REVIEW OPEN ACCESS

Review process for IVIg treatment

Lessons learned from INSIGHTS neuropathy study

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Abstract

Background

This project is an effort to understand how orders for IV immunoglobulin (IVIg) are documented and prescribed by physicians, and subsequently, how they are reviewed by insurance companies for the treatment of immune neuropathies.

Methods

A panel of neuromuscular specialists reviewed case records from 248 IVIg-naive patients whose in-home IVIg infusion treatment was submitted to insurance for authorization. After reviewing a case record, 1 panelist was asked to make a diagnosis and to answer several questions about the treatment. A second panelist reviewed the original record and follow-up records that were obtained for reauthorization of additional treatments and was asked to determine whether the patient had responded to the treatment.

Results

Our specialists believed that only 32.2% of 248 patients had an immune neuropathy and were appropriate candidates for IVIg therapy, whereas 46.4% had neuropathies that were not immune mediated. Only 15.3% of cases met electrodiagnostic criteria for a demyelinating neuropathy. Our specialists believed that 36.7% of 128 cases with follow-up records had responded to therapy. In cases in which the initial reviewer had predicted that there would be a response to IVIg, the second reviewer found that 54% had responded. This is compared with a 27% response rate when the first reviewer predicted that there would be no response ($p = 0.019$).

Conclusions

Our expert review finds that the diagnosis of immune neuropathies made by providers, and subsequently approved for IVIg therapy by payers, is incorrect in a large percentage of cases. If payers include an expert in their review process, it would improve patient selection, appropriate use, and continuation of treatment with this expensive therapeutic agent.

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Allen and Lewis[1] recently reported that 47% of patients referred to a tertiary care neuromuscular practice with a diagnosis of chronic inflammatory demyelinating polyneuropathy

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We intentionally did not provide a specific definition of "objective improvement" to mirror the real-world insurance utilization review process.

(CIDP) failed to meet diagnostic criteria for the disease, raising questions about overdiagnosis in the area of immune neuropathies. Their study used research criteria as the gold standard, which broke the diagnostic process into a "present or not present" dichotomy. The reality, however, is that the review process used by insurance carriers may not always adhere to published standards. Although these reviewers have become the de facto referees for determining when IV immunoglobulin (IVIg) treatment is permitted, there are no systematic studies on how treatment decisions are made or on their accuracy in predicting outcomes.

In this project, we asked clinical experts to review cases and assess pretreatment diagnoses, appropriateness of therapy, and the subsequent responses using records submitted to insurance companies for treatment of CIDP and multifocal motor neuropathy (MMN). This study, called "Immunological and Neurological Study of Immune Globulin Habits, Treatments and Standards" (INSIGHTS), aimed at better understanding how IVIg is prescribed and reviewed across the spectrum of clinical practices and how this relates to outcomes.

Methods

Study cohort

The study was part of a quality assurance/quality improvement (QA/QI) project conducted by NuFACTOR, Inc. ("NuFACTOR"), which provides home-based IVIg infusions. NuFACTOR's program evaluated treatment outcomes associated with disease-specific prescribing regimens in patients who received home-based IVIg treatment provided by NuFACTOR. We conducted a retrospective review of the medical records of 248 patients who received home-based IVIg treatment between October 2011 and November 2016. Patients were referred by 154 distinct physicians in 26 states. Each case had been diagnosed with an immune-mediated peripheral neuropathy by the treating physician, was approved for IVIg therapy by an insurance company, and was naive to previous immunoglobulin therapy. The records included the exact written notes, laboratory data, imaging reports, and electrodiagnostic studies that were supplied to the insurance company, with the exception that all patients' protected health information and information about treating physicians, including names, geography, and type of practice, were redacted before the information was entered into the study. To the best of our knowledge, the insurers did not obtain additional documentation directly from prescribers.

Each redacted record was provided to 1 randomly selected initial expert reviewer (IER), chosen from the panel of 8 practicing neuromuscular clinicians (T.D.L., J.S.K., R.B., D.S.S., T.M., G.I.W., L.K., and M.M.D.). After reviewing the record, the IER answered 4 questions listed in table 1. The IER also completed questions regarding the nerve conduction studies, EMG, laboratory values, and clinical phenotypes (pattern of weakness, reflexes, and sensory loss). From the original 248 cases, we obtained 1 or 2 sets of follow-up records from 145 cases. These records were submitted when the treating clinician ordered additional IVIg or when insurance reauthorization was required. Because there was no standard protocol for the treating physicians, follow-up appointment times, doses and intervals of IVIg, and documentation varied between cases.

A second expert reviewer (SER), blinded to the IER's opinions, evaluated the original note and the follow-up records from these 145 cases under the same redacted protocol. The SER was asked whether, in his/her opinion, the records indicated an "objective improvement" related to IVIg therapy. We intentionally did not provide a specific definition of "objective improvement" to mirror the real-world insurance utilization review process. The SER had the option to deem records as "unreviewable" if records lacked information to form an

Table 1 Questions asked of expert reviewers

1. Choose the best available diagnosis from a comprehensive list of neuropathies (or "other" if the appropriate diagnosis is not listed).
2. Determine whether electrophysiologic studies (1) had no evidence of any demyelination; (2) had at least some evidence of demyelination but did not fulfill definite criteria from the EFNS, AAN, Koski, or Saperstein criteria[1–4]; (3) had evidence of demyelination that met at least one of the above criteria; (4) lacked sufficient information to determine; and (5) were not provided.
3. In the reviewers' opinion, was the course of IVIg therapy appropriate (independent of the answers regarding diagnosis and electrodiagnostic studies).
4. Predict whether, in the reviewer's opinion, the patient would have an objective response to treatment.

Abbreviations: AAN = American Academy of Neurology, EFNS = European Federation of Neurological Societies; IVIg = IV immunoglobulin.

opinion. This was the situation in 17 of these 145 cases, leaving 52% of the original cohort for formal response analysis.

Among the 128 cases with reviewable follow-up records, patients were classified as "responders" when the SER believed that the records indicated an objective response in either the first, second, or both follow-up records. Specifically, in cases with only 1 follow-up record, "responder" was defined as an objective response in that record and "nonresponder" as no objective response in the single follow-up record. The case was excluded if the SER deemed the record as "unreviewable." When there were 2 sets of follow-up records, "nonresponder" meant the SER found "no response" in both records or "no response" in 1 record and deemed the other "unreviewable." The case was excluded if both follow-up records were "unreviewable."

Data analysis

Data were entered into a Research Electronic Data Capture database housed at the University of Kansas Medical Center. Descriptive statistics were used to characterize the study population (n = 248) on demographic and other diagnostic characteristics at baseline. Statistical analysis was completed by G.J.B. Outcome analyses were based on the 128 participants in whom a response could be evaluated. The importance of the association between baseline clinical and electrophysiologic characteristics and objective responses were evaluated with χ^2 tests. In addition, logistic regressions were used to estimate odds ratios and associated 95% confidence intervals for each predictor. Statistical significance was determined based on $\alpha = 0.05$.

Standard protocol approvals, registrations, and patient consents

This study was conducted as part of a QA/QI study, "NuFACTOR IVIg Treatment Outcomes Assessment and Clinical Guidelines Study," by NuFACTOR as part of its health care operations. Before the initiation of the study, an independent institutional review board (IRB), the Copernicus Group IRB, determined that the study was a QA/QI study for which IRB oversight was not required. To cover broader analysis of the data beyond NuFACTOR's QA/QI analyses, the IRB at the University of Kansas Medical Center approved the study and issued a waiver of informed consent for the retrospective analysis of previously collected data.

Data availability

All study data are published within this article.

Results

Assessments by expert reviewers

IER and diagnosis of immune neuropathy

Only 32.3% of overall cases were believed to have an immune-mediated neuropathy; in 46.3% of cases, the documentation supported a non–immune-mediated neuropathy, and in 21.4% of cases, there was insufficient information to make a determination. Table 2 summarizes the diagnoses proposed by the IERs. Responses to questions about the diagnosis, appropriateness of therapy, prediction of a response, and degree of demyelination for each of the original 248 cases are summarized in table 3. Electrodiagnostic studies were not submitted for review in 70 cases.

SER and response to IVIg

The overall "objective response" rate in the 128 reviewable cases was 36.7% (47/128). There was no difference in the mean loading doses of IVIg between responders (1.91 ± 0.28 g/kg) and nonresponders (1.87 ± 0.46 g/kg) ($p = 0.58$). The interquartile range for follow-up was 86–234 days for the overall cohort. The responses based on the original predictions are summarized in table 4 for these 128 patients.

We also collected the various reasons for not having follow-up records in 120 patients who underwent initial review and were not included in the SER evaluation (table 5). The IERs predicted that this cohort was generally more inappropriate for IVIg therapy and less likely to respond to treatment than

Table 2 Neuropathy diagnosis as determined by the initial expert reviewers

Diagnosis	No. of cases	% of total
Immune-mediated neuropathies	80	32.3
CIDP	48	19.4
Multifocal motor neuropathy	16	6.5
GBS	9	3.6
MADSAM/Lewis-Sumner	5	2.0
DADS	2	0.8
Nonimmune neuropathies	115	46.3
Axonal sensorimotor neuropathy	41	16.5
Motor neuron disease	23	9.3
Autonomic neuropathy	18	7.3
Cryptogenic sensory polyneuropathy	10	4.0
Isolated small fiber neuropathy	5	2.0
Radiculopathy	5	2.0
Plexopathy (nondiabetic)	4	1.6
Charcot-Marie-Tooth	4	1.6
Sensory neuronopathy	3	1.2
Plexopathy (diabetic)	2	0.8
Unable to determine	53	21.4
Total	248	100

Abbreviations: CIDP = chronic inflammatory demyelinating polyneuropathy; DADS = Distal Acquired Demyelinating Symmetric Neuropathy; GBS = Guillain Barré Syndrome; MADSAM = Multifocal Acquired Demyelinating Sensory and Motor Neuropathy.

Overall, our findings, consistent with earlier reports suggesting that IVIg is overused in immune neuropathy, call for a change from the current approach.

the 128 cases with follow-up records, but these differences were not significant. In 35 of the 120 cases, the treating physician specifically communicated to NuFACTOR that they did not reorder IVIg because the patient had not responded.

Discussion

There are now more than 20 sets of diagnostic criteria for CIDP and MMN that range from highly specific, where the goal is to select ideal patients for research, to most sensitive, which capture more cases but risk overdiagnosis.[2–5] These multiple efforts reflect a neuropathy field characterized by the absence of a gold standard test for diagnosis and diseases with overlapping findings that require a demanding clinical logic to account for phenotypic, laboratory, and electrodiagnostic features. Complicating the situation, bedside decision makers must calculate the downside of missing a diagnosis in a potentially treatable case that might not fulfill diagnostic criteria.[6–8] It should not be surprising that clinicians with differing experiences and values, and who may have diverse decision-making capabilities, can approach the same problem differently.

As a specialty pharmacy, NuFACTOR has been a first-hand observer of the use of IVIg in neuropathy. In addition, many of our experts (J.S.K., T.D.L., R.B., and D.S.S.) have consulted for insurance payers as reviewers and arbiters or have published diagnostic criteria. A decade after food and drug administration (FDA) approvals of treatments for these conditions,[9–12] our team wondered if the pendulum may have swung toward excessive use. We designed this QA/QI study to learn about clinical practice decisions by mimicking the review processes used by insurance companies. Because of the multiplicity of published criteria that reflect the diagnostic difficulty, we made the assumption that these would be difficult to use alone in making review decisions. Thus, we asked our expert reviewers to rely on real-world records provided to insurers to make individual assessments about diagnoses and expected treatment responses. As the study progressed, it became clear that "ideal" data do not exist to facilitate the required interactions between patients, physicians, infusion companies, and payers.

Using our methods, diagnostic accuracy appears to be even more pessimistic than the report by Allen and Lewis,[1] in

Table 3 Initial expert reviewer's assessments

Clinical condition	Assessment	No. of cases	Percentage of total cases
Immune neuropathy present	Yes	80	32.2
	No	115	46.4
	Unable to determine	53	21.4
Appropriate candidate for therapy	Yes	80	32.2
	No	119	48
	Unable to determine	49	19.8
Positive response to IVIg predicted	Yes	37	14.9
	No	149	60.1
	Unable to determine	62	25
Evidence for demyelination	None	82	33
	Some—does not meet EFNS criteria	42	16.9
	Meets EFNS criteria	26	10.4
	Uninterpretable	20	8
	No NCV submitted	78	31.4

Abbreviations: IVIg = IV immunoglobulin; EFNS = European Federation of Neurological Societies.

Table 4 Positive objective responses based on initial expert reviewer's predictions

		Objective response (%)	Objective response (95% CI)	*p* Value
IVIg deemed appropriate				0.061
No	57	26.3	1.00 (reference group)	
Yes	48	43.8	2.18 (0.95–4.94)	
Unable to determine	23	47.8		
Positive response likely				0.019
No	75	26.7	1.00 (reference group)	
Yes	24	54.2	3.25 (1.25–8.42)	
Unable to determine	29	48.3		
Immune neuropathy present				0.004
No	46	21.7	1.00 (reference group)	
Yes	52	50.0	3.60 (1.48–8.74)	
Unable to determine	30	36.7		
Degree of demyelination				0.29
Meets no criteria	38	23.7	1.00 (reference group)	
Meets some criteria	22	31.8	1.50 (0.47–4.83)	
Meets criteria	18	44.4	2.58 (0.78–8.50)	
Unable to determine	13	30.8		
Not provided	37	51.4		

Abbreviation: IVIg = IV immunoglobulin.

which 53% of cases diagnosed with CIDP met electrodiagnostic criteria. In contrast to the earlier work, we included all forms of demyelinating neuropathies, rather than CIDP alone, and focused only on patients naive to IVIg therapy. We found just 15.3% of the cases in which electrodiagnostic studies were provided, all of which were approved by insurance companies, clearly fulfilled electrodiagnostic criteria for a demyelinating neuropathy. In approximately 12% of the provided cases, electrodiagnostic studies were incomplete or could not be interpreted, and no studies were provided in nearly one-third of cases.

In the judgment of our expert reviewers, only 42% of the reviewable cases and 32% of overall cases clearly met diagnostic criteria consistent with an immune neuropathy, whereas nonimmune neuropathies accounted for more than half of reviewable cases. Notably, these values may be an overly optimistic estimation of real-world practice because our cohort solely included patients already approved for IVIg therapy. The a priori exclusion of insurer-denied cases would have had the effect of increasing our estimate if these cases were the clearest examples of conditions other than immune neuropathy.

The overall 36.7% treatment response rate may represent another overestimate. This value would have been lower had we included cases in which the treating physician explained that IVIg had been discontinued specifically because there was no response. Other key biases may also have affected our response rate. IVIg had been reordered, by definition, in all cases the SER examined. We can presume that the treating physicians reordered IVIg because they believed it worked, but anchoring to the original diagnosis might have affected both how they perceived and documented the outcome. This, in turn, could influence the interpretation by our SER. The effect of anchoring could be magnified if a treating physician relied on subjective responses or failed to carefully document examinations. Patient experience may add to this because placebo responses can be as high as 20%.[3] Biases may have contributed to the surprisingly high 21.7% "objective" response rate in cases in which our first reviewers diagnosed types of neuropathy that are known not to be immune responsive.

Our panel deemed the records "unreviewable" in more than 20% of cases. This problem typically reflected incomplete, poorly written, or difficult-to-follow notes. Follow-up assessments also often lacked key observations to allow for clear conclusions. The SERs had no way to contact the treating physicians, as could be done in controlled studies, because insurance companies rarely use iterative approaches

Table 5 Reason for lack of follow-up evaluations

Reason for lack of follow-up	Number	Percentage
No benefit as reported by the prescribing MD	36	30.0
Study ended before receipt of follow-up evaluation	19	15.8
Second reviewer unable to determine response	17	14.2
One-time order of IVIg with no follow-up	14	11.7
Insurance denied follow-up/site of therapy changed	11	9.2
No follow-up note provided by the prescriber	8	6.7
Adverse reaction to IVIg	7	5.8
Therapy no longer needed	4	3.3
Noncompliance	3	2.5
Patient died	1	0.8
Total	120	100

Abbreviations: IVIg = IV immunoglobulin; MD = medical doctor.

to track missing information. As a result, we adopted the term "AUNTs" (Analytically Uninterpretable Note Taking) to designate this real-world phenomenon of how experts perceive clinical records.[13]

Even given these limitations, predictions about who would and would not respond to IVIg treatment by our IERs, paired with the interpretation of the SERs, were significantly better than the overall SER-determined base response estimates. This provides evidence that input from neuromuscular specialists, who understand the complex reasoning processes involved in differential diagnosis of neuropathies, could improve on the current review process.

Our findings also suggest that prescribing some IVIg for patients who do not have immune-mediated neuropathy is unavoidable. This likely reflects realities related to diagnostic uncertainty. For example, IERs believed that twice as many patients were appropriate candidates for a trial of IVIg (32%) as were likely to respond (15%). These low numbers continue to suggest that only few cases are sufficiently documented not only to clearly warrant treatment but also to demonstrate how reviewers may at times be open to therapy, despite skepticism about the eventual benefit. We have previously used the term "UNCLEs" (UNcertain CLinical Entities) to describe a differential diagnosis that cannot reasonably be narrowed to exclude a treatable condition.[13] Two of the more common examples in our study were cases likely to have primary muscular atrophy, in which MMN remained on the differential diagnosis[14,15] or diabetic neuropathies with features that could not be fully distinguished from CIDP.[6] Weak indications for treatment despite a known diagnosis is another factor. For example, Distal Acquired Demyelinating Symmetric Neuropathy with an Immunoglobulin M paraprotein, which is known to respond poorly to IVIg,[16] and mild Guillain Barré Syndrome, where progression has ceased before treatment was ordered, were considered reasonable for a trial of IVIg by some of our IERs. It may be important to capture these specific clinical entities, to make providers aware of uncertainty, and, therefore, open to discontinuation of therapy when treatment seems ineffective.

Overall, our findings, consistent with earlier reports suggesting that IVIg is overused in immune neuropathy, call for a change from the current approach. Potential areas for improvement include documentation of key observations, inclusion of expertise in review processes, and capturing data to highlight true and perceived uncertainty as it pertains to diagnosis and treatment responses. Given the cost of IVIg, it is worth ensuring that clinicians submit concise information at the onset and at designated intervals during therapy, as has been proven possible in the IGOS study in acute neuropathies.[17] Uncertainty makes it harder to control costs and may foster distrust in communications around treatment decisions. All parties desire to use expensive or scarce resources appropriately and to improve care. Providers might be more enthusiastic about supplying requested documentation and more accepting of decisions to deny insurance coverage for IVIg therapy if they appreciate that decisions were well reasoned, data driven and backed by expert review. Similarly, insurers might be more willing to moderate time-consuming utilization review practices if physicians demonstrate a willingness to participate in a well-validated process to maximize the value of therapy.

Author contributions

T.D. Levine and J.S. Katz developed the study design and organization, served as study codirector during the course of the study, and reviewed data and developed the manuscript. R. Barohn developed the study design and organization and reviewed data and developed the manuscript. L.J. Vaughan ran the day-to-day operations of collecting patient information and acquiring reviews from the expert panel and helped with data analysis and manuscript preparation. M.M. Dimachkie, D.S. Saperstein, T. Mozaffar, and G.I. Wolfe were expert reviewers who analyzed cases during the study and assisted in manuscript preparation. M.S. Mayo was the PI for the Data Coordinating Center for this research project and lead biostatistician. He and his team aided in the design of the study, created and managed the study data capture system, and performed data curation and preliminary and final analyses along with periodic and final study reports to the sponsor. G.J. Badger served to analyze the data at the end of the study and provided statistical support in the preparation of the manuscript. L. Katzin was one of the expert reviewers who analyzed cases during the study. E. Ritt worked on an organizational level during the course of the study and assisted in manuscript preparation. M. Greer, J. DiStefano, and P.M. Schmidt led on an organizational level

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