Symposia Report

Immunoglobulin G for the Treatment of Chronic Pain: Report of an Expert Workshop

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Introduction

Chronic pain carries a heavy burden, in that it has a great impact on patients’ quality of life (QoL) and disability. Despite the availability of different drugs, most patients with chronic nociceptive pain do not receive satisfactory pain relief or report side effects [1,2]. Moreover, no more than 30–40% of patients with neuropathic pain (NP) obtain ≥50% pain reduction by currently available therapies [3,4].

Our incomplete understanding of the pathophysiology of chronic pain may be one of the main reasons why its treatment still represents an unmet need.

Peripheral and central changes are the main factors causing chronification of nociceptive and NP. At the peripheral level, they include peripheral sensitization (i.e., enhanced response to stimuli by peripheral nociceptor) and aberrant activities (ectopic discharges, ephaptic coupling) in the nerve axon and the dorsal root ganglion (DRG). Central sensitization leads to enhanced responses to painful stimuli in the dorsal horn neurons of the spinal cord. According to the commonly accepted pathogenetic view, these phenomena are due to neuronal changes (i.e., dysregulation of the synthesis or the functioning of ion channels, increased release of excitatory neurotransmitters and neuromodulators, and reduced function in descending pain inhibitory systems) [4].

In recent years, converging evidence from animal models and human pain conditions has suggested that interactions between the immune system and pain pathways may be the leading factors and/or contribute to peripheral and central sensitization, as well as aberrant nerve axon and DRG activities. Mast cells, activated macrophages, and secreted immune factors play the main role in the peripheral nervous system, while microglia is the lead actor in the spinal cord. Very recently, the demonstration that pathological autoantibodies to specific neuronal and glial proteins, in particular to components of the voltage-gated potassium channel complex (VGKC-complex), may cause pain added a further piece of information to this topic [5]. Better knowledge of these immune-pain interactions, which are briefly summarized in Figure 1, might ultimately lead to new therapeutic interventions for chronic pain [6].

Human immunoglobulin G (IgG) concentrates are immune-modulating, anti-inflammatory blood plasma-derived products that can be applied either intravenously (intravenous immunoglobulin [IVIg]) or subcutaneously (subcutaneous immunoglobulin [SC Ig]). Converging evidence supports the concept that IgG may represent a valid treatment of pain associated with some established peripheral neuropathies, such as those in diabetes mellitus (DM) and Sjögren’s syndrome (SS), and a range of pain conditions, including fibromyalgia (FM), complex regional pain syndrome (CRPS), post-polio syndrome (PPS), and pain associated with specific autoantibodies that are likely to interfere with specific receptor-targets [5,7]. Despite their pathophysiological heterogeneity, most of these chronic pains are characterized by evidence of abnormal local and/or systemic cytokine production [8–16]. The analgesic action of IgG in these conditions might thus be explained through synergistic effects of some of the large number of already established IVIg...
mechanisms of action, including modulation of cytokine expression and function, and immunosuppression [17].

In recent years, evidence has accumulated suggesting that IgG may play a role in refractory chronic pain, and researchers with experience on this topic organized an investigator-driven expert workshop in Liverpool, UK, in October 2012. During this meeting, published experiences in the use of IVIg and SCIg in these pain conditions, including indications, costs, effectiveness, and side effects, were discussed. The organizers of the workshop sought the support of charities and pharmaceutical companies (see Funding statement for details).

Pain in Diabetic Peripheral Neuropathies

DM is the commonest cause of peripheral neuropathy [18]. IVIg efficacy on pain has been assessed in both diabetic lumbosacral radiculoplexus neuropathy (DLRPN) and in distal symmetric polyneuropathy, the most common DM-associated neuropathy.

DLRPN

DLRPN, which is also known as diabetic amyotrophy, femoral or femoral-sciatic neuropathy, diabetic mononeuropathy multiplex, and proximal diabetic neuropathy, is rare but stands among the most painful complications of DM [19]. DLRPN begins focally and unilaterally, but may spread bilaterally, and has long-term morbidity due to pain and, to a minor extent, limb weakness [20]. Pain in the thoracic or abdominal wall because of multiple radiculopathy and marked weight loss may precede DLRPN onset [20]. Analgesics and drugs for NP often cannot achieve adequate pain reduction in DLRPN. Regarding immune-modulating treatments, the results from a single randomized, controlled trial (RCT), comparing intravenous methylprednisolone vs placebo in DLRPN, indicated an effect on NP but were published in abstract form only [21]. Retrospective case series and reports offer Class III and IV evidence that such therapies, including corticosteroids, IVIg, plasma exchange (PE), or their combination, may reduce pain in DLRPN, with worst side-effect profile for corticosteroids and some discrepancies.

Figure 1 Interactions between the immune system and the pain pathways. ATP = adenosine triphosphate; BK = bradykinin; DRG = dorsal root ganglion; His = histamine; IL = interleukin; NO = nitric oxide; PG = prostaglandin; PNS = peripheral nervous system; TNF-α = tumor necrosis factor alpha.
between these interventions in regard to the onset and amount of pain relief [18,20,22,23]. According to the experience gained by one of the workshop participants (ST), in eight patients (19 IVIg courses), pain intensity was reduced by 62.3% ± 20.5% (range 11–92%), and six out of the eight (75%) patients were responders (i.e., they showed pain reduction >50%) after IVIg (0.4 g/kg/day for 5 days); onset of pain reduction started 5–12 days after IVIg, peaked at 20–45 days, and in most cases, pain did not reappear. Some patients relapsed after 10.1 ± 2.4 (range 6–13) months; no patient reported relevant side effects or discontinued treatment (Table 1). These reports are in keeping with the presumed pathogenesis of DLRPN as an immune-mediated microvasculitis of the nerve roots, lumbosacral plexus, and peripheral nerve, leading to ischemic damage. However, the view that modulating the immune system may improve pain in DLRPN is still not confirmed because DLRPN may improve spontaneously and controlled studies are lacking [20]. Immune-modulating interventions may have a differential effect on DLRPN, in that some patients do respond to IVIg despite no response to corticosteroids [18]. There is no direct comparison of IgG and PE in DLRPN, but general considerations may be in favor of IgG because of the easier handling, option for home treatment and advantageous side-effect profile. In keeping with the view that the underlying cause of DLRPN is not systemic but local microvasculitis, general immune markers (erythrocyte sedimentation rate, rheumatoid factor, antinuclear antibodies, and other markers) are commonly negative, and cerebrospinal fluid (CSF) proteins are only slightly elevated or normal in this condition. Future studies should better support the therapeutic role of IgG in this condition by documenting alterations of inflammatory markers, such as serum or CSF cytokines, in parallel with pain reduction after IgG treatment. Such markers might also offer prognostic information to classify patients as good or bad responder.

Distal Symmetric Painful Polyneuropathy

One randomized open trial has assessed the efficacy of IVIg in distal symmetric painful polyneuropathy. The study included 12 patients with diabetic neuropathy (pain duration: 6 months to 5 years) and pain refractory to conventional therapies, who received either IVIg (0.4 g/kg/day for 5 days), in addition to their regular therapy, or continued with their previous therapy [24]. In the five diabetic patients treated with IVIg, mean pain intensity (visual analog scale [VAS]) significantly dropped (77/100 at baseline, 38 at week 1, 34 after 4 weeks, 33 after 8 weeks) and 80% of patients were responders (i.e., pain reduced by >50%), while pain did not change in the seven diabetic patients of the control group; pain reduction started after 5 days and peaked at 1–2 months [24]; one patient relapsed after 7 months. In contrast, other workshop participants found that symmetrical painful peripheral polyneuropathy of DM usually does not show the same benefit to IVIg as DLRPN [25] and have suggested pathophysiological differences between these two types of neuropathy. An ongoing RCT [26] is currently assessing the IVIg effect in diabetic symmetrical polyneuropathy.

Pain in Neuropathy Associated with SS

SS is associated with a wide spectrum of neuropathic manifestations, including sensory ataxic neuropathy, painful sensory neuropathy without sensory ataxia, multiple mononeuropathy, multiple cranial neuropathy, trigeminal neuropathy, autonomic neuropathy, and radiculoneuropathy [27]. Patients with neuropathy associated with SS may report pain, with both superficial and deep sensory involvement, and there may be an overlap between ataxic and painful neuropathy in some patients [27]. Histopathological findings from SS autopsy cases indicate prominent reduction of small neurons in the DRG of a patient with painful neuropathy and of large neurons in a case with ataxic neuropathy [28]. The hypothesized mechanisms of DRG neuron loss in neuropathies associated with SS is cytotoxic autoimmunity [28].

The NP in some SS patients is very severe and usually not relieved by conventional treatments. Five patients affected by painful neuropathy associated with SS were treated with IVIg (0.4 g/kg/day for 5 days) in an open study; all of them showed a remarkable improvement in NP, in that VAS was reduced by 73% (from 7.6 ± 2.9 to 2.2 ± 1.5) within 2 weeks (onset of pain reduction = 2–14 days) following IVIg therapy treatment, and the observed clinical improvement persisted for 2–6 months (Table 1) [29]. Two patients showed pain relapses over long-term follow-up; IVIg treatment was effective at each relapse, but the effect became less pronounced in one patient after 6 years of treatment [29]. There is no direct comparison between different immunomodulatory treatments in SS-associated painful neuropathy, but the response rate to IVIg (67%) appeared to be higher than that to corticosteroids (17%), which were previously tested in a small case series [27].

Post-Herpetic Neuralgia (PHN) and Peripheral Post-Traumatic NP

In one early open study on five patients with longstanding PHN treated with low-dose IVIg (0.5 g/kg), there was a remarkable response in two patients (>70% pain relief), and a smaller response (>25% pain relief) in two additional patients [30]. However, in a recent small, exploratory, double-blinded, crossover, placebo-controlled RCT (IVIg 0.4 g/kg/day for 5 days vs saline) [31], neither of the three included patients with PHN had any treatment benefit. Diagnosis of NP was confirmed by the Douleur Neuropathique 4 Questions (DN4) [32], but, of note, in neither trial were attempts made to determine positive or negative sensory signs, or nerve fiber density. In these same two studies, only 2 out of 12 (17%) and 0 out of 3 patients, respectively, with post-traumatic NP had beneficial pain relief (i.e., pain reduction ≥50%) to IVIg, suggesting that this group of patients may be generally less or not responsive.
### Table 1  Response to immunoglobulin G and its time course according to the authors’ experience

<table>
<thead>
<tr>
<th>Pain condition</th>
<th>Tx</th>
<th>Dosage</th>
<th>No. of Subjects</th>
<th>Response to Corticosteroids*</th>
<th>Time to Effect Onset</th>
<th>Time to Peak Effect</th>
<th>Duration</th>
<th>RR</th>
<th>Common side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>DLRPN</td>
<td>IVlg</td>
<td>2 g/kg</td>
<td>9</td>
<td>RR ~50% to MTP 1 g/kg/5 days</td>
<td>5–12 days</td>
<td>20–45 days</td>
<td>Indefinite in 8 pts, 3 pts relapsed after 10.1 ± 2.4 (range 6–13) months</td>
<td>75%</td>
<td>Headache, mild hypertension</td>
</tr>
<tr>
<td>DNP</td>
<td>IVlg</td>
<td>2 g/kg</td>
<td>5</td>
<td>NT</td>
<td>5 days</td>
<td>1–2 mos</td>
<td>1 pt relapsed after 7 mos</td>
<td>80%</td>
<td>None</td>
</tr>
<tr>
<td>SS</td>
<td>IVlg</td>
<td>2 g/kg</td>
<td>5</td>
<td>RR 17% to PSE 1 mg/kg/day</td>
<td>2–14 days</td>
<td>Days—months</td>
<td>2–6 mos, IVlg effective at each relapse, but less pronounced after 2–6 years</td>
<td>80%</td>
<td>Headache, pompholyx-like skin reaction</td>
</tr>
<tr>
<td>CRPS (&gt; 6 mos duration)</td>
<td>IVlg</td>
<td>0.5 g/kg</td>
<td>23 (12 of which in the RCT)</td>
<td>None in CRPS &gt; 6 mos duration to PSE 100 mg x 4 days, tapered by 25 mg every 4 days (in preparation)</td>
<td>Median 2 days</td>
<td>Median 5 days</td>
<td>2–10 weeks after single dose, preliminary evidence for induction of remission after maintenance treatment for 3–12 months</td>
<td>~25%</td>
<td>Headache, temporary pain increase</td>
</tr>
<tr>
<td>FM</td>
<td>IVlg</td>
<td>2 g/kg, then 1.2 g/kg/3 weeks (0.4 g/kg/day)</td>
<td>45</td>
<td>None/transient to BMT 6–12 mg IM</td>
<td>5 days</td>
<td>3–6 months</td>
<td>May relapse upon discontinuation</td>
<td>50–75%</td>
<td>Headache, skin rash, fatigue</td>
</tr>
<tr>
<td>PPS</td>
<td>IVlg</td>
<td>90 g</td>
<td>179</td>
<td>NT</td>
<td>2–4 weeks</td>
<td>4–8 weeks</td>
<td>6–12 months</td>
<td>35%</td>
<td>Headache, slight fever</td>
</tr>
</tbody>
</table>

* Most of the data on corticosteroids are from different patients than those treated with IgG. BMT = betamethasone; CRPS = complex regional pain syndrome; DLRPN = diabetic lumbosacral radiculoplexus neuropathy; DNP = diabetic neuropathic pain; FM = fibromyalgia; IM = intramuscular; IVlg = intravenous immunoglobulin; MTP = methylprednisolone; NT = not tested; PPS = post-polio syndrome; PSE = prednisone; pt(s) = patient(s); RCT = randomized, controlled trial; Ref = reference (the Authors reviewed all their treated cases and sometimes the number of reported cases may be higher than the number of cases cited in the reference), references in bold indicate RCTs; RR = responder’s rate (i.e., % of patients achieving pain reduction >50%); SCIg = subcutaneous immunoglobulin; SS = Sjögren’s syndrome; Tx = treatment (type of IgG).
Pain Relief with IVlg

CRPS

Treatment of long-standing CRPS is empirical and often of limited efficacy [33]. Preliminary data suggest that the immune system is involved in sustaining this condition [34], perhaps through an autoimmune mechanism [7,35], and that treatment with low-dose IVlg may substantially reduce pain in some patients. An open trial of repeated low-dose treatment (usually 36 g equal approximately to 0.5 g/kg) in 11 patients was first performed, where 3/11 patients experienced >70% pain relief after repeated treatments and 6/11 patients had no benefit [30]. A subsequent crossover RCT in 13 CRPS patients, who were treated with IVlg (0.25 g/kg/day for 2 days) and saline [36] was positive. The average pain intensity 4–19 days after IVlg treatment was 1.55 units lower than after saline, and in three patients, pain intensity after IVlg was reduced by >50% more than after saline. Median onset of pain reduction and median time to maximal effect were 2 and 5 days, respectively (Table 1). The duration of the effect was variable, but pain returned to baseline by 3 months in all patients. No serious adverse reactions were reported. A larger RCT is currently being conducted aiming to confirm these findings [37]. In a follow-on study, three patients (disease duration >5 years) with >30% pain relief in the RCT received openly first a single dose of either 1 or 0.5 g/kg IVlg, and if they had >30% pain relief, they continued receiving SClg in weekly home applications through a small pump. Two of these three participants experienced profound and sustained pain reduction during their 3–12 months of maintenance SClg treatment; the 1 g/kg doses were not more effective than the 0.5 g/kg doses in the earlier RCT. Both patients remained in remission at 12 months after treatment stop [38]. It should be noted that induction of long-lasting remission was unexpected and had not previously been observed. In earlier studies, patients had been scheduled for repeat treatment only when their pain had become unbearable, usually every 6–12 weeks, and plasma-IgG levels would be assumed to have repeatedly returned to baseline, although this was not measured; in contrast, in this latter study, a higher IVlg trough concentration may have been maintained. It is possible that maintenance of higher IgG-plasma levels over several months induces disease remission in CRPS, as is known in some other IVlg-responsive conditions [39]; however, studies in larger groups would be required both to confidently confirm these clinical results and to clarify trough levels. There is currently no published evidence suggesting a better efficacy for high-dose as compared with low-dose IgG treatment. Use of a Liverpool protocol for future treatments is suggested: patients should first be treated with an intravenous loading dose of 0.5 g/kg; if >40% pain relief is achieved, patients should—commencing 2 weeks after the loading dose—be offered a trial of 6–12 months of low-dose maintenance treatment; this could be either 0.5 g/kg/month divided into weekly portions (or even smaller portions if a “push-technique” is used instead of a pump) for subcutaneous therapy; or 0.5 g/kg every 3 weeks intravenously; after 3–6 months an attempt should be made to halve these doses, and after 6–12 months to stop treatment. In the United Kingdom, such a treatment protocol may be cost-effective [38]. Future research should examine the efficacy of this protocol. The value of establishing an international treatment registry is suggested to enhance such research efforts.

Pain in FM

The current favored paradigm in FM suggests that a central nervous system (CNS) neuromodulatory dysfunction leads to central sensitization, which results in a pain amplification syndrome [40]. Nevertheless, there is some evidence for elevated levels of cytokines (e.g., tumor necrosis factor alpha [TNF-α], interleukin (IL)-1β, IL-6, etc.) in the skin and sera of affected patients. Immune-mediated neurogenic inflammation has also been suggested as an underlying cause of pain in some patients [41]. Pain descriptors reported by FM patients are similar to those used by diabetics with known peripheral NP [42]; however, pain descriptors cannot consistently separate NP from nociceptive pain [43]. It has been reported that a subgroup of FM subjects have clinical evidence of stocking hypesthesia, proximal muscle weakness, and electrodiagnostic findings of demyelinating abnormalities [44]. Significantly reduced epidermal nerve fiber density (ENFD) and an inverse correlation between IL-2 receptor and ENFD in this subgroup of FM patients [45] argue in favor of a peripheral, immune-mediated, neuropathic mechanism. Recently, other investigators, assessing a different patient group, also found epidermal nerve fiber rarification in FM, although without evidence for large fiber involvement in FM [46].

Based on these findings, a peripheral immune-mediated injury was postulated in FM [44,45]. IVlg therapy (0.4 g/kg/day for 5 days) was attempted with good results on pain, tenderness, and proximal muscle strength in an open-label study of 15 FM patients [44]. According to the experience gained by one of the workshop participants (XJC) in 45 patients, 50–75% patients were responders (i.e., pain reduced by >50%) to IVlg (initially 0.4 g/kg/day for 5 days, followed by 1.2 g/kg every 3 weeks, given as 0.4 g/kg/day); median onset of pain reduction was 5 days after IVlg (i.e., the last day of the first IVlg course), and peak effect at 3–6 months; pain might relapse after discontinuation; side effects were usually mild (headache, skin rash, fatigue) and transitory (Table 1).

Pain in PPS

Many patients affected by poliomyelitis experience new or increased symptoms decades after the acute polio infection, a condition known as the PPS [47]. Besides increasing muscle weakness and atrophy, pain is one of the most prominent symptoms of PPS [47,48]. Some PPS patients experience severe chronic pain, which is usually localized to muscle and joint, and considered nociceptive. If NP is present, there is always a concomitant neurological disorder such as compression neuropathy or disc herniation [48]. On the basis of an increase of cytokines in the CSF, an ongoing inflammatory process has been proposed [14].
This is further supported by findings of a proteomic study showing alterations in proteins involved in neuroinflammation and degeneration [49]. An increased concentration of cytokines has also been reported in serum [16], as well as an increased production by peripheral blood mononuclear cells [15], suggesting systemic inflammation.

PPS patients have been treated with IVIg [15,50–53]. After treatment, cytokine levels in CSF were found to be significantly reduced [50] and clinical improvement, including increased muscle power and activity as well as increase of QoL was documented [51]. A decrease of pain in patients with a pain intensity >20/100 and an improvement of QoL for the 36-item Short-Form Health Survey subdomain bodily pain were also found [15,48,51,53]. IVIg-treated patients reported less pain 3 months after treatment in an RCT [54]. In an open clinical study focusing only on IVIg treatment of pain, two thirds of the PPS patients had pain reduction [52]. There was still an effect, including a decrease of the pain intensity 1 year after the IVIg treatment [15]. According to the experience gained by one of the workshop participants (KB), based on 179 PPS patients (298 IVIg courses), response rate (i.e., pain reduced by >50%) was 35%, mean onset time for pain reduction was 2–4 weeks, peak time was around 4–8 weeks, and pain reduction lasted for 6–12 months (Table 1). Good responders to IVIg had more nociceptive pain, muscle weakness in lower extremities, age below 65 years, and no other concomitant disorders apart from PPS [53].

The background for the clinical effect of IVIg in PPS is unclear. A correlation was found between pain and TNF-α in peripheral blood [16], and a decrease of TNF-α was documented during IVIg treatment [51]. These findings may suggest a direct IVIg effect due to dampening of the inflammatory process. Increase in muscle power and activity may be secondary to the decrease of pain [51]. However, other mechanisms must also be considered. An increase of enzymes involved in the prostaglandin pathway was found in blood vessels of PPS patients (E. Melin, personal communication with KB), and IVIg may exert a direct effect on the prostaglandin enzymes. Further studies are, thus, needed to elucidate and increase the knowledge of the effect of IVIg on pain in PPS.

**Pain Associated with Autoantibodies**

It is now clear that pathological autoantibodies to specific neuronal and glial proteins can cause not only peripheral nervous system disease, like in myasthenia gravis but also CNS involvement [55]. Autoantibodies to components of the VGKC-complex are found with acquired neuromyotonia, which results in peripheral nerve hyperexcitability, and these patients often complain of pain. Much of the pain experienced is due to muscle spasms and cramps, but the sensory system is also involved. In a patient-led survey of 56 patients with neuromyotonia or the related condition cramp-fasciculation syndrome, pain was described as aching, cramping, shooting, lancing, or burning (R. Birch, personal communication with AV). In addition, pain, often neuropathic in nature, was reported in 62% of Morvan’s syndrome, a more complex condition with neuromyotonia, autonomic, and CNS involvement [56]. The association of VGKC-complex antibodies with pain has also been described in patients attending the Mayo Clinic [5,57]. Importantly, some of these patients improved after immunotherapies including IVIg, steroids, and PE [5].

VGKC-complexes are multimolecular membrane protein complexes that exist in the nervous system and persist as complexes after detergent extraction of the tissue. The recognized antigenic targets of VGKC-complex autoantibodies are Leucine-rich, Glioma Inactivated protein 1 precursor (LG11), Contactin-associated protein 2 (CASPR2), and contactin-2 [58]. Patients with Morvan’s syndrome or neuromyotonia most often have CASPR2 autoantibodies, but LG11 and contactin-2 autoantibodies are also present in some; in other patients, no known antigen target has been identified so far. In addition to these conditions, which are now thought to be antibody-mediated, pain often accompanies other autoimmune neurological diseases (e.g., multiple sclerosis, neuromyelitis optica) and can be intractable. The involvement of specific autoantibodies to neuronal surface antigens in neuromyotonia and Morvan’s syndrome suggests that pain can sometimes be antibody-mediated and responsive to appropriate treatments. This area is ripe for further investigation.

**Factors which May Influence IgG Availability and Cost in the Future**

Given the potential IgG efficacy in some painful conditions, on the background that moderate or severe chronic pain conditions are not rare [59], and as the supply of polyclonal IgG is restricted, the future of the interlinked topics supply and costs were discussed. Supply issues should be seen on the background that additional factors, including the development of novel, non-pain indications, the aging of the population in developed countries, and improved diagnostic skills in developing countries are expected to contribute to a continuing raise in the number of patients relying on plasma products [60].

The price for IgG is largely governed by costs of both obtaining plasma for fractionation and manufacturing the end-product(s) from plasma, approximately 45% and 20%, respectively [61,62]. IgG costs can be and are currently being kept at lower levels through cost sharing by fractionation of additional products (in addition to IgG) from donated plasma. Further, for any given company, manufacturing costs can be managed best by large-scale fractionation above 1,000,000 L of plasma per year. The latter is one of the driving factors behind consolidation within the fractionation industry [63]. While increasing the volume of fractionated plasma would be expected to both meet increased IgG demand and reduce manufacturing costs, the cost-implications are not linear as demand for the co-fractionated products, such as albumin and coagulation factors, has to rise by similar magnitudes as the IgG demand to ensure economically reasonable cost sharing and to avoid wasting of precious proteins of
human origin [64]. Recovery currently is, at its best, around 50% [61], and one strategy that the industry should follow is to improve the final IgG recovery from donated plasma, although the options available for recovery improvements are by themselves cost-demanding.

An ordinary drug has a life cycle, which primarily depends on the duration of the patent, after which new drugs come up and replace it. At variance, IgG depends on the life cycle of their indications, some of which, such as primary immunodeficiency syndromes, are virtually endless, while new ones, including chronic pain and Alzheimer’s disease [65], may ensure survival of the industry but needs substantial financial input to develop. On the other hand, any single new indication for large number of patients comprises a potential hazard to the overall IgG availability. Stringent application of sophisticated health technology assessment processes adapted to the particular problems of those relatively rare diseases treated with IgG will be needed to both elucidate cost-effectiveness profiles and fairly cover needs of all stakeholders [66]. Ultimately, better understanding of how IVIg works in different conditions is needed in order to maximize its use.

Conclusions

Polyvalent IgG represents a promising treatment in a number of chronic pain (neuropathic, nociceptive, and complex) conditions whose pathophysiology may involve immune changes in the peripheral tissues and/or CNS. While most of these pains are neuropathic in nature, some nociceptive conditions also appear to respond to IgG, suggesting common, immune-mediated pathophysiological grounds. IgG is a relatively safe therapeutic strategy, with uncommon and mild side effects, but high costs, which may represent a limitation for its use. In Italy, 1 g of IVIg costs around 40€/US$50), and the total dosage of IVIg depends on the patient’s weight and the infusion protocol used. A “standard” 2 g/kg IVIg infusion protocol for a patient weighing 80 kg will cost approximately 6400€/US$8,500. Pain is not a common indication for IVIg, and there may be some issues for reimbursement. Most of the published evidence on the use of IgG for pain comes from clinical cases/series and RCTs are needed in this field. To better support the use of IgG for refractory chronic pain, there is a need both to conduct confirmatory RCTs, cost-effectiveness studies, and to develop predictive tests allowing stratification of patients, e.g., by their underlying immune abnormalities, or pharmacogenomic makeup [67].

Key Messages

- IgG, either given intravenously or subcutaneously, represents a promising therapeutic strategy in a variety of chronic pain conditions.
- Most of the data supporting the use of IgG for the treatment of chronic pain come from clinical cases/series, and RCTs are needed in this field.
- Stratification of patients, according to the immune abnormalities underlying their pain, might be a key to better selection of patients who will respond to IgG.

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