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COST COMPARATIVE ANALYSIS OF DEXAMETHASONE-CYCLOPHOSPHAMIDE PULSE THERAPY AND RITUXIMAB THERAPY IN PEMPHIGUS IN A GOVERNMENT TERTIARY CARE HOSPITAL IN NORTHERN INDIA.

Dermatology

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ABSTRACT

Pemphigus vulgaris is the most common autoimmune blistering disorder and the prevalence varies from 0.18 to 6.96 cases per 1,00,000 population worldwide [3].Pulse therapy with high doses of Corticosterids and Cyclophosphamide (most commonly Dexamethasone Cyclophosphamide Pulse (DCP)) for the treatment of pemphigus remained mainstay therapy for past few decades. Targeted immuno-modulation is becoming popular with advent of biological therapies like Rituximab due to lower side effects but its cost is a limiting factor. There is a little literature available on comparison of cost of these therapies which lead us to compare cost of these therapies. In a country like India where cost is a greater parameter to decide therapy a cost effective therapy carries a better compliance and effectiveness as compared to an expensive therapy like Rituximab. In the study we observed DCP therapy was three times cheaper than Rituximab.

KEYWORDS

Dexamethasone-Cyclophosphamide Pulse, Rituximab, Cost analysis.

INTRODUCTION

Autoimmune Bullous disorders are group of antibody mediated chronic disorders characterised by blisters over body and mucosa [1].These disorders can result into life threatening consequences if not treated. Pemphigus vulgaris is the most common autoimmune blistering disorder and its incidence among the dermatology outpatient attendees varies between 0.09 to 1.8% [2]. Its prevalence varies from 0.18 to 6.96 cases per 1,00,000 population worldwide [3]. Corticosteriods have been considered perhaps the best modality to treat and induce remission. Pasricha et al introduced pulse therapy with high doses of Corticosterids and Cyclophosphamide (most commonly Dexamethasone Cyclophosphamide Pulse (DCP)) for the treatment of pemphigus for first time in 1982 and till years it remained mainstay therapy [4]. For the past few years, targeted immuno-modulation is becoming more and more popular with advent of biological therapies like Rituximab due to side effects and other disadvantages associated with bolus doses of Corticosteriods when adminstered through pulses [5]. Rituximab is a novel biological agent which has found its way in the management of Pemphigus, yet its high cost act as an obstacle. To the best of our knowledge there are very few studies that compare the cost of these two highly efficacious and promising therapies.

AIMS and OBJECTIVES

1. To assess the cost of DCP therapy in pemphigus
2. To assess the cost of Rituximab therapy (rheumatoid arthritis protocol)in pemphigus
3. To compare cost of DCP therapy versus Rituximab therapy in pemphigus

MATERIALS AND METHOD

DCP therapy is administered in 4 phases. Data from the record of past 3 years 2016-2019 were extracted from the records and the number of patients who were given Rituximab Pulse therapy and Dexamethasone Cyclophosphamide Pulse therapy were considered. The average cost of therapy for all the patients was considered. All the expenses which patient has to bear during the treatment were calculated and analyzed through tabular forms. These include the investigations and various medications that are required during various phases along with cost of hospital stay. Hospitalization is required only during first two phases which in total comprises of 18 months. While most of the investigations are done at each admission, there are others which are performed every 3 months in phase 1 and 2. During phase 3, all the investigations are repeated every 3 months and phase 4 is observational without any investigation and medication.

According to the Rheumatoid Arthritis Protocol, Rituximab is given in doses of 1 gm each, 15 days apart . All the medications required and investigations performed before these two phases are analyzed and tabulated.

Most of the investigations that are required during therapy were available within the hospital laboratory services and there charges have been tabulated accordingly. Similarly the cost of medicines as well as the material required in these procedures was taken into account considering the minimal cost of products available.

Cost(in Rupees) of DCP therapy in pemphigus			
	Phase 1	Phase 2	Phase 3
Investigation done only at beginning			
Biopsy	150		
Investigation on 1st day of every DCP therapy			
CBC	40	40	
LFTs	180	180	
RFTs	60	60	
Urine C/E	40	40	
RBS	30	30	
S.Electrolytes	90	90	
Lipid profile	150	150	
ESR	10	10	
Total for 9 months	550 *9 =4950	550*9=4950	
Investigations required at 3 monthly interval			
CBC, LFTs, RFTs, Urine C/E, RBS, S. Electrolytes, Lipid profile, ESR			550
X-ray chest	100	100	100
U/S Abdomen	150	150	150
Viral markers	60	60	60
ECG	60	60	60
Total of 9 months	370*3=1110	370*3=1110	920*3= 2760
Hospital stay for 1 pulse	60*3=180	60*3=180	
Total Hospital stay for 9 pulses	180*9=1620	180*9=1620	
Material required during each pulse			
Injection Dexamethasone (20ml)	10/vial *4=40	10 /vial *4=40	
Injection Cyclophosphamide (500 mg)	500	500	
Others like 5%Dextrose,I/V set, Cannula, S.gloves, Syringes	(17*3)+(5*3) +(7.53)+(9*8) +(12*3)=197	(17*3)+(5*3) +(7.5*3)+(9*8) +(12*3)=197	

Total of 9 months	197*9=1773	197*9=1773	
Cost of oral medications (steroids and Cyclophosphamide)	945	720	720
Total	10,548	10,173	3480
Total cost	24,201		

Total cost(in Rupee) of Rituximab therapy (Rheumatoid Arthritis Protocol)		
	Phase 1	Phase 2
Investigations required		
CBC	40	40
LFTs	180	180
RFTs	60	60
ESR	10	10
Urine C/E	40	40
Lipid profile	150	150
Chest x-ray	100	00
U/S abdomen	150	00
ECG	60	00
Biopsy	150	00
S. electrolytes	90	90
Viral markers	60	00
TB Quantiferon gold	1500	00
X-ray LS spine	150	00
Montoux test	00	00
Total charges	2740	570
Hospital stay	1000*2=2000	1000*2=2000
Medicines/ material required		
Inj Rituximab(500 mg)	23000*2=46000	23000*2=46000
Premedications	450	450
Normal saline 500mg	17	17
Syringes	12*2=24	12*2=24
S.gloves	9*3=27	9*3=27
I/V set	5*2=10	5*2=10
Cannula	7.5*2=15	7.5*2=15
Total charges	51,333	49,113
Total cost	1,00,446	

Common Side effects			
DCP therapy		Rituximab therapy	
1	Increase in body weight,transient puffiness,edemas	1	Relapses and partial remissions
2	Metabolic disturbances like hyperglycemias,hyperlipidemias	2	Persistent lesions
3	Increased rate of bacterial,fungal and viral infections	3	Increased rate of bacterial,fungal and viral infections
4	Electrolyte distrbances,hypertension,myopathies ,joint pains		
5	Eye changes like cataract,glucomas		
6	Others like ammenorrhea,hair loss,transient leukopenias		
7	Haematuria due to cyclophosphamide		

DISCUSSION:

In India, the use of DCP therapy by Pasricha in early 80s proved to be a revolutionary measure in the treatment of blistering disorders [4]. Since then, it has become a widely known practice in the country as well as outside the country [6,7]. It has been considered as a rapid mean to control dermatological emergency like pemphigus with least toxicity. In a study conducted by Kanwar et al. it was seen that DCP therapy lead to complete sustained remission of the disease in all the patients in the study group recieving DCP therapy thereby proving it to be highly efficacious with considerable results [8]. Similarly Varala S et al conducted a study over 10 years and observed DCP therapy to be highly efficacious in treatment of Pemphigus [9].

DCP refers to administration of supra-pharmacological doses of Steroids and immuno-suppressant Cyclophosphamide to the patient at regular intervals usually after 28 days to halt the disease process and minimize the side-effects of drugs. The phases include the consolidation phase and maintenance phases.

Dexamethasone Cyclophosphamide Pulse (DCP) therapy - divided into 4 phases.

Phase I: one pulse constitutes of Dexamethasone 100 mg in 5% Dextrose as a slow IV infusion over 2 hours for three consecutive days along with Cyclosphosphamide 500 mg infusion on one of the days. Such DCPs are repeated every 28 days. Cyclosphosphamide 50 mg / day is given orally along with conventional doses of oral corticosteroids to achieve quicker clinical recovery. Addition of daily low dose steroids and short course of antibiotics may be required to control the disease which is slowly tapered off as the lesions heal [10].
Phase II: DCP therapy is given every 28 days for a fixed duration of 9 months along with daily dose of oral immunosuppressant (Cyclophosphamide).

Phase III: Oral Cyclophosphamide 50 mg / day is given for 9 months.
Phase IV: The patient is followed up without any intervention.

Since this treatment involves repeated hospital admissions and long term medications for months to years it can be a burden to the patient's quality of life affecting their socioeconomic and overall well being. Work absenteeism and travelling charges further deteriorates the picture posing a threat to long follow ups and treatment compliance. Owing to loss of follow up patient may land up into relapses of the disease which further has a negative impact over compliance to treatment since patients may resort to other non yielding treatments which are not only economic burden but also toxic to patients health [11]. Therefore it is necessary to look for alternate treatment options which give a long disease free period and a better treatment compliance of the patient besides minimizing the patient and healthcare facilities burden. In this context Rituximab has shown promising results [12].

Rituximab is a 145k-Da chimeric murine-human monoclonal antibody directed against the CD20 antigen present on B lymphocytes. It acts by depleting the CD20 expressing B-cells by either antibody dependant cell killing, complement mediated cytolysis or by inhibition of signaling and apoptosis. Rituximab has been approved by US-FDA in June 2018 for the treatment of moderate to severe Pemphigus. Rituximab has shown promising results as a single agent in treatment of autoimmune bullous disorders [13].

The Treatment protocols include:

1. Lymphoma protocol: dose of 375mg/m^2 body surface area weekly for 4 weeks.
2. Rheumatoid arthritis protocol: 2 doses of 1g Rituximab at a 15 day interval. A dose of 500mg is repeated at 12 months and 18 months thereafter and every 6 months as per the disease process.

Rheumatoid arthritis protocol is mostly employed by dermatologists since it is cost effective as well as requires lesser hospital admissions. Keeping into account such benefits this protocol is being followed at our institute. In view of the cost of the biologicals, biosimilars are usually a choice especially in the developing countries like ours.

Biosimilars as the name implies are the products highly similar to the already FDA approved biological in relation to their safety, efficacy and potency with slight differences in their structures and presence of clinically inactive substances in the biosimilars [14]. Since cost of the drug is a major drawback in compliance of the patient and thus treatment on the whole such product which meets all the requirements is being used in our institute and Rituximab biosimilar is drug adopted. In a study conducted by Sinha P et al. the efficacy of induction and maintenance of remission of Pemphigus with DCP as well as Rituximab was found to be comparable [15]. Therefore, the choice of the therapy is based on other parameters like side/adverse effect profile and cost of the therapy. While use of DCP therapy poses a great threat due to high doses and long duration of steroids along with risk of immunosuppression due to steroid per se and myelotoxicity, gonadal failure and uro-epithelial cancers with the use of cyclophosphamide. Similarly, Rituximab has its own profile of side effects which ranges from transient infusion related and flu like symptoms to severe hypersensitivity reactions, sudden cardiac arrest and prolonged immunosuppression posing threat of infections [16, 17]. Another significant drawback of therapy is failure of remission and relapse of the disease after therapy [18].

In our study we observed that the cost of DCP therapy was In our study the total cost of DCP therapy was 24,201 whereas the total cost for Rituximab therapy was 1,00,446. The cost for DCP is almost thrice as in DCP therapy which in contrast to another study by Rohith et al. where total expenditure for Rituximab therapy was much lesser than DCP therapy [19]. Another study comparing the cost of both therapies in France showed a slight 6% increase in expenditure for Rituximab therapy which is in congruence with our study [20].

CONCLUSION:

The study was conducted to compare cost of two therapies viz. Dexmethasone Cyclophosphamide Pulse therapy and Rituximab pulse therapy and we observed DCP therapy was three times cheaper than Rituximab. In a country like India where cost is a greater parameter to decide therapy a cost effective therapy carries a better compliance and effectiveness as compared to an expensive therapy like Rituximab. Moreover, there is plenty of literature to support efficacy of DCP therapy and side effect profile can be managed with regular follow up and timely treatment of adverse effects related to the DCP therapy. Since there are significant relapses even with Rituximab and the regimens need to be repeated every 6 months the therapy act as a great financial burden thereby compromising compliance of the patient.

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