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Efficacy of azathioprine and methotrexate in patients with chronic inflammatory demyelinating polyneuropathy (CIDP)

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Abstract: The study examined the efficacy of various immunosuppressants in patients with chronic inflammatory demyelinating polyneuropathy. We compared the efficacy of Azathioprine and Methotrexate in the treatment of CIDP**.** Patients of either gender aged ≥ 18 years having chronic polyneuropathy progressive for at least 8 weeks having no serum para protein or any genetic abnormality and fulfilling the Koski criteria. To measure the efficacy, Overall Neuropathy Limitation Scale (ONLS) was used. Group 1 was treated with a combination of oral steroids i.e., Prednisolone and Azathioprine while group 2 was treated with a combination of Prednisolone and Methotrexate. ONLS was statistically insignificant in the patient groups (AZA versus MTX) at the beginning of the therapy (from 1-3 months) in both groups. However, in the 4th month, the AZA group performed better than the MTX group. At the 12th month, the mean ONLS score of the patients in the AZA group was 3.69, while the mean ONLS score of the patients in the MTX group was 5.30 (p-value=0.001). We concluded that Azathioprine was more efficacious as compared to Methotrexate in the treatment of CIDP based on ONLS and should be considered as a first-line immunosuppressant in the treatment of CIDP in low-income countries like Pakistan.

Keywords: Azathioprine (AZA), methotrexate (MTX), prednisolone, chronic inflammatory demyelinating polyneuropathy (CIPD), overall neuropathy limitation scale (ONLS), Koski criteria.

INTRODUCTION

Chronic inflammatory demyelinating polyneuropathy (CIDP) manifests as proximal and distal weakness, areflexia, and sensory impairment progressing. The treatment options for CIDP include intravenous immunoglobulin (IVIG), subcutaneous immunoglobulin, plasma exchange or plasmapheresis, corticosteroids, and other immunosuppressive drugs. Onset is between the ages of 30 and 60 years. In 30% of cases, the disease is relapsing, 60% of cases are chronic and progressive, and 10% of cases are monophasic with full recovery (Yoon *et al*. 2011). The age when the disease evolves, response to the therapy, and duration from diagnosis of the disease till initiation of therapy determine the prognosis. Young individuals with acute onset are more likely than elderly patients to respond to treatment, and proximal weakness has been associated with a better prognosis than distal weakness. Progressive course and axonal degeneration are two major poor prognostic markers in CIDP. Azathioprine ($C_9H_7N_7O_2S$) is a 6-mercaptopurine thiopurine with a 1-methyl-4-nitroimidazol-5-yl group replacing the mercapto hydrogen. Azathioprine (AZA) is an antimetabolite drug that antagonize the purine metabolism, resulting in the inhibition of deoxyribonucleic acid (DNA), ribonucleic acid (RNA), and protein synthesis. Methotrexate belongs to the pteridine family, which includes a monocarboxylic acid amide and a dicarboxylic acid. Methotrexate (MTX $C_{20}H_{22}N_8O_5$) is a folate antagonist that causes a reduction in nucleic acid synthesis by depleting cellular purine pools. Therefore, methotrexate interferes with DNA synthesis, repair, and cellular replication. Patients not responding to conventional treatments showed an improvement in their disability with immunosuppressants. After initial therapy with steroids, AZA is commonly taken to maintain remission. MTX can be effective in refractory cases of CIDP (Hung & Hiew, 2018). The efficacy of plasma exchange and IVIg in CIDP has been proven in several randomized controlled trials but plasma exchange is invasive, requires specialist facilities and extended intravenous access and IVIg has cost issues in the developing countries. So the combination of steroids and immunosuppressants is a valuable alternative in CIDP. Azathioprine is the most often utilized drug, although other options include Ciclosporin, Cyclophosphamide, Mycophenolate, and Rituximab (Hughes *et al*., 2004). It is recommended to start Prednisone with a 100 mg dose taken orally once a day in the morning. Prednisone is gradually decreased by 5mg every 2 to 3 weeks once strength has returned to normal or progress has plateaued, generally within three to six months. Both the patient and the clinician must understand that CIDP is a chronic disease that may need an immunosuppressant for more than one year (Hughes *et al*., 2008). Corticosteroids are simple to use, inexpensive, and when compared to IVIg, are more likely to result in long-term remission in CIDP. Studies show that

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corticosteroids given in pulses over a short period have fewer major adverse effects than corticosteroids taken orally daily (Van Lieverloo *et al*., 2018). There are mixed results concerning the efficacies of Azathioprine and Methotrexate for CIDP in the literature. The purpose of the research was to assess the efficacy of AZA and MTX in the treatment of CIDP. The patients' Overall Neuropathy Limitations Scale was used to measure the efficacy.

MATERIALS AND METHODS

Study setting

A comparative study was conducted in the Department of Neurology, Mayo Hospital, Lahore, Pakistan.

Inclusion and exclusion criteria

Patients of either gender of age $\geq$ 18 years, having chronic polyneuropathy progressive for at least 8 weeks having no serum para protein or any genetic abnormality, and fulfilling the Koski criteria were included who fulfilled the Koski criteria having recordable CMAP in at least 75% of motor nerves and either abnormal distal latency or abnormal motor conduction velocity or abnormal F-wave latency in >50% motor nerves (Gorson, 2012). Patients with other types of inherited or acquired neuropathies, hepatic disease, deranged LFTs, and blood dyscrasias were excluded.

Data collection

Baseline investigations were done for every patient. For monitoring the efficacy, Overall Neuropathy Limitations Scale (ONLS) was used (Graham *et al*., 2006). The criteria require that this scale be completed by adding the total of the Arm scale score based on washing and brushing their hair, turning a key in a lock, using a knife and fork, doing or undoing buttons or zips, dressing the upper part of their body; and if all these functions are prevented can the patient make purposeful movements with their hands or arms, and the Leg scale score (0-7) based on having difficulty in running or climbing stairs, difficulty with walking, gait abnormality, mobility for 10 meters without aid, with one or two sticks or with a wheelchair and if they cannot walk are they able to make some purposeful movements of their legs, e.g. reposition legs in bed and the use of ankle foot orthoses, yielding a total score of 0-12.

Patient groups

Selected patients were divided into two groups. Group 1 was treated with a combination of oral steroids i.e., Prednisolone and Azathioprine (AZA). AZA was started as follows: 50mg daily for 2 weeks, 100mg daily for 2 weeks, and then 150mg daily for 44 weeks afterward. Prednisolone was started at a dose of 1mg per kg body weight (not more than 60mg max.) and continued for the first 12 weeks. At the beginning of the 13th week, gradual taper i.e., 5mg per week was started and eventually tapering stopped at 10mg dose at the end of the 24th week. This dose was continued till the end of the study afterward. Clinical response was assessed by ONLS criteria after every month. CBC and LFTs were monitored weekly for the first month and then monthly afterward.

Group 2 was treated with the combination of oral steroids i.e., Prednisolone and Methotrexate (MTX). MTX was started as follows: 7.5mg once a week for 4 weeks, 10mg once a week for the next 4 weeks, and then 15mg once a week for 40 weeks and the same protocol would be followed for oral steroids i.e., Prednisolone for commencement and tapering afterward, as described for group 1. Clinical response was assessed by ONLS criteria after every month. CBC and LFTs were monitored weekly for the first month and then monthly afterward with PFTs.

Because there are various dangers associated with long-term corticosteroid treatment, a PPD skin test was performed before the initiation of corticosteroids to determine whether isoniazid is required in previously exposed patients. We obtained a baseline bone DEXA (dual-energy X-ray absorptiometry) scan and started the patients on calcium and vitamin D supplementation. In case the patient complained of stomach pain, proton pump inhibitors were given. Patients and their relatives were encouraged to report any changes in personality or mental side effects. Patients were advised to reduce their salt and carbohydrate intake, as well as maintain blood pressure and glycemic levels.

Ethical approval

The study was conducted with the approval of the institutional review board (IRB) [Reference No. 336/PEC/RC/KEMU]. Informed consent was taken from the patient or family member.

STATISTICAL ANALYSIS

Data was analyzed in SPSS version 26. Numeric variables like age were presented as means $\pm$ standard deviation. Categorical variables like gender were presented as frequencies and percentages. Chi-square test applied to compare the two groups, Prednisolone with AZA and Prednisolone with MTX. A p-value of less than 0.05 was considered significant.

RESULTS

66 patients were enrolled who fulfilled the inclusion/exclusion criteria. The mean age of the patients was 50 years, there were 18 female and 48 male patients.

Comparisons of ONLS scores (1st – 11th months)

ONLS scores were calculated on the monthly interval of all the patients. At 1st month, In the AZA group, the mean

ONLS score was 8.09 while in the MTX group, the mean ONLS was 7.69. The difference in both the groups was insignificant i.e., p-value=0.156 (table 1). At 2nd month, in the AZA group, the mean ONLS score was 6.82 while in the MTX group, the mean ONLS score was 6.94 (insignificant difference p-value=0.674) (table 2). At 3rd month, in the AZA group, the mean ONLS score was 6.33 while in the MTX group, the mean ONLS score was 6.69 (insignificant difference) (table 3). At the 4th month, In the AZA group, the mean ONLS was 5.96 while in the MTX group, the mean ONLS score was 6.54 (significant difference) (table 4). At the 5th month, in the AZA group, the mean ONLS score was 5.79 while in the MTX group, the mean ONLS score was 6.33 (significant difference) (table 5). At the 6th month, in the AZA group, the mean ONLS score was 5.45 while in the MTX group, the mean ONLS score was 6.18 (significant difference) (table 6). At 7th month, in the AZA group, the mean ONLS score was 5.06 while in the MTX group, the mean ONLS score was 6.00 (significant difference) (table 7). At the 8th month, in the AZA group, the mean ONLS score was 4.91 while in the MTX group, the mean ONLS score was 5.79 (significant difference) (table 8). At the 9th month, in the AZA group, the mean ONLS score was 4.61 while in the MTX group, the mean ONLS score was 5.57 (significant difference) (table 9).

Table 1: Comparison of ONLS Scores at 1st month between the study groups

ONLS		Study Groups		p-value
		AZA	MTX	
1st Month	n	33	33	0.156
	Mean	8.09	7.69	
	Std. Deviation	1.26	0.95	

Table 2: Comparison of ONLS at 2nd month between the study groups

ONLS		Study Groups		p-value
		AZA	MTX	
2nd Month	n	33	33	0.674
	Mean	6.82	6.94	
	Std. Deviation	1.36	0.93	

Table 3: Comparison of ONLS at 3rd month between the study groups

ONLS		Study Groups		p-value
		AZA	MTX	
3rd Month	n	33	33	0.186
	Mean	6.33	6.69	
	Std. Deviation	1.22	0.98	

At the 10th month, in the AZA group, the mean ONLS score was 4.24 while in the MTX group, the mean ONLS score was 5.48 (significant difference) (table 10). At the 11th month, in the AZA group, the mean ONLS score was 3.91 while in the MTX group, the mean ONLS score was 5.33 (significant difference) (table 11). In this study, the overall mean ONLS score at the 12th month of the patients was 4.50 (fig. 1). At the 12th month, In the AZA group, the mean ONLS score was 3.69 while in the MTX group, the mean ONLS score was 5.30 (significant difference) (table 12).

Table 4: Comparison of ONLS at 4th month between the study groups

ONLS		Study Groups		p-value
		AZA	MTX	
4th Month	n	33	33	0.028 (significant result)
	Mean	5.96	6.54	
	Std. Deviation	1.16	0.90	

Table 5: Comparison of ONLS at the 5th month between the study groups

ONLS		Study Groups		p-value
		AZA	MTX	
5th Month	n	33	33	0.047 (significant result)
	Mean	5.79	6.33	
	Std. Deviation	1.22	0.96	

Table 6: Comparison of ONLS at the 6th month between the study groups

ONLS		Study Groups		p-value
		AZA	MTX	
6th Month	n	33	33	0.010 (significant result)
	Mean	5.45	6.18	
	Std. Deviation	1.20	1.01	

Table 7: Comparison of ONLS at 7th month between the study groups

ONLS		Study Groups		p-value
		AZA	MTX	
7th Month	n	33	33	<0.001 (significant result)
	Mean	5.06	6.00	
	Std. Deviation	1.06	1.00	

Table 8: Comparison of ONLS at the 8th month between the study groups

ONLS		Study Groups		p-value
		AZA	MTX	
8th Month	n	33	33	0.002 (significant result)
	Mean	4.91	5.79	
	Std. Deviation	1.18	1.05	

Table 9: Comparison of ONLS at the 9th month between the study groups

ONLS		Study Groups		p-value
		AZA	MTX	
9th Month	n	33	33	0.001 (significant result)
	Mean	4.61	5.57	
	Std. Deviation	1.03	1.15	

DISCUSSION

This study found that at the commencement of the treatment (from 1-3 months) in both groups, the overall Neuropathy Limitations Scale was statistically insignificant between the patient groups. Up to the follow-up of 3rd month, both drugs were statistically equally effective in the measurement of ONLS. But from the 4th months onwards, we found significantly better responses with the AZA group as compared to the MTX group. At the 12th month, In the AZA group, the mean ONLS score of the patients was 3.69 while in the MTX group, the mean ONLS score of the patients was 5.30 (p-value=<0.001). Although we found improvement in the MTX group, patients from the 1st month to the 12th-month follow-up in comparison with the AZA group, the MTX drug was less effective. Alternative immunosuppressants, such as Azathioprine, Methotrexate, or Rituximab, are widely seen as alternatives to IVIg, especially in healthcare systems that may be unable to deliver invasive therapies like plasma exchange or IVIg (Castle *et al*. 2019). Moderate-quality data suggested that 6-month usage of high-dose monthly oral dexamethasone did not improve disability more than daily oral prednisolone (Oaklander *et al*. 2019). Azathioprine is the most often used immunosuppressive drug in the management of CIDP for steroid-sparing. A small trial found Azathioprine unsuccessful, even though it could not detect or rule out all but the most severe therapeutic effects, was too short in length, and employed a lower dosage of Azathioprine than has been used in other autoimmune diseases (Dyck *et al*. 1985). Though Azathioprine can induce bone marrow toxicity, acute pancreatitis, and liver damage, it has a lot of clinical experience and looks to be reasonably safe to use. Yoon *et al*. (2011) revealed that Azathioprine often requires 3-6 months to acquire full effectiveness as seen in our study too. Azathioprine is well tolerated by most people. A dosage of 2.5-3.0mg/kg was preferable.

Table 10: Comparison of ONLS at the 10th month between the study groups

ONLS		Study Groups		p-value
		AZA	MTX	
10th Month	n	33	33	<0.001 (significant result)
	Mean	4.24	5.48	
	Std. Deviation	1.03	1.034	

Table 11: Comparison of ONLS at the 11th month between the study groups

ONLS		Study Groups		p-value
		AZA	MTX	
11th Month	n	33	33	<0.001 (significant result)
	Mean	3.91	5.33	
	Std. Deviation	1.13	1.051	

Table 12: Comparison of ONLS at the 11th month between the study groups

ONLS		Study Groups		p-value
		AZA	MTX	
12th Month	n	33	33	<0.001 (significant result)
	Mean	3.69	5.30	
	Std. Deviation	1.10	1.04	

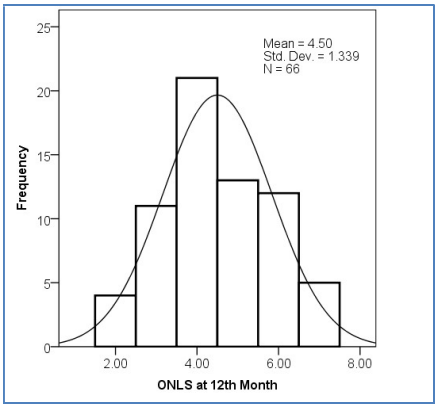

Fig. 1: Distribution of ONLS at the 12th month

Mahdi-Rogers *et al*. (2017) found that there was no significant difference in the change in the ONL scale at the end of the Methotrexate experiment at 40 weeks. Diaz-Manera *et al*. (2009) discovered that individuals with CIDP who were resistant to standard therapy reacted well to MTX (20mg/week). Gorson *et al*. (2012) revealed that AZA is beneficial in certain patients not only for stabilizing the illness course but also for allowing prednisone dosage to be reduced. For CIDP patients who require either IVIg or corticosteroids, a multicenter, randomized double-blinded controlled study compared oral MTX (7.5mg per week for four weeks, 10mg for the following four weeks, and ultimately 15mg for the remaining 32 weeks) with placebo (RMC Trial, 2009). The most widely used medicine is Azathioprine, however, there are no case studies describing its usage, and the one randomized study conducted was ineffective (Dyck *et al*. 2018). MTX's apparent broad-range anti-inflammatory activity is ideal for a condition like CIDP, where the pathophysiology is unknown but likely involves macrophages and both B and T cells. Methotrexate, there may be little or no difference in disability change between MTX and placebo after 40 weeks of therapy, as judged by the ONLS (Kuitwaard *et al*. 2009). In another study 52% of patients who took MTX and 44% percent of patients who had a placebo were able to reduce the dose of corticosteroids or IVIg dose >20%, indicating that oral methotrexate had no substantial advantage over placebo (van Schaik & Eftimov, 2011).

CONCLUSION

Azathioprine was more efficacious as compared to Methotrexate in the treatment of chronic inflammatory

demyelinating polyneuropathy based on the Overall Neuropathy Limitation Scale. Though, initially, both groups were equally effective but with time, azathioprine was found to be more efficacious. Being a cost-effective drug, Azathioprine should be considered a first-line immunosuppressant in the treatment of CIDP in low-income countries like Pakistan. It is recommended that future studies should be done with a larger sample size with better methodology and data must be taken in multicenter settings rather than single-center.

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