Effect of Immunomodulating Medications in Complex Regional Pain Syndrome

A Systematic Review

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Background: Different mechanisms are involved in a complex network of interactions resulting in the painful and impairing disorder, complex regional pain syndrome (CRPS). There is convincing evidence that inflammation plays a pivotal role in the pathophysiology of CRPS. Immunomodulating medication reduces the manifestation of inflammation by acting on the mediators of inflammation. Therefore, as inflammation is involved in the pathophysiology of CRPS, immunomodulating medication in CRPS patients may prove beneficial.

Objectives: To describe the current empirical evidence for the efficacy of administering the most commonly used immunomodulating medication (ie, glucocorticoids, tumor necrosis factor-α antagonists, thalidomide, bisphosphonates, and immunoglobulins) in CRPS patients.

Methods: PubMed was searched for original articles that investigated CRPS and the use of one of the abovementioned immunomodulating agents.

Results: The search yielded 39 relevant articles: from these, information on study design, sample size, duration of disease, type and route of medication, primary outcome measures, and results was examined.

Discussion: Theoretically, the use of immunomodulating medication could counteract the ongoing inflammation and might be an important step in improving a disabled hand or foot, leading to further recovery. However, more high-quality intervention studies are needed.

Key Words: complex regional pain syndrome (CRPS), immunomodulating medication, efficacy

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Complex regional pain syndrome (CRPS) is a complication that may occur after surgery or trauma, but spontaneous development is also described. It was formerly known by many names, but was most commonly referred to as "reflex sympathetic dystrophy" (RSD).

The diagnosis of CRPS is based on signs and symptoms. Of the several diagnostic criteria sets available, the most commonly used are the Veldman et al,[1] the IASP,[2] and the "Budapest Criteria."[3]

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Most patients with CRPS have a burning spontaneous pain, disproportionate in intensity to the initial eliciting event, most often being a fracture of an extremity.[4] In the acute stages of CRPS, the affected limb is generally warmer than the contralateral limb, with edema as a common symptom. Hypohidrosis or hyperhidrosis is present in many patients. About 70% of the patients have weakness of all muscles in the affected region and a decrease in the active range of motion. The upper extremities are affected more frequently than the lower extremities.[5] The estimated overall incidence rate of CRPS is 26.2 per 100,000 person years.[5] Females are affected at least 3 times more often than males. The highest incidence occurs in females in the age category of 61 to 70 years.[5]

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.[6] CRPS often displays the classic aspects of inflammation.[1] There is convincing evidence that inflammation is one of the mechanisms playing a pivotal role in the pathophysiology of CRPS.[6] The presence of local inflammation was shown in a scintigraphic study on CRPS in which vascular permeability for macromolecules was demonstrated.[7] Increased systemic calcitonin gene-related peptide levels in patients with acute CRPS suggest neurogenic inflammation as a pathophysiologic mechanism.[8] Increased levels of the pro-inflammatory cytokines have been detected in fluid from artificially raised skin blisters in the involved extremity in comparison to the contralateral site; however, no correlation has been found between levels of pro-inflammatory cytokines and the characteristics or duration of the disease.[9–12] This is an indication that inflammation explains a part, but not the whole picture of the pathophysiology.

Analysis of blister fluid with a multiplex array (testing for 25 different cytokines) revealed a pro-inflammatory expression profile, with increased markers for activated monocytes and macrophages.[13] Also, a pro-inflammatory cytokine expression profile was demonstrated in the cerebrospinal fluid of CRPS patients.[14] Venous blood of patients with CRPS showed elevated mRNA levels of the pro-inflammatory cytokines, tumor necrosis factor (TNF) and interleukin (IL)-2 and serum IL-2 protein, as well as a reduction of mRNA levels of the anti-inflammatory cytokines IL-4 and IL-10.[15] Plasma demonstrated higher levels of soluble TNF-α receptor.[16] After performing technetium 99m-anti-TNF-α antibody scintigraphy, a recent case report showed that TNF-α was only localized in the affected hands of patients with early CRPS.[17] In addition, the contribution of inflammation in the pathophysiology of CRPS is suggested by the successful reports from

open-label studies on treatment with immunomodulating agents such as infliximab[18] and immunoglobulin.[19]

Immunomodulating medication reduces the manifestation of inflammation by influencing mediators of inflammation, such as cytokines, neuropeptides, eicosanoids, and amino acids. If inflammation does play a role in the pathophysiology of CRPS, then immunomodulating medication may be beneficial for CRPS patients.

Despite the fact that, especially in higher doses, nonsteroidal anti-inflammatory drugs (NSAIDs) also show anti-inflammatory effects, these drugs are not included in the group of immunomodulating medications. For this reason, we excluded them from this review. In general we know that NSAIDs have no effect in the CRPS.[20] In the Netherlands there is some popularity for treating CRPS with free radical scavengers.[21] Due to a lack of convincing evidence for effectiveness, these drugs never gained general international acceptance. For this study we decided to exclude them. This review presents the current empirical evidence for the benefit of administering the most commonly used immunomodulating drugs in CRPS patients.

GLUCOCORTICOIDS

Glucocorticoids are anti-inflammatory that prevent phospholipid release and decrease eosinophil action and a number of other mechanisms. Interactions between the nervous system, the hypothalamic-pituitary-adrenal axis, and components of the innate and adaptive immune system play a key role in the regulation of inflammation and immunity. Glucocorticoids can also inhibit prostaglandin production through some independent mechanisms.[22]

TUMOR NECROSIS FACTOR-α ANTAGONISTS

Tumor necrosis factor alpha (TNF-α) is a cytokine that promotes an inflammatory response. Although principally produced by macrophages, other cells (including lymphocytes and mast cells), and tissue cells (such as epithelial cells and fibroblasts) can also secrete TNF.[23] The possible mechanism of action of anti-TNF agents are inhibition of inflammatory "cytokine cascade" mediated by TNF; sequestration of TNF by binding; complement-mediated lysis of cells expressing TNF; altered leukocyte recruitment and endothelial activation; reduction of vascular endothelial growth factor expression and neovascularization; restoration of function of regulatory T cells, and induction of T lymphocyte apoptosis.

THALIDOMIDE

Thalidomide inhibits TNF-α production by human blood monocytes, without influencing either general protein synthesis or the expression of 3 other monocyte-derived cytokines. Thalidomide exerts a selective effect by suppressing only TNF-α secretion, neither IL-1β, IL-6, nor granulocyte macrophage colony-stimulating factor production is influenced by the drug.[24] Thalidomide was introduced as a sedative drug in the late 1950s. It was withdrawn from the market in the early 1960s due to teratogenicity and neuropathy. There is growing interest due to its immunomodulatory properties. Thalidomide is also a potent inhibitor of new blood vessel growth.[25] On the basis of this finding clinical trials were initiated, which have reported its effectiveness against multiple myeloma.[26]

BISPHOSPHONATES

The most important biological effect of bisphosphonates is the reduction of bone remodeling through the inhibition of osteoclastic activity, but there is evidence of extra-skeletal biological effects of bisphosphonates.[27] Bisphosphonates exert their effects also on cells of the immune system with an "immunomodulating" effect, influencing the production of pro-inflammatory and anti-inflammatory cytokines and changing the molecular expression involved in the immune process and anti-inflammatory response. The exact identification of target cells and interference mechanisms of bisphosphonates with the immune and inflammatory responses are not yet totally clear.

IMMUNOGLOBULINS

The mechanism of action of immunoglobulins involves modulation of expression and function of Fc receptors, interference with activation of complement and the cytokine network, provision of anti-idiotypic antibodies, regulation of cell growth, and effects on the activation, differentiation, and effector functions of dendritic cells, T and B cells.[28] Modulation of the production of cytokines and cytokine antagonists by intravenous immunoglobulin is a major mechanism by which immunoglobulin exerts its anti-inflammatory effects. The anti-inflammatory effects are not restricted to monocytic cytokines, but are also largely dependent on the ability of intravenous immunoglobulin to modulate Th1 and Th2 cytokine production.

MATERIALS AND METHODS

The PubMed database was searched from inception up to the end of August 2010. The search was for original articles (in the English language) that met our inclusion criteria. The initial search strategy included {[complex regional pain syndrome (Title/Abstract) OR reflex sympathetic dystrophy (Title/Abstract)] AND [glucocorticoids/steroids (Title/Abstract)] OR [TNF-α antagonist/anti-TNF (Title/Abstract)] OR [thalidomide (Title/Abstract)] OR [bisphosphonate/biphosphonate (Title/Abstract)] OR [immunoglobulin (Title/Abstract)]}.

The abstracts of retrieved articles were manually reviewed to assess suitability for inclusion using the following criteria: adult humans having CRPS (the previously used names for this syndrome were also allowed, eg, shoulder-hand syndrome, RSD), together with the use of one of the abovementioned immunomodulating medications. The references of the selected articles were also checked for additional relevant papers. Finally, from all studies fulfilling the inclusion criteria, the following information was examined: type of study, sample size, duration of disease, type and route of medication, primary outcome measures, and results

RESULTS

The literature search yielded 39 articles, 10 case reports, 19 observational studies, and 10 randomized controlled trials (RCTs: 7 blinded and 3 nonblinded). The results of the various medications are described below (and in Table 1).

Glucocorticoids

A total of 3 case reports, 13 open-label studies, and 5 RCTs (2 of which were blinded) were found. The 3 case

TABLE 1. Overview

Author	Type	Sample Size	Duration of Disease (Mean)	Medication	Route	Primary Outcome Measure	Outcome	Country
Glucocorticoids								
Russek et al[29]	OL	17	6.5 wk	Cortisone	Oral or intramuscular	Clinical improvement	Five complete relief of signs and symptoms, 8 marked improvement, 3 moderate improvement, and 1 no response	US
Steinbrocker et al[30]	OL	13 14		Corticotropin/ cortisone or both vs. sympathetic block		Clinical features (pain, signs, swelling, trophic changes), graded: complete recovery, greatly improved, slightly improved, or no improvement	All symptoms and signs were abolished in 4, great improvement in 4, 1 failed to respond. Recovery function depended on stage disease, complete relief of shoulder or hand pain in all but 2 patients	US and Canada
Rosen and Graham[31]	OL	15 7 20 31	1 d-4 y	ACTH/cortisone vs. stellate ganglion block, physiotherapy, other, or no specific treatment		Grading of results of treatment: excellent, good, fair, or poor	10 of 15: excellent or good result; 1 of 7: excellent or good response; 9 of 20: excellent or good result; none: excellent or good	Canada
Glick[32]	OL	17		Prednisolone	Oral	Clinical improvement: poor, no improvement, good, very good, excellent	Only 3 failed to derive any benefit	UK
Mowat[33]	CR	3	2-7 mo	Prednisolone Hydrocortisone	Local in bursa		Reduction in volume, improvement in all other symptoms & signs relieve of pain	UK
Glick and Helal[34]	OL	21		Prednisolone or methylpredniso-lone/ACTH	Oral or intramuscular	Improvement, grading very good, good, fair and poor	Relief of pain, > 50% improvement of function: 10; constituted reduction of pain, 20% improvement in range of movement: 3; relief of pain but still requiring analgesics, no improvement of movement: 5; no significant change: 3	UK
Kozin et al[35]	OL	11	4-60 wk	Prednisone		Shoulder range of motion, grip strength, tenderness and ring size	In 4 patients: improvement in all measurements, significant for swelling and tenderness	US
Kozin et al[36]	OL	55	75.9 ± 67.9 wk	Prednisone vs. stellate ganglion blockade	Oral	Subjective estimate: poor, fair, good, or excellent	Prednisone: 63% good to excellent response Stellate blockade: fair 15%, poor 85%	US
Christensen et al[37]	RCT	23	3 mo	Prednisone vs. placebo	Oral	Activity of RDS: pain, edema, volar sweating and finger-knitting ability	All prednisone-treated: more than 75% response to treatment; Placebo: 2 of 10 had improvement	Denmark
Poplawski et al[38]	OL	27	2-36 mo	Methylprednisolone	ivrb	Grading: excellent, very good, good, fair, poor	21 of 28 extremities improved significantly: 11 excellent, rest substantial improvement; 7 poor results	Canada
Dirksen et al[39]	CR	1	3 mo	Methylprednisolone	Cervical epidural		Marked pain relief, improved motor control, reduced muscular contracture and trophic changes occurred	The Netherlands
Tountas and Noguchi[40]	OL	17	< 6 mo	Methylprednisolone	ivrb	Grading: excellent, good, fair and poor	Overall late results: excellent: 9, good: 2 and fair: 4 patients	

(*continued*)

TABLE 1. (*continued*)

Author	Type	Sample Size	Duration of Disease (Mean)	Medication	Route	Primary Outcome Measure	Outcome	Country
Braus et al[41]	RCT[1]	36		Methylprednisolone vs. placebo	Oral	Shoulder-hand syndrome score	Placebo: no significant improvement; 34 treated with corticoids: 31 of them symptom free	Germany
Grundberg[42]	OL	47	8-36 wk	Methylprednisolone	intramuscular	Pain, motion PIP joint, swelling, pinch strength	In all patients: relief of night and rest pain, improvement of motion in PIP joint, swelling improved	
Zyluk[43]	OL	36	1-8 mo	Methylprednisolone	ivrb	Overall results, graded good, moderate or poor	Good: 25 patients; moderate: 8; poor: 3	Poland
Okada et al[44]	CR	1	> 3 mo	Methylprednisolone			Symptoms were dramatically improved	Japan
Taskaynatan et al[45]	RCT	22	3.1 ± 1.4 mo	Methylprednisolone vs. placebo	ivrb	VAS, range of motion and volumetric edema	No benefit in both groups	Turkey
Kalita et al[46]	RCT	60	7-100 d	Prednisolone vs. piroxicam	Oral	CRPS score	Prednisolone: improvement 83.3%; Piroxicam: 16.7%	India
Bianchi et al[47]	OL	31	10-204 d	Prednisone		VAS, clinical severity (scale 0-22)	VAS: reduction of score Clinical severity: significant improvement	Italy
Zyluk and Puchalski[48]	OL	75	< 4 mo	Dexamethasone	Intravenous	VAS; Loss of finger flexion, grip strength; CRPS score	Mean VAS decreased; mean loss of finger flexion decreased, grip strength did not improve; CRPS score decreased	Poland
Munts et al[49]	RCT	21	4.5 y	Methylprednisolone vs. placebo	Intrathecal	Change in pain	No effect on pain–> trial stopped prematurely	The Netherlands
TNF-α antagonists								
Huygen et al[18]	CR	2	2-m & 5-y	Infliximab	Intravenous	Clinical examination: pain, temperature, edema, motor function	1 slight improvement and 1 considerable improvement	The Netherlands
Bernateck et al[50]	CR	1	3 mo	Infliximab	Ivrb	Pain, temperature, hand grip strength, ROM wrist and QST	Substantial improvement of pain intensity, temperature difference, and range of motion	Germany
Thalidomide								
Rajkumar et al[51]	CR	1	3 y	Thalidomide			Improvement and near resolution of symptoms	US
Ching et al[52]	CR	1	6 y	Thalidomide			Pain and other symptoms disappeared	New Zealand
Schwartzman et al[53]	OL	42	longstanding	Thalidomide		Objective and subjective responses including increased function, healing of lesion, pain reduction, and lower analgesic requirements	17% "dramatic responses" 14% modest pain relief and/or some reduction in need for medication	US
Bisphosphonates								
Maillefert et al[54]	OL	11	> 6 mo	Pamidronate	Intravenous	VAS and Physical global assessment	Mean VAS decreased 4: no improvement/1: moderate improvement/3: significant improvement/3: excellent improvement	France
Cortet et al[55]	OL	23	15 ± 13 mo	Pamidronate	Intravenous	Decrease of pain (VAS and PVS)	Significant decrease of VAS and PVS: day 0 and day 30/day 0 and day 60/day 0 and day 90.	France
Adami et al[56]	RCT[1]	20	5-34 wk	Alendronate vs. placebo	Intravenous	VAS; arbitrary score of motion and	Diminution in VAS, tenderness and swelling; improvement in	Italy

						circumference of affected joints	motion significantly different	
Varenna et al[57]	RCT[1]	32	4.0 ± 2.3 mo	Clonadrate vs. placebo	Intravenous	VAS	Significant decrease	Italy
Siminoski et al[58]	CR	1	> 1 y	Pamidronate	Intravenous		Pain decrease— > gone	Canada
Kubalek et al[59]	OL	29	41.89 ± 38.90 wk	Pamidronate	Intravenous	Complete disappearance of pain Functional improvement: increase in range of movement more than 20	25 patients (86.2%) 14 patients (70%)	France
Robinson et al[60]	RCT	27	3 mo-6 y	Pamidronate vs. placebo	Intravenous	VAS; patient's global assessment of disease severity; functional assessment	VAS: overall score was significantly lower and percentage change significantly greater at 3 mo; global assessment of disease severity score: overall improvement at 3 mo; physical function: significantly higher scores at 1 and 3 mo	New Zealand
Manicourt et al[61]	RCT[1]	40	7 ± 2 mo	Alendronate vs. placebo	Oral	VAS pressure tolerance, edema and joint mobility	Significant decrease in mean VAS increase in mean pressure tolerance and joint mobility	Belgium
Breuer et al[62]	OL	10	4.3 ± 3.1 y	Ibandronate	Intravenous	Brief pain inventory, neuropathic pain scale patient's global impression of change scale	Patient global impression of change: 4 much improvement, 6 minimally improved; brief pain inventory: improvement; neuropathic pain qualities (9 of 10) and average and worst pain levels improved significantly	US
Santamato et al[63]	CR	1	2 mo	Clonadrate	Intramuscular	Pain level with VAS	Great improvement	Italy
Immunoglobulin								
Goebel et al[64]	OL	11 of 130	> 3 mo	Immunoglobulin	Intravenous	Ratio average pain intensity (API) value after or before therapy	20%: > 70%pain relief; 27.7%: pain reduction 25%-70%; 4.6%: moderately increased pain levels, returned to pretreatment levels; rest: no effect, or pain reduction < 25%	Germany
Goebel et al[19]	CR	1		Immunoglobulin	Intravenous		> 50% pain reduction	UK
Goebel et al[65]	RCT	13	6-30 mo	Immunoglobulin vs. placebo	Intravenous	Pain intensity	Average pain intensity was 1.55 units lower	UK

CR indicates case report; ivrb, intravenous regional block; OL, open label; PVS, pain verbal score; QST, quantitative sensory testing; RCT, randomized controlled trial; RCT[1], RCT followed by open label; ROM, range of motion; VAS, visual analogic scale.

reports described 5 patients: in all cases the signs and symptoms improved after administration of glucocorticoids.[33,39,44]

In the 13 open-label studies, various dose regimens were prescribed and different routes of administration were used.[29–32,34–36,38,40,42,43,47,48] In 3 of the open-label studies, patients who received medication were analyzed, as were those who received stellate ganglion blockade, physiotherapy, or no specific treatment. These treatments were then compared with each other.[30,31,36] Although the results of the open-label studies were based on different parameters, like clinical improvement and visual analog scale, the use of glucocorticoids seems to cause predominantly improvement in outcome. Only one of these studies described 2 major adverse events (arterial occlusion below the femorals and manic psychosis[30]); in the remaining studies only minor events (eg, weight gain) were described.

Of the 5 RCTs[37,41,45,46,49] 2 were double-blinded.[45,49] The first double-blinded study showed no improvement of CRPS using a Bier block with methylprednisolone compared with placebo.[45] The second study, in which patients received medication intrathecally, was stopped early owing to no effect after interim analysis.[49] In 2 of the remaining 3 nonblinded RCTs, use of glucocorticoids resulted in a significantly greater improvement in activity of CRPS[37] or in shoulder-hand syndrome score[41] compared with placebo. The third RCT showed a significantly greater improvement in the signs and symptoms of CRPS among patients receiving glucocorticoid compared with those receiving piroxicam.[46]

In 3 of the 5 RCTs, the patients with CRPS for a period of about 3 months.[37,45,46] In another study, patients has CRPS for a mean duration of 4.5 years,[49] and in 1 study the duration of disease was not reported.[41] The studies used different primary outcome measures. In 1 RCT, the placebo group could also receive medication afterwards (Table 1).[41] In contrast to the open-label studies, no serious side-effects were described.

TNF-α antagonists

Two case reports were found describing 3 patients.[18,50]

All 3 patients received infliximab and showed improvement in pain, temperature, and motor function. The 2 patients who had CRPS for 2 to 3 months showed greater improvement than patients with CRPS for 5 years. No adverse effects were observed.

Thalidomide

Two case reports and 1 open-label study were found.

In the case reports, thalidomide was introduced for CRPS patients with a comorbid condition.[51,52] In this case thalidomide had a beneficial effect on CRPS. In the open-label study 42 patients were treated.[53] A "dramatic response" occurred in 17% of the patients, and 14% experienced at least modest pain relief and/or showed some reduction in the need for concurrent medications. No results for the remainder of the patients were reported.

In 1 patient, due to persistent paresthesia, thalidomide was temporarily stopped after which the pain re-occurred.[52] Although patients often felt worse during the first weeks of therapy (eg, increased pain and edema) no major side-effects were reported.

Bisphosphonates

Two case reports, 4 open-label studies, and 4 double-blind RCTs were found. In the case reports the 2 patients experienced pain relief.[58,63] In the open-label studies pamidronate or ibandronate was used.[54,55,59,62] These studies reported a positive effect of both drugs on pain intensity.

Patients who participated in the RCTs were prescribed alendronate (oral or intravenous),[56,61] clonadrate,[57] or pamidronate.[60] All were compared with placebo. In 2 of the RCTs, patients had CRPS for less than 6 months,[56,57] compared with about 7 months to 6 years in the other 2 studies.[60,61] In all RCTs there was a significant decrease of pain. Apart from pain, the other primary outcome measures were different but all showed improvement. Three RCTs were followed by an open-label study in which continuation of the medication showed an additional effect; however, the difference was not significant.[56,57,61]

Side-effects were minimal (eg, transitory flu-like symptoms); 1 patient dropped-out of one of the trials due to upper gastrointestinal intolerance.[61] No serious adverse events were described.

Immunoglobulin

The search yielded 1 case report, 1 open-label study, and 1 double-blinded RCT. In the case report the patient recorded more than 50% pain reduction, accompanied by cessation of autonomic signs.[19] In the open-label study, only 11 of the 130 described patients were had CRPS,[64] in the total group of patients, 20% had more than 70% pain relief, and 27.7% reported pain relief ranging from 25% to 70% relief.

The RCT was a double-blind, randomized, placebo-controlled study.[65] Patients received either the intervention in the first period and placebo in the second, or placebo in the first period and the intervention in the second. Pain intensity was the primary outcome measure and was 1.55 units lower after treatment with immunoglobulins compared with placebo. The treatment was associated with very few adverse events, except for moderate or severe headache and transient pain increase. No serious adverse events were reported.

DISCUSSION

This literature review was conducted to assess empirical evidence for the efficacy of various immunomodulating medication in CRPS patients. The assessment is complicated by the fact that the cited studies show extensive methodological variability, that is, presence or absence of a control group, use of different designs, and varying sample compositions, diagnostic criteria, and primary outcome measures. The exact impact of the outcome is often unclear.

The CRPS criteria applied for diagnosis vary between studies. The most common criteria are the IASP criteria,[66] a revision of the criteria set has been proposed for both diagnostic and research purposes.[67] Because different criteria for diagnosing CRPS were used in the studies in this review, it is unlikely that all patients in these studies are comparable.

The studies covered the treatment of both acute and chronic conditions. A scintigraphic study to investigate whether inflammatory characteristics were present showed significantly more patients with early CRPS (existing for

≤5 mo) with a positive scintigraphy compared with patients who had CRPS for a longer period.[7] Also, although the presence of local inflammation was confirmed in the first 2 years of CRPS, cytokine levels did not correlate with either the characteristics or duration of the disease.[10] Therefore, the acute versus chronic classification is probably inadequate, and the time factor thus becomes less important.

It seems difficult to determine the appropriate period for treatment with immunomodulating medication. It is more important to determine in each patient whether or not there is still an (ongoing) inflammatory process. In addition, different primary outcome measures were used in the studies. In none of the studies was an improvement in inflammation measured. We suggest that a selection of 2 or 3 representatives from the inflammatory cytokines panel, the Th1/Th2 cytokines panel and the chemokines panel would be sufficient to indicate the activity of the CRPS disease; during the course of the disease, this selected panel could also be used to indicate the effectiveness of therapeutic intervention.[13] This might allow to better determine which patients are likely to benefit from treatment with immunomodulating drugs.

Because the studies have different designs, the degree of empirical evidence yielded also differs. Most of the included articles were case reports or uncontrolled open-label studies. On the basis of these studies, TNF-α antagonists and thalidomide were reported to have a positive effect. Noteworthy, an open-label study, in which CRPS patients received lenalidomide (a thalidomide analog), showed that lenalidomide's pain and functional improvement sustained over 52 weeks of treatment. There would be some serious adverse events, suspected to be related to lenalidomide. However, this study only appeared in a poster presentation at a congress, and these results have not been published.[68]

The immunoglobulins were also investigated by means of a randomized double-blind placebo-controlled trial; this trial also showed a positive effect, albeit a small one. However, for the glucocorticoids and bisphosphonates, more RCTs have been performed. The glucocorticoids yielded 5 RCTs, of which the 2 blinded RCTs showed no benefit. However, a disadvantage is that the intervention in these 2 latter studies was administered by means of a Bier block, or intrathecally. In contrast, in the nonblinded trials, the oral glucocorticoids had a positive effect. Oral and intravenous bisphosphonates also appeared to have a positive effect. In our opinion, the use of bisphosphonates can be recommended; however, which medication, which dose, and for how long remains unclear. Our recommendation is in contrast to another group that also reviewed the 4 RCTs of bisphosphonates,[69] they concluded that, although bisphosphonates have the potential to reduce pain, there is insufficient evidence to recommend their use.

In summary, there is increasing evidence to show that inflammation does play a role in the pathophysiology of CRPS. Immune involvement brings a mechanism-based treatment within reach. On the basis of the results of this review, the use of immunomodulating medication may counteract the ongoing inflammation and might be an important step in the recovery of the disabled hand or foot. However, as might be evident from the studies described above, this literature is of a very poor quality. Therefore, there is a need for more high-quality intervention studies.

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