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Original Research Article

Patterns of Drug Use and Adverse Drug Reactions in Patients with Autoimmune Bullous Disease (AIBD)

S.B. Nishitha[1], Anuradha S[2], Mary Augustine[3]

[1]Postgraduate, Department of Pharmacology, St. John's Medical College, Bangalore, Karnataka, India
[2]Assistant Professor, Department of Pharmacology, St. John's Medical College, Bangalore, Karnataka, India
[3]Professor, Department of Dermatology, St. John's Medical College, Bangalore, Karnataka, India

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Corresponding author: Dr. Anuradha S
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Abstract

Background: AIBD is an autoimmune dermatological disorder affecting predominantly the skin and mucous membrane. Though newer biologic Rituximab has been introduced in the last decade, systemic corticosteroids form the mainstay of the treatment. Comprehensive studies reporting drug use pattern, adverse effects and costs involved with treatment have been few in India.

Objectives: To evaluate the pharmacotherapy its adverse effects of AIBD, and costs incurred for treatment.

Methods and Materials: Prospective observational study that enrolled adults with AIBD, who were followed up at 1 and 3 months. Data on demographics, disease characteristics, treatment, and treatment costs were collected. Data were summarized using descriptive statistics and compared using chi-squared and t-tests.

Results: Of the 47 patients recruited, 66% were females, mean age (SD) of participants being 46.6 (±11.1) years. Median (IQR) duration of AIBD was 0.83 (0.46-1.50) years. Mean no. of drugs was 9.2 ± 2.80. Thirty three (70.2%) patients received topical and 47 (100%) received systemic corticosteroid therapy and 18 (38.2%) received rituximab therapy. Most commonly prescribed topical drugs were supplements (calcium) 100%, oral prednisolone 100%, anti-inflammatory agents (79%). The median treatment cost including admission was INR 26702.1 (SD 21971.2).

Conclusion: Patients had moderate severity of disease and poor QoL at baseline compared to other studies. They received rational treatment and there was an improvement in the DLQI score. There was a high economic burden due to hospital and drug costs. We recommend that health insurance coverage should be increased to help these patients.

Keywords: AIBD; Autoimmune bullous disease/ Pemphigus/ Bullous pemphigoid, drug therapy, Administration, Corticosteroids, Rituximab, Health Care Costs, Drug Costs.

INTRODUCTION

Autoimmune bullous diseases are characterized by blisters in the skin and mucos membrane. Predominantly seen in Ashkenazi Jews, Southeast Asians and elderly. Based on site of bullae formation, they are grouped- 'Pemphigus' (intraepidermal blisters) and 'Pemphigoid' (subepidermal bullae) group. Auto antibodies target components of the epidermis or dermoepidermal junction

(DEJ) leading to inflammatory cascade and blister formation. [1]

Drugs, trauma, radiotherapy, UV radiation and vaccination (influenza vaccine) are known to trigger AIBD.[2] Drug induced AIBD was first seen in 1970 in a patient on Salicylazosulphapyridine. [3] Other drugs identified to cause AIBD- furosemide, Spironolactone, Phenothiazines, ACE- I, anticoagulants and diuretics. Involvement of connective tissue leads to exanthema, itching or scaling. Life-threatening complications due to infections and sepsis may occur.

AIBD runs a chronic course, corticosteroids are mainstay of treatment, followed by Azathioprine, Mycophenolate mofetil as a second-line treatment. [4-5] Rituximab (anti-CD20 monoclonal antibody), immunoadsorption, Cyclophosphamide, Dapsone or Methotrexate are relatively newer treatment options. Both Corticosteroids and Rituximab have shown considerable disease control. [6] Prolonged treatment pose a threat due to adverse effects like hyperglycemia, hyperlipidaemia, insulin resistance, ischemic cardiac events etc.

Expensive newer treatment regimens, chronic treatment and regular investigations add to the financial burden. As the disease is rare, very few studies have been done. A search of previous studies conducted in India in this area did not yield a comprehensive study looking at the disease characteristics, treatment pattern and cost of disease/ treatment.

MATERIAL AND METHODS

The study was conducted by the Department of Pharmacology in collaboration with the Department of Dermatology at St John's Medical College Hospital, Bangalore, tertiary care hospital. Patients visiting the hospital come from different geographical regions with a fair representation of both urban and rural populations. The present study was conducted among the outpatients and inpatients with AIBD. Institutional Ethics Committee (IEC) approval was obtained for the conduct of the study [IEC Study Ref No: 967 / 2018]. We conducted a hospital-based prospective observational study for 21 months (18 months recruitment with additional 3 months for follow-up). Patients were recruited from January 2019 to June 2020. There were 2 follow ups at 1 month and 3 months from the time of recruitment. One of the primary objectives of our study is to evaluate the pattern of drug use. Using previous studies, the minimum sample size was calculated to be 36. Taking an account of dropout rate of 30% the final sample size would be 47 patients.

The clinical outcomes (remission relapse) and average monthly cost of medical care were the secondary objectives. All registered patients with Dermatologist confirmed diagnosis of AIBD, Age >18 years, both males and females were included in the study. Patients in whom the three month follow up is not possible or Patients with severe cognitive impairment were excluded from the study.

The informed consent form (ICF) was designed to obtain voluntary, informed consent from all the patients participating in the study. The Case Record Form (CRF) was designed to capture demographic characteristics, treatment data, costs of treatment. Recruitment began from January 2019. After which the patients were followed up at 1 month and 3 months via telephonic conversation. Details of medications prescribed were also recorded from the daily treatment charts. During the designated follow-ups at 1 month and 3 months, data on complications, hospitalizations, relapses, remission, ADRs and frequency of follow-ups were recorded.

We summarized the baseline and demographic data of patients using descriptive statistics. Continuous variables like duration of illness, hospitalization, monthly family income etc., were

summarized using mean (± SD) or median with interquartile range (IQR). All continuous variables were checked for normality. Parametric data were analysed using an Independent sample t-test and non-parametric data were analysed using Mann Whitney U test. Categorical variables were analysed using Chi-squared tests. In analyses, a p-value of <0.05 was considered significant for all tests. All data were entered into the EpiInfo software (version 7), and statistical analyses were performed using commercially available software (SPSS version 20).

RESULTS

This study was conducted over a period of 23 months. A total of 47 patients with AIBD were recruited. Of the 47 patients, 45(96%) completed the first follow up and 42(89%) completed the 2nd follow-up. Five (10%) patients were considered lost to follow-up by the end of the study.

Among the study population had 31(66%) were females and 16(34%) were males with a male to female ratio of 1:5. The mean age of the patients was 46.6 (SD 11.1). Twenty-eight (59.6%) patients were from the urban areas and 19(40.4%) were from the rural areas. Thirty-five (74.5%), 10 (21.3%), and 2(4.3%) patients belonged to the High, Moderate and Low classes respectively. A majority of patients, 22 (46.8%) had school education followed by 8(17%) who were professionals or graduates. Mean no. of family members for the patients was 4.7 (SD 1.4). Only 5(10.6%) patients followed a vegetarian diet. 23.4% patients were occasional alcoholics and 21% were smokers. The patients' demographic characteristics and distribution by percentage are given in Table no. 1.

Table 1: Demographic profile at baseline

Variables		**Total Sample (N=47) n (%)**
Age (mean± SD)		46.6±11.1
Gender	Female	31 (66.0%)
	Male	16 (34.0%)
Domicile	Rural	19 (40.4%)
	Urban	28 (59.6%)
Marital Status	Married	40 (85.1%)
	Unmarried	7 (14.9%)
Median monthly family income (in Indian rupees)		12000.00 (7500.00-30000.00)
Non vegetarian diet		42 (89.4%)
Substance abuse	Smoking	10 (21.3%)
	Alcohol	11 (23.4%)
	Tobacco chewing	8 (17.0%)
Education	Illiterate	17 (36.2%)
	Primary/middle/high school	22 (46.8%)
	Diploma/graduate/professional	8 (17.0%)
Occupation	Unemployed	16 (34.0%)
	Elementary/ Agriculture/ Fisheries	15 (31.9%)
	Sales-workers/ Clerks/ Technicians	11 (23.4%)
	Professionals/ Managers	5 (10.6%)
No: of Family members (mean± SD)		4.7± 1.4

The median duration of AIBD was 0.83 years (IQR 0.46-1.50) and the mean age at diagnosis of AIBD was 45 (SD 11.9) years. In 5(10.6%) patients, the duration of disease was more than 5 years. Forty (85.1%) patients were in-patients and 7 (14.9%) were out-patients. 22(46.8%) patients had at least one co-morbidity,

diabetes mellitus being the most frequent at 27.7%, followed by hypertension and at 25.5%, coronary artery disease, asthma and hypothyroidism 4.3% each and vitamin B12 deficiency at 1.2% .

The commonest type of AIBD among the patients was Pemphigus vulgaris at 87.2%. Bullous pemphigoid was present in 8.5% patients, IgA bullous disease and Pemphigus follicaeous in 2.1% each. Oral Mucosa was affected in 74.5% patients, trunk in 53.2% patients, followed by Lower Limb Flexor in 38.3% and Upper Limb Flexor in 36.2% patients. Scalp was affected in 34% patients, Head & Neck in 21.3% patients and Genitals in 10.6% patients. 65.9% patients presented at the hospital with complaints of blisters followed by complaints of itching in 8.5% and those who came for routine therapy 25.5% patients. Severity of the disease was measured using the ABSIS (Autoimmune bullous skin disorder intensity score) and OMS (oral mucosal score). The median ABSIS score of the study population was 2.50 (IQR 1.50-8.50). The median OMS score of the study population was 3.00 (IQR 3.00-5.00). 23.3% patients had severe AIBD, at baseline. At baseline 25 (53.2%) of the patients were reported to have an aggravation of the condition.

Details of clinical characteristics are given in table no.2

Table 2 : Baseline clinical characteristics

Variables		**Total sample (N=47) n (%)**
Age at diagnosis (years) (mean± SD)		45.03 ± 11.92
Duration of AIBD (years)	Median, IQR	0.83 (0.46-1.50)
	>5 years	42 (89.4%)
	< 5 years	5 (10.6%)
Duration of treatment of AIBD (years) (median, IQR)		0.50 (0.29-0.83)
Hospital site	In-patient	40 (85.1%)
	Out-patient	7 (14.9%)
Mean no. of days of admission (mean ± SD)		3.7± 0.84
Co-morbidities	Total	22 (46.8%)
	Diabetes Mellitus	13 (27.7%)
	Hypertension	12 (25.5%)
	Coronary Artery Disease	2 (4.3%)
	Thyroid disorders	3 (6.4%)
	Asthma	2 (4.3%)
	Neurological disorder	11 (2.1%)
	Chronic nutritional deficiency	1(2.1%)
	Fungal infection	1(2.1%)
Type of AIBD	Pemphigus Vulgaris	41 (87.2%)
	Bullous Pemphigoid	4 (8.5%)
	Pemphigus Folliacious	1 (2.1%)
	IgA disease	1 (2.1%)
Areas affected	Lower limbs	26 (55.3%)
	Upper limbs	29 (61.7%)
	Chest/ breasts	25 (53.19%)
	Scalp	16 (34.04%)
	Genitals	5 (1.06%)
	Oral mucosa	34 (72.34%)
	Abdomen &back	20 (42.5%)
Presenting	Blisters	31 (65.95%)

complaints	Itching	4 (8.51%)
	Routine pulse/ rituximab therapy	12(25.53%)
OMS score	Median (IQR)	3.00 (3.00-5.00)
ABSIS score	Median (IQR)	2.50 (1.50-8.50)

The mean no. of drugs prescribed was 9.21 (SD 2.80) and polypharmacy (>6 drugs) was seen in 93.6% patients. All 47 patients received systemic steroids, 38.3% received rituximab therapy, 48.9% received other adjuvant therapy, like azathioprine, cyclophosphamide and 70.2% received topical therapy. Among topical medications, anti-inflammatory drugs like benzydamine were the most commonly prescribed (36.2%), antibiotic creams at 34% and steroid combinations at 23%. Among steroid combinations, betamethasone plus fusidic acid combination was the most commonly prescribed (17%), followed by clobetasol plus gentamicin combination at 4.9%.

Details of the topical drugs prescribed is described in Figure no. 1. The commonest drug prescribed as systemic treatment was steroids like Prednisolone, supplements like calcium at 100% each. Systemic adjuvant medications were prescribed in 48% of the patients with Azathioprine being the most frequently prescribed drug (36%), Cyclophosphamide 46.3%, Doxycylcine and Methotrexate 4.2% each (Figure no. 2). Biologic adjuvant treatment, Rituximab was prescribed in 38% patient. Details of systemic treatment is given in Table no. 3. 14.6% patients gave a history of using complementary alternative medicines.

Figure 1: Pattern of use of topical agents

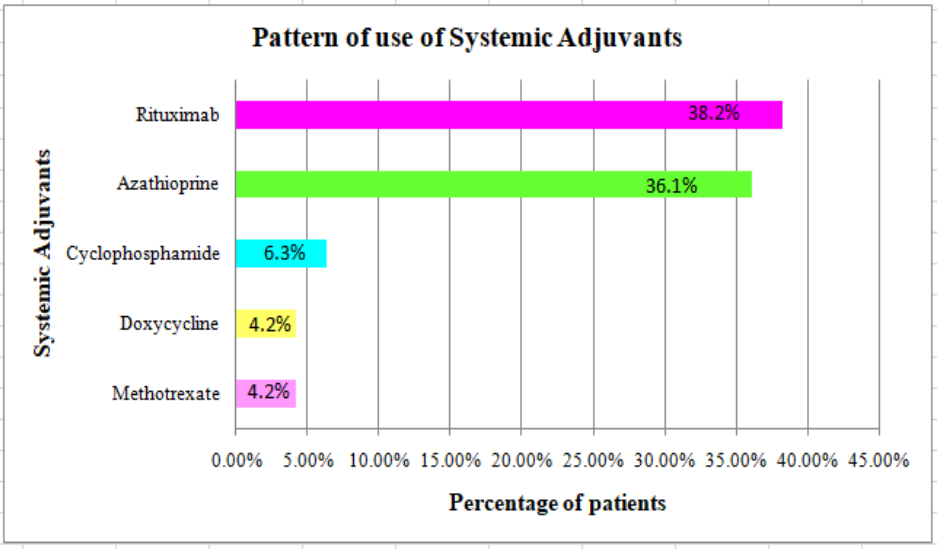

Table 3 : Treatment details (baseline)

Variables		**Total sample (N=47) n (%)**
Mean total no. of drugs (±SD)		9.2 ± 2.80
No. of medications	Polypharmacy (>6 drugs)	(93.6%)
Topical medications	Total	33 (70.21%)
	Steroids	3 (6.38%)
	Steroid combinations	13 (27.65%)
	Topical antibiotics	15 (31.91%)
	Topical anti-inflammatory	19 (40.42%)
	Topical Antifungal	1(2.12%)
Systemic medications	Systemic steroids	47 (100%)

	Rituximab	18 (38.2%)
	Pulse therapy	20 (42.5%)
	Adjuvants	23 (48.9%)
	Anti-hypertensives	15 (31.91%)
	Anti-diabetics	13 (27.7%)
	Anti- viral drugs	6 (12.7%)
	Anti- fungal drugs	4 (8.5%)
	Antibiotics	18 (38.2%)
	Analgesics	4 (8.5%)
	Antacids	47(100%)
Complementary alternative medicine	Total	7 (14.89%)
	Ayurveda	3 (6.38%)
	Homeopathy	5 (10.63%)

Among the study population, 70.2% patients complained of ADRs. The most common ADR was gastritis, seen in 18 (70.2%) patients. Other ADRs seen include tiredness (36.2%), urinary tract infections (20%) and hyperglycemia (17%). A complete list of treatment emergent ADRs is given in Table no. 4.

Table 4: Treatment emergent adverse drug events reported by patients

Variables	Total sample (N=47)
Presence of ADRs	33 (70.2%)
GIT adverse reactions	18 (38.3%)
Tiredness	17 (36.2%)
Skin manifestations	1 (2.1%)
Hematological changes	3 (3%)
Opportunistic infections	1 (1%)
Hyperglycemia	8 (17.0%)
Infections	9 (20.0%)
Neurological	2 (4.3%)

The median family income of patients in the study population was INR 12000.00 (IQR 7500.00-30000.00). Hospital costs for in-patients and out-patients were similar as most patients got admitted either for pulse or rituximab therapy. The costs calculated included the admission, registration, travel, drug and investigation costs. The mean duration of hospital stay for inpatients was 3.7 days (SD 0.3). The mean total hospital cost including admission was INR 26702.1 (SD 21971.2), mean cost for investigation and travel costs (2-way) was INR 1006.3 (SD 546.7) and INR 1176.60 z(SD 1152.7) respectively. The mean registration costs was INR 195.3 (SD 26.1). Details of the estimated costs are given in Table no. 5.

Table 5: Details of costs incurred by patients

Variables	Total Sample (N=47)
Registration costs	Rs 195.32 ± 26.11
Travel costs (2-way)	1006.38± 546.69± 1152.73
Treatment cost (Including admission charges)	Rs 26702.13 ± 21971.24 Median cost Rs 15000 (6500- 50000)
Investigation charges	Rs 1006.38± 546.69

At baseline 25(53.2%) patients were in flare which decreased to 15(33.3%) at first follow up and 10(22.2%) at second follow up. At first follow-up (1 month), 10(22.2%) patients had undergone remission, 6(13.3%) reported relapse of their condition and 29(64.4%) patients reported no change in their condition from

baseline. At the second follow-up (3 months), 18(40.0%) patients reported remission with 7(15.6%) and 20(44.4%) patients reporting relapse and no change in their condition compared to previous follow up, respectively.

DISCUSSION

This was a prospective, observational, hospital-based study. Of the 47 patients recruited, 45 completed 1st follow-up and 42 completed 2nd follow-up, with a loss-to-follow-up rate of 10.6%. In our study, the mean age of the participants was 46.62 (SD±11.1) years. Study done by Mini et al (2019) in India reported a similar result with age in the range of 40–59 years.[7] The mean age of onset in our study was 43 years (SD ± 9.11). Studies in the western population have shown a later age of onset between 53-73 years (Baican et al, 2010) [8]. Our study had a female preponderance (M: F ratio 1:5) with 66% patients being females. Other studies showing similar results were done by Kiran et al (2018) [9] - female preponderance (60.7%) and Davatchi et al (2005) (59.9%)[10].

The median duration of disease was 0.83 (IQR 0.46-1.50) years with 10.6% patients having the disease for > 5 years, similar to study from Eastern India (mean duration of 0.68 years) [11].

PV is more common in India. (12) In our study the commonest type of AIBD found was PV (87.2%), followed by BP (8.5%) and PF, IgA bullous disease (2.1%). This was also seen in a study done by Mini et al (2019) in Kerala- PV (83.72%) [13]. 65.95% patients complained of blisters over skin and oral cavity, 8.51% had itching. 74.5% of our patients had oral lesions. This is also seen in the study done by Kiran et al (2018), where 89.65% patients presented with oral lesions. None of our patients had family history of AIBD. Drugs are common triggers for AIBD; in our study 2 patients reported Nemusilide and telmisartan as triggers for onset of the skin condition. Another study done in India by Kanwar et al (2006) reported to have no triggers or precipitating factors for AIBD. [14]

The mean no. of drugs in our study was 9.21 (SD± 2.8). In a study done by Försti et al in Finland (2013), 49.8% of the study population with BP had polypharmacy (>6 drugs) and this was associated with 7.6 folds increase in mortality with 16.7% having 1-year mortality [15]. 93.6% of our patients had polypharmacy.

Topical therapy is only the supportive treatment and 70.21% patients received topical treatment. 36.2% received anti-inflammatory topical agents, like benzydamine, 8.5% patients received topical steroid mono-therapy, 23.4% received topical steroid combinations. In a study done by Sheth et al (2019) topical betamethasone (25.11%) was most frequently prescribed [15]. A study by Jolly et al (2002) showed superiority of topical clobetasol to systemic steroids in moderate to severe pemphigus patient. 49.8 % patients received topical steroid therapy with clobetasol, the study showed that one-year survival rate 76 % in the topical-corticosteroid group versus 58 % in the oral-prednisone group. Disease was controlled at 99 % topical steroids and 91 % oral prednisolone group (P=0.02) [16].

All patients in our study received steroids oral prednisolone (100%). 38.3% patients received rituximab and 48.9% corticosteroids pulse therapy with adjuvant drugs. 36.1% patients received DAP pulse therapy and 6.3% DCP pulse therapy. Study done in Gujarat (kiran et al, 2018) showed similar trend. A 10-year retrospective study done in Iran showed that 75.7% of AIBD patients were on DCP, 19.6% received DAP. Though corticosteroid pulse therapy is being used for the treatment of AIBD in India, there is no evidence that it is superior to conventional oral corticosteroids but may be useful for rapid disease control in patients with severe disease [17]. Karwar et al first introduced rituximab therapy in

2010 [18]. A systematic review and meta-analysis done by Tavakolpour et al has shown that the number of studies done on rituximab therapy has increased from 2 to 11 from 2010 to 2018.

70.2% of our study population experienced an ADR during the course of the study. The most common ADR reported was gastritis (38.3%), tiredness (36.2%) and infections (20.0%). In a study by Kiran et al (2018) 23.6% patients developed infections, 10% had pedal edema. Similar to our study, 55% patients complained of malaise or tiredness in a study done by Kanwar et al [14].

In our study 85.1% of patients were in-patients with mean duration of hospital stay being 3.7 (SD± 0.84) days. The mean total costs for in-patients which included admission costs and medication costs were around INR 26702 per month. In a study by Kiran et al (2018), the mean cost of treatment was much higher (51,371.40 INR).

Being a tertiary care hospital, we had a fair representation of patients from different sections of the society. We managed to include a good representation of patients from both the rural and urban areas, and from the out-patient and inpatient wards and also patients with varying types and severity of AIBD.

The study was conducted in the dermatology outpatient and in-patient wards and required a random sampling strategy to ensure a representative sample. We could not strictly follow this sampling strategy and this is a limitation of our study

Details of investigations done every month and costs involved could not be accurately assessed as patients often had no records during the time of interview. Finally, as this study was done in a single centre with a small number of patients (n=47), and being AIBD is a rare disease, the findings of this study cannot be generalized to other population. We suggest that further multi-centre studies be undertaken in India to widen the scope of available knowledge about AIBD, and to quantify the social and economic burden of those living with AIBD, that will help establish policies to benefit them.

CONCLUSION

Our study evaluated the pharmacotherapy, cost of treatment, in patients with AIBD in a tertiary care hospital in India. A majority of our patients received systemic corticosteroid therapy, followed by adjuvant treatment. In our study, patients were found to have a physical, psychosocial and financial burden. This burden was increased by the presence of co-morbidities and frequent relapses or flares. To combat the challenges posed by this disease, early screening for co-morbidities, triggers should become routine and appropriate interventions to be done. To ease the financial burden of the patients, insurance schemes should be made available. In conclusion, our study though an important one in generating treatment data was limited by short duration and relatively small number of patients. The findings from our study may be used to design larger studies, preferably, multi-centre studies with larger sample size, to generate more meaningful information about AIBD patients.

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