Aswan University Medical Journal. volume 3 / No.1/ June 2023 (34-46) Online ISSN: **2735-3117**

REVIEW ARTICLE

Evaluation of the Effect of Narrowband Ultraviolet B Versus Methotrexate on Serum TWEAK Level in Psoriasis

Ali Mohamed Younis[1], El-Hassan M. Rageh[1*], Moustafa A. El Taieb[1], Nour Mohammed Ahmed[2], Eisa Mohamed Hegazy[3]

[1] Dermatology, Venerology, and Andrology department, Faculty of Medicine, Aswan University, Egypt

[2] Clinical pathology Department, Faculty of Medicine, Aswan University, Egypt

[3] Dermatology, Venereology, and Andrology department, Faculty of Medicine, South Valley University, Egypt

ABSTRACT

Keywords: NB-UVB, MTX, Psoriasis, TWEAK, Anti-inflammation

*Corresponding Author: El-Hassan Mohsen Mansour Mahmoud
Email: hassanrageh92@gmail.com
Mobile: +201151222522

Psoriasis is a chronic inflammatory disease that affects the skin and joints, with a worldwide prevalence of 2-3%. The management of psoriasis is individualized and may involve a combination of different treatment modalities. NB-UVB is a commonly used phototherapy, while MTX is an immunosuppressive drug with anti-proliferative and anti-inflammatory effects. TWEAK, a member of the TNF-ligand superfamily, plays a role in the pathogenesis of psoriasis by promoting the expression of proinflammatory mediators from various cell types. Studies have shown that NB-UVB and MTX can inhibit keratinocyte growth and downregulate the expression of cell adhesion molecules, which can moderately decrease systemic TWEAK levels in psoriasis patients. However, more research is needed to fully understand the role of TWEAK in psoriasis and its relation to different treatment methods. Therefore, this review article aims to discuss the role of TWEAK levels in NB-UVB phototherapy and MTX in the treatment of psoriasis.

INTRODUCTION

1. Psoriasis

Psoriasis is a chronic, immune-mediated disorder of the skin and joints, characterized by abnormal proliferation and differentiation of keratinocytes, as well as infiltration of inflammatory cells such as T-lymphocytes, macrophages, and neutrophils. The exact cause of psoriasis is not known, but it is believed to have a genetic component. It is a inflammatory and proliferative disease of the skin and joints **(1).**

1.1. Epidemiology of psoriasis:

Psoriasis is a common condition that affects people of all ages, genders, and ethnicities worldwide. The prevalence of psoriasis ranges from 1.5-5%, with higher rates observed in

Submission date: (25/1/2023) - acceptance date: (11/2/2023)

developed countries. Children are also affected by psoriasis, with a prevalence rate of 0.1-1.5%. The median age of onset is between 7-10 years, with early-onset cases being more likely to have a positive family history and a poor prognosis. The prevalence in adults is bimodal, with the highest rates observed in the age groups of 18-39 years, 50-69 years, and particularly 61-70 years **(2).**

1.2. Risk factors of psoriasis

Psoriasis is a chronic, multigenetic disorder that affects people of all ages, genders, and ethnicities worldwide. The exact cause of psoriasis is not known, but it is believed to be triggered by various factors in genetically predisposed individuals. The risk factors for psoriasis can be divided into two groups: extrinsic factors, such as environmental triggers, and intrinsic factors, such as genetic predisposition.Recent research suggests that the onset, development, and clinical presentation of psoriasis is a result of a complex interplay between environmental, genetic, and epigenetic factors. Twin studies have estimated the heritability of psoriasis to be among the highest of all multifactorial genetic diseases, at 60-75%. **(2).**

1.3. Pathogenesis of psoriasis

Psoriasis is an immune-mediated, inflammatory disorder that primarily affects the skin and joints. It is genetically determined and influenced by epigenetic mechanisms, potentially triggered by environmental factors. The pathogenesis of psoriasis is complex and not fully understood **(3)**. The early development of psoriasis is characterized by an autoinflammatory response, with a burst of neutrophils and cytokines related to the IL-1 family, such as IL-1α, IL-1β, and IL-36, which initiate the disease. In later stages, characterized by plaque psoriasis, IL-12 induces differentiation of naive T cells to TH1 cells which in turn secrete IFN-γ and TNF-α, leading to keratinocyte proliferation, increased expression of angiogenic mediators and endothelial adhesion molecules, and infiltration of immune cells into lesional skin **(Figure 1) (4).**

1.4. Role of T lymphocytes and cytokines in the pathogenesis of psoriasis:

1.4.1. T lymphocyte stimulation:

T cells in psoriasis are activated by responding to peptides presented by antigen presenting cells (APCs) including self-proteins, microbial pathogens, and microbial superantigens. However, it has also been observed that T cells can be activated without antigens or superantigens, but rather through direct contact with accessory cells **(6).**

In psoriasis, T cells recognize antigens via presentation by mature antigen presenting cells (APCs) in the skin rather than lymphoid tissues. APCs expose antigenic peptides via class I or II major histocompatibility complex (MHC) molecules, to which receptors are present on the T-cell surface. The second signal for T lymphocyte activation is the antigen-independent cell-cell interaction known as co-stimulation. Both mechanisms regulate T-cell signaling and is referred to as the immunologic synapse. Co-stimulation involves pairing of receptors with ligands on the T cell, such as the B7 family of molecules, which interact with cluster of differentiation (CD) molecules such as CD28 on T cells, lymphocyte function associated antigen (LFA)-1 on the T cell, which interacts with ICAM-1 on an APCs or endothelial cell and LFA-3 on APCs binds

Submission date: (25/1/2023) - acceptance date: (11/2/2023)

with CD2 on the T cell. This leads to a cascade of inflammatory cytokines that contribute to the development of psoriasis **(Figure 2) (6).**

1.3.1. Role of cytokines in the pathogenesis of psoriasis

Cytokines are small, biologically active glycoproteins that play a key role in the development of psoriasis. They function as signals to produce inflammation, tissue repair and remodeling, fibrosis, angiogenesis, and restriction of neoplastic growth. Several chemokines and growth factors have been identified within psoriatic lesions, and the cutaneous and systemic overexpression of various proinflammatory cytokines, such as IL-1, IL-12, IL-17, IL-22, IL-23, IFN- γ, and TNF-α has been observed **(Figure 3) (7).**

1.4. Psoriasis-specific Measures, Area and Severity Index

The Psoriasis Area and Severity Index (PASI) is currently the gold standard for the assessment of the extent and severity of psoriasis. Four sites of affection, the head (h), upper limb (u), trunk (t) and lower limbs (l), are separately scored by using three parameters, erythema (E), induration(I) and desquamation(D), each graded on a severity scale of 0 to 4. Area-wise percentage involvement of the affected sites is calculated with a formula. The final formula for PASI score is: PASI = 0.1 (Eh + Ih + Dh) Ah + 0.2 (Eu + Iu + Du) Au + 0.3 (Et + It+ Dt) At + 0.4 (El + Il + Dl). The maximum score of PASI is 72. A PASI 75 is a 75% reduction of baseline PASI score, and is commonly considered as a denominator for satisfactory results of any treatment modality for psoriasis. **(8).**

1.5. Treatment of psoriasis

Psoriasis is a chronic relapsing disease that often requires long-term therapy **(Figure 4)**. A variety of treatment options are available, including topical therapy, oral medication, biological therapy, phototherapy, and parenteral therapy. The choice of therapy is determined by disease severity, comorbidities, access to healthcare, patient psychological aspects, and the patient's ability to comply with treatment **(10).** Unfortunately, there is no cure for psoriasis at present, and most treatments aim to control symptoms while neglecting the importance of avoiding risk factors. Topical therapy is typically the first line of treatment for mild disease, while immunosuppressive agents, oral retinoids, and phototherapy are used for moderate to severe disease. Biologic agents, which are less toxic and more effective than traditional therapies, represent a newer treatment option for severe cases of psoriasis. **(11).**

2. Phototherapy

The sun emits a broad spectrum of electromagnetic radiation that includes gamma rays, ultraviolet radiation (UVR), and visible light as well as infrared, microwaves, and radio waves. The Earth is protected by its magnetic field, the ozone layer, that restricts the penetration of electromagnetic radiation and absorbs radiation below 280 nm, meaning that only UVA and UVB, visible, and infrared radiation will come into contact with human skin. revise it **(13).**

Ultraviolet radiation (UVR) is a type of electromagnetic radiation with wavelengths ranging from 200 to 400 nm **(figure 5)**. It is divided into three categories:

Submission date: (25/1/2023) - acceptance date: (11/2/2023)

A. UVA (320-400 nm) has the longest wavelength and lowest energy; it can penetrate deep into the dermis and cause aging effects. It is further divided into UVA2 (320-340 nm) and UVA1 (340-400 nm).

B. UVB, with wavelengths between UVC and UVA, is readily absorbed by the epidermal chromophores and causes redness of the skin. It is divided into BB-UVB (290-320 nm) and NB-UVB (311-313 nm).

C. UVC (200-290 nm) is completely blocked by the ozone layer and the atmosphere and is not used in phototherapy **(13).**

2.1. Indications of phototherapy:

Phototherapy is a therapeutic method used to treat several skin conditions including vitiligo, psoriasis, atopic dermatitis (AD), parapsoriasis, cutaneous T-cell lymphoma (CTCL), scleroderma, graft versus host disease (GVHD), and Idiopathic photodermatoses. It is also used to treat other dermatological conditions such as lichen planus, seborrheic dermatitis, chronic eczema, and chronic idiopathic urticaria **(14).**

2.2. Narrow band UVB (NB-UVB):

NB-UVB phototherapy is considered the first-line treatment option for plaque-type psoriasis. The light source used for this type of phototherapy is the TL-01 lamp, which delivers monochromatic light at 311-nm UVB **(14).**

2.3. Mechanism of action of NB-UVB in psoriasis:

NB-UVB phototherapy has multiple mechanisms of action which have not been fully elucidated **(Figure 6).** It reverses several pathologic alterations in psoriasis: the number of epidermal T lymphocytes and DCs decrease during phototherapy, also, it reduces keratinocyte proliferation **(15).**The most significant molecular target of NB-UVB is cellular DNA. UVB exposure reduces DNA synthesis in epidermal cells particularly through the formation of pyrimidine dimers and through injury to the cellular membrane. UVB exposure upregulates expression of tumor suppressor gene p53 resulting in either cell cycle arrest or apoptosis of keratinocytes **(16).** In addition, Activation of NF-κB at the cell membrane following UVB exposure leads to T-lymphocytes apoptosis. Langerhans cells, the most important epidermal APCs, are highly susceptible to UVB irradiation, which reduces their number and density by about 20% and alters their antigen-presenting function. UVB inhibits Th-1 axis by IL-12, IFN-γ and IL-8 and can selectively reduce proinflammatory cytokine production in individual T cells. It also causes decreased expression of the ICAM-1. Moreover, it induces apoptosis of intraepidermal T cells by increasing Fas ligand (FasL) expression on the surface of keratinocytes, which then bind to infiltrated T cells in the epidermis to trigger apoptosis **(17).**

2.4. Dosage and Administration:

The starting dose for NB-UVB therapy can be based on minimal erythema dose (MED) or skin phototype. The MED should be tested in a sun-protected area, such as the hip or buttock. In subsequent visits, the patient's response to phototherapy is evaluated by the degree and duration of skin erythema and any subjective symptoms of burning, stinging, pain, or itch **(21).**

Submission date: (25/1/2023) - acceptance date: (11/2/2023)

The effect of skin erythema on UVB dosing will be as follows: minimal erythema lasting less than 24 hours following treatment - increase dose by 20%, erythema persistent for more than 24 hours but less than 48 hours - hold dose at previous level until erythema lasting less than 24 hours, erythema lasting more than 48 hours - no treatment on that day followed by return of dose to the last lower dose that did not cause persistent erythema. Another approach is to plan the starting dose for phototherapy according to the Fitzpatrick skin phototypes (SPT); a scale for individual's response to sunlight. The skin type is based on the person's reaction to 30 minutes of mid-day sunlight for the first time in the summer **(Table 2) (19).**

2.5. Frequency of NB-UVB sessions:

A frequency of twice or thrice weekly is effective. Twice-weekly treatments tend to take about 1.5 times longer to achieve skin disease clearance compared to thrice-weekly treatments. The maintenance therapy taper protocol is treatment twice weekly for 4 weeks and then once weekly for 4 weeks. The dose should be held constant. For prolonged maintenance therapy, the patient should receive treatment every 1-2 weeks. The final dose should be decreased by 25% and held constant for all maintenance treatments. **(21).**

3. Methotrexate (MTX)

MTX is a synthetic analog of folic acid that disrupts DNA synthesis, repair, and cell replication. It is a derivative of aminopterin, an early folic acid antagonist discovered in the 1940s, known for its anti-inflammatory and anti-proliferative properties. It binds to the active sites of enzymes that typically use folate as a coenzyme for DNA precursor biosynthesis and protein biosynthesis. MTX is considered one of the first immune-modifying agents and is widely used to treat inflammatory diseases that do not respond to steroids. **(21).**

3.1. Mechanism of Action:

3.1.1. Folate Antagonism

As a competitive inhibitor of DHFR and thereby prevents the regeneration from dihydrofolate of tetrahydrofolate (THF) **(Figure 7)**, it blocks the production of purines and pyrimidines, which are necessary for DNA and RNA synthesis. This inhibition of the regeneration of tetrahydrofolate (THF) from dihydrofolate by binding to the enzyme dihydrofolate reductase (DHFR), leads to a reduction in the proliferation of rapidly dividing cells such as lymphocytes, which are responsible for inflammation. **(22).**

3.1.2. Adenosine release

Adenosine is a powerful anti-inflammatory agent that interacts with different types of immune cells, such as neutrophils, macrophages, and T cells, through its four receptors (ADOR). The activation of ADORA2A and ADORA3 receptors leads to a decrease in pro-inflammatory cytokines, such as IL-1β, TNF-α, and IL-6, as well as a reduction in matrix metalloproteinase (MMP) production. **(23).**

3.1.3. Polyamine inhibition

MTX reduces the production of downstream polyamine mediators such as methionine and S-Adenosylmethionine (SAM) by decreasing the production of tetrahydrofolate (THF) and methyl THF which are involved in the conversion of polyamines by monocytes into lymphotoxic products **(23).**

3.1.4. Generation of ROS

MTX is a potent inhibitor of DHFR which catalyzes the reduction of dihydrobiopterin to tetrahydrobiopterin, a cofactor required for the synthesis of NO. Depletion of

Submission date: (25/1/2023) - acceptance date: (11/2/2023)

tetrahydrobiopterin leads to a loss of NO synthesis and an increase in ROS production. This induces apoptosis of transformed T cells and modulates different cell functions such as suppression of cytokine production and cell proliferation through the generation of ROS **(24).**

3.2. Effects on cytokine and MMPs production

MTX treatment reduces the production of proinflammatory monocytic/macrophagic cytokines (IL1β, IL6, and TNF-α), adhesion molecules (E-selectin and VCAM-1) and decreases the gene expression of Th1 proinflammatory cytokines (IL2 and IFN-γ). MTX also disrupts T cell crosstalk signals by inhibiting the expression of IL-15, IL-6, and IL-8. Additionally, it reduces MMPs production and stimulates their tissue inhibitors of MMPs (TIMPs), which is mediated by the downregulation of IL-1β rather than a direct effect on MMP gene expression **(Figure 8) (24).**

3.3. JAK / STAT pathway inhibitor

MTX has been classified as an inhibitor of the (JAK/STAT) signaling pathway by reducing constitutive JAK1 phosphorylation and reducing both STAT1 and STAT5 phosphorylation **(25).**

3.4. Dosage and monitoring of MTX in psoriasis

Starting dose: In general, 7.5–15 mg/week by oral, i.m. or s.c. delivery, Maintenance dose: 5–25 mg/week depending on efficacy and tolerability and Folate supplementation: 5 mg/week of folic acid taken 24 h after administration of MTX. Laboratory tests, including a full blood count with differential, RFTs, LFTs including albumin and bilirubin constitute a baseline work-up and periodically along with treatment with MTX. A chest radiograph is important for patients with underlying pulmonary disease (**26).**

4. TWEAK

TWEAK is a member of the TNF family, such as TNF α, FASL, and TNF-related apoptosis-inducing ligand **(Figure 9)**, that has multiple effects, including cell growth, apoptosis, angiogenesis, and modulation of immune responses. TWEAK is mainly expressed by cells from the monocyte/macrophage family and is found in high levels in inflamed tissues during autoimmune and chronic inflammatory diseases (AICID) **(27).**

4.1. TWEAK structure

The human TWEAK gene, located on chromosomal position 17p13.1, is initially synthesized as a 249-amino-acid type II transmembrane protein. It has a C-terminal extracellular region (206 amino acids; including a stalk region and a prototypical TNF-homology domain), a transmembrane domain (25 amino acids), and an N-terminal intracellular domain (18 amino acids; containing a potential protein kinase C phosphorylation site) **(28).**

4.2. TWEAK receptor (TWEAKR)

In 2012, **Gaudineau et al**. discovered a cDNA clone encoding a TWEAK-binding cell surface molecule, named TweakR. DNA sequence analysis revealed that the predicted TweakR protein sequence was identical to that of human Fn14 **(29).**

4.3. Role of TWEAK in skin

The interaction between TWEAK and Fn14 has been shown to increase the expression and secretion of various molecules that contribute to local inflammatory reactions. This interaction

Submission date: (25/1/2023) - acceptance date: (11/2/2023)

also promotes the proinflammatory activities of cytokines such as TNF-α, IL-1, IL-6, and INF-γ, which play a role in the development of inflammatory skin disorders **(30).**

4.4. TWEAK and psoriasis

Psoriasis is one of the most common inflammatory skin diseases. There is a great debate about TWEAK levels in psoriasis patients. In 2016, **Cheng et al. reported that** both TWEAK and Fn14 are highly expressed in lesional skin of patients with psoriasis and can upregulate multiple proinflammatory and chemoattractive cytokines such as CCL20 and IL-19 with accumulation of RANTES, IL-8, IP-10, and MCP-1 in lesional skin **(30).**

In 2021, according to **Wang et al.** there was a statistically significant correlation between TWEAK and IL-17A/IFN-γ in PV and IL-36γ in EP. **(31).**

In disagreement with the previously mentioned studies, **Elesawy et al., 2020** showed that the serum TWEAK levels were significantly decreased in patients with severe psoriasis vulgaris **(32).**

Although another study, **Myśliwiec et al., 2017** reported that Treatment with NB-UVB caused concurrent increase in serum TWEAK **(33).**

Conclusion

In conclusion, both NB-UVB and MTX have been shown to effectively inhibit keratinocyte growth and decrease the expression of certain cell adhesion molecules and cytokines in psoriasis patients. TWEAK may serve as a new marker for disease activity in psoriasis, which could aid in determining treatment decisions and prognosis. However, further research is needed to fully understand TWEAK's role in the development of psoriasis and its relationship with different treatment methods.

References

1) **Manchiryala, B.R., Tirupathi, U.R. and Anand, T., 2020.** Psoriasis and Its Association with Various Biochemical Parameters--A Clinico-Epidemiological Study. Journal of Evolution of Medical and Dental Sciences, 9(12), pp.900-905.

2) **Parisi, R., Iskandar, I.Y., Kontopantelis, E., Augustin, M., Griffiths, C.E. and Ashcroft, D.M., 2020.** National, regional, and worldwide epidemiology of psoriasis: systematic analysis and modelling study. bmj, 369, p. m1590.

3) **Li, Q., Chandran, V., Tsoi, L., O' Rielly, D., Nair, R.P., Gladman, D., Elder, J.T. and Rahman, P., 2020.** Quantifying differences in heritability among psoriatic arthritis (PsA), cutaneous psoriasis (PsC) and psoriasis vulgaris (PsV). Scientific reports, 10(1), pp.1-6.

4) **Campanati, A., Marani, A., Martina, E., Diotallevi, F., Radi, G. and Offidani, A., 2021.** Psoriasis as an immune-mediated and inflammatory systemic disease: From pathophysiology to novel therapeutic approaches. Biomedicines, 9(11), p.1511.

5) **Abdallah, H.B., Johansen, C. and Iversen, L., (2021).** Key Signaling Pathways in Psoriasis: Recent Insights from Antipsoriatic Therapeutics. Psoriasis: Targets and Therapy, 11, p.83.

6) **Hugh, J.M. and Weinberg, J.M., (2018).** Update on the pathophysiology of psoriasis. Cutis, 102(5S), pp.6-12.

Submission date: (25/1/2023) - acceptance date: (11/2/2023)

7) **Gupta, G., Singh, Y., Tiwari, J., Raizaday, A., Alharbi, K.S., Al‐Abbasi, F.A., Kazmi, I., Satija, S., Tambuwala, M.M., Devkota, H.P. and Krishnan, A., 2020.** Beta-catenin non-canonical pathway: A potential target for inflammatory and hyperproliferative state via expression of transglutaminase 2 in psoriatic skin keratinocyte. Dermatologic therapy, 33(6), p.e14209.

8) **Otero, M.E., Van Geel, M.J., Hendriks, J.C.M., van de Kerkhof, P.C.M., Seyger, M.M.B. and de Jong, E.M.G.J., 2015.** A pilot study on the Psoriasis Area and Severity Index (PASI) for small areas: Presentation and implications of the Low PASI score. Journal of Dermatological Treatment, 26(4), pp.314-317.

9) **Feldman, S.R. and Krueger, G., 2005.** Psoriasis assessment tools in clinical trials. Annals of the rheumatic diseases, 64(suppl 2), pp.ii65-ii68.

10) **Bakshi, H., Nagpal, M., Singh, M., Dhingra, G.A. and Aggarwal, G., 2020.** Treatment of psoriasis: a comprehensive review of entire therapies. Current drug safety, 15(2), pp.82-104.

11) **Rendon, A. and Schäkel, K., 2019.** Psoriasis pathogenesis and treatment. International journal of molecular sciences, 20(6), p.1475.

12) **Jabbar-Lopez, Z.K., Wu, K.C.P. and Reynolds, N.J., 2014.** Newer agents for psoriasis in adults. Bmj, 349, p. g4026.

13) **De Assis, L.V.M., Tonolli, P.N., Moraes, M.N., Baptista, M.S. and de Lauro Castrucci, A.M., 2021.** How does the skin sense sun light? An integrative view of light sensing molecules. Journal of Photochemistry and Photobiology C: Photochemistry Reviews, p.100403.

14) **Garmyn, M., Young, A.R. and Miller, S.A., 2018.** Mechanisms of and variables affecting UVR photoadaptation in human skin. Photochemical & Photobiological Sciences, 17(12), pp.1932-1940.

15) **McKenna, K. and Ibbotson, S., 2016.** Principles of phototherapy. Rook's Textbook of Dermatology, Ninth Edition, pp.1-21.

16) **Musters, A.H., Mashayekhi, S., Harvey, J., Axon, E., Lax, S.J., Flohr, C., Drucker, A.M., Gerbens, L., Ferguson, J., Ibbotson, S. and Dawe, R.S., 2021.** Phototherapy for atopic eczema. Cochrane Database of Systematic Reviews, (10), p. CD013870.

17) **Bernard, J.J., Gallo, R.L. and Krutmann, J., 2019.** Photoimmunology: how ultraviolet radiation affects the immune system. Nature Reviews Immunology, 19(11), pp.688-701.

18) **Wang, H., Wang, S., Li, L., Wang, X., Liu, C., Lu, M., Xia, Y. and Liu, Y., 2021.** Involvement of the cytokine TWEAK in the pathogenesis of psoriasis vulgaris, pustular psoriasis, and erythrodermic psoriasis. Cytokine, 138, p.155391.

19) **Farid, A., Tawfik, A., Elsioufy, B. and Safwat, G., 2020.** Narrow band ultraviolet B therapy deactivates Th1/Th17 pathway and activates Th2 cytokines secretion in Egyptian psoriatic arthritis patients. Journal of Radiation Research and Applied Sciences, 13(1), pp.356-361.

20) **Kostović, K., Šitum, M. and Nola, I., 2002.** Phototherapy (UVB) and photochemotherapy (PUVA) for psoriasis. Acta clinica Croatica, 41(2), pp.103-112.

21) **Elmets, C.A., Lim, H.W., Stoff, B., Connor, C., Cordoro, K.M., Lebwohl, M., Armstrong, A.W., Davis, D.M., Elewski, B.E., Gelfand, J.M. and Gordon, K.B., 2019.** Joint American Academy of Dermatology–National Psoriasis Foundation guidelines of care for the management and treatment of psoriasis with phototherapy. Journal of the American Academy of Dermatology, 81(3), pp.775-804.

Submission date: (25/1/2023) - acceptance date: (11/2/2023)

22) **Griffith, J.L., Zarbo, A.J. and Lim, H.W., 2018.** Phototherapy and photochemotherapy. In Evidence-Based Psoriasis (pp. 31-53). Springer, Cham.
23) **Brown, P.M., Pratt, A.G. and Isaacs, J.D., 2016.** Mechanism of action of methotrexate in rheumatoid arthritis, and the search for biomarkers. Nature Reviews Rheumatology, 12(12), pp.731-742.
24) **Thomas, S., Fisher, K.H., Snowden, J.A., Danson, S.J., Brown, S. and Zeidler, M.P., 2015.** Methotrexate is a JAK/STAT pathway inhibitor. PloS one, 10(7), p.e0130078.
25) **Amatore, F., Villani, A.P., Tauber, M., Viguier, M., Guillot, B. and Psoriasis Research Group of the French Society of Dermatology (Groupe de Recherche sur le Psoriasis de la Société Française de Dermatologie), 2019.** French guidelines on the use of systemic treatments for moderate-to-severe psoriasis in adults. Journal of the European Academy of Dermatology and Venereology, 33(3), pp.464-483.
26) **He, Z., Wang, S., Wu, J., Xie, Y. and Li, B., 2022.** Lower Expression of TWEAK is Associated with Poor Survival and Dysregulate TIICs in Lung Adenocarcinoma. Disease Markers, 2022, p. 8661423.
27) **Lammens, A., Baehner, M., Kohnert, U., Niewoehner, J., Proff, L.V., Schraeml, M., Lammens, K. and Hopfner, K.P., 2013.** Crystal structure of human TWEAK in complex with the Fab fragment of a neutralizing antibody reveals insights into receptor binding. PLoS One, 8(5), p.e62697.
28) **Gaudineau, B., Fougère, M., Guaddachi, F., Lemoine, F., De La Grange, P. and Jauliac, S., 2012.** Lipocalin 2, the TNF-like receptor TWEAKR and its ligand TWEAK act downstream of NFAT1 to regulate breast cancer cell invasion. Journal of cell science, 125(19), pp.4475-4486.
29) **Zimmermann, M., Koreck, A., Meyer, N., Basinski, T., Meiler, F., Simone, B., Woehrl, S., Moritz, K., Eiwegger, T., Schmid-Grendelmeier, P. and Kemeny, L., 2011.** TNF-like weak inducer of apoptosis (TWEAK) and TNF-α cooperate in the induction of keratinocyte apoptosis. Journal of Allergy and Clinical Immunology, 127(1), pp.200-207.
30) **Cheng, H., Xu, M., Liu, X., Zou, X., Zhan, N. and Xia, Y., 2016.** TWEAK/Fn14 activation induces keratinocyte proliferation under psoriatic inflammation. Experimental Dermatology, 25(1), pp.32-37.
31) **Wang, H., Zhang, M., Xu, X., Hou, S., Liu, Z., Chen, X., Zhang, C., Xu, H., Wu, L., Liu, K. and Song, L., 2021.** IKKα mediates UVB-induced cell apoptosis by regulating p53 pathway activation. Ecotoxicology and Environmental Safety, 227, p.112892.
32) **Elesawy, F.M., Salem, R.M., Elfallah, A. and Sarhan, A.A., 2020.** Serum Levels of Tumor Necrosis Factor-Like Weak Inducer of Apoptosis (TWEAK) in Patients with Severe Psoriasis Vulgaris. Benha Journal of Applied Sciences, 5(4 part (2)), pp.1-4.
33) **Myśliwiec, H., Kiluk, P., Myśliwiec, P., Żelazowska‐Rutkowska, B., Baran, A. and Flisiak, I., 2017.** Influence of narrowband ultraviolet B phototherapy on serum tumour necrosis factor-like weak inducer of apoptosis (TWEAK) in patients with psoriasis. Clinical and experimental dermatology, 42(7), pp.786-790.

Submission date: (25/1/2023) - acceptance date: (11/2/2023)

Plaque characteristic	Lesion score	Head	Upper Limbs	Trunk	Lower Limbs
Erythema	0 = None 1 = Slight 2 = Moderate 3 = Severe 4 = Very severe				
Induration/Thickness					
Scaling					
Add together each of the 3 scores for each body region to give 4 separate sums (A).					
Lesion Score Sum (A)					

Percentage area affected	Area score	Head	Upper Limbs	Trunk	Lower Limbs
Area Score (B) *Degree of involvement as a percentage for each body region affected (score each region with score between 0-6)*	0 = 0% 1 = 1% - 9% 2 = 10% - 29% 3 = 30% - 49% 4 = 50% - 69% 5 = 70% - 89% 6 = 90% - 100%				
Multiply Lesion Score Sum (A) by Area Score (B), for each body region, to give 4 individual subtotals (C).					
Subtotals (C)					
Multiply each of the Subtotals (C) by amount of body surface area represented by that region, i.e. x 0.1 for head, x 0.2 for upper body, x 0.3 for trunk, and x 0.4 for lower limbs.					
Body Surface Area		x 0.1	x 0.2	x 0.3	x 0.4
Totals (D)					
Add together each of the scores for each body region to give the final PASI Score.					

PASI Score = ☐

Table (1): PASI score **(9).**

Skin type	Reaction to first sun exposure of 3 MED	MED (mJ/cm3) for UVB
I	Always burn, never tan	20-30
II	Usually burn, tan less than average	25-35
III	Sometimes burn, tan about average	30-35
IV	Rarely burn, tan more than average	45-60
V	Brown-skinned persons	60-100
VI	Dark-skinned persons	100-200

Table (2): Skin photo types and corresponding MED **(20).**

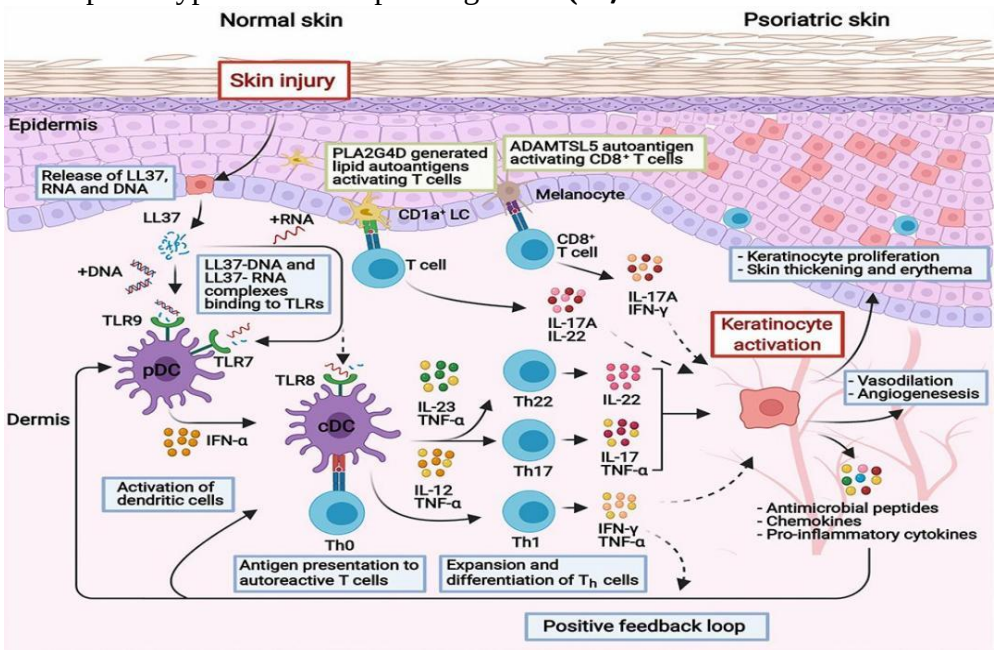


Figure (1): Overview of the immunopathophysiology of Psoriasis **(5).**

Submission date: (25/1/2023) - acceptance date: (11/2/2023)

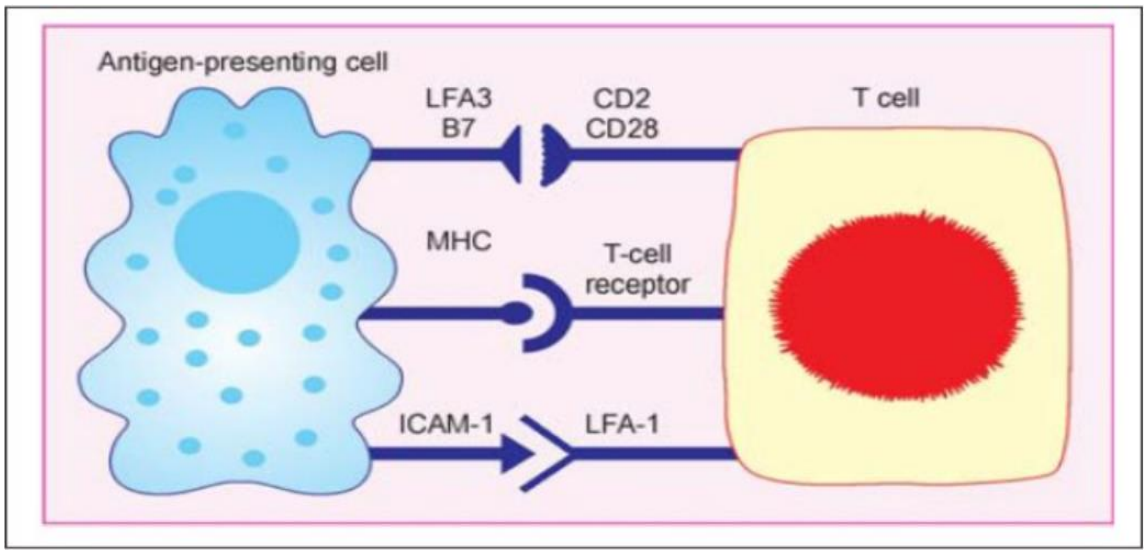


Figure (2): Immunological synapse model between Langerhans and DCs in the skin and T lymphocyte **(6).**

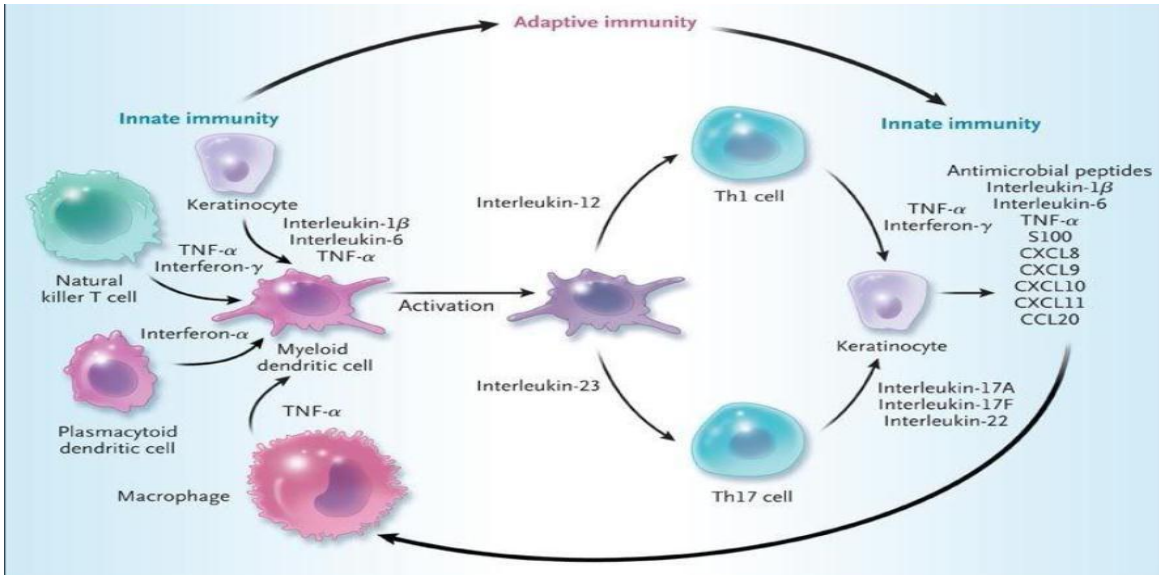


Figure (3) Key Cells and Mediators in the Transition from Innate to adaptive Immunity in Psoriasis **(7).**

Submission date: (25/1/2023) - acceptance date: (11/2/2023)

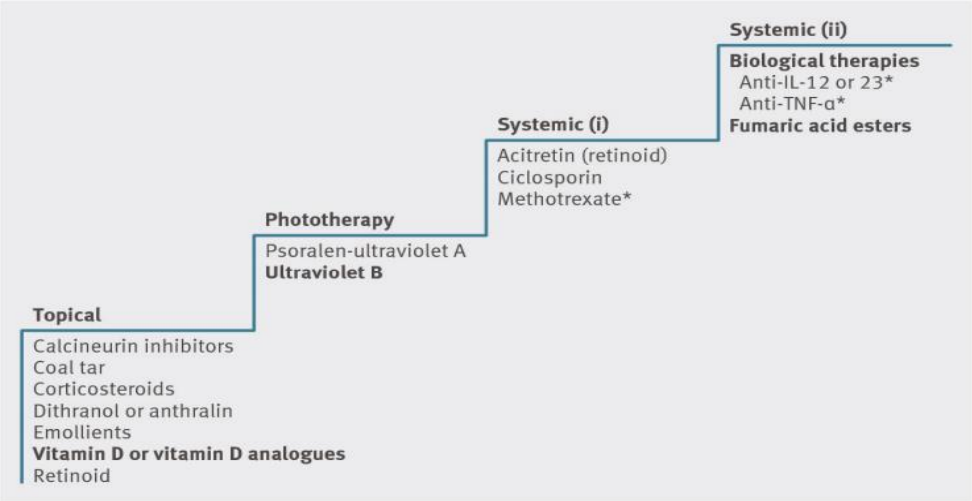


Figure (4): Psoriasis treatment ladder **(12).**

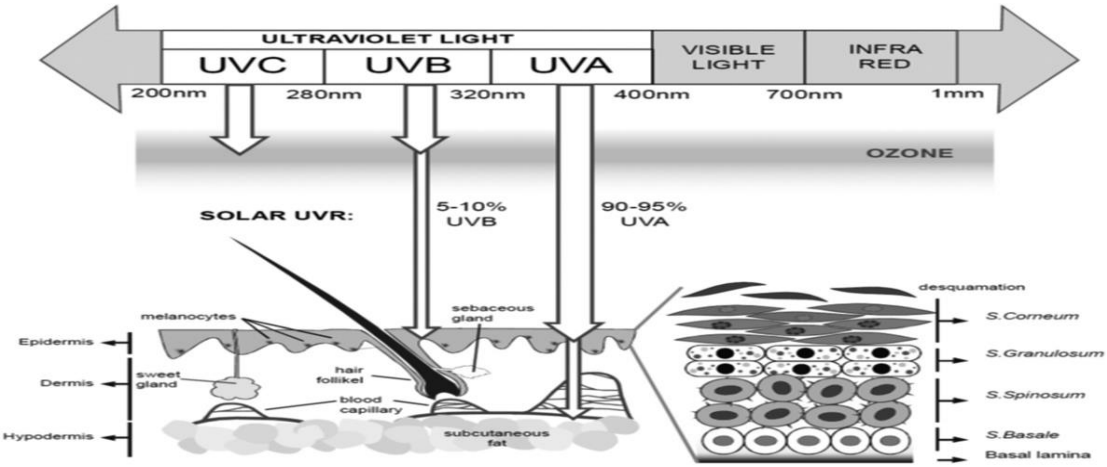
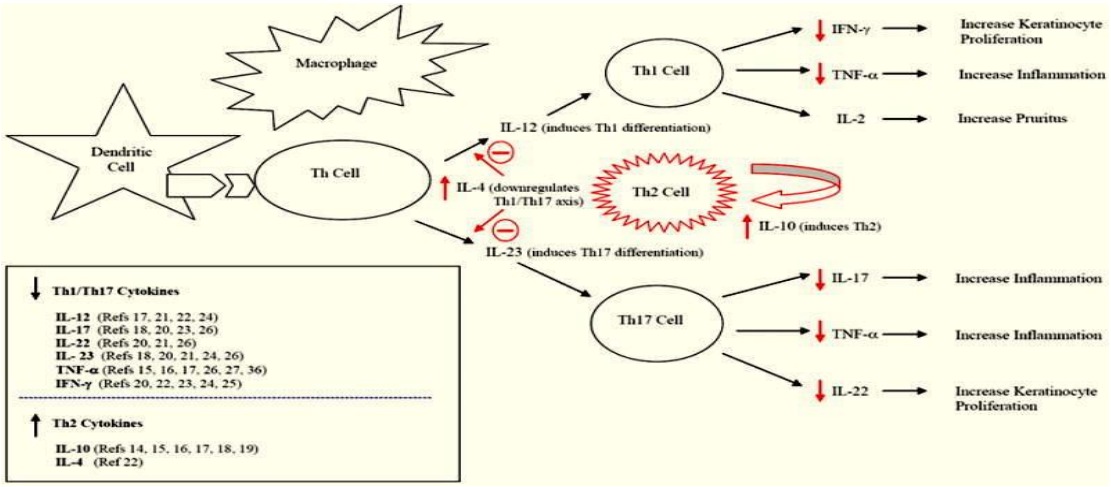


Figure (5): The electromagnetic spectrum of sunlight and the penetration of UVR in the different skin layers **(13).**



Submission date: (25/1/2023) - acceptance date: (11/2/2023)

Figure (6): Immunopathogenesis of psoriasis and the impact of phototherapy on altering the cytokine profile **(18).**

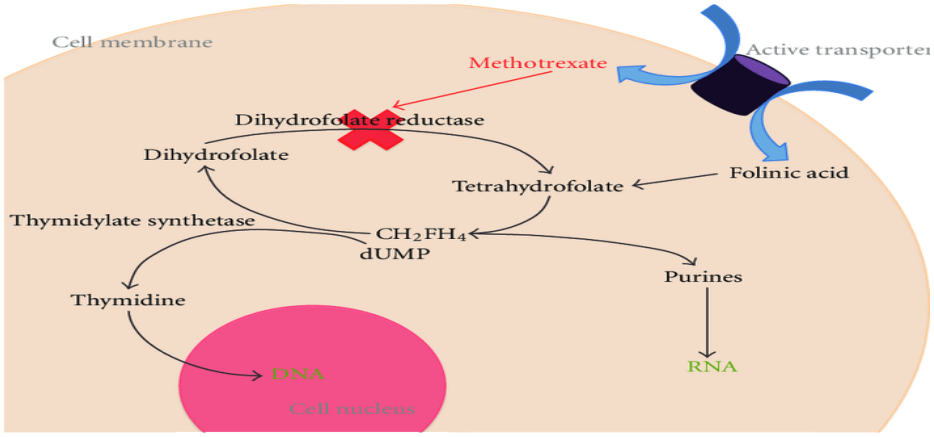


Figure (7): The mechanism by which MTX inhibits cellular proliferation **(22).**

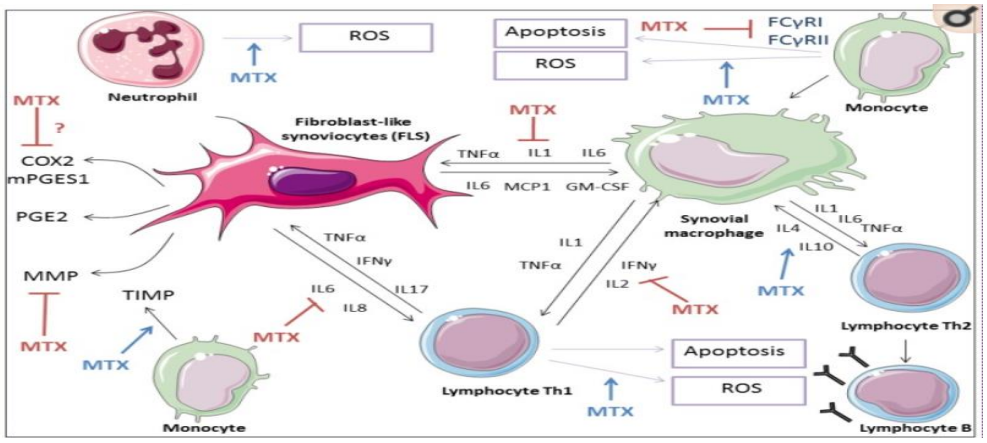


Figure (8): Immune regulatory action of MTX **(24).**

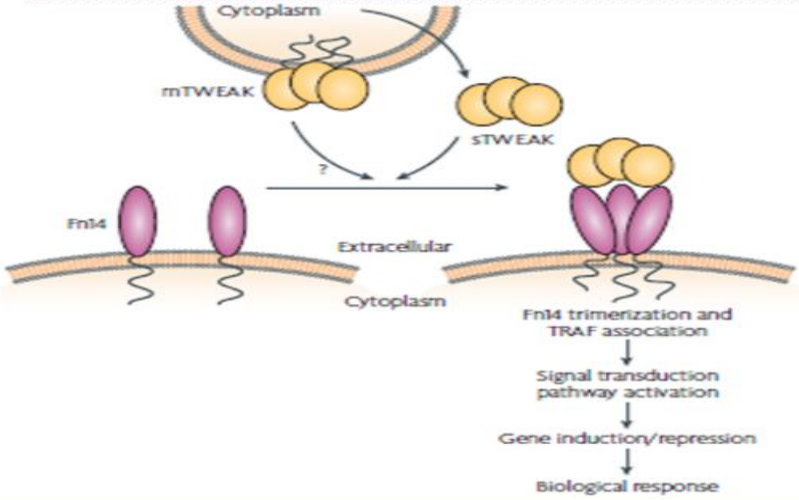


Figure (9): TWEAK/Fn14 Interaction **(29).**

Submission date: (25/1/2023) - acceptance date: (11/2/2023)