociceptive fibers in response to various triggers. Neuropeptide mediators involved in neurogenic inflammation include substance P, calcitonin gene-related peptide, and bradykinin (which is also involved in initiating cytokine release).

Over time, various studies have report the role of inflammation in the pathophysiology of CRPS. In venous blood of patients with CRPS elevated mRNA levels of proinflammatory cytokines, TNF and IL-2 have been found, as well as a reduction in mRNA levels of the anti-inflammatory cytokines IL-4 and IL-10.\(^9\) However, local rather than systemic inflammatory responses appear to be relevant in CRPS.\(^10\) No significant changes in serum parameters in CRPS were found compared with control groups, indicating the local formation of mediators. The presence of a local inflammation was already suspected based on evidence found in a scintigraphic study on CRPS, which demonstrated vascular permeability for macromolecules.\(^11\) Technetium 99 m-anti-TNF-α antibody scintigraphy revealed that TNF-α was only localized in the affected hand of patients with early CRPS.\(^12\)

Increased levels of proinflammatory cytokines have been detected in fluid from artificially raised skin blisters in the involved extremity in comparison with the contralateral site; however, no correlation was found between levels of proinflammatory cytokines and the characteristics or duration of the disease.\(^13\)–\(^15\) Using multiplex bead array assays to establish the involvement of cytokines in inflammatory processes revealed 10 detectable representative cytokines in blister fluid of CRPS patients.\(^16\) This finding suggests that these mediators were generated by a homogenous cell population. Because T cells are apparently not involved, the most likely candidates are monocytes, macrophages, and, possibly, fibroblasts and skin mast cells.

Mast cells are known to be involved in CRPS.\(^6\) Tryptase is a specific proteolytic enzyme and a good marker of the presence of mast cells. Activated mast cells synthesize and release tryptase. Significantly higher levels of tryptase have been demonstrated in the involved extremity compared with the contralateral extremity. A significant correlation between levels of IL-6 and TNF-α in the involved extremity was observed, but no significant correlation was found between levels of tryptase, IL-6, and TNF-α. Also, a significant correlation was found between the reported pain intensity as measured on a visual analog scale (VAS) and tryptase levels in the involved extremity, but not between the VAS and IL-6 or between the VAS and TNF-α.\(^6\)

Proinflammatory cytokines and neuropeptides are responsible for peripheral sensitization leading to increased nociceptive responsiveness. Persistent or intense noxious input resulting from tissue damage or nerve injury triggers increased excitability of nociceptive neurons in the spinal cord, a phenomenon called “central sensitization”.\(^8\) An objective phenomenon associated with central sensitization is windup, which is reflected in increased excitability of spinal cord neurons. CRPS patients display significantly greater windup to repeated stimuli.\(^8\)

The anatomical proximity of mast cells to neurons in both the central nervous system (CNS) and peripheral nervous system, their migratory ability, and their ability to release potent vasoactive and inflammatory mediators, constitutes an important neuroimmune axis.\(^17\) The presence of “cross-talk” has been shown between mast cells and cells of the CNS in various neurodegenerative diseases having an inflammatory and/or autoimmune component. The CNS interacts with the immune system by means of its neuropeptides, neurohormones, and neurotransmitters; in turn, the immune system feeds back to the brain which subsequently induces changes both in behavior (sickness response) and in the immune system.\(^18\) Neural plasticity and remodeling occur extensively during an inflammatory process, in that there is an increase in nervous innervation as well as mast cell density.

NEW PATHOPHYSIOLOGY-BASED PERSPECTIVES FOR PHARMACOLOGICAL INTERVENTION

Mast cells are bone-marrow-derived cells capable of secreting many active molecules: mediators stored in specific granules (such as histamine and heparin); small molecules produced immediately upon stimulation (such as nitric oxide); and many constitutively secreted, pleiotropic cytokines.\(^19\) They play an important role in
innate or acquired immunity, in bacterial infections, and also in autoimmunity. A number of cytokines (eg, IL-1, IL-6, TNF) are synthesized de novo and released several hours after stimulation.

Thus, because mast cells are known to be involved in inflammation in CRPS, it can be assumed that controlling these cells might (in part) improve inflammation in CRPS. Counteracting the effects of the mast cell can be achieved by the following: (1) prevention the division of, or killing the cell, (2) prevention of release, or (3) use of anti-TNF/anti-IL 6 therapy when TNF-α/IL-6 is released.

Prevention of Division/Killing the Mast Cell

This effect is achieved by means of tyrosine kinase inhibitors. They inhibit the intrinsic tyrosine activity of several specific proteins, including KIT. KIT is a transmembrane protein expressed on a variety of cells, including mast cells. In mast cells, KIT acts as a receptor for the stem cell factor. Binding of the stem cell factor on KIT is essential for the survival, differentiation, chemotaxis, and functional activity of mast cells. Thus, inhibition of KIT results in decreased mast cell population and activity.

Inhibition of the intrinsic activity of several proteins also results in reduced tumor vessel growth or carcinogenesis. Examples include imatinib, which became clinically available in 1998 for the treatment of patients with chronic myeloid leukemia in the chronic phase resistant to interferon-α and sunitinib, an anticancer drug currently used in the palliative treatment of metastatic renal cell carcinoma and gastrointestinal stomal cell tumors. As far as we know, these 2 drugs have not yet been used in CRPS.

Prevention of Release from the Mast Cell

This effect can be achieved by means of glucocorticoids. Besides the fact that glucocorticoids are anti-inflammatory via a number of mechanisms, they also appear to affect mast cells degranulation. They could rapidly inhibit IgE-mediated exocytosis and histamine release of mast cells. This effect is not accomplished by direct action on secretion machines, but is mediated by a reduction in the [Ca(2+)] (i) elevation.

The second type is the antihistamines. Cytokine production by human mast cells can be modulated (to some extent) by the H1-antagonists (eg, azelastine, loratadine, and cetirizine) as well as by the H2-antagonist ranitidine. Of the cytokines studied, TNF-α has been shown to be the most susceptible to inhibition by antihistamines. The exact mechanism of action of antihistamines on cytokine secretion from mast cells remains to be elucidated.

Finally, there is the cell stabilizer. Disodium cromoglycate is a cell stabilizer which inhibits the release of preformed and newly synthesized chemical mediators from a variety of cells involved in allergic and inflammatory responses. It is assumed that cromoglycate acts on the lipid bilayer membrane and thereby regulates the degranulation of mast cells by stabilizing membrane fluidity.

Although the use of glucocorticoids in CRPS appears to have a positive effect, empirical evidence for their use is scarce. The mechanism by which this effect is achieved is not yet clear. Neither cromoglycate nor antihistamines have been used in the treatment of CRPS.

Use of Anti-TNF Therapy/Anti-IL-6

If release of cytokines does occur, it might be useful to administer drugs which affect these cytokines.

**Anti-TNF.** Tumor necrosis factor-α antagonists – Tumor necrosis factor alpha (TNF-α) is a cytokine which promotes the inflammatory response. The possible mechanisms of action of anti-TNF agents are, for example, inhibition of the inflammatory “cytokine cascade” mediated by TNF, sequestration of TNF by binding, and complement-mediated lysis of cells expressing TNF.

The effect of using this drug in the treatment of CRPS has been described in 2 case reports of 3 patients. In both cases, there was a beneficial effect on CRPS. An open-label study, in which 42 patients were treated, has shown a “dramatic response” in 17% of the patients, and 14% experienced at least modest pain relief and/or showed some reduction in the need for concurrent medication. No results for the remainder of the patients have been reported.
Anti-IL-6. Interleukin (IL)-6 is a pleiotropic proinflammatory cytokine that is produced by multiple cell types. IL-6 signal transduction is mediated by membrane-bound and soluble IL-6 receptors. Tocilizumab (TCZ) is a recombinant humanized anti-human IL-6 receptor monoclonal antibody. TCZ binds to both of these receptors and inhibits signaling via this route. TCZ has been approved for the treatment of rheumatoid arthritis in patients who have an inadequate response to one or more TNF-α inhibitors. Until now, TCZ has not been used in CRPS.

**SUMMARY AND CONCLUSION**

Woolf and Decosterd advocated a form of pain treatment based on the mechanisms involved in the pathogenesis of pain. The aim should be to identify in each patient which mechanisms are responsible for their pain and specifically target treatment to those mechanisms. Following this recommendation, the treatment of CRPS should be based on knowledge of the pathophysiological mechanisms underlying this condition.

It is assumed that several mechanisms play a role in CRPS, one of which appears to be inflammation. Mast cells generate proinflammatory cytokines which are involved in the inflammatory process of CRPS. Also, central sensitization is common in CRPS. In general, mast cells appear to be involved in the cross-talk with the CNS; this process could play a role in central sensitization in CRPS.

It appears appropriate to correct the baseline inflammatory status to lower disease activity and, thus, lower production of pro-inflammatory cytokines. Treating the inflammatory component of CRPS might also prevent central sensitization. Therefore, following the recommendations of Woolf and Decosterd, it is reasonable to tackle the mast cell.

It is difficult to decide which of the above-mentioned strategies for modulating mast cell activity might be preferred. Therefore, in selecting a drug for study, it seems wise to take into account the safety profile, side effects, ease of treatment, and the cost of the drugs associated with each of the options.

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