

## Intravenous Immunoglobulin to Fight Complex Regional Pain Syndromes: Hopes and Doubts

Chronic pain is multifaceted. It involves changes in somatosensory processing from the primary afferent neurons to the brain; it induces negative emotions, such as fear and depression; and it often entails serious consequences for working ability and personal life. Long-standing complex regional pain syndrome (CRPS) has all of these features and may be associated with substantial reduction of limb function, leading to physical impairment (1).

In recent years, we have made progress in understanding CRPS. Studies of the acute phase of posttraumatic CRPS show the importance of cytokines (2) and growth factors (3) for pain and hyperalgesia; the involvement of peptides in changes in skin perfusion (4), edema (5), and sweating (6); and the effect of sympathetic neurotransmission on pain in selected patients (7). We have learned that in long-standing CRPS, cortical reorganization of sensory (8), motor (9), and autonomic function (10) might underlie the profound disturbances of the body reference scheme (11). Although acute CRPS can be challenging to treat, the outcome is often favorable. Treatment of chronic CRPS, when central neuroplastic changes are fully established, is especially difficult. Strict adherence to ongoing multimodal treatment is the current gold-standard approach but is often unsuccessful (12).

Consequently, patients with CRPS and their physicians welcome innovative and easier-to-implement treatments, such as those reported by Goebel and colleagues in this issue (13). In their randomized crossover trial, these investigators treated 13 patients with long-standing CRPS with infusions of intravenous immunoglobulin (IVIG) (0.5 g/kg) or placebo and evaluated outcomes over 4 weeks. Patients reported a significant reduction in pain with IVIG treatment compared with placebo. Intravenous immunoglobulin is typically used to treat immunodeficiency or autoimmune disorders. The rationale for investigating IVIG for the treatment of CRPS is the recent detection of antineuronal (the exact autoantigen remains to be determined) autoantibodies in patients with CRPS (14, 15). Intravenous immunoglobulin not only potentially interferes with these autoantibodies but also downregulates proinflammatory cytokines, which are important in the mechanisms of CRPS pain and hyperalgesia, in the peripheral and the central nervous systems (16). Pathophysiologic findings support a mechanism that may explain the results of this trial. However, despite enthusiasm for these findings, we must recognize the limitations of this preliminary clinical trial, which relate to the study design and the feasibility of treating CRPS with IVIG.

The researchers note the limitations of the study design, which include the involvement of a single center; the small number of participants; the short observation period;

and the lack of objective measures, such as edema, skin temperature, and range of motion, all of which characterize CRPS and are important to document treatment success in this disorder. Moreover, some of the measures used to assess effectiveness in this trial, such as the CRPS limb symptom scale, have not been externally validated.

In our opinion, a less obvious but critical limitation is the missing placebo response, which raises doubts about the adequacy of blinding. The observed response to IVIG (20% to 30% pain reduction from baseline) is in the range that one would expect for the placebo response. Another concern relates to the definition of “refractory to standard treatment” as a criterion for patient eligibility. Study participants had not tried certain treatments that have been shown to have some effectiveness in randomized, controlled trials, such as motor or sensory learning (12, 17), steroids, bisphosphonates, and sympathetic blocks (1).

In addition to concerns about study design, the cost-effectiveness ratio compared with alternative therapies makes IVIG an unrealistic treatment option for CRPS. It is available in limited quantities and is very expensive. Patients with long-standing CRPS may need intensive, long-term treatment. While Goebel and colleagues were conducting their trial, other randomized trials evaluated ketamine (18), magnesium (19), and tadalafil (20) for long-standing CRPS. These trials showed that some therapies have similar efficacy to IVIG and are much less expensive. We remain skeptical that those who make payment decisions will cover IVIG in CRPS—a pain syndrome with proven heterogeneous pathophysiology and substantial psychological comorbidity (21, 22)—without much more convincing evidence that IVIG is more effective than other therapies.

Multicenter randomized, controlled trials that provide data on the long-term efficacy of IVIG versus other therapies are needed to provide such evidence. However, we should not treat CRPS as a single disease entity. Several pathophysiologic mechanisms, each of which might be present to different degrees in individual patients, contribute to CRPS symptoms. Accordingly, only 40% of patients with CRPS have serum antineuronal autoantibodies (15), and inflammatory cytokines might be most relevant if pinprick hyperalgesia is present (16). Future IVIG studies should therefore focus on patients with these characteristics.

A close look at the individual treatment responses in Goebel and colleagues' study shows another reason that future trials should use “enriched” designs. Although 3 of 13 patients had very positive responses, the remaining 10 patients had no or only a transient response. If one could identify patients likely to respond, the efficacy of treatment

and the cost-effectiveness ratio might be greatly improved. Only then might IVIG offer what we have long looked for: a safe, effective, easy-to-adhere-to, and scientifically validated treatment for CRPS.

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