Effect of Ivermectin Cream in Imiquimod-Induced Psoriasis like Inflammation in Mice

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ABSTRACT

Psoriasis is an erythematous, scaly, inflammatory infiltrate with increases thickness of skin lesions. Ivermectin has anti-inflammatory role in T cell disease. It is investigated in psoriasis like model. The objective of this study is to investigate the pharmacological action of ivermectin and its combination with steroid on imiquimod mice model. Thirty-six albino male mice, aged six weeks were used in the present study which are divided into six groups (6 in each group) as follows: Group I is a healthy control group, Group II imiquimod induction group in which imiquimod applied topically once daily five days. Group III, IV, V, and VI were the treatments groups in which Group III Clobetasol 0.05%, group IV Ivermectin, group V Ivermectin with clobetasol combination, and Group VI Glycerin. All treatments used for five days. The immunohistochemistry of interleukin -17 and signal transducer and activator of transcription 3 were done in addition to histopathology reading scores and the results showed that for the interleukin -17 percent, a significant decrease showed when comparing induced group with clobetasol, ivermectin, clobetasol with ivermectin combination groups. A significant change in interleukin -17 intensity and percent between all the treatment groups were found. In conclusion, Ivermectin and ivermectin/ clobetasol combination has a promise role in imiquimod induced psoriasis model.

Keywords: IL-17; STAT3; Imiquimod; Inflammation; Ivermectin; Psoriasis.

INTRODUCTION

Psoriasis is an erythematous, scaly, inflammatory infiltrate with increases thickness of skin lesions[1]. Different diseases associated with psoriasis like cardiovascular diseases, metabolic syndromes, and psychological/psychiatric disorders[2,3] where the most common psychological problems associated with psoriasis are depression and anxiety[3]. The pathogenesis of psoriasis showed that interleukin (IL)-17, IL-23, and tumor necrosis factor (TNF) have an important role as demonstrated by clinical dermatological studies. Also, a genome-wide association study showed genetic predisposition in psoriasis patient to T helper 17 (TH17) reply and inflammatory signal disturbances in nonimmune part like keratinocytes and immune part. This may have a role in psoriasis development particularly due to suggesting a specific role of signals from keratinocyte. This is identified in familial psoriasis type as gene mutations was found[4]. In addition to that, a previous studies found a significant increase of Staphylococcus colonization especially the species Staphylococcus aureus in skin psoriasis lesions[5,6]. Therefore, the infection that may occur interact with the body immune system and may have a significant role in psoriasis pathogenesis[7]. From this point of view, a new treatment approach, is looking for as the routinely used drugs are not completely curable. The series B1 ivermectin which is a naturally product fermented from Streptomyces avermitilis soil bacteria contain the semisynthetic compound ivermectin[8]. In vitro and in vivo researches refer to the beneficial effect of ivermectin in many medicinal approaches in addition to its parasite growth inhibition[9]. Ivermectin showed a potential anti-cancer, antiviral, antibacterial, with wide spectrum anti-parasitic effect potentially[10]. It has anti-inflammatory role against induced T cell skin disease[11]. Ivermectin have both redox effect where it was found as an oxidant and antioxidant behavior. The oxidative effect showed in osteosarcoma through mitochondrial dysfunction and induction of oxidative stress damage in target cells[12]. Ivermectin can be used topically[13]. It is approved as 1% cream in 2014 by the food and drug administration for inflammatory rosacea treatment. It was found that ivermectin decrease the rosacea inflammation in addition to its anti-parasitic action against Demodex folliculorum[14]. The topical application of ivermectin was tolerated sufficiently and it was found with a beneficial use in seborrheic dermatitis, mild to moderate dermatitis (perioral type) and in acne vulgaris[15]. In addition to that, another study showed no adverse reaction occur due to topical use of ivermectin that need replacement or decrease the drug dose. Those mild adverse reactions on Hartwig Seigel calibre will be subsided with no need for additional treatment[16]. The aim of study to investigate the pharmacological action of ivermectin and its combination with steroid on imiquimod mice model.

METHODS

Study Design: An animal study designed in AL- Nahrain University /College of pharmacy/ pharmacology and toxicology department. It is approved by AL- Nahrain University- college of pharmacy ethical committee (Approval number: nah.co.pha. 22).

Thirty-six albino male mice, six weeks' age were used in this study. All mice were divided randomly to six groups (each six animals). Group I (G-I)) healthy animals. Group II (G-II) inducer group, Imiquimod 12.5mg (5% cream) used once daily (Glenmark company) at the skin of the mice back for five consecutive days[17]. Group III, IV, V and VI (G-III, IV, V and VI) used imiquimod with same procedure but

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after three hours' different treatment was given. Group III a steroid clobetasol 0.05% (the state company for drugs industry and medical appliances. SDI), ointment[18], group IV ivermectin 1% (Associated Biotech, India)[19], and group V Ivermectin with clobetasol combination (0.5% and 0.025% respectively), group VI glycerin (Local markets). All treatment groups continued used treatment for five days.

Immunohistochemistry (IHC) measurement: Interleukin -17 IHC and Signal transducer and activator of transcription 3 (STAT3) IHC kits are used. The used catalogs and company (FNab04224, and FNab08298, Fine Test, China) respectively. The procedure of IHC was done by a pathologist according to the above referred catalogs.

Histopathology Procedure: After the end of the experiment (After five days) all animals were anesthetized by chloroform and sacrificed. Harvested mice back skin tissue taken and buffered formaldehyde used for storage [20]. Histopathology scoring system was used. Each histopathology parameter given a value where Munro's abscess (1.5), acanthosis (1), hyperkeratosis (0.5), parakeratosis (1), dermis lymphocytic infiltrate (0.5–1.5), and length of rete ridges (0.5–1.5)[21].

Statistical Analysis: Statistical analysis using version 26 of SPSS to calculate range and median. Kruskal Wallis and Mann Whitney also done that consider probability value significant, if it is less or equal to 0.05[22,23].

RESULTS

As showed in table (1) and (2), all the parameters are significantly changed when compare the healthy group with the induced group. Table (1) show significant decrease in intensity of IL-17 when clobetasol and induced groups are compared.

A significant increase in IL-17 intensity was shown when compare the clobetasol and glycerin group. There is a significant change in IL-17 intensity and percent between all the treatment groups. (Table 1) and (Figure 1).

In relation to IL-17 percent, a significant decrease showed when comparing induced group with clobetasol, ivermectin, clobetasol with ivermectin combination groups and no significant change with glycerin. A significant increase in IL-17 percent when comparing clobetasol and glycerin groups and also significant increase when compare the clobetasol with ivermectin combination with glycerin group.

In relation to STAT3 percent parameter, only a significant decrease was found when comparing the induced group with all treatment groups. No significant difference between the treatment groups. (Table 1) and (Figure 2).

In relation to histopathology scores (Table 2), this study showed significant decrease in Munro's abscess when clobetasol, ivermectin, clobetasol with ivermectin combination compared to induced group. A significant decrease in hyperkeratosis showed when ivermectin compared to induced group and significant difference between treatment group. For parakeratosis parameter, significant decrease showed when clobetasol, ivermectin, clobetasol with ivermectin combination compared to induced group. A significant increase in parakeratosis showed when clobetasol with ivermectin combination compared to glycerin. A significant difference was found between treatment groups. For lengthening and clubbing of rete ridges, no significant difference was found when the treatment groups are compared to induced group.

A significant decrease in acanthosis was found when clobetasol with ivermectin combination was compared with induced group. A significant decrease in dermis lymph infiltrate was found when clobetasol, ivermectin, ivermectin with clobetasol combination groups compared with induced group. A significant difference between treatment groups were found. (Table 2) and (Figure 3).

DISCUSSION

Psoriasis is an inflammatory chronic skin disease with T cells, neutrophils, and monocyte infiltration in skin tissue at the same time of parakeratosis and keratinocytes hyper proliferation. The pathogenesis of the disease involves many cytokines like tumor necrosis factor-a (TNF alpha), IL-17A, IL-22, and IL-23[24]. It is not clear what is the causes of inflammation in patient skin with psoriasis. The cause may be due to that the T lymphocyte cells can recognize the skin autoantigen. T cell will have activated and secrete inflammatory cytokines like IL-17, TNF alpha, and IL-22[25]. These inflammatory cytokines then activate the skin cells such as keratinocytes. As a result, chemokines are produced and initiated skin neutrophils infiltration occur[17].

The continued discover of new uses of ivermectin like possible antiviral, antibacterial, and anticancer[26] encourage further investigation for ivermectin in order to investigate the suspected use and mechanism of action of ivermectin in psoriasis. This psoriasis model of study was chosen because the mice imiquimod induced psoriasis symptoms resembles the human psoriasis symptoms[27]. The neutralizing treatment against TNF alpha, IL-17A, and IL-12/IL-23-p40 were investigated and had been found a benefit in psoriasis[28]. Also the draw of neutrophils to the skin tissue was inhibited when IL- 17 keratinocytes signal is absent[17]. An active STAT3 was found in psoriasis of both skin keratinocyte and immune cells that lead to epidermal hyperplasia. Interleukin -23 stimulate T cells IL-23R leads to induction of JAK2/TYK2 signal and STAT3 activation downstream. The expression of IL-22, IL-23, IL-17A, and IL-17F are regulated by STAT3 significantly[29]. For overall of the above causes, IL-17 and STAT3 were chosen as investigated parameter in this research to identify the action of ivermectin.

When healthy and induced group are compared, the significant increase in IL-17 and STAT3 percent are comparable with the result of Zhang et al., in which the imiquimod causes IL-17 activation, in addition to NF-kappa B and STAT3 pathways activation in psoriasis[30]. The significant decrease in intensity and percent of IL-17 when clobetasol and induced groups are compared in this study are identical with the study that showed the effectiveness of clobetasol on skin psoriasis imiquimod induced[31].

The effect of glycerin showed no therapeutic benefit when it is compared with clobetasol cortisone as showed by the result of this study when IL-17 percent is measured indicate no benefit of glycerin when compared to a steroid drug in addition to no significant decrease in IL-17 intensity and percent when compared to induced group which increase the impact of no benefit of glycerin. The significant change between the treatment group in relation to the intensity and percent of IL-17 indicate that not all of the treatment groups may have a benefit in relief the psoriatic lesion.

In relation to IL-17 percent, it was found a significant decrease when comparing induced group with ivermectin, clobetasol with ivermectin combination, which is identical with a study that showed high significantly reduction in the tissue skin IL-17 among induced group when compared to petrolatum, clobetasol , ivermectin , clobetasol combined with ivermectin groups, although in this study an ELISA technique was used[32]. It was found before that ivermectin act to improve skin allergic inflammation through a mechanism that include T cells inflammatory response when used topically[33].

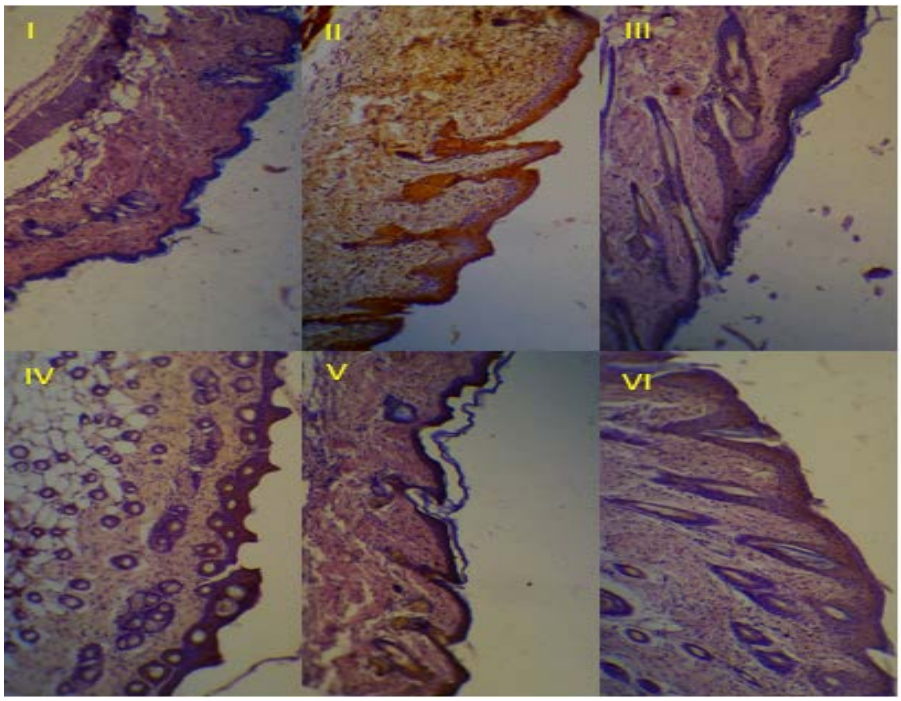

Figure 1. Immunohistochemistry expression of IL-17 in mice skin tissue.
Group I: Apparently healthy. Group II: Strong brown with intensity: 3+, Percentage: 3+. Group III: Low brown with intensity: 1+, Percentage: 1+. Group IV: Low brown with intensity: 2+, Percentage: 1+. Group V: Low brown with intensity: 2+, Percentage: 1+. Group VI: Moderate brown with intensity: 2+, Percentage: 2+. Olympus lens power of 10 microscope used. Samples taken after 5 days.

Table 1. Comparison of immunohistochemistry parameters between the mice groups

Parameter		G-I N=6	G-II N=6	G-III N=6	G-IV N=6	G-V N=6	G-VI N=6
IL-17 intensity	Median (Range)	0 (0-0)	2.5 (2-3)	1 (1-2)	2 (2-2)	2 (2-2)	2 (2-3)
	P value [a]		0.002	0.002	0.002	0.002	0.002
	P value [b]			0.015	0.180	0.180	0.699
	P value [c]				0.065	0.065	0.026
	P value [d]					1.000	0.394
	P value [e]						0.394
	P value [f]			0.005			
IL-17 %	Median (Range)	0 (0-0)	3 (3-3)	1 (1-1)	1.5 (1-2)	1 (1-2)	2 (2-3)
	P value [a]		0.002	0.002	0.002	0.002	0.002
	P value [b]			0.002	0.002	0.002	0.065
	P value [c]				0.180	0.699	0.002
	P value [d]					0.394	0.065
	P value [e]						0.009
	P value [f]			0.002			
STAT3 %	Median (Range)	0 (0-0)	3 (3-3)	1 (1-1)	2 (1-2)	1 (1-2)	1.5 (1-2)
	P value [a]		0.002	0.002	0.002	0.002	0.002
	P value [b]			0.002	0.002	0.002	0.002
	P value [c]				0.065	0.699	0.180
	P value [d]					0.180	0.699
	P value [e]						0.394
	P value [f]			0.066			

a: p value by comparison of healthy group with each other group by Mann Whitney test
b: p value by comparison of induced with each treatment group by Mann Whitney test
c: p value by comparison of clobetasol with ivermectin, clobetasol with ivermectin and glycerin by Mann Whitney test
d: p value by comparison of ivermectin with clobetasol with ivermectin and glycerin by Mann Whitney test
e: p value by comparison between clobetasol with ivermectin and glycerin by Mann Whitney test
f: p value by comparison among treatment groups by Kruskal Wallis test

Table 2. Comparison of skin histopathological parameters between mice groups

Parameter		G-I N=6	G-II N=6	G-III N=6	G-IV N=6	G-V N=6	G-VI N=6
Munro's abscess	Median (Range)	0 (0-0)	2 (0-2)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-2)
	P value [a]		0.015	1.000	1.000	1.000	0.394
	P value [b]			0.015	0.015	0.015	0.180
	P value [c]				1.000	1.000	0.394
	P value [d]					1.000	0.394
	P value [e]						0.394
	P value [f]			0.099			
Hyperkeratosis	Median (Range)	0 (0-0)	0.5 (0.5-0.5)	0.25 (0-0.5)	0 (0-0)	0.5 (0-0.5)	0.5 (0.5-0.5)
	P value [a]		0.002	0.180	1.000	0.065	0.002
	P value [b]			0.180	0.002	0.394	1.000
	P value [c]				0.180	0.699	0.180
	P value [d]					0.065	0.002
	P value [e]						0.394
	P value [f]			0.007			
Parakeratosis	Median (Range)	0 (0-0)	1 (1-1)	0 (0-0.5)	0 (0-0)	0 (0-0.5)	1 (1-1)
	P value [a]		0.002	0.699	1.000	0.394	0.002
	P value [b]			0.002	0.002	0.002	1.000
	P value [c]				0.699	0.699	0.002
	P value [d]					0.394	0.002
	P value [e]						0.002
	P value [f]			<0.001			
Lengthening and clubbing of rete ridges	Median (Range)	0 (0-0)	1.5 (1.5-1.5)	0.75 (0-1.5)	1.5 (1.5-1.5)	1.5 (0-1.5)	1.5 (1.5-1.5)
	P value [a]		0.002	0.180	0.002	0.015	0.002
	P value [b]			0.180	1.000	0.699	1.000
	P value [c]				0.180	0.394	0.180
	P value [d]					0.699	1.000
	P value [e]						0.699
	P value [f]			0.075			
Acanthosis	Median (Range)	0 (0-0)	0.5 (0.5-0.5)	0.25 (0-0.5)	0.25 (0-0.5)	0 (0-0)	0.5 (0.5-0.5)
	P value [a]		0.002	0.180	0.180	1.000	0.002
	P value [b]			0.180	0.180	0.002	1.000
	P value [c]				1.000	0.180	0.180
	P value [d]					0.180	0.180
	P value [e]						0.002
	P value [f]			0.009			
Dermis lymph infiltrate	Median (Range)	0 (0-0)	2 (2-2)	0.5 (0.5-0.5)	0.5 (0.5-1)	0.5 (0.5-0.5)	1.5 (1-2)
	P value [a]		0.002	0.002	0.002	0.002	0.002
	P value [b]			0.002	0.002	0.002	0.180
	P value [c]				0.699	1.000	0.002
	P value [d]					0.699	0.004
	P value [e]						0.002
	P value [f]			<0.001			

a: p value by comparison of healthy group with each other group by Mann Whitney test
b: p value by comparison of induced with each treatment group by Mann Whitney test
c: p value by comparison of clobetasol with ivermectin, clobetasol with ivermectin and glycerin by Mann Whitney test
d: p value by comparison of ivermectin with clobetasol with ivermectin and glycerin by Mann Whitney test
e: p value by comparison between clobetasol with ivermectin and glycerin by Mann Whitney test
f: p value by comparison among treatment groups by Kruskal Wallis test

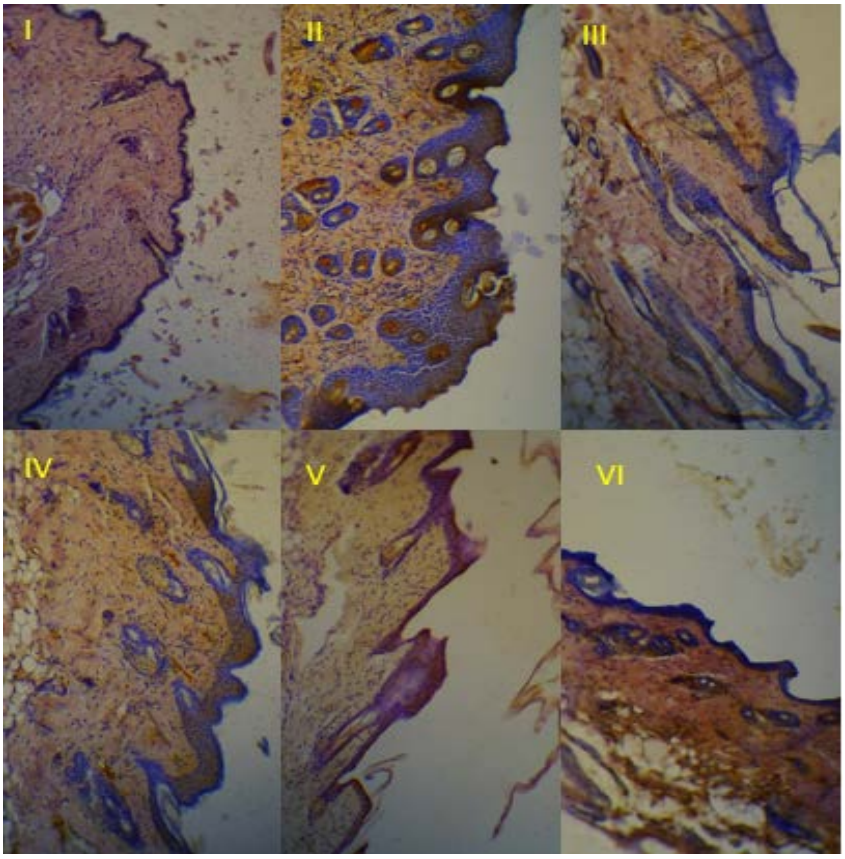

Figure 2. Immunohistochemistry expression of STAT3 in mice skin tissue.
Group I: Apparently healthy. Group II: Strong brown with Percentage: 3+. Group III: Low brown with Percentage: 1+. Group IV: Moderate brown with Percentage: 2+. Group V: Low brown with Percentage: 1+. Group VI: Moderate brown with Percentage: 2+. Olympus lens power of 10 microscope used. Samples taken after 5 days (Figure 4).

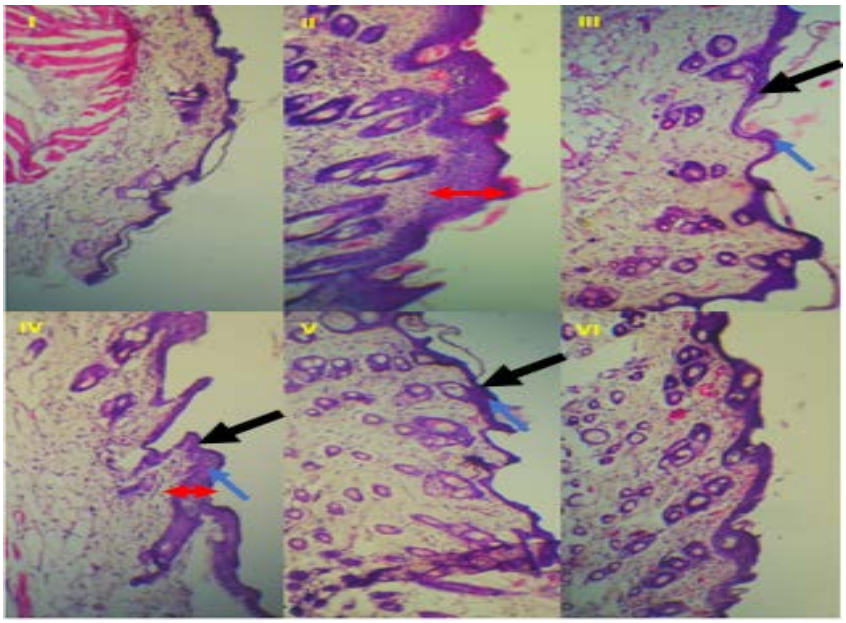

Figure 3. Histopathology mice skin sections.
I: Healthy group, II: induction group show histopathology picture of psoriasis (Munro's abscess, parakeratosis, hyperkeratosis, lengthening of rete ridges, dermis lymphocytic infiltrate, and acanthosis. III: Clobetasol group, IV: Ivermectin group, V: Ivermectin and clobetasol combination group, and VI: Glycerin group. Treatment groups III, IV, and V had better Munro's abscess (Black arrow), parakeratosis, and few dermis lymphocytic infiltrate (Blue arrow). Group IV had better hyperkeratosis (Red arrow),while group II had more hyperkeratosis (Red arrow). Group V had decrease acanthosis. Stain of hematoxylin and eosin of mice skin back. Olympus lens power of 10 microscope used. Samples taken after 5 days.

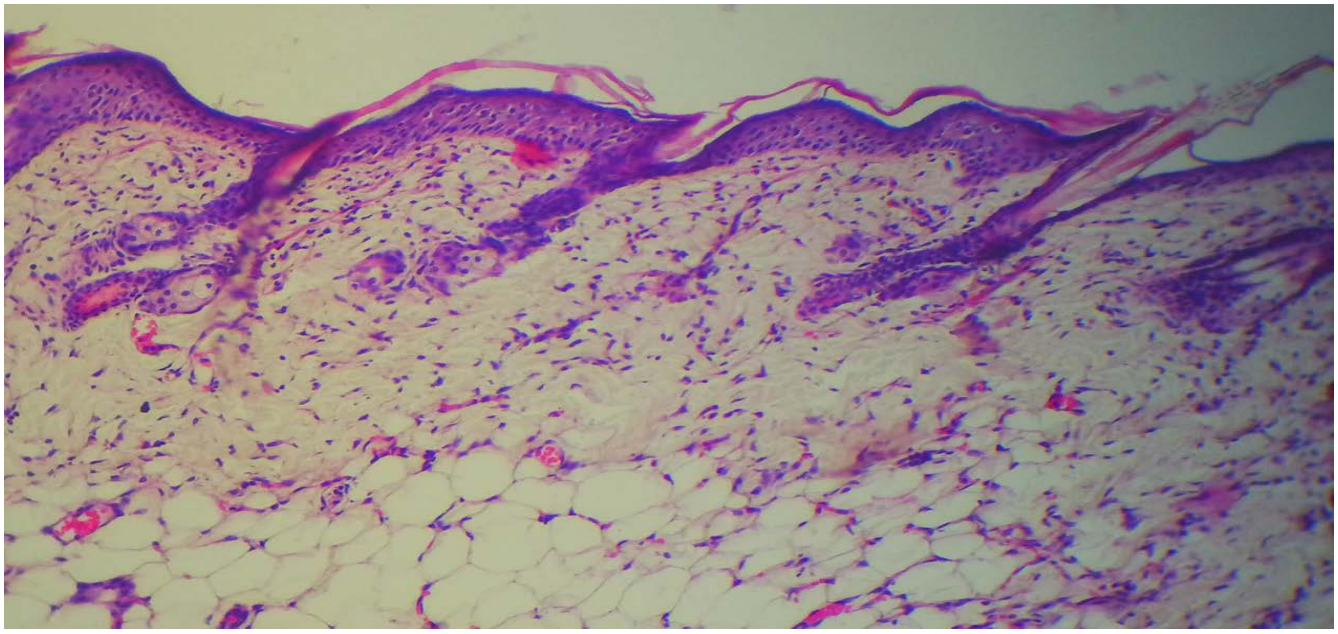

Figure 4. Histopathology of group IV (ivermectin) mice skin additional section
The section show decrease munro abscess in epidermis stratum corneum in addition to decrease the dermis lymphocytic infiltrates. Stain of hematoxylin and eosin of mice skin back. Olympus lens power of 10 microscope used. Sample taken after 5 days.

The combination of ivermectin with clobetasol group used half of the doses (0.5% and 0.025% respectively) of both of them in order to decrease the side effect of each drugs and as shown in this study they are still effective when used in combination. Furthermore, they are better than ivermectin alone because the median number of IL-17 and STAT 3 percent are less. The expression of p-STAT3 and STAT3 in skin imiquimod psoriasis model was detected. In addition to that, when comparing human healthy skin tissue to psoriasis skin tissue, increased expression levels of METTL14, p-STAT3, TRIM27, and IL-6 where found[34].

The significant decrease in STAT3 percent in clobetasol, ivermectin, and clobetasol with ivermectin combination when compared to the induction group indicate the similarity to the previous study that state ivermectin decrease the level of STAT3/STAT5 phosphorylation and encourage autophagy proteins expression[35]. Also, the result is similar to a study showed a reduced STAT3 protein level expression intensity for the clobetasol group[36]. It was documented that in psoriasis, STAT1 in addition to STAT3 are participate in the differentiation of Th1 cells with Th17 cells where the dendritic cells activation occurs[37,38], as it was suggested before that IL-23 but not IL-12 cytokine participate in the pathogenesis of psoriasis[39].

The binding of IL-23 with its receptor will activate Janus kinases and then an additional activation of STAT3. Interleukin -23 will cause Th-17 cells production of cytokine where IL-17 is the main psoriasis pathogenic cytokine[40]. The decreased level of STAT3 and IL-17 in the psoriatic lesion will eventually lead to a decrease in the inflammatory process in skin tissue as shown in the study.

For the histopathology readings, the ivermectin group when compared with induced group several parameters showed significant decrease like Munro's abscess, hyperkeratosis, parakeratosis, and dermis lymph infiltrate those indicate a response of the tissue to ivermectin. This is similar to the description of the research that stated in the ivermectin group, mild keratosis and papillary thinning, no Munro's abscess and parakeratosis shown in the skin. In addition to mild epidermal acanthosis and few of rete ridges[32]. This model of imiquimod used to evaluate the ivermectin effectiveness because this 5 days' model highly used in studies[27, 41] and the five days' treatment as shown above have an effect on psoriatic tissue. The neutrophil cells infiltrations happened in the beginning of psoriasis as a Munro abscesses[42]. The significant reduction in the Munro's abscesses by ivermectin indicate decrease in the inflammation process which indicate starting healing process although only five days ivermectin treatment used. Furthermore, as the significant decrease in parakeratosis occur in ivermectin group, this indicate cell proliferation slowing down and increase normal turnover of skin. When clobetasol group compared to the induction group also a significant decrease in Munro's abscess, parakeratosis, and dermis lymph infiltrate showed and no significant decrease in hyperkeratosis which show the benefit of ivermectin for this parameter. The parakeratosis is similar to the study that showed high significant decrease in it for the clobetasol group in the mouse ear pinna[43].

The best histopathology readings response was found in the clobetasol with ivermectin combination. When it is compared with induced group it was found that Munro's abscess, parakeratosis, acanthosis, dermis lymph infiltrate showed significant decrease. This indicate that more than one mechanism of action used in this group combination give better wide range skin tissue response. This is similar to the note that present in the study in which the absence of parakeratosis and Munro's abscess in addition to mild acanthosis in the epidermis and a little chronic lymphocyte dermal infiltrations are present. It is showed also that ivermectin with clobetasol combination is the best treatment used group[32]. The significant difference between the treatment group indicate that those treatment group are of different potency in modulate the investigated parameter.

CONCLUSIONS

The study suggests that ivermectin and combination of ivermectin with clobetasol may have a promise role in imiquimod induced psoriasis with preferring the ivermectin/clobetasol combination due to decrease IL-17 inflammatory cytokine and decrease the STAT3 protein in the skin in addition to other ameliorating effect on histopathology readings like Munro's abscess, parakeratosis,

and dermis lymph infiltrate. Other pathway has to be investigated in order to clearly understand all the suspected mechanism of action of ivermectin.

Study limitation and future suggestion

The study limitation includes using the imiquimod induction in mice which may not represent all the clinical and pathological features or genetic changes of human psoriasis although it represents the inflammation process and other showed feature in addition to that, it is highly used induction protocol in researches. Farther Future studies should be focus on the use of ivermectin in other longer inflammation study model in animals to simulate the psoriasis chronicity and discover longer ivermectin activity. In addition to that, more attention could be paid for the changes in skin microbiome of psoriasis model.

Authorship Contribution: Mohammed and Iqbal design the study and wrote the draft. Mohammed performs the pharmacology part and analyzed and interpreted data. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

Potential Conflicts of Interest: None

Competing Interest: None

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