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Response to therapy in patients with chronic inflammatory demyelinating polyradiculoneuropathy: An observational study

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Abstract

Background & Objective: The existing practice in chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is to initiate therapy with steroids, intravenous immune globulin (IVIg), or plasma exchange (PLEX) followed by period of immunosuppression. The objective of this study is to assess disability outcomes at 6 months after starting therapy. *Methods:* Patients who were diagnosed as having CIDP from the Army Hospital of Research and Referral, Delhi; who were initiated and maintained on therapy by treating neurologists with a six month follow up were included in this study. They were retrospectively divided into three groups based on initial therapy received. The primary outcome was comparison of the Inflammatory Neuropathy Cause and Treatment (INCAT) group overall disability sum score (INCAT-ODSS) at 6 months. Secondary outcomes were difference in score at 1 and 3 months, proportion with at least 20% response at 3 and 6 months ("responders") and proportion who needed "rescue" therapy during the 6 months. *Results:* Sixty patients (26 retrospective, 34 prospective) were included in this study. They were treated with IVIg (33), steroid (19) and PLEX (8). Baseline INCAT-ODSS score (±SD) was 7.2(2.2), 7.2(1.5) and 7.5(1.9) respectively. All received some form of oral immune suppression during follow up. Twenty one (35%) needed additional rescue therapy. There was an overall significant reduction in the mean INCAT-ODSS disability score from 7.2 to 3.1 (Mean difference 4.2; CI 3.6-4.8); p<0.01). Nearly 88% of patients (51/58) showed at least 20% improvement from baseline. Two were lost to follow up (1 IVIg, 1 steroid). There was no difference in the ODSS at 6 months [2.9(2.4), 3.5(2.7) and 2.7(1.3)] respectively. No difference in ODSS at 1 and 3 months. Proportion of responders at 6 months and proportion who needed rescue therapy were also similar.
Conclusion: Irrespective of initial therapy and maintenance oral immunosuppression used, the overall disability reduction in treatment with IVIg, steroid or PLEX is significant; however the three modalities are comparable in terms of disability reduction at 6 months. At least a third may need additional rescue therapy.

Keywords: CIDP, comparison, IVIg, steroid, plasma exchange

INTRODUCTION

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is an autoimmune condition affecting peripheral nerves and nerve roots. It is characterized by a relapsing-remitting or progressive course of symmetric weakness of proximal and distal muscles. CIDP can be identified using a combination of clinical features, electrodiagnostic studies and laboratory features. There is evidence to suggest that both cellular and humoral immunity is involved in the pathogenesis of CIDP.[1] The goal of treatment is to stop the immune attack against the myelin sheath of peripheral nerves so that secondary axonal degeneration is minimized.[2] Therefore, early administration of immunosuppressive or immunomodulatory treatment with glucocorticoids, intravenous immune globulin, or plasma exchange (PLEX) is the mainstay of treatment. This can improve symptoms and function and can prevent or minimize long-term disability. Any of the above three treatment modalities is considered as initial therapy as per European Academy of Neurology

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and Peripheral Nerve Society.[3] This is based on randomized trials and observational studies where mostly IVIg has been compared to steroids or PLEX.[3,4] A more recent Cochrane review also concludes that the response is similar.[5]

We collected and analysed the data from a cohort of CIDP patients with the aim to assess response to therapy using IVIg, steroid or PLEX, in the form of disability reduction at six months.

METHODS

The study was a single centre, pragmatic, "real world experience", observational study with no intervention in a cohort of patient seen in the Army Hospital of Research and Referral, Delhi. Patients were included if they were aged 18 years or above and satisfied the definite, probable or possible diagnostic criteria of European Federation of Neurological Societies/Peripheral Nerve Society Guideline on management of chronic inflammatory demyelinating polyradiculoneuropathy (EFNS/PNS) criteria of 2006.[6] The exclusion criteria mentioned in the same guidelines were used, which included Lyme disease, diphtheria, drug or toxin exposure likely to have caused neuropathy, hereditary demyelinating neuropathy, multifocal motor neuropathy (MMNCB) and other secondary causes, including POEMS syndrome, diabetic and non-diabetic radiculo-plexopathy, PNS lymphoma and amyloidosis.

Recruitment of patients could be either retrospective or prospective. For retrospective recruitment, previous two years records were screened for discharge diagnosis with key word "CIDP". Patients were considered for inclusion if their clinical, electrodiagnostic and other supportive studies and records were available. Patients could be recruited prospectively if they were newly diagnosed and could be examined on follow up.

A proforma was filled for each selected patient where the following details at baseline were recorded: demographic data, presence of comorbidities like diabetes, malignancy, autoimmune disease, use of immunosuppressive drugs, status of HIV, hepatitis B and C infection, duration of neurological symptoms and examination findings, CSF cytology and biochemistry and certain laboratory parameters. All patients had their Inflammatory Neuropathy Cause and Treatment (INCAT) group overall disability sum score (INCAT-ODSS) recorded at baseline.[7] This is a twelve-point disability score, five points for the arm and seven for the leg. The score for patients who were recruited retrospectively was calculated from records by second author and verified by any of the other authors. The patients recruited prospectively were examined and score calculated at baseline by any one of the authors. The type of initial therapy received was recorded. This was decided by the treating neurologist, the authors had no role in choosing the type of therapy or dose administered.

During the follow up period of six months, the following variables were recorded: use of immunosuppressive medications if any, INCAT-ODSS score at 1, 3 and 6 months and the need for "rescue" therapy. Patients were deemed to have received "rescue" therapy during the six month follow up if the treating neurologist and team decided that the disease had relapsed or there was poor response to initial therapy. The "rescue therapy could be repetition of the same initial therapy, a change to another initial therapy or the use of another agent like rituximab or cyclophosphamide.

The patients completing six months of follow up were divided into three groups based on the initial therapy received. Primary outcome measure was difference in INCAT-ODSS score at 6 months between groups. Secondary outcome measures were difference in the score at 1 and 3 months. Another secondary outcome measure was based on "responder" status at 3 and 6 months. A "responder" was defined as ≥ 20% improvement from baseline in the INCAT-ODSS score. The proportion of responders in each group were then compared. Also, proportion of patients who needed some form of "rescue" therapy any time during the follow up period of 6 months were also compared.

Sample size was calculated using an online sample size calculator for analysis of variance (ANOVA) assuming type 1 error to be 0.05 and power of study to be 80%. It was assumed that most patients would be at least moderately disabled at start of therapy and the mean INCAT-ODSS score was kept between 6.5-8 with a standard deviation of 1.5. It was calculated that a sample size of at least 20 patients would be needed in each group to demonstrate a difference between groups. Categorical variables were presented in number and percentage (%). Continuous variables were presented as mean ± SD. Statistical analysis was done by comparing the three groups using a non-parametric test one way ANOVA on ranks (Kruskal Wallis test). A p value of <0.05 was taken as significant. The study was approved by the Institute's Ethics Committee. Informed

consent was obtained from all patients who were examined.

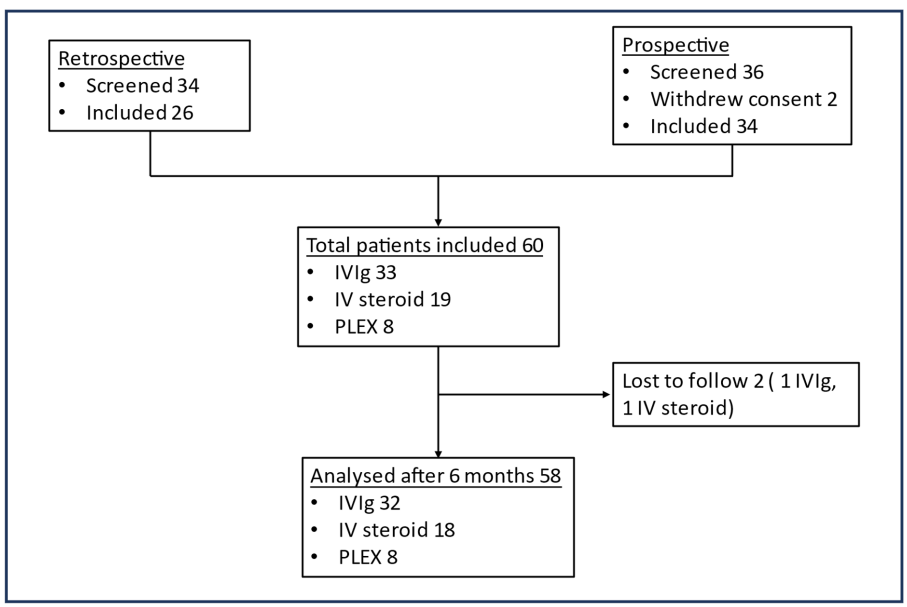
RESULTS

After an initial screening process, a total of 60 patients with CIDP were included, 34 were recruited prospectively while 26 were retrospective (Figure 1). Two patients were lost to follow up, one having received IVIg and the other IV methylprednisolone. Follow up data of 58 patients was available for analysis. They were divided into three groups based on initial therapy received. Table 1 shows the baseline characteristics of the three groups before receiving the therapy. They were mostly matched.

Initial treatment in the form of either IVIg, pulse steroids or PLEX was given at the discretion of the treating neurologist in standard doses. IVIg was given in a dose of 2gm/kg, divided over 5 days. Steroid was given in the form of IV pulse methylprednisolone 500-1000mg per day for 3-5 days. Plasma exchange was performed on TerumoBCT Cobe-Spectra apheresis system® or on B-Braun Dialog+ dialysis system®, depending on the availability of the machine in hospital on that day. Around 35-40ml/kg of exchange was performed every alternate day for five cycles. Replacement was done with either fresh frozen plasma or albumin.

All patients received some form of continued oral immunosuppression at the discretion of treating neurologist after the initial therapy, the details are shown in Table 2. There was no difference among the groups for oral immunosuppression received (p=0.12). Two patients (1 each from IVIg and pulse steroid group, both recruited prospectively) were lost to follow up after initial inclusion. Data of 58 patients was finally analysed, 32 in IVIg group, 18 in pulse steroid group and 8 in plasma exchange group. During the six month follow up, there were twenty-one patients who needed "rescue therapy" due to perceived poor response or relapse, the breakup is shown in Table 3. Although, there was no significant difference among the groups for the need for rescue therapy, the proportion of patients needing it was higher in the steroid group (50%) than the other two.

There was no difference in the INCAT-ODSS among the three treatment groups at 6 months (Table 4). There was also no difference among them at 1 and 3 months although there was trend favouring IVIg with the least response in the steroid group. When the groups were analysed at 3 and 6 months for the number of patients with responder status (defined as >20% reduction at ODSS at defined times) there was a significant difference in favour of IVIg at 3 months suggesting a possible faster response. However, at 6 months there was no difference among groups (Table 5).



IVIg= Intavenous Immunoglobulin, PLEX= plasma exchange

Figure 1: Flow design of the study

Table 1: Baseline characteristics

Sr No	Characteristic at presentation	All patients (n=60)	IVIg (n=33)	Pulse steroids (n=19)	PLEX (n=8)	P value
1	Age in years (SD)	51.3 (13.6)	49.9 (13.8)	51.2 (13.8)	56.8 (12.5)	0.39
2	Males (%)	41 (68.3)	19 (57.6)	15 (78.9)	7 (87.5)	0.13
3	Diabetes (%)	37 (61.7)	16 (48.5)	16 (84.2)	5 (62.5)	0.04
4	HBsAg positive (%)	4 (6.7%)	1 (3)	3 (15.8)	0	0.15
5	HCV positive (%)	6 (10)	2 (6.1)	3 (15.8)	1 (12.5)	0.51
6	Presence of other autoimmune diseases (%)	11 (18.3)	8 (24.2)	2 (10.5)	1 (12.5)	0.42
7	Malignancy or premalignant condition (%)	9 (15)	4 (12.1)	3 (15.8)	2 (25)	0.65
8	On immunosuppressive drugs (%)	12 (20)	7 (21.2)	2 (10.5)	3 (37.5)	0.27
9	Mean duration in months of symptoms(SD)	5.7 (7.5)	6.1 (9.8)	5.8 (3.8)	4 (1.5)	0.84
10	Sensorimotor presentation (%)	51 (85)	25 (75.8)	18 (94.7)	8 (100)	0.1
11	Mean power (MRC)of weakest limb at presentation (SD)	3.5 (0.7)	3.4 (0.9)	3.6 (0.5)	3.3 (0.5)	0.47
12	CSF cells > 5/cmm (%)	16 (26.7)	10 (30.3)	3 (15.8)	3 (37.5)	0.40
13	CSF proteins (mg/dL)	119.8 (73.4)	125.1(90.1)	102.3 (29.8)	139.7(39.6)	0.43
14	CRP in mg/dL(SD)	8.8 (7)	8.3 (6.3)	10 (8.7)	7.7 (5.5)	0.94
15	TSH (SD)	4 (1.9)	3.8 (1.8)	4.1 (1.9)	4.2 (2.6)	0.88
16	Serum Protein Electrophoresis (%)	4 (6.7)	2 (6.1)	2 (10.5)	0	0.59
17	ANA positive (%)	19 (31.7)	8 (24.2)	9 (47.4)	2 (25)	0.21

IVIg= Intavenous Immunoglobulin, PLEX= plasma exchange, HBsAg= hepatitis B surface antigen, HCV= hepatitis C virus, MRC= Medical Research Council, CSF= Cerebro Spinal Fluid, CRP= C Reactive protein, TSH= Thyroid Stimulating Hormone, ANA= Anti Nuclear Antibody

DISCUSSION

The European Academy of Neurology/Peripheral Nerve Society guideline on diagnosis and treatment of chronic inflammatory demyelinating polyradiculoneuropathy of 2021 recommends the initiation of therapy with either IVIg, steroids or plasma exchange, all being equally efficacious.[3] This is based on studies where IVIg has been compared to either steroids or plasma exchange

Table 2: Immunosuppression used during the follow up period

Sr No	Continuation Phase Drugs	IVIg (n=33)	Pulse steroids (n=19)	PLEX (n=8)	P value
1	Oral steroids	6	6	2	0.12
2	Mycophenolate Mofetil (MMF)	16	6	2	
3	Azathioprine	5	2	1	
4	Oral steroid + MMF	3	5	3	
5	Oral steroid + azathioprine	3	0	0	

IVIg= Intavenous Immunoglobulin, PLEX= plasma exchange

Table 3: Distribution of patients who needed rescue therapy during the follow up 6 months

Sr No	Rescue therapy	IVIg (n=32; 1 lost to follow up)	Pulse steroids (n=18; 1 lost to follow up)	PLEX (n=8)	P value
1	Rituximab	3	3	0	
2	IVIg + Rituximab	3	1	0	
3	IVIg	2	3	0	
4	PLEX	1	1	1	
5	PLEX + Rituximab	2	1	0	
	Total (%)	11 (34.3)	9 (50)	1 (12.5)	P=0.41

IVIg= Intavenous Immunoglobulin, PLEX= plasma exchange

Table 4: Comparison of the ODSS of patients in the three treatment groups

Sr No	Parameter	All patients	IVIg (n=32; 1 lost to follow up)	Pulse steroids (n=18; 1 lost to follow up)	PLEX (n=8)	P
1	Baseline ODSS	7.2 (4)	7.2 (2.2)	7.2 (1.5)	7.5 (1.9)	0.91
2	ODSS at 1 month	5.8 (2.3)	5.4 (2.6)	5.9 (1.8)	7 (1.6)	0.1
3	ODSS at 3 month	4.5 (2.2)	3.9 (2.3)	5.1 (1.9)	5.1 (1.7)	0.08
4	ODSS at 6 month	3.1 (2.4)	2.9 (2.4)	3.5 (2.7)	2.7 (1.3)	0.66

IVIg= Intravenous Immunoglobulin, PLEX= plasma exchange, ODSS= overall disability sum score

Table 5: Responder status (>20% improvement in ODSS from baseline)

Sr No	Time from base line	IVIg (n=32; 1 lost to follow up)	Pulse steroids (n=18; 1 lost to follow up)	PLEX (n=8)	P value
1	No At 3 months (%)	30 (93.8)	11 (61.1)	6 (75)	0.01
2	No At 6 months (%)	30 (93.8)	14 (77.7)	7 (87.5)	0.66

IVIg= Intavenous Immunoglobulin, PLEX= plasma exchange, ODSS= overall disability sum score

with varying dosages, routes of administration of steroids and duration of follow up.[8-12] These studies have been summarized in a recent Cochrane review.[5] As noted in the review, there is a great variability among studies for the outcome and follow up period. Most patients usually require a maintenance therapy which be either the same as induction therapy or another medication like azathioprine or mycophenolate.[3]

Our cohort of CIDP patients had a mostly "typical" profile. Majority were males in their sixth decade. A large number had associated comorbidities like diabetes, malignancies, autoimmune disorders, and hepatitis infection. CSF suggested albumin cytological dissociation. After the initial induction therapy, all received some form of oral immunosuppression. Around a third of the cohort needed additional "rescue" therapy due to relapse or poor response. At the end of six months all patients showed good response to immunosuppression, there was an overall significant reduction in the mean INCAT-ODSS disability score from 7.2 to 3.1 (Mean difference 4.2; Confidence Interval 3.6-4.8); p<0.01). Nearly 88% of patients (51/58) showed at least 20% improvement from baseline. This was similar to a previous study and a very recent systematic review and meta-analysis.[4,13]

Like previous studies, we too found that there is no difference in disability reduction between the three initial therapies. However, there was significant bias in our study in that, irrespective of the initial treatment for induction all patients received maintenance immunosuppression. Therefore, it is difficult to conclude whether the disability reduction at the end of six months was

due the effect of initial therapy or contributed significantly by follow up immunosuppression. Some needed additional "rescue therapies during the six months.

There are several limitations of our study, the chief among them being that it has an observational design. Nearly half of our patients were recruited in a retrospective manner by chart review. During the follow up period, the maintenance immunosuppressive therapy given was variable and not standardized for each arm leading to a bias in outcome. Several patients in each arm needed rescue therapy due to worsening of functional neurologic status. These rescue therapies included the repeat use of the same first line therapy or a different first line therapy. Some patients were given rituximab, a powerful anti CD20 therapy. This could have been a further source of treatment bias. Statistical analysis suggested that the three treatment groups were comparable for the rescue therapy as a treatment class, however, due to small sample size these could not be analysed individually for each type of rescue therapy. Lastly despite recruiting sixty patients (two dropped out on follow up), we could not achieve the calculated sample size of twenty for the steroid and plasma exchange group. This was due to the skewed choice towards IVIg.

In conclusion, our study, despite the above limitations, demonstrates an overall good response in disability reduction to immunosuppression in CIDP. Our study supports the existing evidence that the three initial therapies have equal efficacy. Other considerations like existing comorbidities and cost can help choose the optimum therapy in a resource constrained setting. It may spur a researcher to plan a randomized trial comparing the three options and adjusting for the variables contributing to bias in our study brought out in the discussion.

DISCLOSURE

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