Human Pooled Immunoglobulin in the Treatment of Chronic Pain Syndromes

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ABSTRACT

Objective. To examine the use of intravenous immunoglobulin (IVIG) in chronic pain.

Design. A prospective multiple-dose, open-label cohort study in 130 consecutive patients who suffered from 12 chronic pain syndromes. The largest symptom groups were (number of patients): Fibromyalgia (48); Spinal pain (20); Complex regional pain syndrome (CRPS, 11); Peripheral neuropathic pain (12); and Atypical odontalgia or atypical facial pain (11). All patients had insufficient pain relief with established treatments. Pain relief was recorded using average pain intensity values as documented in standardized diaries. A specific treatment protocol was developed, and patients were enrolled over a 36-month period.

Results. Overall, 20% of patients had >70% pain relief and 27.7% of patients reported relief between 25% and 70%. Six patients (4.6%) had moderately increased pain levels for a duration of up to 9 weeks. Good relief, of more than 70%, was found in all major symptom groups. Patients with pain of short duration (<2 years) reported high relief rates (33.8% of patients in this group reported relief of >70%). No serious adverse events were reported.

Conclusions. IVIG may be effective in patients suffering from chronic pain. Controlled studies are needed to evaluate the efficacy of IVIG in these patients. Patients with a good response to IVIG may be models for the study of neuroimmune interactions in chronic pain.

Key Words. IVIG; Fibromyalgia; CRPS; Neuropathic Pain; Trigeminal Neuralgia; Myofascial Pain Syndrome

Introduction

In 1988, we treated a patient for primary hypogammaglobulinemia with intravenous immunoglobulin (IVIG). This patient had idiopathic widespread pain. The IVIG treatment gave unexpected, reproducible pain relief. We subsequently applied IVIG in the treatment of other patients, without known immunopathology, who suffered from idiopathic chronic pain syndromes. We observed marked pain relief in some patients, while others did not show any effect. Based on this experience, we developed a protocol for unblinded IVIG administration (Figure 1).

Human pooled immunoglobulin for intravenous application (IVIG) is derived from the pooled plasma of between 3,000 and 60,000 healthy blood donors. IVIG was originally administered to patients with humoral immunodeficiency [1,2]. In the beginning of the 1980s it appeared that IVIG was effective in the treatment of idiopathic thrombocytopenic purpura in children [3]. Since then, the list of therapeutic indications for IVIG has increased, and it now includes neurological diseases, such as inflammatory demyelinating neuropathies (an acute form of which is the Guillain-Barré syndrome) and multifocal motor neuropathy [4,5].

IVIG has been used to prevent and treat postherpetic neuralgia. Neu [6] successfully treated a small number of patients using 5 g of IVIG on two consecutive days. Recently, the application of IVIG enriched with anti-Varicella antibodies has been
shown to reduce the incidence of post-herpetic neuralgia when given at the acute phase of zoster neuralgia [7]. To our knowledge, no further reports exist on the treatment of chronic pain syndromes with IVIG.

We report an evaluation of the response to IVIG therapy over a 36-month study period in 130 consecutive patients suffering from chronic (>3 months), continuous noncancer pain. Therapy was based on a treatment protocol developed at our unit (Figure 1). In all patients, pain was insufficiently relieved by conventional methods (Table 1).

Methods

Study Medication

The following IVIG preparations were used: Sandoglobulin (Sandoz/Novartis, Basel, Switzerland); and Intraglobin (Bioprost, Dreieich, Germany). Both preparations contain primarily (>98%) complete (including Fab and Fc fragments) antibodies of the IgG isotype.

Patient Recruitment, Diagnoses, and Pain Recording

During a 36-month period, all consenting patients between 18 and 65 years of age who were referred to our pain clinic for chronic noncancer pain and who had insufficient pain relief with all appropriate established treatments (Table 1) were considered candidates for IVIG therapy. For the purpose of this study, “chronic” was defined as pain of duration of more than 3 months. Patients were diagnosed according to IASP (International Association for the Study of Pain) guidelines [8].

Selective IgA deficiency is a contraindication for the use of IVIG (see below) [9]. A serological test was performed on all patients on enrollment in the study to evaluate total serum IgA. Patients with an IgA level of less than 95% of the healthy population (70 mg/dL) were excluded from the study [9,10]. We only included patients with insufficient benefit from established pain therapy. Insufficient benefit was assessed in each patient using the following question: “Are you satisfied with the pain relief from treatment received so far from us/from others?” We required that a standard repertoire had been tried in each patient before commencement of IVIG therapy. This repertoire included, either as monotherapy or in combination, nonsteroidal anti-inflammatory drugs, Metamizol (Novalgin®, a pyrazolin derivate and a mainstay of pain therapy in Germany, not approved in the United States), dextropropoxyphene,

![Figure 1 Treatment algorithm for IVIG therapy.](image-url)
Human Pooled Immunoglobulin in Chronic Pain Syndromes

Table 1 Diagnoses and response to IVIG therapy

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number of patients</th>
<th>Prior pharmacotherapy</th>
<th>Patients with 25-70% pain relief (%) (group D)</th>
<th>Patients with &gt;70% pain relief (%) (group E)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRPS (Complex Regional Pain Syndrome)</td>
<td>11</td>
<td>a,b,c,e</td>
<td>2 (18.2%)</td>
<td>3 (27.3%)</td>
</tr>
<tr>
<td>Post herpetic neuralgia</td>
<td>5</td>
<td>a,b,c,d,e,t</td>
<td>2 (40%)</td>
<td>2 (40%)</td>
</tr>
<tr>
<td>Trigeminal neuralgia</td>
<td>6</td>
<td>a,b,c,d,e</td>
<td>1 (16.6%)</td>
<td>4 (66.6%)</td>
</tr>
<tr>
<td>Peripheral neuropathic pain postrauma or of unknown etiology</td>
<td>12</td>
<td>a,b,c,d,e,t</td>
<td>2 (16.6%)</td>
<td>2 (16.6%)</td>
</tr>
<tr>
<td>Phantom limb pain</td>
<td>3</td>
<td>a,b,c,d,e,t</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fibromyalgia and specific myofascial pain syndromes</td>
<td>48</td>
<td>a,b,c,e</td>
<td>17 (35.4%)</td>
<td>8 (16.6%)</td>
</tr>
<tr>
<td>Chronic tension headache</td>
<td>5</td>
<td>a,b,c,e</td>
<td>2 (40%)</td>
<td>0</td>
</tr>
<tr>
<td>Lateral epicondylitis</td>
<td>6</td>
<td>a,b,e</td>
<td>2 (33.3%)</td>
<td>2 (33.3%)</td>
</tr>
<tr>
<td>Odontalgia not associated with lesions and atypical facial pain</td>
<td>11</td>
<td>a,b,c,e</td>
<td>3 (27.3%)</td>
<td>1 (0.9%)</td>
</tr>
<tr>
<td>Spinal pain of unknown or uncertain origin, exclusive of clinical myelopathy</td>
<td>20</td>
<td>a,b,c,e</td>
<td>3 (15%)</td>
<td>3 (15%)</td>
</tr>
<tr>
<td>Central pain postspinal cord injury</td>
<td>1</td>
<td>a,b,c,e</td>
<td>1 (100%)</td>
<td>0</td>
</tr>
<tr>
<td>Chronic abdominal pain without obvious pathology</td>
<td>2</td>
<td>a,b,e</td>
<td>0</td>
<td>1 (50%)</td>
</tr>
</tbody>
</table>

*Classified according to the International Association for the Study of Pain criteria [8]; formula for pain modulation: (average pain intensity after/average pain intensity before × 100%) -100%.

Prior pharmacotherapy: a = NSAID (nonsteroidal anti-inflammatory drug); b = opioid (weak); c = opioid (strong); d = anticonvulsant; e = antidepressant; t = transcutaneous electrical nerve stimulation (TENS).

tildine/naloxone, slow-release morphine preparations, other opioid analgesics, carbamazepine, amitryptiline, and transcutaneous electrical nerve stimulation (TENS) where applicable (Table 1). Gabapentin was not readily available for clinical use at the beginning of this study [11]. Patients were asked before each application of IVIG for symptoms of an acute viral or bacterial infection (e.g., the common cold or flu). In patients with infection, IVIG application was deferred.

Participants were asked to record, in the evening, their average pain intensity (API) over the previous 24 hours on a 0-10 box-scale, with 0 representing “no pain” and 10 “the worst pain imaginable.” Patients also noted any adverse events with therapy. In all patients, the treatment was given on an outpatient basis.

**Treatment Protocol**

Patients continued to take their pain-related medication if commenced more than 3 weeks before enrollment. In each patient, therapy was initiated using a total dose of 9-18 g of IVIG (at the discretion of the treating physician, Figure 1), divided into three applications, given over 1 week (“cycle”). If no pain relief was reported following the first cycle, patients were considered nonresponders and therapy was not continued. If, after 28 days, incomplete pain relief was reported, i.e., a relief that was considered unsatisfactory (see above) by the patient, a relief that lasted less than 4 weeks, or both, we applied IVIG at a higher dose (3 × 10 g given over 1 week). This 28-day time period was chosen based on our experience from patients treated before the commencement of this study. Treatment efficacy was evaluated at 28-day intervals for the duration of the study. When the patient noted additional, yet still unsatisfactory, pain-relieving effect, therapy was repeated for as long as additional effects were seen with repeated treatment or until the patient was pain free.

In cases where treatment was stopped due to satisfactory pain relief, patients were encouraged to continue using their pain diary. IVIG treatment was reestablished in those patients with pain recurrence.

Some patients with pain relief following IVIG therapy reported side effects of the concomitant pain medication. In these cases, concomitant pain medication could be reduced upon discussion with the treating physician.

The primary outcome variable was the ratio of the API value recorded 28 days after administration of the last IVIG therapy to that of the API value directly before that therapy. The percentage pain reduction or increase (Table 1) was classified into one of five groups: A = marked increase in pain (>25%); B = moderate increase in pain (0-25%); C = no or minimal pain reduction (0-25%); D = 25-70% pain reduction; and E = greater than 70% pain reduction, including complete pain relief.

Statistical analysis was performed using the software program INSTAT

**Results**

During the 36-month study period, 130 patients were enrolled: 82 female, 48 male, mean age (± standard deviation, SD) = 46.5 (± 13.2) years, mean duration of disease (± standard error of the
mean, SEM) = 6.1 (± 0.6) years. Patients were classified according to IASP guidelines into one of 12 chronic pain syndromes (Table 1). No patient had autoimmune disease with recognized efficacy of IVIG.

**Pain Relief**

Twenty-six patients (20%) of our 130 study population reported more than 70% pain relief after a median of three treatment cycles (range = 1-23 cycles, Figure 2A). The response pattern in this group was variable, with some patients needing treatment in weekly intervals throughout the study, while others required only one treatment cycle for lasting pain relief. Thirty-six patients (27.7%) reported a pain reduction of between 25% and 70%. No patient experienced a severe pain increase (Group A), although six patients (4.6%) reported moderately increased pain levels (Group B), which returned to pretreatment levels within 9 weeks of stopping IVIG therapy.

All patients in Group B and 43 patients in Group C were considered nonresponders after the first treatment cycle and did not receive further treatment. We found no differences in age (Wilcoxon’s nonparametric test), sex (Chi-squared test), or any of the clinical or anatomical pain characteristics among response groups to IVIG therapy. Patients

![Figure 2 A) Treatment outcome in 130 patients with 12 chronic pain syndromes; calculated as (average pain intensity (API) after treatment/API before treatment × 100%) - 100%. (B) Pain reduction in Group E (>70% reduction or complete pain relief) related to pretreatment pain duration. *P<0.03 versus all other patients.](image-url)
with greatest therapeutic benefit (Group E) had significantly shorter pretreatment duration of symptoms (disease duration, DD) when compared with all other patient groups combined (average = 3.8 versus 6.7 years, \( P < 0.02 \), Wilcoxon’s nonparametric test). We analyzed the pain relief provided by IVIG in relation to the duration of pain symptoms (Figure 2B). Patients with a DD of less than 1 year (20 patients, 8 in Group E, \( P < 0.03 \)) or less than 2 years (first and second bar in Figure 2B: 48 patients, 15 in Group E, \( p = 0.0116 \)) had a significantly higher Group E response rate than all other patients (Table 2; Chi-squared test).

**Adverse Events**

One or more adverse events were reported by 19.2% of patients (25 patients). Each of these were less than 2 days duration and included fevers, chills, sweating, postural hypotension, nausea, vomiting, diarrhea, lethargy, anxiety, restlessness, sleep disturbances, bilateral headache, and symptoms or signs suggestive of an anaphylactoid reaction (wheezing, nasal congestion, itch, or exanthema, see below). No patient received anti-allergic treatment, however, nausea and vomiting were treated with oral metoclopramide. No correlation was observed between reported side effects and treatment outcome. Two days of absence from work were recognized as linked to side effects from this treatment. Forty-six of our patients (35.4%) reported a transient pain increase, other than headache, following the administration of IVIG. This lasted less than 4 days, except in those six cases reported above who had a pain increase lasting more than 4 weeks.

### Table 2 Diagnoses and Group E* response to IVIG treatment in patients (DD ≤2 years)

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number of patients</th>
<th>Patients with &gt;70% pain relief</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRPS</td>
<td>5</td>
<td>2 (40%)</td>
</tr>
<tr>
<td>Post herpetic neuralgia</td>
<td>3</td>
<td>2 (66%)</td>
</tr>
<tr>
<td>Peripheral neuropathic pain post trauma or of unknown etiology</td>
<td>6</td>
<td>1 (16.6%)</td>
</tr>
<tr>
<td>Phantom limb pain</td>
<td>1</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Fibromyalgia and specific myofacial pain syndromes</td>
<td>18</td>
<td>6 (33%)</td>
</tr>
<tr>
<td>Chronic tension headache</td>
<td>2</td>
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<td>1 (33%)</td>
</tr>
<tr>
<td>Spinal pain of unknown or uncertain origin, exclusive of clinical myelopathy</td>
<td>5</td>
<td>1 (20%)</td>
</tr>
<tr>
<td>Total number of patients with DD ≤2 years</td>
<td>48</td>
<td>15 (31.3%)</td>
</tr>
</tbody>
</table>

*Group E = more than 70% pain relief; DD = disease duration.

**Discussion**

The treatment of patients with chronic idiopathic pain continues to pose a challenge to physicians both at a community level and in specialized pain centers. Despite improved knowledge of underlying mechanisms and better treatment regimens, many patients who have chronic pain respond insufficiently to established medication and pain management [12].

We examined a new treatment in patients who responded insufficiently to conventional pain therapy. One hundred and thirty patients with 12 idiopathic chronic pain syndromes were treated. We observed pain relief, of more than 70% of the average pain intensity, in 8% to 40% of patients, depending on the disease duration (Figure 2B). Overall, 20% of patients had pain relief of more than 70% following a median of three treatment cycles.

**Mechanisms**

A summary of proposed mechanisms in other disorders where IVIG is currently applied is given in Figure 3 [1,4,13-16]. With one exception [15], the mode of action is not known with certainty in any of these disorders. It is not known which mechanism(s) may be responsible for the action of IVIG in chronic pain. We recently demonstrated a higher frequency of serum antibodies against intestinal pathogens in patients with CRPS compared with healthy controls [17,18]. It is tempting to speculate that protective antibodies present in CRPS may bind and deactivate pathogenic, postinfectious antibodies present in the patient’s serum. In a different approach, Sommer at al. demonstrated altered expression of tumor necrosis factor (TNF) in neural and perineural tissue in animal models of neuropathic pain [19]. IVIG may work by binding to perineural TNF, or indeed, by modulating TNF mRNA expression in neurons, glial cells, or perineural macrophages. At this point, our results may generally be seen as clinical evidence for a neuroimmune interaction [20,21] in a subgroup of patients with chronic pain.

**Inclusion Criteria**

For patients with *intermittent* chronic pain syndromes, the consideration of the time *interval* between attacks has an important role in judging the treatment effect. Treatment benefit based on lengthening intervals between attacks is difficult to compare with benefit based on reduction in *constant* pain. Therefore, although we have previously used IVIG in the treatment of patients with intermittent...
chronic pain syndromes, such as migraine, we excluded this group from our study. Indeed, all patients with trigeminal neuralgia in this study had daily symptoms.

Study Design and Measurement of Pain Reduction

As this study was not controlled, we cannot determine the magnitude of a possible placebo response to IVIG. The time course of the placebo effect has not been sufficiently studied [22]. In pain literature, placebo effects are frequently reported to mimic the “true” drug effect in the short term following placebo application, and to last shorter than the effect of the “true” drug [23]. From this, it may be concluded that the effect observed at 28 days following IVIG administration in unlikely to be due to a placebo effect. However, placebo responses have also been reported as varying systematically with the efficacy of the active analgesic medicine [24]. In addition, our design does not allow for the natural history of chronic pain (some patients, although impossible to determine who, may have improved without any treatment). Clearly, placebo-controlled studies are needed to confirm our results.

Three details in the study design may have caused a bias toward a too low reporting of pain relief with IVIG. First, an incremental treatment effect is evident in some patients with repeated administration of IVIG. We stopped analyzing patient diaries at the end of the 36-month time period. Patients who were admitted toward the end of the study period may not as yet have obtained maximal benefit. Second, the primary outcome variable was defined as the ratio of the API value after therapy to the API value before the last therapy cycle within the study period. A comparison of the API value after the last with the API value before the first IgG application was not applied as it may have resulted in an invalid comparison of pain values recorded at two ends of what was either a long or variable time interval. The API values before the last therapy cycle, however, in some patients, already reflected a reduction from the original API value before initiation of IVIG therapy. It may be argued that, using a one-point measurement to describe treatment benefit, we may have overestimated such benefit, as we do not control for possibly higher pain levels within the 28-day period. However, clinically, we rarely observed pain increases (except in the first 3 days following IVIG administration, see below) within the 28-day period when there was pain relief after 28 days (data not shown).
Finally, the threshold for patients to be included into Group E was a >70% pain reduction. This is more stringent than criteria commonly used for efficacy in pain trials, which require a >50% pain relief [25].

During the course of the study, we observed that the variability in the first treatment step, where “at the physicians discretion” a dose of either 3 × 3 g or 3 × 6 g was prescribed, may unnecessarily have prolonged attempts to treat pain with IVIG in particular patients, especially when a dubious response was noted following the application of 3 × 3 g. We, therefore, recommend for future trials to commence with a full dose of 3 × 10 g.

We also realized that IVIG therapy may not only reduce pain levels, but it may independently influence the mood of patients with pain. For example, in spite of unchanged pain levels, some patients expressed that they felt better overall following IVIG therapy. IVIG treatment has been shown to reduce neuropsychiatric symptoms in rheumatic disease [26].

The failure of traditional pain treatment was assessed by recording patient satisfaction. This has, however, not been specifically documented with respect to IVIG therapy. In controlled studies, the effects of IVIG on mood, enjoyment of life [27] and patient satisfaction should be measured.

**Dosage and Costs of IVIG Application, Predictive Factors for Treatment Outcome, and Long-term Treatment**

The dosage used in our study is on the lower end of dosages commonly applied in antibody replacement therapy [10]. It constitutes approximately one quarter to one fifth of those dosages used in other immune-mediated diseases, including the Guillain-Barré syndrome [5]. In preliminary observations before the commencement of this study, we found that increasing the dosage of IVIG above 3 × 10 g rarely enhanced the treatment effects.

IVIG treatment at our clinic currently costs $800 for one cycle of three applications with 10 g of IVIG each. In the United States, costs of IVIG therapy are higher. We believe that IVIG therapy is most economic if applied when other medical treatment modalities have been exhausted. To reduce costs, it will be essential to find predictive factors for a positive response to treatment. In parallel with results from IVIG use in studies of other disorders [28], the outcome in our study was correlated with disease duration (Figure 2B), but was not influenced by either age or sex. Patients with the best response to IVIG were found in most diagnostic groups (Table 1), and the power of this study was too low to determine intergroup differences.

Future research may show if the efficacy of IVIG remains constant in patients who require repeated drug administration over several years and who are treated from early on. If that were the case, this would support the use of IVIG as early as possible in the development of a chronic pain disorder. Alternatively, IVIG may lose its efficacy with time. We have observed that the overall Group E response rate is 15% or less when IVIG was given several years after the onset of pain (Figure 2B).

We do not know if IVIG treatment will “cure” chronic pain. Our observation period was too short for definitive answers to this question, however, some patients, particularly in the trigeminal neuralgia group, reported complete relief of pain following the first treatment and for the remainder of the trial (data not shown) [29].

**Adverse Events**

Twenty-five of our patients (19.2%) reported one or more adverse events with IVIG therapy (see above). Such events started either at the time of the IVIG infusion or with a several hour delay. Most reactions occurred on the first or second infusion. All of the reactions we observed are commonly described with IVIG treatment [1,9,10], were self-limiting (with less than a 2-day duration), and did not require treatment other than metoclopramide in rare cases of nausea. In our experience, the administration of IVIG during the course of an infection (e.g., the flu or common cold) will result in an enhancement of side effects.

In patients with an absence of IgA or severe IgA deficiency, it is believed that IVIG administration will result in the formation of immune complexes between IgA antibodies present in the drug and traces of preformed anti-IgA in patients [1,10]. In some cases, this may result in life-threatening anaphylaxis. Therefore, the use of IVIG is contraindicated in these patients.

We did not observe any of the more serious adverse events that have been reported with IVIG therapy: Thrombosis, neutropenia, acute renal failure, and severe aseptic meningitis (with severe headache, vomiting, and fever, which responds to strong analgesia and subsides in 24–48 hours) [1,10,30,31]. These complications are known to develop as late as 7 days following IVIG infusion, yet they are rarely described with low-dose IVIG therapy such as ours. An adverse event not previously de-
scribed, although commonly encountered in our patients, was pain increase other than headaches or low back pain [32]. Forty-six of our patients (35.4%) reported some degree of pain increase for a period of no longer than 3 days. We found no correlation between this symptom and the response to treatment from Day 3 onward.

Several prophylactic options to prevent or ameliorate early side effects with IVIG are available. These include a slow infusion rate, the preemptive use of cortisone and antihistamines [10,33], and possibly the subcutaneous administration of IgG (using parallel dosages) [34,35]. In this study, we applied a slow infusion rate (10 g given over 1.5 hours) when possible.

**Safety**

IVIG is derived from the pooled serum of a large donor group. This is thought to guarantee that IVIG preparations contain as “complete” a spectrum of “protective” antibodies as possible. By using methods of careful donor selection and several chemical, mechanical, and microbiological steps of processing, the risk of viral transmission from infected donor blood is drastically reduced compared with unprocessed serum. These steps are ensured in all IVIG preparations licensed for European and U.S. markets. Safety standards are being improved with the advent of new technologies [36,37]. Since 1994, there has been no published report anywhere of hepatitis A, B, or C or HIV transmission following IVIG application. As the risk of viral transmission is not, and probably never will be zero, patients must be informed about this.

There are no reports of human-to-human transmission of prion disease by blood products. In addition, there is a reassuring absence of cases of a new prion disorder, Variant Creutzfeld-Jakob Disease, among patients with hemophilia [38]. However, persons who have spent time in Great Britain (where most cases of Variant Creutzfeld-Jakob Disease have emerged) have been excluded from blood donation. At this point, the risk of prion infection following the application of serum-derived products from infected human subjects appears to be very low.

**Conclusions**

The use of intravenous immunoglobulins may provide a new, effective treatment for patients with chronic pain syndromes. Treatment comes at considerable cost and other therapeutic options should be fully evaluated before initiating IVIG treatment. Future research into the mechanism of action of IVIG may help in distinguishing responders from nonresponders to IVIG and may open a new page in obtaining a mechanism-based classification in chronic pain [39]. The effects of subcutaneous administration of IVIG and preemptive methylprednisolone on an early pain increase should be further explored. Prospective, randomized, and blinded studies are now needed to assess the efficacy of IVIG in chronic pain.

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