Research Article**Prevalence, pathophysiology and guideline-based management of dose related diarrhea during Apremilast treatment in psoriasis patients****Ganesh Dhavalshankh¹, Archana Dhavalshankh^{2*}**¹Professor and Head, Dept. of Dermatology, RSCSMGMC, Kolhapur, Maharashtra, India²Professor and Head, Dept. of Pharmacology, D Y Patil Medical College, Kolhapur, Maharashtra, India

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Abstract

Background- Diarrhea is frequently observed in moderate to severe plaque Psoriasis patients treated with Apremilast. Though, it is known about the Apremilast associated diarrhea in but dose related prevalence varies in patients of psoriasis. **Objective:** To estimate the Prevalence of Apremilast associated diarrhea in mod to severe plaque psoriasis patients receiving various doses of Apremilast. **Materials and Methods:** The study was done in 152 Psoriasis patients attending skin and V.D. department in a tertiary care center receiving Apremilast treatment in dose of 30 mg twice a day to estimate the prevalence of diarrhea. **Results:** The prevalence of grade I diarrhea was 67% and 53%, grade II was 9% and 4% in male and female respectively. The grade III diarrhea was 2% both in male and female whereas grade IV diarrhea reported in male (1%) patient only. The Study data suggested that the diarrhea after Apremilast therapy is self-limiting and 4% discontinued therapy after diarrhea. **Conclusion:** It was observed that most of the Psoriasis patients receiving Apremilast suffered from diarrhea but these patients should be counselled and monitored regularly for Apremilast induced diarrhea.

Keywords: Plaque psoriasis, apremilast, diarrhea, gastrointestinal

Introduction

Apremilast is an inhibitor of phosphodiesterase-4 (PDE4) that is available as an oral tablet formulation approved by the United States Food and Drug Administration (FDA) for the treatment of patients with moderate and severe plaque psoriasis (PlqPso). The mode of action of Apremilast in PlqPso is related to modulation of inflammation via intracellular inhibition of PDE4; the resultant increase in levels of cyclic adenosine monophosphate (cAMP) and reduction in AMP diminishes cellular inflammation and keratinocyte activation/proliferation (Tom et al., 2015; Papp et al., 2015; Paul et al., 2015; Schafer, 2012; Schett et al., 2010; Chimenti et al., 2015). Gastrointestinal (GI) side effects (e.g., nausea, changes in bowel movement quality and/or frequency) have been reported to be the most common adverse reactions associated with Apremilast use (Tom et al., 2015; Papp et al., 2015; Paul et al., 2015).

Approaches suggested for the management of nausea include:

- Ingesting Apremilast with food
- Eating smaller more frequent meals
- Avoiding excessive liquid intake with meals
- Using anti-nausea medications, such as diphenhydramine (Benadryl: OTC), promethazine (Phenergan; Rx), or prochlorperazine (Compazine; Rx)

Approaches suggested for the management of diarrhea include: (Abraham et al., 2016)

- Ingesting Apremilast with food
- Maintaining adequate hydration (without large volume ingestion with food)
- Eating smaller more frequent meals
- Limiting caffeine, dairy, and artificial sweetener intake
- Using anti-diarrheal medications, such as loperamide (Imodium: OTC), fiber-bulk forming agents (OTC),
- Bismuth subsalicylate (Pepto-Bismol, Kaopectate; OTC)

Methodology

This study was done in a tertiary care hospital Maharashtra for a period of six months (November 2017 to April 2018)

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over 152 patients by random selection. Indoor and outdoor adult patients (age group 15-55yrs) from department of dermatology diagnosed for moderate to severe plaque psoriasis and taking Apremilast (30 mg twice a day) were selected and analyzed for gastrointestinal side effects. Cases were excluded with pediatric, geriatric, pregnancy, immune-compromised state, history of Irritable or Inflammatory Bowel disease and history of GIT disease or GIT surgery. Approval from institutional ethics committee was taken before starting the study. Consent from patient was also taken.

Data Collection

Gastrointestinal side effects are assessed like: (1) Diarrheal frequency, change in quality, any intervention for management (2) Nausea onset, duration, associated or relief with vomiting, any intervention for management, discontinuation

Statistical Analysis

The data was compiled and subjected to descriptive statistical analysis.

Observations and results

One hundred and fifty-two patients were enrolled into the study. Out of 152 patients, 22.37% (n=34) belonged to 15 – 25 years, 36.18% (n=55) belonged to 26 – 35 years, 34.21% (n=52)

belonged to 36 – 45 years and 7.24% (n=11) belonged to 46 – 55 years. Maximum number of patients on Apremilast were 34.21% (n=52) and 36.18% (n=55) belonged to age groups 36 – 45 years and 26 – 35 years respectively. Only 138 patients were reported diarrhea and therefore assessed during the study. There were 90.8% (n= 138/152) patients involved in study without dropouts. Out of 138 patients, 79 (57.25%) were males and 59 (42.75%) were females who were on Apremilast suffered from diarrhea according to table 1&2.

Diarrhea was graded from grade I to grade V where Grade I (less than 4), Grade II (more than 4), Grade III (less than 7), Grade IV (more than 7) and Grade V (fatal) is considered. In this study it was identified that incidence of diarrhea was more of grade I with male (67%) and female (53%). The incidence of diarrhea as per different grades was shown in Table 3. It was observed that most of the patients 61% continued Apremilast as diarrhea recovered on own. 35% required treatment or interventions and 04 % discontinued (Figure 1).

Discussion

Psoriasis being a chronic persistent infection require a long durational treatment. Despite the various drugs and

Table 1. Age and Sex wise distribution

S.N.	Sex- Age	15-25 years (%)	26-35 years (%)	36- 45 years (%)	46- 55 years (%)	Total (%)
1	Male	12(13.95)	31(36.05)	35(40.70)	08(9.30)	86 (56.58)
2	Female	22(33.33)	24(36.37)	17(25.76)	03(4.54)	66 (43.42)
3	Total	34 (22.37)	55 (36.18)	52 (34.21)	11(7.24)	152

Table 2. Prevalence of diarrhea

S.N.	Sex- Age	15-25 years (%)	26-35 years (%)	36- 45 years (%)	46- 55 years (%)	Total (%)
1	Male	11(13.92)	29(36.71)	32(40.51)	07(8.86)	79 (57.25)
2	Female	21(35.59)	21(35.59)	15(25.42)	02(3.40)	59 (42.75)
3	Total	32 (23.19)	50 (36.23)	47 (34.06)	09(6.52)	138

Table 3. Frequency of diarrhea

S.N.	Sex- Age	15-25 years (%)		26-35 years (%)		36- 45 years (%)		46- 55 years (%)		Total (%)	
		M	F	M	F	M	F	M	F	M	F
1	I (less than 4)	09	20	28	18	27	13	03	02	67	53
2	II (more than 4)	02	01	01	02	04	01	02	00	09	04
3	III (less than 7)	00	00	00	01	00	01	02	00	02	02
4	IV (more than 7)	00	00	00	00	01	00	00	00	01	00
5	V (fatal)	00	00	00	00	00	00	00	00	00	00

Figure 1. Management of diarrhea

remedies available for the treatment of Plaque Psoriasis, safety and efficacy related problems still persist. All these patients require new drug with high efficacy and low toxicity. In the present study we have observed a total of 138 Plaque Psoriasis patients receiving Apremilast in the dose of 30 mg twice daily and suffering from diarrhea. Out of 138 patient's majority i.e. n=86 were male and amongst these 79 of them had diarrhea. The mean age of patients in this study was 38 years as compared to the mean age of 45.8 years in Kim A et al study with n= 562 patients (Papp et al., 2015) and this is also comparable to a study done by Tina zenili et al. (2015) where majority are males (78.38%), with the median age of 36 years. During this study patients received, Apremilast and 53% patients suffered from grade I diarrhea whereas 4% from grade II and only 2% from Grade III. This goes parallel with Reich et al. (2017). No reporting for Grade IV and Grade V diarrhea. During Study 61% Continued Apremilast where diarrhea resolve on own, 35% required treatment or intervention whereas only 04% discontinued Apremilast therapy.

Conclusion

The findings from above study revealed that Apremilast is effective, safety drug for moderate plaque psoriasis. Though very common, frequent gastrointestinal side effect like diarrhoea reported with Apremilast therapy but it is found that it gets recovered early without intervention and does not required discontinuation of therapy.

Conflicts of interest

The authors declare there is no conflict of interests.

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