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Implications of a local over-production of tumor necrosis factor-α in complex regional pain syndrome

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Running title: TNF-α in complex regional pain syndrome

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Abstract

Objective. To review the implications of a local over-production of tumor necrosis factor-α for the pathogenesis and treatment of complex regional pain syndrome.

Background. Elevated local production of tumor necrosis factor-α contributes to prolonged inflammation in the early stages of complex regional pain syndrome. Consequences could include hypoxia and necrosis of local tissues.

Method. We conducted a review of papers published since 2000 on tumor necrosis factor-α in complex regional pain syndrome.

Results. We propose that exaggerated local inflammation, subsequent inhibition of N-type calcium channel currents in sympathetic vasoconstrictor neurons and reduced sympathetic neurotransmitter release from perivascular terminals disrupt sympathetic cutaneous vasoconstrictor activity in complex regional pain syndrome. The resultant microvascular disturbance could exacerbate inflammation in the affected limb. In addition, an under-active cholinergic anti-inflammatory pathway might lead to overproduction of tumor necrosis factor-α. The results of large, randomized controlled treatment studies that test the efficacy of selective anti-tumor necrosis factor-α drugs in complex regional pain syndrome are not yet available. However, numerous small-scale studies and case reports indicate that anti-inflammatory drug treatments that directly or indirectly target tumor necrosis factor-α ameliorate pain and other symptoms in some cases.

Conclusions. An exaggerated inflammatory cytokine cascade may contribute to sensory and autonomic disturbances in complex regional pain syndrome. Further investigation of anti-tumor necrosis factor-α therapy as a cost-effective treatment option for this devastating disease is required. Whether increased activity in the cholinergic anti-inflammatory pathway provides therapeutic benefits for complex regional pain syndrome also warrants further investigation.

Key Words: complex regional pain syndrome (CRPS); tumor necrosis factor-α (TNF); cholinergic anti-inflammatory pathway; efferent vagus nerve; N-type voltage-gated calcium channels; ‘sterile’ inflammation

Introduction

Complex regional pain syndrome (CRPS) involves sensory disturbances such as spontaneous stabbing and burning pain, exaggerated stimulus-evoked pain and impaired tactile discrimination in the affected limb; autonomic nervous system dysfunction associated with vascular and sweating abnormalities; trophic changes in skin, hair, nails and bone; motor disturbances resulting in weakness, tremor and dystonia; and persistent edema in the CRPS-affected extremity [1-10]. Symptoms can develop after minimal direct injury to peripheral nerves (termed CRPS type 1), or may be associated with major nerve trunk injury (termed CRPS type 2).

Potential CRPS-inciting events include crush injury, compression injury, ischemia-reperfusion, fracture, contusion (soft tissue injury), sprain, strain, stroke, shock, hypoxia, cardiac ischemia, surgery (usually involving the distal part of an extremity such as carpal tunnel release), invasive procedures (venipuncture, intramuscular injection) and overly tight casting or immobilisation. These events may trigger an inflammatory cascade that results in prolonged and excessive ‘sterile’ inflammation and, in some unfortunate cases, the development of CRPS [1-13]. Nerve and tissue injury activates mast cells, macrophages and other tissue-resident cells, resulting in the release of inflammatory mediators such as tumor necrosis factor-α (TNF) and histamine and the recruitment of circulating neutrophils and monocytes [14]. Excess local TNF production may then play a key role in perpetuating an exaggerated inflammatory cascade that, if not resolved, triggers painful CRPS.

To explore this question, we conducted a review of papers listed in PubMed since 2000 on TNF in CRPS, supplemented by targeted searches using the Google search engine. In addition, references by key authors and those cited in relevant papers were traced.

This paper begins by providing an overview of the role of TNF in CRPS. We then examine the possibility that excess local TNF might not only mediate chronic inflammation and pain in CRPS but could also contribute to sympathetic dysfunction and associated vascular deficits. We subsequently review the role of the parasympathetic nervous system in CRPS – specifically the prospect that an under-active cholinergic anti-inflammatory pathway increases the likelihood of TNF over-production and chronic pain. Finally, we examine the efficacy of drugs that directly or indirectly target TNF in CRPS.

TNF in animal models of CRPS

As a master cytokine, TNF has a lead role in activating an inflammatory cytokine cascade that involves release of the pro-inflammatory cytokines interleukin (IL)-1β, IL-6 and IL-8 [15-18]. Additionally, TNF plays an important part in hypernociception during antigen-induced inflammation [19] and acts on sensory neurons to induce hyperalgesia [20]. Increased TNF levels may also lead to up-regulation of the voltage-gated sodium channels Nav1.3 and Nav1.8 in uninjured dorsal root ganglion neurons following neuronal injury, hence implicating not only injured but also uninjured neurons in neuropathic pain [15,18,21-26].

In a rat model of CRPS type 1 involving distal tibia fracture, increased production of TNF and the inflammatory cytokine cascade was detected in the hindpaw skin of the fractured limb [27-30]. Contributing to this response was substance P-mediated mast cell degranulation, which increased IL-1β release and contributed to nociceptive sensitization [31]. In addition, tibia fracture led to keratinocyte activation and proliferation, and heightened expression of TNF and other inflammatory mediators in the fractured hindpaw [30]. Conversely, the cytokine inhibitor pentoxifylline decreased cytokine expression and CRPS-like symptoms in this model [32].

The chronic post-ischemia pain (CPIP) model of CRPS involves an ischemia-reperfusion injury induced by a tight tourniquet on the hind limb of anaesthetized rats for three hours.

Removal of the tourniquet results in immediate blood reperfusion, hyperemia, plasma extravasation and edema. CPIP animals demonstrate spontaneous pain, hyperalgesia and allodynia in the affected paw and spread of symptoms to the uninjured hindpaw [4]. This model also involves sympathetic dysfunction, increased activity of the DNA transcription factor nuclear factor κB (NFκB) that triggers production of TNF, and high levels of TNF and other pro-inflammatory cytokines. The ischemia-reperfusion injury evokes microvascular disturbances that result in poor tissue perfusion, chronic tissue ischemia and tissue damage with reduced small-diameter nerve fibre endings in the skin and abnormal capillary endothelial cells in skeletal muscle and tibial nerve [4,33-35]. Preventing the translocation of NFκB into the nucleus inhibits the production of TNF, IL-1β and cyclooxygenase-2 in macrophages and other immune cells, and impedes the development of hyperalgesia in inflammatory and neuropathic pain models [36-39]. Inhibition of NFκB also prevents TNF-mediated expression of cell adhesion molecules in endothelial cells, thereby reducing the extravasation of circulating leukocytes and attenuating inflammation [40]. Pyrrolidine ditiocarbamate, a NFκB antagonist, and free radical scavenger drugs such as N-acetylcysteine and Tempol that reduce NFκB activation [41-43], decrease signs of hyperalgesia in CPIP rats [4,34,44]. Thus, NFκB and TNF appear to be pivotal in this model of CRPS.

The TNF receptor 1 is involved in thermal hyperalgesia and mechanical allodynia evoked by chronic constriction injury in mice [45]. Neutralizing antibodies to TNF reduce pain behaviours both in this model and after partial sciatic nerve transection, possibly due to decreased TNF or nerve growth factor in the injured nerve or reduced anterograde transport of TNF in the intact and injured nerves [46,47]. Etanercept, a selective anti-TNF drug, reduces hyperalgesia in the chronic constriction injury model [48] and significantly decreases mechanical allodynia in the spinal cord injury model [49].

Together, these studies indicate that TNF is an important mediator of pain and inflammation in a diverse range of neuropathic pain models, both in studies with minimal direct injury to peripheral nerves that attempt to replicate CRPS type 1, and also after direct injury to peripheral nerves (CRPS type 2).

The role of TNF in CRPS patients

An exaggerated posttraumatic ‘sterile’ inflammatory response that includes a persistently elevated pro-inflammatory cytokine profile, delayed resolution of the inflammatory cascade and depressed anti-inflammatory cytokine expression may contribute to the onset and maintenance of CRPS [17,50-52]. In an elegant study by Üçeyler et al. [50], 42 CRPS patients (median disease duration 12 weeks; range 3 to 70 weeks) were found to have a higher pro-inflammatory cytokine profile than age- and gender-matched healthy controls (n=34). Specifically, CRPS patients had greater pro-inflammatory TNF and IL-2 serum levels and lower anti-inflammatory IL-4 and IL-10 mRNA serum levels than controls. Notably, IL-10 (an anti-inflammatory cytokine) could not be detected in 27 of 42 CRPS patients, whereas pro-inflammatory IL-2 was absent in 32 of 34 controls [50]. Findings from similar studies have confirmed that the early stages of CRPS are characterized by increased pro-inflammatory cytokine activity [6,7,53,54], particularly TNF and IL-6 [55].

It is becoming increasingly clear that *local*, as opposed to *systemic*, inflammation is likely to contribute significantly to CRPS [17,56]. In a study based on 3-phase bone scintigraphy, TNF overproduction was detected in the CRPS-affected hands of three early-stage CRPS patients but not in the contralateral hands or in patients with chronic CRPS [57]. In another study that involved assessing both skin and serum TNF levels, skin punch biopsies and blood samples were taken from 10 patients with osteoarthritis, ten with acute traumatic upper limb bone fracture, and from the affected limb of another ten patients with CRPS type 1 [17]. TNF levels were greater in skin samples from CRPS patients than in skin punch biopsies from the other patient groups, whereas serum TNF was similar in patients with osteoarthritis and CRPS. Together, these findings signify the importance of locally-produced TNF in the pathogenesis of CRPS. From a practical point of view, the findings also suggest that skin punch biopsies could be used as a minimally invasive diagnostic tool to quantify local TNF levels in the CRPS-affected limb [17].

In association with local leukocyte accumulation [58], the elevated local production of TNF may mediate persistent ‘sterile’ inflammation and tissue damage in the acute CRPS-affected limb [3,59-63]. For example, in a study involving 66 primarily acute-stage patients, higher local TNF and IL-6 levels were observed in most of the induced skin blisters [64]. On the other hand, IL-6 levels in blister fluids of chronic CRPS patients (n=12; median duration=6 years) were significantly reduced compared with levels shortly after CRPS onset, and TNF levels also trended down [65]. Together, these findings suggest that increased TNF, IL-6 and other pro-inflammatory agents are associated with tissue damage, necrosis and pain during the early stages of CRPS, whereas additional mechanisms may contribute later on.

How might locally-increased TNF contribute to tissue damage and necrosis in CRPS?

TNF can stimulate both inflammation and cell death [66]. Thus, poor resolution of a TNF-induced inflammatory cytokine cascade might evoke an exaggerated posttraumatic ‘sterile’ inflammatory response that contributes to symptoms of CRPS [50-52] (Figure 1). Specifically, excess TNF and other inflammatory cytokines may result in local tissue damage that includes necrosis of sympathetic cutaneous vasoconstrictor and other small-diameter nerve fibers, mitochondrial dysfunction, abnormal endothelial cell activity, poorly-formed capillaries and dysfunctional capillary outgrowth, pericyte damage and skeletal muscle fibre losses in the CRPS-affected limb [67-69]. In turn, hypoactive or degenerating sympathetic efferent fibres could prevent blood from being diverted from arterioles into local capillary beds in CRPS-affected tissue, thereby limiting oxygen and nutritive supply and delaying waste removal. While the affected extremities of ‘warm limb’ patients may appear flushed and hyperemic, the tissues below the skin could actually be ‘paradoxically ischemic’ [67,70,71]. Indeed, increased skin lactate in CRPS-affected limbs is consistent with tissue ischemia [72]. Local tissue damage could contribute to the maintenance of many CRPS symptoms including neuropathic pain, autonomic dysregulation, motor dysfunction and edema [3,13,67,68,70,71,73-75].

Prolonged production of TNF by macrophages and other immune cells may mediate persistent ‘sterile’ secondary inflammation, pain, severe tissue damage and necrosis [76]. Necrosis involves rapid cell membrane lysis and the passive release of intracellular contents including high mobility group box-1 (HMGB1) protein from the nuclei of necrotic cells [77,78]. HMGB1 interacts with Toll-like receptor 4 expressed by macrophages, activates NFκB and stimulates further production of TNF and other pro-inflammatory agents, leading to the activation of dendritic and endothelial cells [78-80]. A vicious circle involving extravasation of neutrophils and monocytes from the circulation, activation of macrophages, TNF production and an exaggerated inflammatory cytokine cascade could then result in persistent and excessive ‘sterile’ inflammation in CRPS-affected limbs. The ongoing passive release of excess HMGB1 by necrotic cells may further exacerbate tissue damage and necrosis [81-84] (Figure 1).

Does TNF-mediated inhibition of the N-Type calcium current contribute to impaired sympathetic cutaneous vasoconstriction in CRPS?

Whole-body cooling and warming provokes three distinct patterns of cutaneous blood flow in CRPS patients: increased blood flow and warmth in the symptomatic limb irrespective of body temperature, consistent with impaired sympathetic cutaneous vasoconstriction; decreased flow and coolness in the symptomatic limb irrespective of body temperature; or an intermediate type where the symptomatic limb is warmer or cooler than the contralateral limb at different body temperatures [85,86]. The cold pattern is most common in CRPS patients with the longest duration of pain [87], possibly due to the development of adrenergic supersensitivity or up-regulation of vasoconstrictors such as endothelin-1 as the condition progresses [61,88,89].

Reductions in venous concentrations of sympathetic neurotransmitters and their metabolites in the warm or cool CRPS-affected limb indicate that sympathetic neurotransmission is compromised in at least some patients [85,90-95]. This may be due to a combination of sympathetic denervation [67] and altered control of sympathetic neural activity [94,96-98]. Although much evidence points toward a central disturbance in regulation of autonomic activity in CRPS [85,93,97-100], a sympathetic deficit distal to the site of trauma may also contribute to local hypoxia and decreased nutritive supply in the CRPS-affected limb [101-103]. In addition, animal models of neuropathic pain suggest that peripheral nerve injury triggers novel sympathetic neurite sprouting. Pathologic coupling between these sprouts and nociceptive neurons in the dorsal root ganglia and upper dermis may underpin sympathetically maintained pain [3,104-107].

An additional mechanism involving excess local TNF production could disrupt sympathetic vasoconstrictor activity in the CRPS-affected extremity. Normal N-type calcium channel function in sympathetic efferent fibres is essential for release of the vasoconstrictor neurotransmitters noradrenaline, ATP and neuropeptide Y [108,109]. In vitro studies have demonstrated that excess TNF stimulates the signaling of transcription factor NFκB, leading to reduced calcium entry into N-type calcium channels, selective inhibition of the N-type calcium channel current and decreased sympathetic neurotransmitter release from the perivascular terminals of postganglionic sympathetic neurons [110,111] (orange arrows in Figure 1). Selective TNF-mediated inhibition of the N-type calcium channel current in sympathethic efferents is linked with Crohn’s disease and Guillain-Barré syndrome [110-114], but whether this mechanism also contributes to CRPS has yet to be established.

Does impairment of the cholinergic anti-inflammatory pathway play a role in CRPS?

It is widely accepted that an autonomic imbalance that involves the sympathetic nervous system results in altered tissue perfusion and hyper- or hypohidrosis in CRPS. However, there is a paucity of research that investigates whether changes in parasympathetic activity also contribute to autonomic dysfunction or other disturbances in CRPS. Persistently impaired parasympathetic vagal outflow may contribute to cardiovascular disease [115-120], postoperative pain [121], fibromyalgia [122,123], chronic fatigue syndrome, postural orthostatic tachycardia syndrome [124,125], migraine [126], depression [127,128], inflammatory bowel disease [113,114] and various inflammatory autoimmune diseases (rheumatoid arthritis, systemic lupus, primary Sjögren syndrome, polymyalgia rheumatica and scleroderma) [129,130]. Whether vagal outflow is also compromised in CRPS warrants further investigation, as the efferent vagus nerve forms part of the cholinergic anti-inflammatory pathway.

An overview of the cholinergic anti-inflammatory pathway (Figure 2)

Innate immune responses are regulated in various ways via humoral and neural pathways. The humoral pathway controls the release of hormones and cytokines via the hypothalamic-pituitary-adrenal axis. This pathway mediates systemic and local effects on target tissues via circulating anti-inflammatory hormones (corticosteroids, glucocorticoids, IL-10) and tissue repair agents (lipoxins, resolvins) [37,39,81,131]. The neurally-based cholinergic anti-inflammatory pathway, on the other hand, comprises the centrally-controlled efferent arc of the anti-inflammatory reflex. This involves the fine-tuned, targeted and rapid release of acetylcholine into local regions via selected motor branches of the vagus nerve. The efferent vagus nerve is able to exert systemic and local anti-inflammatory effects in a ‘real-time’ manner, relative to the slower and more diffuse humoral pathway [37-39,81,131].

Most fibres in the vagus nerve are visceral afferents that supply major organs such as the heart, lungs, liver, spleen and gastrointestinal tract. The remaining 10% - 25% of the vagus nerve comprises efferent fibres that not only provide parasympathetic innervation to the cardiovascular system, liver, spleen, gut and other visceral organs, but also significantly contribute to proper regulation of the cholinergic anti-inflammatory pathway [81,132-134]. Efferent vagal cholinergic release leads to activation of the α7 subunit of the nicotinic acetylcholine receptor expressed by monocytes, macrophages and other cytokine-producing cells (mast cells, B cells, T cells, dendritic cells and microglia), and may also act on vascular endothelial cells and certain neurons.

The afferent arc of the anti-inflammatory reflex fulfils a sensory function by detecting inflammatory stimuli (e.g., IL-1β) in the periphery via afferent vagal fibres. This leads to glutamate release in the nucleus tractus solitarius (NTS) of the medulla oblongata. The NTS neurons project to numerous central structures involved in pain processing and other functions, including brainstem nuclei (locus coeruleus, rostral ventrolateral medulla, parabrachial nucleus in the pons, nucleus raphe magnus), central nucleus of the amygdala, paraventricular nucleus in the hypothalamus, insular cortex, anterior cingulate cortex and medial prefrontal cortex. The NTS neurons also project via the medial lemniscus to the ventral posterior medial nucleus of the thalamus, and then to the somatosensory cortex in the parietal lobe (parietal superior operculum). Afferent vagal fibres in the NTS project to, and form synapses with, the central terminals of efferent vagal fibres in the dorsal motor nucleus and nucleus ambiguus. Thus, the NTS is a major intersection for afferent and efferent vagal fibres involved in immunomodulation. This neuroanatomical configuration enables the efferent arc of the anti-inflammatory reflex to act reflexively and in a precise manner following central processing of noxious inflammatory stimuli detected by afferent vagal fibres in the periphery [37-39,81,134-136].

Efferent vagal fibres, immune cells (B cells, T cells, dendritic cells, neutrophils), keratinocytes and vascular endothelial cells all release acetylcholine [37-39,137,138]. Transient exposure to acetylcholine results in α7-mediated JAK2/STAT3 activation that prevents the translocation of NFκB from the cytoplasm into the nucleus. This leads to suppression of pro-inflammatory cytokine production by macrophages and other immune cells, without altering the anti-inflammatory cytokine profile (IL-10, corticosterone, transforming growth factor-β) [16,37-39,81,131,139,140]. Conversely, disruption of the efferent arc of the anti-inflammatory reflex may lead to decreased vagal cholinergic outflow and increased pro-inflammatory cytokine production by activated immune cells (Figure 2). If left unchecked, this could result in persistent and exaggerated 'sterile' inflammation, tissue injury and necrotic cell death.

As the efferent vagus nerve does not directly innervate the limbs, exactly how the cholinergic anti-inflammatory pathway is able to control inflammation at distal sites is not clear. Nonetheless, in animals with experimentally-induced paw inflammation, vagal nerve stimulation inhibits foot-pad edema [141]. Acetylcholine released from endothelial cells regulates leukocyte trafficking via modulation of adhesion molecule expression [37-39]. Cholinergic agonist-induced activation of the α7 subunit inhibits TNF-induced adhesion molecule expression in human microvascular endothelial cells, hence blocking monocyte and neutrophil adhesion to these cells. This decreases recruitment, extravasation and migration of circulating leukocytes into localized inflamed tissue sites and reduces local TNF production [138,142-144]. Similarly, electrical stimulation of the vagus nerve decreases the activity of circulating dendritic cells and monocytes that release TNF, IL-6 and IL-12 [145].

The efferent vagus nerve targets the spleen via the splenic nerve to modulate both *systemic* and *localized* inflammation [38]. The splenic nerve may deliver specific anti-inflammatory signals that modify circulating neutrophils, monocytes and lymphocytes as they pass through the spleen. Once altered, these circulating white blood cells might then migrate to distal inflamed sites where they exert anti-inflammatory effects. Alternatively, circulating immune cells may no longer be chemo-attracted to distal inflamed regions due to vagally-altered down-regulation of relevant receptors during their transit through the spleen [81,132].

Disruption of the cholinergic anti-inflammatory pathway might contribute to symptoms of CRPS. In support of this possibility, Kohr et al. [146] reported that the serum from a subset of CRPS patients contained surface-binding autoantibodies against autonomic neurons. In particular, autoantibody binding to primary cultured autonomic neurons was detected in 13 of 30 (43.3%) CRPS patients. Furthermore, an inducible surface cholinergic antigen in differentiated SH-SY5Y neuroblastoma cells was recognized by the sera of 18 of 30 CRPS patients [146]. Recent work suggests that autoantibodies in CRPS form a functionally-active subclass of immunoglobulin G, and that the antigens for these agonistic autoantibodies are contained within the second extracellular loop of muscarinic-2 receptors and β_2-adrenoceptors [147]. Muscarinic M2 receptor agonists may decrease neurogenic inflammation and desensitize nociceptors [148]. In addition, however, central muscarinic acetylcholine receptors play an important role in the activation of the cholinergic anti-inflammatory pathway. In particular, acetylcholine is negatively regulated by the presynaptic M2 autoreceptor in several brain regions. Activation of the M2 autoreceptor (by acetylcholine or other cholinergic agonists) can lead to reduced acetylcholine release in the synaptic cleft in the central terminal of the efferent vagus nerve, leading to decreased central cholinergic neurotransmission and reduced vagal output [149]. As such, agonistic autoantibodies to muscarinic-2 acetylcholine receptors could disrupt vagal outflow in CRPS.

Importantly, significant pain relief was obtained by 3 of 12 CRPS patients following intravenous immunoglobulin treatment to neutralize serum autoantibodies [150] (see below and Table 1). Further research is warranted to clarify the role of autoantibodies in CRPS.

Effect of the cholinergic anti-inflammatory pathway on TNF

The cholinergic anti-inflammatory pathway has been explored extensively in animal models involving ischemia-reperfusion injury and hemorrhagic (circulatory) shock. For example, aortic occlusion restricted blood flow and mediated an exaggerated innate immune response with excess cytokine release. Conversely, vagal nerve stimulation before or after aortic occlusion inhibited the cytokine response [37-39,151]. Similarly, vagal nerve stimulation reversed hypotension, inhibited NFκB signaling and reduced TNF production in a model that involved clamping the splanchnic arteries for 45 minutes [152]. In a bilateral renal ischemia-reperfusion injury model, pretreatment with nicotine or a selective α7 agonist reduced renal dysfunction and tubular necrosis via decreased TNF production [153]. Finally, vagal outflow provided protection against hemorrhagic (circulatory) shock, likely via decreased translocation of NFκB into the cell nucleus, reduced TNF synthesis, and decreased hypotension [37-39,154,155].

At present, little is known about the effects of vagal nerve stimulation on hyperalgesia in animal models of neuropathic pain. It may be useful to explore this further, as findings could have important implications for CRPS.

Is TNF a useful target for treating CRPS?

A range of clinical and experimental evidence suggests that anti-inflammatory drug treatments (e.g., corticosteroids) alleviate CRPS by reducing TNF and other inflammatory mediators [15,17,18,50]. Infliximab selectively targets TNF, similar to other TNF monoclonal antibodies (adalimumab, certolizumab pegol, afelimomab and golimumab).

Other drugs not widely appreciated for their anti-inflammatory effects but that nonetheless have demonstrated treatment benefits in CRPS include intravenous immunoglobulin, pregabalin (and gabapentin), thalidomide (and its newer generation derivative lenalidomide), memantine, N-acetylcysteine and bisphosphonate drugs (pamidronate, ibandronate, clodronate, alendronate). Representative examples of treatment studies are listed in Table 1 and described below.

Infliximab has been used to treat lumbar radicular pain including severe sciatica [156-160] and rheumatoid arthritis [161]. Analysis of blister fluid from CRPS-affected limbs of two patients indicated that local concentrations of TNF and IL-6 were significantly decreased following selective anti-TNF (infliximab) treatment. This was accompanied by amelioration of pain, vascular disturbances, edema, motor dysfunction and other symptoms [162]. In addition, a patient with acute CRPS type 1 showed near complete remission following infliximab treatment for eight weeks [163]. Furthermore, a controlled trial involving 13 CRPS type 1 patients showed positive results for the infliximab-treated patients (n=7) compared with the placebo group (n=6) (Nederlands Trial Register 449 ISRCTN 75765780).

Corticosteroid treatment inhibits local inflammation and reduces serum TNF [17]. In a randomized controlled trial that compared corticosteroid (oral prednisolone) to NSAID (oral piroxicam) treatment for up to one month in 60 CRPS patients following stroke, symptoms improved significantly in 25 of the 30 patients who received prednisolone compared with only 5 of the 30 patients in the piroxicam control group [164]. Lasting therapeutic results, including significant pain relief, were reported in other controlled trials and numerous case series following corticosteroid therapy [93,165-175]. Thus, further research involving corticosteroid and other anti-inflammatory (TNF-inhibiting) drug treatments for CRPS appears warranted [176].

Intravenous immunoglobulin not only inhibits certain autoantibodies but may also reduce pro-inflammatory cytokine levels [177] and exert potent anti-inflammatory activity [178]. In particular, intravenous immunoglobulin treatment may result in saturation of macrophage Fc receptors, suppression of pro-inflammatory mediators (TNF, macrophage colony-stimulating factor and monocyte chemoattractant protein-1), up-regulation of anti-inflammatory cytokines and inhibition of endothelial cell activation and inflammation [179-184]. This treatment was recently reported to decrease immune activation, reduce pain and improve autonomic disturbances in patients with CRPS [150].

Pregabalin (and gabapentin) is approved for treatment of post herpetic neuralgia and painful diabetic peripheral neuropathy, and may also be prescribed ‘off-label’ for CRPS and other neuropathic pain conditions. Varying degrees of success with this drug have been reported for CRPS [185-189]. Pregabalin (and gabapentin) bind with the α2δ1 calcium channel subunit, leading to inhibition of translocation of NFκB into the cell nucleus and reduced gene transcription for inflammatory agents including IL-6 [190,191] and (likely) TNF.

Thalidomide offers various degrees of relief in CRPS patients [192-198]. Lenalidomide, an analogue with greater potency and less toxicity, also extends certain benefits for some CRPS patients. Specifically, 14 of 40 CRPS patients who took oral lenalidomide treatment for more than 2 years showed overall improvement in symptoms including improvements in pain, allodynia and sleep [199]. An earlier study reported similar results following 12-week lenalidomide treatment [200]. The therapeutic effects may be mediated by degradation of TNF mRNA [50]. Thalidomide also inhibits TNF-induced NFκB activation, hence preventing further TNF synthesis [201,202]. Due to known risks of severe teratogenicity, availability of thalidomide is limited to patients beyond child-bearing age.

Promising results have also been reported for memantine and memantine/morphine treatment in CRPS patients. Specifically, pain decreased in three CRPS patients following 8-week oral memantine treatment [203] and in six CRPS patients in a follow-up study [204]. More recently, 10 CRPS patients benefited significantly following memantine/morphine combination treatment [205]. As administration of memantine hydrochloride decreases TNF expression in animals [206], studies are warranted to determine whether memantine decreases local TNF in CRPS patients (in addition to effects on NMDA and other receptors). N-acetylcysteine may also benefit certain ‘cold’ CRPS type 1 patients [207] by inhibiting NFκB translocation and reducing TNF production [41,43].

Bisphosphonate treatment evokes apoptosis of macrophages and macrophage-derived osteoclasts, and decreases production of TNF and other inflammatory mediators in vitro and in vivo [208-213]. A pilot study involving ibandronate (a third generation amino-bisphosphonate) indicated that pain ratings decreased in patients with upper limb CRPS [214]. Numerous studies involving bisphosphonates, including pamidronate, clodronate and alendronate treatment, have demonstrated varying degrees of success in CRPS patients [198,215-232].

Together, the findings reviewed above suggest that drugs that reduce the availability of TNF and other inflammatory cytokines contribute significantly to the amelioration of pain and ‘sterile’ inflammation in CRPS. As such, the ability to block TNF may play a key role in the treatment of pain and edema in CRPS. It is noteworthy that complete remission from CRPS was reported in small subset of patients following TNF-inhibiting drug treatment (Table 1).

Although effective in some cases, drug treatments that target TNF may increase the risk of secondary infections or other adverse events. Hence, it is important to establish whether prolonged stimulation of the cholinergic anti-inflammatory pathway decreases TNF production and ameliorates symptoms in CRPS. Non-invasive techniques that increase vagal outflow include acupuncture, controlled deep breathing (via deep breathing exercises, yoga, Tai Chi, Qigong) and meditation [81,122,233-235]. Benefits of diaphragmatic breathing exercises, mental imagery, music therapy, hydrotherapy, proprioception training, tactile desensitisation (for allodynia), physical/gym rehabilitation, recreational/socialisation therapy, massage, relaxation (for stress management) and problem solving/assertiveness training have been reported for children with CRPS [236]. Whether these treatment gains involve increased vagal outflow or reductions in TNF is unknown.

Conclusions

Increased local production of TNF may contribute to the onset and maintenance of CRPS by promoting chronic ‘sterile’ inflammation and secondary microvascular disturbances including impaired sympathetic cutaneous vasoconstriction. Thus, it may be desirable to reduce local TNF levels by means of selective anti-TNF drug treatment or via pharmacological, electrical or non-invasive stimulation of the cholinergic anti-inflammatory pathway. From an experimental and clinical perspective, research into anti-TNF therapy may offer additional insights into the pathogenesis of CRPS, and result in the development of cost-effective treatment options for this devastating disease.

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Figure legends

Figure 1. Effects of an over-supply of TNF on symptoms of CRPS. The blue arrows represent pathways for the prolonged manufacture of TNF and other inflammatory mediators, and for the production of symptoms. A deficit in sympathetic vasoconstrictor regulation that results in microcirculatory ischaemia and hypoxia may augment necrosis in local tissues (red arrows). Inhibition of N-type calcium channel currents in sympathetic vasoconstrictor fibres (orange arrows) could further aggravate this cycle.

Figure 2. The cholinergic anti-inflammatory pathway. Under normal conditions, inflammatory mediators detected by vagal afferent fibres activate vagal efferent fibres with cell bodies in the dorsal motor nucleus and nucleus ambiguus. This prevents the production of TNF (blue arrows). However, failure of this inhibitory process could contribute to heightened production of TNF and “sterile” inflammation (red arrows).

Table 1. Drug trials that target an action of TNF (and other primary mechanisms) in CRPS *

	Diagnosis	Design	Intervention	N	Patient details including age, gender, duration of painful CRPS and inciting event	Results including the number of patients that benefited from intervention via reduced pain and other clinical benefits
Infliximab (a therapeutic monoclonal antibody that selectively targets TNF)						
Huygen et al. [162]	CRPS type 1	Case reports	Infliximab	2	Case 1: F, 50 Spontaneous onset of CRPS in left leg 5 years earlier, followed by CRPS in right leg 2 years later. Case 2: F, 55 Acute CRPS caused by a left Colles' fracture 2 months earlier (resulting in affected limb being casted for 2 months).	Infliximab treatment of <1 month led to decreased localized TNF and IL-6 in blister fluid. Amelioration of CRPS symptoms including pain, temperature, edema and motor dysfunction occurred in both patients.
Bernateck et al. [163]	CRPS type 1	Case report	Infliximab	1	F, 62. Acute CRPS caused by a left Colles' fracture 3 months earlier.	Near complete remission following infliximab treatment for 8 weeks.
Trial Register 449 ISRCTN 75765780	CRPS type 1	Controlled trial	Infliximab (n=7) Placebo (n=6)	7	Aged 18 - 65	Positive results for infliximab-treated patients, compared to placebo group.
** **Corticosteroids** (corticosteroid treatment inhibits local inflammation and serum TNF [15])						

Wasner et al. [93]	CRPS type 1	Case report	Treatment also included sympatholytic blocks, NSAIDs and physiotherapy for 6 weeks.	1	F, 52. Acute CRPS in right forearm and hand (following right distal radius fracture and plaster).	Full recovery from CRPS within one year, post fracture.
Kalita et al. [164]	Patients who developed CRPS after stroke	Randomized controlled trial	Corticosteroids (prednisolone) for up to one month (n=30). Control patients received NSAID (piroxican) (n=30). Both groups underwent ongoing physiotherapy.	60	CRPS developed within 7 to 100 days following stroke in all 60 patients (40 males, 20 females; 40 - 70 years; mean age=56)	25/30 (83.3%) CRPS patients benefited significantly from daily corticosteroid (oral prednisolone) treatment, compared with 5 of 30 (16.7%) CRPS patients following NSAID (piroxican) treatment.
Bianchi et al. [166]	CRPS	Case reports	Corticosteroids (prednisone)	25	Various	21 of 25 CRPS patients derived lasting benefits following corticosteroid treatment.
Braus et al. [167]	Shoulder-hand syndrome after stroke in hemiplegic patients	Randomized placebo-controlled non blinded trial	Corticosteroids (oral methylprednisolone)	36	Various	31 patients became ‘almost symptom free’ following daily low doses of corticosteroids (oral methylprednisolone) for up to 10 days.
Kozin et al. [168]	RSD	Comparative non-randomized	Comparison of systemic oral prednisone (n=35) to stellate ganglion	55	Various	Prednisone treatment resulted in ‘excellent’ results for 14 patients (40%) and ‘good’ results for 8 patients (23%). However, 17 patients had ‘poor’ results

		study	blockade (n=20)			and 3 patients had only ‘fair’ results following stellate ganglion blocks (n=20).
Grundberg [169]	RSD	Case reports	Corticosteroids (methylprednisolone injections)	69	Various	47 of 69 patients obtained significant benefits.
Christensen et al. [165]	Acute RSD	Randomized placebo-controlled trial	Corticosteroids (oral prednisone for a maximum of 12 weeks) (n=13). Placebo (n=10).	23	22/23 had sustained a fracture while 1 had an abscess following an incision. Mean duration from trauma to RSD diagnosis was 92 days (range 50-194 days).	All 13 patients in the prednisone treatment group showed greater than 75% clinical improvement within 12 weeks.
Glick [170]	RSD (acute and chronic)	Case reports	Corticosteroids	17	RSD caused by elbow injury (n=4), post surgery (n=3), wrist fracture (n=1), finger injury (n=1), leg injury (n=1) and shoulder-hand syndrome (n=7).	12 of 17 RSD patients had fair to excellent results following daily corticosteroid treatment for 10-70 weeks.
Glick & Helal [171]	Post-traumatic neuro-dystrophy	Case reports	All patients were given daily oral prednisolone for 6-8 8 months except for 2 patients who received intramuscular methylprednisolone	21	Various	10 had ‘very good’ results (pain relief and good movement) and 3 had ‘good’ results (limited pain requiring nil analgesics and some movement).
Zyluk [172]	Painful RSD of upper limb	Case reports	A solution of methylprednisolone, lidocaine and heparin was injected	36	23 females; 13 males; 44-73 years. RSD-inciting events included distal radius fracture (n=22), fasciectomy (n=5)	At 1-year follow-up, 25 patients (69%) reported ‘good’ relief of spontaneous pain and normal finger movements.

			into the dorsal side of the affected hand or wrist, and a 20-25 minute occlusion block was maintained.		and other hand injuries (n=9). RSD duration was less than 1 year in all cases.	
Poplawski et al. [173]	Post-traumatic dystrophy of the extremities	Case reports	Regional IV blocks involving a solution of corticosteroid (methylprednisolone and lidocaine for ~30 minutes)	27	13 males; 14 females; aged 31- 81 years. Duration ranged from 2-36 months	10 patients (11 limbs) had ‘excellent’ results that included little or no pain and edema as well as a full range of motion. Five patients obtained ‘good’ or ‘very good’ results, and required nil or infrequent analgesia.
Tountas & Noguchi [174]	RSD	Case reports	Regional IV blocks involving a solution of corticosteroid (methylprednisolone sodium succinate) and lidocaine	17	Inciting event included distal radius fracture Duration ranged from 2 days to almost 6 months.	At 6 months, 11 patients showed complete or almost complete relief from symptoms.
Zyluk & Puchalski [175]	Acute CRPS type 1	Case reports	Mannitol and dexamethasone combination treatment (daily for 1 week)	75	75 patients (68 females; 7 males; aged 38-82; Duration less than 4 months. Various inciting events.	After 1-week treatment, pain from a mean Visual Analogue Scale (VAS) dropped from 6.7 to 2.3. After 8-12 months, at the final assessment, 70 patients had a mean VAS of 1.8. Other variables also improved significantly.
Thalidomide or lenalidomide (these agents act intracellularly, resulting in inhibited production of TNF and other cytokines) [193,194]						
Rajkumar et al. [192,196]	RSD	Case report	Thalidomide	1	F, 43 3 years duration.	After 1-month thalidomide treatment RSD was almost entirely resolved, and the leg

					Caused by traumatic injury to her left hand.	ulcer and edema were completely healed. The patient no longer needed her wheelchair and walked normally. She no longer took pain medication and regained function in her left hand several months later. When the patient was followed up 30 months later, she remained free of CRPS.
Schwartzman et al. [197]	CRPS	Case reports	Thalidomide	42	Long-standing CRPS disease.	7 (17%) patients showed a ‘dramatic response’ following thalidomide treatment, while 6 (14%) patients had ‘modest pain relief’ and/or reduced their pain medication.
Ching et al. [194]	CRPS type 1	Case report	Thalidomide	1	F, 33. CRPS caused by a fall on left knee 6 years earlier	CRPS pain in her left knee disappeared, post thalidomide treatment.
Bengtson et al. [193]	Chronic upper limb CRPS	Phase II trial	Thalidomide	12	CRPS duration exceeded 1 year in all patients	Thalidomide treatment for 6 months resulted in significant pain reduction in 4 patients.
Prager et al. [195]	CRPS type 1	Case reports	Thalidomide	9	2 males, 7 females	Pain decreased significantly in 7 of 9 patients after thalidomide treatment.
Manning [199]	CRPS type 1	Case reports	Lenalidomide	40	Genders/ages not specified	14 of 40 patients took oral lenalidomide treatment for >2 years. These patients showed overall improvement in symptoms including improvements in pain, allodynia and sleep.
Schwartzman et al. [200]	Chronic CRPS type	Case reports	Lenalidomide. Multicenter (6	40	Average duration 6 years, 75% female	Daily oral lenalidomide treatment resulted in sustained symptom reduction including

	1		centers), open label, 12-week study (the core phase), plus option to extend for a further 40 weeks			pain reduction in all 31 patients that completed the core phase. 18 (of 31) also completed the extended 40-week period (and continued into 2nd year of treatment.
Intravenous immunoglobulin (macrophage Fc receptor inhibition may suppress TNF production and reduce endothelial cell activation [174], and also neutralize autoantibody effects in some autoimmune diseases [176])						
Goebel et al. [150]	CRPS	Randomized, double-blind, placebo-controlled crossover trial	Intravenous immunoglobulin	13	6 to 30 months duration. Various inciting events	3 of 12 CRPS patients who completed the trial had significant pain relief following intravenous immunoglobulin therapy.
Gabapentin and pregabalin (bind with the α2δ1 calcium channel subunit. In addition to decreased neurotransmitter release, this may inhibit translocation of NFκB into the cell nucleus and decrease the production of inflammatory agents including TNF [34,38,182,183])						
Mellick & Mellick [187]	RSD	Case reports	Gabapentin	6	42-68 years, all female. Various durations/ inciting events	Pain reduction ranged from 85% to 100% in 5 patients and 60% in the other patient.
Wheeler et al. [188]	Childhood RSD (acute)	Case report	Gabapentin	1	Girl, 9 years. Inciting event: ingrown nail with purulent drainage in left big toe	Complete resolution of all CRPS symptoms following gabapentin treatment.
Memantine (in addition to effects on NMDA and other receptors/channels [195,196,197], memantine may decrease TNF expression [198])						
Sinis et al. [203]	CRPS	Case reports	Oral memantine for 8 weeks	3	F, 60; M, 58; M, 49. CRPS duration 1-7 months; various trauma-inciting events	Nil ‘resting’ pain was present in 3 patients at the 6 month follow-up.

Sinis et al. [204]	CRPS	Case reports	Memantine	6	4 men and 2 women (29-64 years; mean age 48.3 years). CRPS duration: 4-23 months; various trauma-inciting events	Pain decreased significantly and ‘continuous’ pain was abolished in 6 patients after 8 weeks of memantine treatment (as reported at the 6 month follow-up). This was accompanied by an improvement in motor symptoms and autonomic changes in all patients.
Gustin et al. [205]	CRPS	Double-blind randomized placebo-controlled study	Memantine + morphine (n=10) Placebo + morphine (n=10)	20	8 men and 12 women; 29-69 years; mean age 50.9 years. CRPS duration 6-36 months; various trauma-inciting events	Pain decreased significantly in 10 CRPS patients after the memantine/morphine combination treatment for 8 weeks.
N-acetylcysteine (a free radical scavenger [199] that may also inhibit NFκB and cytokine production including TNF [39,41])						
Perez et al. [207]	CRPS type 1	Randomized actively controlled trial	CRPS patients were randomly assigned to either N-acetylcysteine (n=74) or DMSO (n=71) for 17 weeks (regardless whether they were ‘warm’ or ‘cold’ CRPS).	74	20 males; 54 females; mean age 48.94 years; 18 ‘cold’ CRPS patients and 56 ‘warm’ CRPS patients. Median duration of CRPS pain: 102 days.	The 18 ‘cold’ CRPS patients benefited from N-acetylcysteine treatment whereas the 56 ‘warm’ CRPS patients did not.

*Bisphosphonate treatment for CRPS may also exert inhibitory effects on TNF production, but these studies are not included in the table.

**Additional corticosteroid-related studies were reviewed by Fischer et al. [167].