OFF-LABEL USE OF APREMILAST FOR AUTOIMMUNE SKIN DISORDERS TREATMENT

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Abstract **-** "Off-label use" refers to when a medication is prescribed for a use or in a way that has not been approved by the Food and Drug Administration. Apremilast (APR) is an oral phosphodiesterase 4 inhibitor that can be used off-label for autoimmune skin disorder treatment such as pyoderma gangrenosum, Behc et's disease, and neutropholic ulcerative dermatosis. The primary goal of this study is to discuss about off-label use of apremilast for autoimmune skin disorders treatment so that researchers can enhance their knowledge about off-label use of apremilast that certainly required to treat autoimmune skin disorders. Autoimmune skin disorders occur worldwide and affected individuals in everyday life because of the discomfort caused by skin lesion. The method of this paper was through reviewing of published research datas and books that focused on off-label use of apremilast for autoimmune skin disorders treatment. The result indicates that off-label use of apremilast is an effective medication to decrease the intense inflammation of skin lesion. In conclusion, this paper describes apremilast as a potential off-label drug for autoimmune skin disorders treatment where the safety and efficacy of medications are needed.

Keywords - Apremilast, Autoimmune skin disorder, Off-label use, Therapeutics

I. INTRODUCTION

In and ideal world, medical drugs should be safe and effective. In our real world, there are many justifications given for that, it would cost too much.
"Off-label use" refers to when a medication is prescribed for a use or in a way that has not been approved by the Food and Drug Administration (FDA). The prevalence off-label use of drug increase through many pathways but usually entails the use of drugs for unapproved clinical indications or in unapproved subpopulations. Off-label use may originate from a presumed drug class effect, extension to milder forms of an approved indication, extension to related conditions, expansion to distinct conditions sharing a physiological link, or extension to conditions whose symptoms overlap with those of an approved indication [1].
Apremilast is a drug which is phosphodiesterase-4 inhibitor that regulates the immune response associated with psoriasis. In 2014, oral apremilast was approved by the FDA for active psoriatic arthritis and moderate to severe plaque psoriasis treatment in adult patients [2]. Furthermore, apremilast can be used off-label for autoimmune skin disorders treatment such as pyoderma gangrenosum, Behc et's disease, and neutropholic ulcerative dermatosis [3].
Autoimmune skin disorders occur worldwide until now and affected individuals in everyday life because of the discomfort caused by skin lesion [4]. Apremilast is an attractive alternative option for the patient because it is administered per oral, decreased laboratory monitoring requirements, its lack of blackbox lymphoma risk, and the adverse effects for this drug is also well tolerated [3].
So, the primary goal of this study is to discuss about off-label use of apremilast for autoimmune skin disorders treatment so that researchers can enhance their knowledge about off-label use of apremilast that certainly required to treat autoimmune skin disorders.

II. METHODOLOGY

This study was conducted through reviewing of published research datas and books that focused on off-label use of apremilast for autoimmune skin disorders treatment. ScienceDirect, PubMed (Medline), and ResearchGate were used to retrieve online publications related to autoimmune skin disorders, apremilast, and off label use of apremilast for autoimmune skin disorders treatment. Around 5 articles about autoimmune skin disorders, 5 articles about apremilast and 5 articles about off label use of apremilast for autoimmune skin disorders treatment were used in this paper for references.

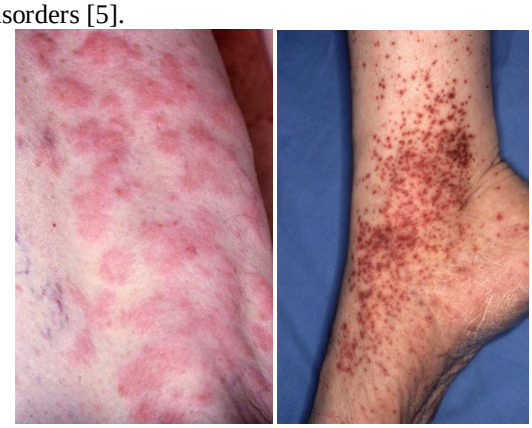
III. AUTOIMMUNE SKIN DISORDERS

The term autoimmunity indicate the presence of specific symptoms immune reactions that are directed against one or more self-antigens. Related condition of autoimmunity is determined in terms of immunoglobulins that react with either unknown from external body or well defined as human antigen [5]. Autoimmune disease first step is the process of dysregulation involves a skin barrier breakdown in

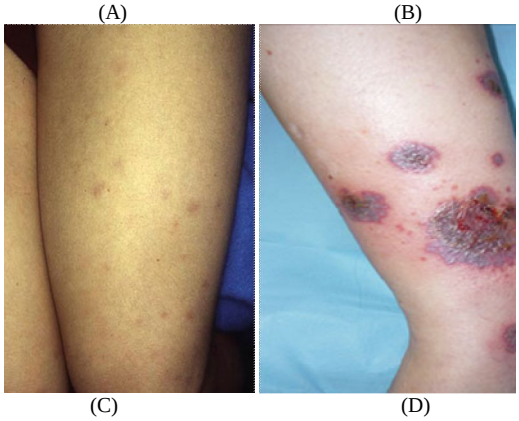
addition to dysfunctional innate and adaptive immune response, including an unbalanced increase in T-helper 2 (Th2) cells and hyperimmunoglobulinemia E [6]. Additionaly, dysregulation of multiple pro-inflammatory and anti-inflammatory mediators occurs in dendritic cells, monocytes, macrophages, neutrophils, keratinocytes, chondrocytes, and synoviocytes [7]. Classical examples are rheumatoid arthritis, myasthenia gravis, pemphigus vulgaris, lupus erythematosus and multiple sclerosis [5].

IV. CLINICAL APPEREANCE OF AUTOIMMUNE SKIN DISORDERS

Autoimmunity is a relatively frequent event. Most likely, any individual raises immune reactions against numerous self antigens. Autoimmunity leads only very rarely to overt autoimmune disease. Therefore, the development of autoimmune disease requires trespassing of a large number of additional security levels, beyond autoimmune reactivity. Clinical precence in every induvidual depends on their reactivity of immune reaction against self-antigens. Skin vasculitis presents as a spectrum of clinical lesions including erythema, purpura, papules, pustules, nodules, livedo, necrosis, ulcerations and bullae. These various lesions come often altogether giving a pleomorphic appearance of the eruption. Significant geographic variation has been noted in the prevalence of psoriasis, likely reflecting the fact that environmental and genetic factors influence this disorders [5].



(A) (B)



(C) (D)

(A) Infiltrated purpura of the ankles
(B) Urticarial vasculitis on the limbs
(C) Nodules on the lower limbs in a patient with cutaneous periarteritis nodosa
(D) Necrotic lesions secondary to a vasculitis involving both the superficial and deep dermal vessels.

V. MECHANISM OF ACTION

Apremilast is an oral small molecule phosphodiesterase-4 (PDE4) inhibitor. Phosphodiesterase4 (PDE4) is one of the major cAMPselective PDEs expressed in epithelial cells, such as those lining the airways. Hematopoietic cells controlled by PDE4 include dendritic cells, T cells, macrophages, and monocytes. Mesenchymal cells that express PDE4 include keratinocytes within the dermis, smooth muscle, vascular endothelium, and chondrocytes involved in the structure of the joint [7]. PDE4 mediates the conversion of cyclic adenosine monophosphate (cAMP) to AMP that can contribute to the occurrence of inflammation. Apremilast is PDE4 inhibitor, through this targeted inhibition apremilast increases intracellular cAMP concentrations, inhibiting the production of many proinflammatory mediators such as TNF-a, IFN-g, and IL-2 production from peripheral blood monocytes and T cell, and increasing the production of some anti-inflammatory mediators such as IL-10 [7] [8].

VI. PHARMACOKINETICS AND PHARMACODYNAMICS

Apremilast has an absolute bioavailability of 73% with peak plasma concentrations occurring at a median time (Tmax) of 2,5 hours. Administration with food does not alter the extent of its absorption. Apremilast has human plasma protein binding approximately 68%. Mean apparent volume of distribution (Vd) is 87 L, and the half-life (t ½) is 6 to 9 hours. Apremilast is primarily metabolized by CYP3A4 metabolic pathway with subsequent glucuronidation and hydrolysis. Mostly eliminated in the urine (58%) with 3% being unchanged and excretion in feces accounts for 39% with 7% being unchanged and mean clearance of apremilast is 10L/hr [9].

VII. DOSING AND ADMINISTRATION

The dosage of apremilast for adult patients is titrate over the first 5 days of treatment. On day 1, a dose of 10 mg is administered in the morning, on day 2, 10 mg twice daily administered in both the morning and evening; on day 3, 10 mg is administered in the morning and 20 mg in the evening; on day 4, 20 mg twice daily administered in both the morning and evening; on day 5, 20 mg is administered in the

morning and 30 mg in the evening; and the maintenance dosage is 30 mg twice daily administered in the morning and evening starting on day 6.
In pediatrics, the effectiveness and safety of apremilast not established in patients under 18 years of age. Meanwhile, for patients with severe renal impairment which is creatinine clearance (CrCL) less than 30 ml/minute, the dosage of apremilast should be reduced. Initiate with 10 mg in the morning, with maintenance dosage is 30 mg once a day. For patient with pregnancy, apremilast should only be used during pregnancy if the potential benefit justifies the potential risk to the fetus and use it caution when apremilast is administered to a breast feeding woman, because it is not known whether the drug is excreted in human milk [8] [10].

VIII. ADVERSE EFFECT AND PRECAUTIONS

The most common adverse effect associated with apremilast are nausea, diarrhea, and headache. Upper respiratory tract infection and vomitting were also reported in some patients. Dosage titration is recommended to reduce those gastrointestinal symptoms associated with initial therapy. Some patients also experienced depression and weight loss during treatment. Patients should be advised of the potential emergence or worsening of depression, suicidal thoughts, or other mood changes, and patient's weight should be monitored regularly. If excessive weight loss occurs, discontinuation of apremilast should be considered [8] [10].

IX. DRUG INTERACTION

The use of apremilast with CYP3A4 inducers such as rifampin, carbamazepine, phenobarbital, and phenytoin resulted in a reduction of serum concentrations of apremilast, which may result in a loss of efficacy [8] [10].

X. OFF-LABEL USE OF APREMILAST FOR AUTOIMMUNE SKIN DISORDERS TREATMENT

Psoriatic arthritis and psoriasis, often referred to as psoriatic diseases, are autoimmune diseases characterized by chronic inflammation, tissue and organ - involvement, and the accelerated growth cycle of skin cells. Plaque psoriasis is the most common form of psoriasis and is characterized by raised, red patches covered with a silvery white build up of dead skin cells or scale [11]. These plaques typically appear on the scalp, knees, elbows, and lower back. They are often painful, and they can crack and bleed [11]
On March 21, 2014, the FDA approved apremilast (Otezla; Celgene) for the treatment of adults with active psoriatic arthritis [12] Apremilast is a small molecule that specifically inhibits phosphodiesterase 4 (PDE-4) resulting in an elevation of cyclic-AMP levels in cells, which in turn decreases T-cell secretion of pro-inflammatory cytokines and other mediators including TNFα, interferon-gamma, nitric oxide synthase, interleukin-2, interleukin-7 and interleukin-23 [13], is the first oral therapy to receive FDA approval for the treatment of adults with active psoriatic arthritis.

Apremilast, given orally at 20 or 30 mg twice daily, seems tobe efficacious, safe, and tolerable for patients with moderate to severe plaque psoriasis. Importantly, no opportunistic infections occurred and adverse events commonly associated with phosphodiesterase 4 inhibition (headache, diarrhoea, nausea, vomiting) were generally mild to moderate and transient. These findings, along with oral dosing and apparent lack of need for monitoring of liver and kidney function, suggest that apremilast offers an efficacious treatment option with an acceptable safety and tolerability profile and improved convenience compared with present options and could help to fill a gap in the management of psoriasis.

CONCLUSION

The result indicates that off-label use of apremilast is an effective medication to decrease the intense inflammation of skin lesion. In conclusion, this paper describes apremilast as a potential off-label drug for autoimmune skin disorders treatment where the safety and efficacy of medications are needed.

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