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Subcutaneous immunoglobulin proves to be an effective alternative to intravenous immunoglobulin in the treatment of chronic inflammatory demyelinating polyneuropathy

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ABSTRACT A clinical decision report appraising van Schaik IN, Bril V, van Geloven N, et al. Subcutaneous immunoglobulin for maintenance treatment in chronic inflammatory demyelinating polyneuropathy (PATH): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Neurol.* 2018;17(1):35-46. https://doi.org/10.1016/S1474-4422(17)30378-2.

Keywords: *CIDP, SCIG, IVIG, neurological weakness*

Clinical Context

Tyler Brown (pseudonym) is a 67-year-old man with a history of myelodysplastic syndrome status post bone marrow transplant and subsequent graft versus host disease. He also suffers from insulin dependent diabetes mellitus type 2, diabetic neuropathy, and hypertension. The neurology team was consulted due to progressive bilateral lower extremity weakness over 5 months eventually leading to his inability to stand up. On neurological exam he presented with loss of reflexes and diminished sensation in his lower extremities. Based on clinical presentation, nerve conduction studies, and his lab workup, Mr. Brown was given a diagnosis of chronic inflammatory demyelinating polyneuropathy (CIDP) and was started on a treatment regimen of 500 mg methylprednisolone twice daily for 5 days followed by 2 gm/kg intravenous immunoglobulin (IVIG) over 4 days. Upon his initial improvement after receiving the IVIG to the point where he was able to walk around the hospital with the help of physical therapists, Mr. Brown and his wife were informed that he would need continued therapy and further IVIG infusions over the coming months to continue improving his mobility. Living 4 hours from the hospital, Mr. Brown inquired about the option of receiving care closer to his home and was told that he could find a physical therapist nearby, but due to his insurance coverage he would still need to return to the hospital where he is being treated every 2 weeks for the future rounds of IVIG over the following 6 months. The idea of Mr. Brown receiving home infusion services was initially brought up, but it was found out that his insurance would not fully cover the costs of home infusion of IVIG as it does for inpatient treatment. Even though Mr. Brown's insurance fully covered the cost of his inpatient IVIG infusion, he still was faced with the issue of being unable to drive and relying on his wife to take time off work every 2 weeks in order to drive him over the next 6 months. Mr. Brown was not given another option and was forced to figure out a way to return to the hospital every 2 weeks, but access to an equally effective and more easily administered treatment option such as subcutaneous

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immunoglobulin (SCIG) would have allowed for him to receive optimal care without the excessive time or costs spent on traveling.

Clinical Question

Compared to IVIG, can SCIG be an effective maintenance treatment option for patients with CIDP who prefer to self-infuse at home?

Research Article

van Schaik IN, Bril V, van Geloven N, et al. Subcutaneous immunoglobulin for maintenance treatment in chronic inflammatory demyelinating polyneuropathy (PATH): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Neurol.* 2018;17(1):35-46. https://doi.org/10.1016/S1474-4422(17)30378-2.

Related Literature

Initially a search of Up-to-Date using the terms "subcutaneous IVIG" was performed to look into the current landscape regarding the comparison between IVIG and SCIG.[1] The advantages of SCIG included fewer systemic side effects, more consistent physiologic IG levels due to fewer peaks and valleys, the convenience of infusing at home, and monetary savings due to avoiding hospital and associated travel costs.[2,3,4,5] Since most of the information on Up-to-Date focused on various different immunodeficiencies and not CIDP specifically, a PubMed search was done next using the terms "CIDP IVIG treatment." The initial search yielded 621 results, many of them only tangentially related to CIDP or other neurologic syndromes. To make the results more manageable, an advanced search was done next with the terms "CIDP treatment" and "IVIG" and "SCIG" which narrowed the results to only 33 studies. These 33 studies were further narrowed down by reading through all of the abstracts to find only high-quality randomized controlled trials, which led to 3 studies comparing IVIG and SCIG treatment for CIDP.

One of the Markvardsen et al. studies was ruled out because it focused on treatment naïve patients and did not apply to Mr. Brown who had already received IVIG.[6] The final two studies were the PATH trial[7] and another randomized, double-blind placebo controlled study by Markvardesen et al.[8] Both studies found that SCIG can be effective at maintaining stable treatment in patients who previously relied on IVIG. The PATH trial was chosen because it had a larger sample size (57/58) compared to the Markvardsen trial (30), and the PATH trial also compared both a low and a high-dose treatment with the placebo group which could potentially have an added benefit of decreasing the necessary infusion time by using a lower effective dose.

Overall, the PATH trial was the most applicable high-quality study as it was a randomized, double-blind, placebo-controlled, phase 3 trial of patients with CIDP. Patients given SCIG at both high and low doses had reduced percentages of CIDP relapse when compared with patients who were given placebo. Given this body of evidence, this would be a Strength of Recommendation B based on Strength of Recommendation Taxonomy (SORT) criteria.[9]

Critical Appraisal

The PATH trial is a randomized, multicenter, double-blind, placebo-controlled, parallel-group phase 3 trial. Adult patients with definite or probable CIDP as determined by the European Federation of Neurological Societies/Peripheral Nerve society 2010 Criteria who responded to IVIG were chosen from 69 neuromuscular centers across North America, Europe, Israel, Australia, and Japan.[10] According to the SORT criteria, this study would be Level 1 due to it being a high-quality randomized controlled trial.[9] The study meets Level 1 criteria since the treatments were randomized, patients and study personnel were blinded to treatment allocation, groups were treated equally aside from the intervention, no patients were lost to follow-up, and the primary outcome was assessed in an intention-to-treat analysis. The study was prospectively registered on clinicaltrials.gov, with no deviations from the initial study protocol or different reported outcomes. Funding for the study was provided by CSL Behring who had no role in collecting data while an independent statistician from a steering committee reviewed all results. Inclusion criteria consisted of CIDP diagnosis, an IVIG treatment within the previous 8 weeks, and being age 18 and above. The study excluded patients with any other

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polyneuropathy, any disease that would interfere with treatment, patients with thrombotic episodes in the 2 years prior to the trial, or those allergic to blood products.

All patients meeting the study criteria had baseline activity level and limb disability measured using the Inflammatory neuropathy cause and treatment (INCAT) disability score and an Inflammatory-Rasch-built Overall Disability Score (I-RODS), and then entered into an IgG dependency period of up to 12 weeks where they were withheld from receiving IVIG. Those who showed clinical deterioration based on INCAT or I-RODS were moved into the IVIG restabilization period. The restabilization period consisted of patients receiving standard doses of IVIG until their INCAT score increased to their initial level and remained constant at the end of 7-10 weeks. Patients were given a randomized treatment via a system maintained by Parexel International in a 1:1:1 ratio (57 given placebo, 57 given low-dose SCIG, and 58 given high-dose SCIG). The three treatment groups were given either 2% human albumin (placebo), 0.2 g/kg body weight of IgPro20 human immunoglobulin (low-dose), or 0.4 g/kg body weight of IgPro20 human immunoglobulin (high-dose) weekly for 24 weeks.

The primary outcome was the proportion of patients who either withdrew from the study for any reason or had a CIDP relapse based on increases of at least 1 point on INCAT scores from the baseline level at the end of the restabilization period. Secondary outcomes included any changes in INCAT scores, changes in grip strength scores, or I-RODS changes.

The researchers used the INCAT score to determine how the patients were responding to SCIG clinically in order to assess the primary outcome of CIDP relapse. At the end of the trial there were 77 patients that withdrew due to relapse, 36 from the placebo group, 22 from the low-dose group, and 19 from the high-dose group. This difference in relapse rates shows overall superiority of treatment compared with placebo leading to a statistically significant p-value of 0.0007 when using the Exact Cochran-Armitage test, and absolute risk reductions (ARR) for CIDP relapse of 25% (p=0.007) and 30% (p=0.001) for the low- and high-doses respectively when compared with placebo. When using these values to perform a relapse analysis where all of the patients who withdrew for reasons besides a relapse were assumed not to have a relapse, the number needed to treat (NNT) to prevent one relapse was reported to be 2.7 for high-dose and 4.4 for low-dose SCIG. When using the ARR calculated from all patients regardless of their reason for withdrawal, the NNT to prevent one relapse changes to 3.3 for high-dose and 4.0 for low-dose SCIG treatments.

The demographics of the participants in the study were 64% male with the mean age being 57 years, which is younger than Mr. Brown by 10 years. This difference could potentially affect the applicability of the study to Mr. Brown and future studies would need to be done using a more similar patient population to show whether the treatment is effective in an older population as well. Mr. Brown would have been excluded from this study due to his underlying diabetic neuropathy, so further trials would need to be done in patients with baseline neuropathy to show that SCIG is just as effective as IVIG in this population as well. Overall, the therapeutic maneuver of using SCIG as CIDP maintenance therapy is feasible in patients who wish to receive treatment at home, and thus makes the study clinically relevant.

Clinical Application

The PATH study concluded that SCIG, in both low and high-dose treatments, was able to maintain disease stability over 24 weeks in CIDP patients who had previously been dependent on IVIG treatment.[7] With regards to Mr. Brown, he would additionally benefit from the ease of administration of SCIG due to it eliminating his transportation barrier that would put significant strain on his life if required to travel 4 hours one way every two weeks for IVIG treatment. Based on the results of the study, the treatment could be effectively applied to the patient. Even though he would be ruled out through exclusion criteria due to diabetic neuropathy, other smaller studies regarding SCIG treatment for CIDP did not have this exclusion and showed similar positive treatment results.8 Overall, Mr. Brown would benefit from transitioning to SCIG as he already responded well to IVIG treatment, and SCIG would give him the independence that he prefers so that he can spend more time at home instead of traveling to the treatment hospital for his treatment for a couple days every other week.

New Knowledge Related to Clinical Decision Science

Clinical decision science is built upon effective clinical treatment in addition to how well the treatment can be implemented with regards to patients with complicating social determinants. When Mr. Brown was diagnosed with CIDP and told he would need IVIG

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infusions every two weeks, this led to some concern due to socioeconomic constraints. During their everyday practice physicians should not rely solely on the same treatment plan for every patient but should take each patient's individual circumstances to try and find what works best for them. With seeing how Mr. Brown was only offered a less than ideal treatment plan for his situation it became clear that an additional benefit of using clinical decision science is it requires physicians to address the patient's whole situation and to stay up to date on emerging therapies that may be more practical in certain social circumstances. SCIG was newly approved for CIDP in March of 2018, but it was not presented to Mr. Brown as an alternative to receiving IVIG infusions. The extension study to the PATH trial demonstrated the long-term efficacy of SCIG and other advantages of SCIG Mr. Brown could have received such as increased independence, less time spent during subcutaneous treatment, and less felt side effects when compared with IVIG.[11] Had first-rate clinical decision science been implemented with regards to Mr. Brown's treatment he may have been offered something more compatible with his needs as a whole and not just for his medical needs.

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