An Evaluation of Pharmacological Management of Pemphigus Vulgaris and Its Impact on Quality of Life

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ABSTRACT

Objectives: To study use, effect and adverse drug reaction (ADR) of the drugs and its impact on quality of life in patients suffering from Pemphigus vulgaris (PV). Materials and Methods: Prospective, observational study was carried out in newly diagnosed patients of PV. Baseline and follow-up data at 2, 6 and 12 weeks; disease severity (Kumar’s score), Quality of Life (Dermatology Life Quality Index (DLQI)) and ADR were recorded. Data analyzed by one-way and repeated measure ANOVA test. Results: Total 84 patients were included (Group A: Corticosteroid (n=29), Group B: Corticosteroid + Azathioprine (n=30), Group C: Corticosteroid + rituximab (n=26)). Significant reduction (P<0.001) observed in Kumar’s and DLQI score at 2nd and 3rd follow-up as compared to baseline and 1st follow-up and at 3rd follow-up as compared 2nd follow-up in group A, B and C. Mean difference between baseline and 3rd follow up of Kumar’s score and DLQI was significantly higher in group C as compared to group A (p<0.01 and p<0.001, respectively) and B (p<0.05 and p<0.05, respectively). Correlation between Kumar’s and DLQI score was significant in group C (P<0.05). ADRs were reported in group A (68.96%), B (63.33%) and C (52%). Cost of rituximab was significantly higher (p<0.001) than corticosteroid alone / in combination with azathioprine for the treatment of Pemphigus vulgaris.

Key words: Pemphigus vulgaris, Kumar’s score, Dermatology life Quality Index, Corticosteroid, Rituximab.

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INTRODUCTION

Pemphigus vulgaris is a rare autoimmune blistering disease of skin and mucous membranes. The Worldwide incidence of Pemphigus vulgaris is 0.5 to 3.2 cases per one lakh populations/year.1 In India, incidence of Pemphigus vulgaris is 4.4 cases per million populations/year.2 Patients of Pemphigus vulgaris are presented with flaccid, thin walled vesicles and/or bullae which are commonly rupture to leave an area of erosion and ulceration. Involvement of various mucosal surfaces such as oral, ocular, nasal, pharyngeal, laryngeal, upper respiratory and anogenital mucous membrane is present in Pemphigus vulgaris. Majority of patients with Pemphigus vulgaris develop painful erosions of the oral and skin lesion due to involvement of peripheral nerves.3 The choice of therapy depends on severity of the disease, efficacy, safety, availability and cost of drugs.4 Corticosteroid are preferred therapy for Pemphigus vulgaris, azathioprine is used for its corticosteroid-sparing effect and it is first line adjuvant immunosuppressant agent.5 Rituximab, an anti-CD20 monoclonal antibody is indicated for moderate to severe refractory cases, contraindication or severe ADR to systemic corticosteroids and immunosuppressants.6 High-dose Intravenous immunoglobulin G (IVIG) and plasmapheresis can also be indicated in resistant cases.5 Disease symptoms e.g. painful lesions, disease severity and complications due to treatment e.g. ADR may adversely affect the quality of life of patients.7 Therefore, quality of life measures can be used to guide and evaluate treatment interventions.

During extensive literature search, we observed studies reported from different countries about efficacy (i.e. Pemphigus area and activity score, Pemphigus disease area index), evaluation of quality of life (i.e. skin-dex-29, short form-36, autoimmune Bullous Disease Quality of Life Questionnaire) and correlation of efficacy and QOL in patients of Pemphigus vulgaris.8 11 We did not find any Indian study showing efficacy and correlation of efficacy with QOL over a period of time. Hence, this study was carried out to study the use and effect of the drugs as well as its impact on quality of life in patient suffering from Pemphigus vulgaris.

MATERIALS AND METHODS

Permissions to conduct the study were obtained from the Institutional Ethics committee (IEC No –208/15) and the Head of Department of Dermatology and Venereology. All newly diagnosed patients of Pemphigus vulgaris by Dermatologist, between 18 to 65 years of either gender, who are willing to participate in the study and gave written informed consent were enrolled. Patients who were suffering from severe or uncontrolled cases of hypertension, diabetes mellitus, hepatic, renal, pulmonary, hematologic disorders and pregnant as well as lactating women were excluded. This was an observational, prospective, single center study carried out at department of skin and venereal disease of a tertiary care teaching hospital over a period of 24 months from November 2015 to November 2017. The baseline data like demographic details, clinical history, details of laboratory investigation, disease of severity (Kumar’s
Based on prescribed treatment by dermatologist, patients were Grouped as: Group A (n=29): {corticosteroid group [inj. dexamethasone 4 to 6 mg once a day intravenously followed by tab prednisolone 20 to 40 mg once a day and maintained by 10 to 20 mg of prednisolone once a day]}, Group B (n=30): {corticosteroid [inj. dexamethasone 4 to 6 mg once a day intravenously followed by tab prednisolone 20 to 40 mg once a day and maintained by 5 to 20 mg of prednisolone once a day] plus azathioprine [50 mg twice daily group] and Group C (n=25): {corticosteroid [inj. dexamethasone 4 to 6 mg once a day intravenously followed by tab prednisolone 20 mg once a day and maintained by 5 to 20 mg of prednisolone once a day] plus rituximab [1 gm Injection 2 times at 15 days interval (Total 2 injections)]}. All study treatments were allocated to patients by government supply and treatment selection was based on decision of dermatologist. All patients were followed at 2 (1st follow up), 6 (2nd follow-up) and 12 weeks (3rd follow up). Disease severity was assessed by Kumar's score\(^1\) and Quality of Life was assessed by Dermatology Life Quality Index (DLQI).\(^2\) At each follow up visit, presenting complaints, any change in drug treatment, Kumar’s score and quality of life was recorded and analyzed at the end of the study. Details of the adverse drug reaction (ADR) if any, was recorded in the CRF. Analysis of cost of drug incurred was calculated for given treatment from time of enrollment to 3rd follow up visit.

The data was recorded in Microsoft Excel Worksheet version 2013. The statistical evaluation was done using Analysis of Variance (ANOVA) test with the help of Graph Pad demo version 3.1. Intra-group comparison was done between baseline and at each follow up visits by repeated measure ANOVA test. Intergroup comparison was done between group A, B and group C by one way ANOVA test. \(p<0.05\) was considered to be statistically significant.

**RESULTS**

Total 84 patients were included in the study according to inclusion and exclusion criteria. Patients were followed up at the 2 weeks (1st follow up), 6 weeks (2nd follow up) and 12 weeks (3rd follow up) of treatment.

As shown in Table 1, the mean age of total number of patients was 45.42 ± 1.58 years, 33 (39.28%) male and 51 (60.72%) were female patients with higher female to male ratio. (Table 1)

Mean of baseline Kumar’s score was comparable between all groups [4.31 ± 0.14 (group A), 4.70 ± 0.13 (group B) and 4.68 ± 0.22 (group C)]. There was significant reduction \((p<0.001)\) in oral and skin score and total Kumar’s score and at 2nd and 3rd follow-up as compared to baseline and 1st follow up and at 3rd follow up as compared to 2nd follow up in all treatment groups. At 3rd follow up, there was an \(p<0.01\) reduction in Kumar’s score in group C as compared to group A and group B. (Figure 1) Mean difference of Kumar's score between baseline and 3rd follow up data was significantly higher in group C as compared to group A \((p<0.01)\) and group B \((p<0.05)\). (Table 2) Total 3 patients (10.34%) in group A, 4 patients (13.33%) in group B and 12 patients (48%) in group C achieved complete reduction in Kumar’s score at 3rd follow up (12 weeks). (Table 3)

**Quality of life**

Mean baseline DLQI score was comparable between all groups [13.75 ± 0.30 (group A), 13.76 ± 0.38 (group B) and 14.08 ± 0.42 (group C)]. Total DLQI score was significantly \((p<0.001)\) reduced at 2nd and 3rd follow-up as compared to baseline and 1st follow up and also at 3rd follow up as compared to 2nd follow up in group A, B and C. At 3rd follow up, there was significant \((p<0.01)\) reduction in DLQI score in group C as compared to group A and group B. (Figure 2)

![Figure 1: Comparison of efficacy (Kumar's score) between corticosteroid (group A), corticosteroid + azathioprine (group B) and corticosteroid + rituximab (group C) in patients suffering from pemphigus vulgaris (n=84).](image)

![Figure 2: Table 1: Comparison of demographics characteristics and presenting symptoms of patients suffering from PV (n=84).](image)
Table 2: Comparison of Kumar’s score, DLQI score and each parameter of DLQI score in corticosteroid (group A), corticosteroid + azathioprine (group B) and corticosteroid + rituximab (group C) (Mean ± SEM) (n=84).

<table>
<thead>
<tr>
<th>Score (Mean difference between baseline and 3rd follow up)</th>
<th>Group A Corticosteroid (n=29)</th>
<th>Group B Corticosteroid + Azathioprine (n=30)</th>
<th>Group C Corticosteroid + Rituximab (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kumar’s Score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral site score</td>
<td>1.17 ± 0.10</td>
<td>1.43 ± 0.11</td>
<td>1.64 ± 0.16</td>
</tr>
<tr>
<td>Skin site score</td>
<td>1.55 ± 0.19</td>
<td>1.53 ± 0.10</td>
<td>2.24 ± 0.14</td>
</tr>
<tr>
<td>Kumar’s total Score</td>
<td>2.72 ± 0.24</td>
<td>3.03 ± 0.16</td>
<td>3.88 ± 0.25</td>
</tr>
<tr>
<td>DLQI Score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptoms and feeling</td>
<td>1.79 ± 0.14</td>
<td>2.03 ± 0.13</td>
<td>2.4 ± 0.12</td>
</tr>
<tr>
<td>Daily activities</td>
<td>1.68 ± 0.16</td>
<td>1.7 ± 0.16</td>
<td>1.92 ± 0.16</td>
</tr>
<tr>
<td>Leisure</td>
<td>0.93 ± 0.12</td>
<td>1.2 ± 0.16</td>
<td>1.08 ± 0.17</td>
</tr>
<tr>
<td>Work or school</td>
<td>0.65 ± 0.10</td>
<td>0.8 ± 0.11</td>
<td>0.88 ± 0.14</td>
</tr>
<tr>
<td>Personal relationship</td>
<td>0.65 ± 0.12</td>
<td>0.5 ± 0.10</td>
<td>0.60 ± 0.11</td>
</tr>
<tr>
<td>Treatment</td>
<td>0.62 ± 0.11</td>
<td>0.56 ± 0.10</td>
<td>0.92 ± 0.09</td>
</tr>
<tr>
<td>DLQI total Score</td>
<td>6.34 ± 0.28</td>
<td>6.80 ± 0.28</td>
<td>7.80 ± 0.20</td>
</tr>
</tbody>
</table>

Intergroup comparison was done by primary ordinary ANOVA test followed by post hoc analysis using Tukey-Kramer multiple comparison test.

* p < 0.05 in group C as compared to group A

** p < 0.01 in group C as compared to group A

* p < 0.01 in group C as compared to group B

* p < 0.05 in group C as compared to group B

Table 3: Analysis of complete remission, cost of drug incurred and adverse drug reactions (ADR) in patients suffering from pemphigus vulgaris (n=84).

<table>
<thead>
<tr>
<th>Sr. no</th>
<th>Parameters</th>
<th>Group A (n=29)</th>
<th>Group B (n=30)</th>
<th>Group C (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Complete remission</td>
<td>10 %</td>
<td>13 %</td>
<td>48 %</td>
</tr>
<tr>
<td>2</td>
<td>Cost of drug incurred</td>
<td>1787.66 ₹</td>
<td>2620.84 ₹</td>
<td>51371.40 ₹</td>
</tr>
<tr>
<td>3</td>
<td>Adverse drug reactions (Total)</td>
<td>20 (68.96 %)</td>
<td>19 (63.33 %)</td>
<td>13 (52 %)</td>
</tr>
</tbody>
</table>

QOL at 2nd follow up:
In group A, each parameter of QOL (except treatment parameter) was significantly (p<0.001) reduced at 2nd follow up as compared to baseline and 1st follow up. Treatment parameter was significantly (p<0.01) reduced at 2nd follow up as compared to baseline. In group B, symptoms and feelings, daily activities, leisure and school parameter of QOL was significantly (p<0.001) reduced at 2nd follow up as compared to baseline and 1st follow up while treatment parameter was significantly (p<0.05) reduced at 2nd follow up as compared to 1st follow up (2 weeks). In group C, each parameter of QOL was significantly (p<0.001) reduced at 2nd follow up as compared to baseline. Symptoms and feeling, daily activities, leisure, personal relationship and treatment parameter was significantly (p<0.001) reduced at 2nd follow up as compared to 1st follow up while work and school parameter was significantly (p<0.01) reduced at 2nd follow up as compared to 1st follow up in group C.
QOL at 3rd follow up:
Mean score of each parameter of QOL significantly (p<0.001) reduced at 3rd follow up as compared to baseline and 1st follow up in all treatment group. Significant (p<0.001) reduction in symptoms and feeling parameter of QOL at 3rd follow up as compared to 2nd follow up and significant (p<0.01) reduction in work and school parameter of QOL at 3rd follow up as compared to 2nd follow up was seen in group A. In group B, significant (p<0.001) reduction in symptoms and feeling, work and school and personal relationship parameter of QOL at 3rd follow up as compared to 2nd follow up and significant (p<0.01) reduction in daily activities and treatment parameter of QOL at 3rd follow up as compared to 2nd follow up was observed. In group C, significant (p<0.001) reduction was seen in symptoms and feeling and treatment parameter of QOL at 3rd follow up as compared to 2nd follow up and also significant (p<0.05) reduction in work and school parameter of QOL at 3rd follow up as compared to 2nd follow up.
Mean difference of DLQI score was significantly higher in group C as compared to group A (p<0.001) and group B (p<0.05). Mean difference of symptoms and feelings parameter at 3rd follow up was significantly higher in group C as compared to group A (p<0.01). (Table 2)

Correlation between Kumar’s Score and Quality of Life
Correlation between Kumar’s score and QOL was carried out using Pearson parametric correlation test. Weak positive correlation in group A (0.39) and B (0.49) and strong positive correlation in group C (0.58) was observed. (Figure 3) Significant correlation was seen in group C (p<0.05).

Adverse drug reaction
Out of 52 adverse drug reaction, 20 (38.46%), 19 (36.53%) and 13 (25%) ADRs were reported in group A, B and C respectively. All ADRs were reported to regional ADR monitoring center of Pharmacovigilance Programme of India (PvPI). All ADRs were assessed as possible except weight gain, infection and vomiting which were assessed as probable by using WHO-UMC causality assessment score. All ADRs were assessed as not preventable by using modified Schumock and Thornton scale. (Table 3)13
Mean cost of drug incurred per patient was 1787.66 ≠, 2620.84 ≠ and 51,371.40 ≠ in group A, B and C respectively. It was observed that the mean and individual cost of drug incurred was significantly (p<0.001) higher in group C as compared to group A and B. (Table 3)

DISCUSSION
In the present study, efficacy of drugs and QOL in newly diagnosed patients suffering from Pemphigus vulgaris were studied. In our study, we observed higher number of female patients suffering from Pemphigus vulgaris (60.72%). Corticosteroid alone/in combination with azathioprine/or in combination with rituximab significantly (p<0.001) reduced disease severity (Kumar’s score) and improve QOL (DLQI) at 2nd (6 weeks) and 3rd follow-up (12 weeks) as compared to baseline and 1st follow-up (2 weeks). We observed that nearly half of the patients in group C achieved complete remission (complete reduction in Kumar’s score) at 3rd follow-up (12 weeks) which was higher as compared to group A (10%) and group B (13 %). Patients treated with corticosteroid plus rituximab therapy developed less ADRs (25%) than corticosteroid alone (38.46%) and corticosteroid with azathioprine treated group (36.53%). In our study, 60.72 % were female patients followed by labourers (22.61%) and farmers (15.47%). Estrogen (increases immunity, autoantibody production)14 may be contributing factor for higher number of female patients (particularly housewives) in our study.15 Sun exposure can worsen the Pemphigus vulgaris particularly in patients who are working in open space e.g. farmers, labourers.16
Our study shows corticosteroid alone or in combination with azathioprine or rituximab significantly (p<0.001) decrease severity of disease by reducing both oral and skin site of Kumar’s score at 2nd and 3rd follow-up i.e. 6 and 12 weeks respectively. Similar results were observed in different studies with corticosteroid alone,17 corticosteroid plus azathioprine18 and corticosteroid plus rituximab19 treatment in Pemphigus vulgaris. Corticosteroid decreases inflammation by suppressive effects on cytokines and other mediators of inflammation.20 In addition, azathioprine plus corticosteroid combination decreases the proliferation by inhibiting synthesis of purines and impaired the lymphocyte function after 4-8 weeks.21 Rituximab decreases the precursor of autoantibody producing plasma cells and marked decrease in anti-desmoglein-3 antibodies within 4-6 weeks.22 Thus disease severity is reduced by corticosteroid alone or in combination with azathioprine or rituximab.
At the end of 12 weeks, we observed that, there was significant (p<0.01) reduction in both oral and skin site Kumar’s score in group C as compared to group A and group B. Mean difference (Baseline to 3rd follow up) of Kumar’s score was also significantly higher in group C as compared to group A (p<0.01) and group B (p<0.05). This suggest better efficacy of corticosteroid plus rituximab therapy as compared to corticosteroid alone and corticosteroid plus azathioprine therapy.
In our study, nearly half of the patients in group C achieved complete remission of disease at 3rd follow-up which was higher as compared to group A (10%) and group B (13 %). Kanwar study (2012) reported 40% complete remission where rituximab 375 mg/m² was given once weekly
for 4 weeks. In our study, 1 gm of rituximab dose was prescribed for 2 times at 15 days interval. This could be the contributing factor for higher rate of complete remission in our study.

Corticosteroid alone, corticosteroid plus azathioprine and corticosteroid plus rituximab therapy improves QOL by reducing score of each parameter and total DLQI score after 6 and 12 weeks of treatment. This suggests reduction in disease severity over a period of 12 weeks and hence patients feel better, taking interest in daily activities, able to participate in social activities (including improvement in relation with family members and friends) and improvement in work output at working place. At the end of 12 weeks, we observed that, there was significant (p<0.01) reduction in DLQI score in group C as compared to group A and group B. Mean difference (Baseline to 3rd follow up) of DLQI score was significantly higher in group C as compared to group A (p<0.001) and group B (p<0.05). Analysis of each parameter of QOL between treat ment groups suggest that there was significant improvement in symptoms and feeling parameters in corticosteroid plus rituximab group than corticosteroid alone patients. Intergroup comparison suggest that there was significant improvement in QOL in patients treated with cortico steroid plus rituximab therapy as compared to corticosteroid alone and corticosteroid plus azathioprine therapy.

Positive correlation between Kumar’s score and DLQI score was seen in all groups which suggest that when Kumar’s score decreases (decrease in disease severity), the DLQI score also decreases (improvement in QOL). All groups were associated with positive correlation between efficacy and QOL indicating decrease in disease severity associated with improvement in QOL. The correlation between Kumar’s score and QOL was significant in treatment group C (p<0.05) as compared to group A and B which suggests patients treated with corticosteroid plus rituximab lead to more improvement in QOL than corticosteroid alone and corticosteroid plus azathioprine therapy. Complete remission in disease severity in corticosteroid plus rituximab group can lead to better correlation between efficacy and QOL.

Decrease in inflammation and inflammatory cytokines (corticosteroid), inhibition of synthesis of purines, impairment in lymphocyte function (corticosteroid plus azathioprine), reduction in autoantibodies (dsg-1 and -3) and depletion of B cell (corticosteroid plus rituximab) can lead to decrease in disease severity and hence improve QOL. In corticosteroid plus rituximab group, better reduction in disease severity and improvement in QOL was observed as compared to corticosteroid alone/plus azathioprine group (prednisolone-10-20 mg). In addition, maintenance dose of prednisolone requirement is less (5-10 mg) in corticosteroid plus rituximab group which may contribute to less ADR particularly ADR due to corticosteroid. In our study, patients developed pedal edema, fever, acne, oral candidiasis, urinary tract infection, weight gain, hyperglycemia, infection, pneumonia, diabetes mellitus and hypertension who administered dexamethasone or prednisolone. In a study carried out by Lihi et al., (2016) it was reported that the patient treated with corticosteroid therapy also developed ADRs such as oral candidiasis, pulmonary edema, hyperglycemia, secondary infections, electrolytes imbalance, gastritis, lung abscess, psychosis, and sepsicaemia. Major disadvantage with rituximab is higher cost as rituximab is too expensive.

CONCLUSION

Our study concludes, all treatment groups are efficacious for the treatment of Pemphigus vulgaris. Corticosteroid alone and corticosteroid plus azathioprine having similar efficacy for treatment and improvement of the QOL in patients suffering from pemphigus vulgaris. Corticosteroid plus rituximab combination therapy is more efficacious, can cause complete remission and associated with significant improvement of QOL with less ADRs but too expensive than corticosteroid alone or in combination with azathioprine therapy. We have evaluated efficacy and QOL over a period of time and done correlation between efficacy and QOL. Due to chronic nature of disease, longer study duration with large sample size will help to better analysis of correlation between efficacy and QOL.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

ADR: Adverse drug reaction; ANOVA: Analysis of variance; CRF: Case record form; DLQI: Dermatology life quality index; IVIG: Immunoglobulin; PV: Pemphigus vulgaris; PVP: Pharmacovigilance programme of india; QoL: Quality of life.

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