An overview about Uses of Isotretinoin in Management of psoriasis

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Abstract

Background: Psoriasis is a common chronic, recurrent, immune mediated disease of the skin and joints. It can have a significant negative impact on the physical, emotional, and, psychosocial wellbeing of affected patients. Psoriasis is found worldwide but the prevalence varies among different ethnic groups. It has a strong genetic component but environmental factors such as infections can play an important role in the presentation of disease. There are several clinical cutaneous manifestations of psoriasis but most commonly the disease presents as chronic, symmetrical, erythematous, scaling papules and plaques. Systemic retinoids address many pathological features of psoriasis including modulating inflammatory cells, keratinocyte hyperproliferation, and differentiation. Some studies suggest that isotretinoin is ineffective in treating certain types of psoriasis, particularly plaque-type psoriasis. In fact, in early head-to-head studies, etretinate was found to be superior to isotretinion in treating most forms of psoriasis. However, with a lengthy teratogenic half-life of 120 days and reports demonstrating its presence in serum up to two years post-therapy, etretinate was removed from the market in 1997. Its successor acitretin became the only systemic retinoid with a psoriasis-approved indication. sotretinoin has been shown to manage pustular-type psoriasis with dosages ranging from 40mg/day for children to 1.5 to 2.0mg/kg/day for adults with success rates exceeding 90 percent.

Keywords: Isotretinoin, psoriasis

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Psoriasis is a common chronic, recurrent, immune mediated disease of the skin and joints. It can have a significant negative impact on the physical, emotional, and, psychosocial wellbeing of affected patients. Psoriasis is found worldwide but the prevalence varies among different ethnic groups. It has a strong genetic component but environmental factors such as infections can play an important role in the presentation of disease. There are several clinical cutaneous manifestations of psoriasis but most commonly the disease presents as chronic, symmetrical, erythematous, scaling papules and plaques. **(1).**

Psoriasis is chronic, inflammatory, immune-mediated systemic disease with proliferative skin disorder in which both genetic and environmental factors have a critical role **(1).**

It is a common disease characterized by scaly, sharply demarcated, itchy, erythematous plaques that commonly affect areas such as the knees, scalp and sacral region **(2).** Due to the chronic nature of the disease and need for long-term treatment, psoriasis is associated with substantial disease burden and negative impact on patients' quality of life **(3).**

Epidemiology:

Worldwide burden of psoriasis is between 2-3% of the whole population. **(4).** Men and women are equally affected with a peak age between 20-30 years old while 50-60 years old is another peak to a lesser extent (**5).**

Etio-pathogenesis of psoriasis :

Although the exact cause of psoriasis is unknown, it is possible that immunological, environmental, and genetic variables interact to cause the skin disorder**.** While autoimmune diseases may be the cause of psoriasis, no specific auto antigen has been identified as the cause until now. Both internal and external factors, including as minor trauma, sunburn, infections, systemic medications, and stress, can potentially cause psoriasis **(6).**

Treatment of psoriasis:

Numerous topical and systemic therapies are available for the treatment of the cutaneous manifestations of psoriasis. Treatment modalities are chosen based on disease severity, relevant comorbidities, patient preference (including cost and convenience), efficacy, and evaluation of individual patient response **(7).**

1. Topical therapy:

Mild disease may be effectively treated with topical therapies, including corticosteroids, vitamin D derivates, retinoids, tar, keratolytic agents that break down scale (urea, salicylic acid), and emollient moisturizers. The choice of topical agent depends on anatomical area, size and thickness of the plaque, and whether the agent is being used for initiation or maintenance therapy **(8).**

A combination product of betamethasone dipropionate and calcipotriol is recommended to initiate treatment on the trunk or extremities because this preparation is more efficacious than monotherapy **(9).**

This product is too strong for the face or folds. When disease control has been established, vitamin D derivates are recommended for maintenance therapy. Further, thick plaques (clinical thickness >0.75 mm) respond to keratolytic agents including salicylic acid or urea, the use of emollients (lubricating moisturizers), and higher-strength topica**l** corticosteroids (ointment formulation) **(9).**

The choice of topical corticosteroid depends on the anatomical location of the plaque, the thickness of the plaque, and the age of the patient. For thick plaques on the trunk or limbs, mid- to highpotency corticosteroids should be used. For infants and young children, body folds, and the face, low- to mid-potency corticosteroids should be used. The palms and soles require high- to very high potency corticosteroids **(8).**

Table (1): Common Topical Therapies for Psoriasis **(8).**

Therapy category	**Mechanism of Action**	**Adverse Effects**	**Evidence Level**
Corticosteroids	Anti-inflammatory	Use of potent and super potent class should be limited to 2-4wk; inappropriate use may cause skin atrophy, contact dermatitis, rebound plaques, and systemic adverse effects.	A
Vitamin D analogs	Normalization of keratinocyte function and anti- inflammatory.	FDA category C; usually well tolerated; most common adverse reaction is irritant contact dermatitis.	A
Tazarotene 0.05% - 0.1%	Normalization of keratinocyte function and anti-Inflammatory	FDA category X, most common adverse effect is irritant contact dermatitis.	A

Salicylic acid 3%- 10%	Degrades the stratum corneum by dissolving intracellular components holding keratinocytes together	Concentration of ≥ 10% and application on ≥ 20% of body surface area may cause systemic adverse effects including metabolic acidosis and nausea.	C
Coal tar/LCD (20% LCD= 4% crude coal)	Decreased keratinocyte proliferation	Irritant and allergic contact dermatitis, staining of clothes and furniture, possible increased risk of non melanoma skin cancer.	A
Calcineurin inhibitors (tacrolimus, pimecrolimus)	Anti- inflammatory	FDA black box warning of increased lymphoma risk; however, no clinical or epidemiological evidence of increased risk, usually well tolerated, relatively safe, but use small quantities with caution during pregnancy.	A

Abbreviation: LCD, liquor carbons detergents.
Fetal abnormalities have been demonstrated in animals or humans according to the FDA.

Table (2): Recommended corticosteroids by body area **(8).**

Application	**Corticosteroids (Vehicles)**
Face, body folds, and infants/ young children	Hydrocortisone 1 (cream, lotion) Desonide 0.05% (cream, lotion) Mometasone furoate 0.1% (cream, lotion)
Plaques on trunk and limbs	Betamethasone furoate 0.1% (cream, ointment). Fluocinonide 0.05% (cream, ointment). Triamcinolone acetonide 0.5% (cream)
Palms and Soles	Clobetasol proionate 0.05% (cream, ointment). Betamethasone dipropionate 0.05% (cream, ointment)
Scalp	Betamethasone valerate 0.1%, 0.05% (lotion) Fluocinonide 0.05% (gel) Mometasone furoate 0.1% (lotion)

Phototherapy:

Photo-chemotherapy modalities commonly used to treat psoriasis include narrowband ultraviolet B (NB-UVB; 311–313 nm), broadband ultraviolet B (BB-UVB; 280–320 nm), targeted or excimer UVB laser (308 nm) and a combination treatment of oral or topical 8- methoxypsoralen and UVA (PUVA; 320–400 nm). Initiation of Photo- chemotherapy is usually considered when at least 10% of the BSA is involved or in patients who have not responded to topical therapies. In contrast, the excimer laser may be utilized as a third-line treatment of localized or treatment resistant lesions; however, NB-UVB is the most commonly used first line photo-chemotherapy because of a decreased photo damage profile **(10).**

Ultraviolet light exerts its effects by inhibiting the ability of epidermal Langerhans cells to present antigens to T cells, thus down regulating the immune response. The PUVA therapy works as photo chemotherapy by crosslinking DNA and inducing apoptosis **(10).**

Absolute contraindications to phototherapy include systemic lupus erythematosus, xeroderma pigmentosum, and porphyria. Relative contraindications include a history of skin cancer, extensive photodamage, immunosuppression, and use of photosensitizing medication other than the prescribed topical or systemic psoralens. Phototherapy is usually well tolerated. **(8).**

However, acute adverse effects may include erythema, a burning sensation, blisters, and pruritus. In addition, PUVA may be associated with an increased risk of skin cancer because the psoralens act as a photosensitizer and UVA penetrates deeper into the skin **(8).**

Systemic Treatments:

Conventional systemic treatments are usually initiated when:

1. 10% or more of the BSA is affected.
2. The psoriasis has a debilitating effect on the patient's quality of life (e.g., involvement of the palms or soles).
3. Response to topical treatments and phototherapy is not sufficient**. (11).**

Methotrexate, cyclosporine, acitretin, and sulfasalazine are the most often prescribed systemic medicines. First-line systemic agents include acitretin, methotrexate, and cyclosporine. Among other things, sulfasalazine and apremilast may be utilized when Treatment with first-line systemic agents does not produce the desired effect, First line therapy is contraindicated, and the medication causes undesirable adverse reactions **(12).**

A 2018 review reported a strong consensus statement on the use of methotrexate and cyclosporine for first-line systemic induction therapy. Absolute contraindications to methotrexate include hepatic impairment (excessive alcohol consumption and active hepatitis B or C), pregnancy, and tuberculosis or other active infection**.** Benefits of methotrexate include evidence of efficacy for psoriatic arthritis and the best safety profile out of all commonly used systemic agents and biologic therapies. **(13).**

Absolute contraindications to cyclosporine include renal impairment, uncontrolled hypertension, active tuberculosis or other infection, and some current and past malignancies. Further, cyclosporine is activated through the CYP3A4 pathway, resulting in multiple drug interactions. A benefit of cyclosporine is the fast onset of action. The previously mentioned review concluded that acitretin is less efficacious than both methotrexate and cyclosporine for chronic plaque psoriasis **(13).**

Further, acitretin has teratogenic potential; therefore, in women of childbearing age, it should be started on the second to third day of a menstrual period. Contraception should be initiated 1 month prior to and continued up to 3 years after discontinuation of the acitretin. Moreover, acitretin is contraindicated for women who are breastfeeding and patients with severe renal or hepatic dysfunction (**14)**.

Acitretin and UVB phototherapy combination treatment may be used, especially for patients with thicker plaques, and results in lower doses of both acitretin and UVB. However, acitretin and the oral biologic agent apremilast does not cause immunosuppression that is associated with methotrexate, cyclosporine, or the other biologic agents **(13).**

Medication	Mechanism of action	Benefits	Common dosing	Adverse effects	Evidence level
Methotrexate	Inhibits production of proliferating cells such as lymphocytes	Some evidence for psoriatic arthritis and best safety profile of systemic agents	Once weekly 7.5-25mg + 1-5 mg folic acid daily on other days.	FDA pregnancy category X; hepatotoxicity, bone marrow suppression, pulmonary toxicity.	A
Cyclosporine	Inhibits immune response through inhibition of calcineurin	Fast acting	3-5 mg/kg daily	Renal toxicity, hypertension, limit continuous long term use.	A
Acitretin	Modulates epidermal differentiation and has anti-inflammatory effects	Evidence for generalized pustular and erythrodermic psoriasis and patients who are HIV- positive	10-50 mg/d with meals	FDA pregnancy category X, hypertriglyceridemia, dryness of oral and nasal mucosa, brittle nails, alopecia, hepatotoxicity.	A
Sulfasalazine	Exact mechanism unclear, has anti-inflammatory effects.	Low adverse effects profile, some evidence for psoriatic arthritis.	1-4g daily	Rash, nausea	A

Table (3): Traditional systemic medications for psoriasis **(8).**

Abbreviation: HIV, human immunodeficiency virus.
Fetal abnormalities have been demonstrated in animals or humans according to FDA. No FDA approval in the US.
No FDA pregnancy category because not approved for use in the US.

Biological therapy:

Biologics used to treat moderate to severe plaque psoriasis represent one of the most significant therapeutic advancements in the field of dermatology. The 4 classes of biologics used to treat psoriasis are

TNF inhibitors, IL-12/23 inhibitor, IL-17 inhibitors, and IL-23 inhibitors. Biologics that inhibit TNF-α, p40IL-12/23, and IL-17 are approved by the US Food and Drug Administration to treat psoriatic arthritis **(15).**

All biologics used to treat psoriasis are administered subcutaneously except infliximab. Overall, there are no increased rates of serious infections or internal malignancies in patients with psoriasis who are treated using biologics. Adverse effects that occur at slightly higher rates than placebo and are common to all biologics include injection site reaction, nasopharyngitis, and upper respiratory tract infections **(15).**

Table (4**):** US Food and Drug Administration–Approved Biologic and Oral Systemic Treatments for Psoriasis **(15)**

Isotretinoin is termed 13-cis-retinoic acid (13-CRA) and considered a retinoid approved by U.S. Food and Drug Administration for the treatment of severe acne. Isotretinoin exerts its biological action by serving as retinoic acid and/or 9-CRA isomers can efficiently activate retinoic acid receptors **(16).**

Mechanism of action:

Isotretinoin has anti-inflammatory and immunomodulatory effects on skin conditions. Retinoic acid isomers were initially discovered because of their role in cell differentiation and prevention of epithelial tumorigenesis through lysosome stabilization and regulation of epithelial cell growth.

Isotretinoin, like all metabolites of retinoids, binds to nuclear receptors known as retinoic acid receptors (RAR and RXR). Once activated, these receptors regulate gene transcription leading to cellular activity changes ranging from cell-cycle progression, differentiation of keratinocytes, and apoptosis to modulation of interleukin-2 (IL-2), interferon γ (IFN-γ), and T and B lymphocyte function **(17).**

Further, isotretinoin can be exploited for keratolysis and decreased neutrophil migration, a trait useful in conditions such as psoriasis and hidradenitis suppurativa. It can also be used to modulate signaling factors, such as epidermal growth factor (EGF) and cyclic adenosine monophosphate (cAMP), responsible for epidermal proliferation and differentiation in cutaneous neoplasms **(17).**

Isotretinoin's exact mechanism of action is unknown, but isotretinoin induces apoptosis (programmatic cell death) in various cells in the body. Cell death may be important for treatment of acne in sebaceous gland cells. Isotretinoin has a low affinity for retinoic acid receptors (RAR) and retinoid X receptors (RXR) but may be converted intracellularly to metabolites that act as agonists of RAR and RXR nuclear receptors **(18).**

FoxO1 and FoxO3 are p53 target genes for isotretinoin, which are apoptosis-promoting transcription factors. In a recent RNAseq analysis, Kovács et al. noted that gene expression changes were mostly related to altered growth factors and other differentiation pathways, which has the key role in sebocytes differentiation and not the lipid metabolism **(19).**

Isotretinoin also have anti-inflammatory effect through suppression of mTORC1 in a subgroup of isotretinoin-responsive patients **(20).** The anti-inflammatory role of isotretinoin through down regulation of inflammatory driving protein, S100a7a **(21).** In addition, isotretinoin targeting the Th17 pathway may offer an additional pathway for their therapeutic response **(22).**

Pharmacokinetics:

Isotretinoin, aka13-cis-retinoic acid, is a vitamin A derivative naturally present in very small quantities in the blood and tissues of humans. It is relatively water-soluble and metabolized in the liver by the cytochrome p450 system. In the liver, isotretinoin is oxidized to 4-oxo-isotretinoin and isomerized into several metabolites including tretinoin.

Maximum plasma concentrations of isotretinoin are reached between 1 and 4 hours following oral administration. By 6–20 hours, peak levels of 4-oxo-isotretinoin are seen in the plasma. Retinoids levels return to baseline after 1 month of discontinuing oral isotretinoin. The drug's metabolites are excreted primarily in the feces (53–74%) and small amounts in the urine **(23).**

Oral Isotretinoin is best absorbed when taken with a high-fat meal, because it has a high level of lipophilicity. The efficacy of isotretinoin doubles when taken after a high-fat meal compared to when taken without food.

Due to Isotretinoin's molecular relationship to Vitamin A, it should not be taken with Vitamin A supplements due to the danger of toxicity through cumulative overdosing **(24).**

Dosage:

The conventional recommended dose of ISO is 0.5–1 mg/kg/day for a period of 16–32 weeks with a maximum cumulative dose of 120–150 mg/kg. However, there are other dosing schedules for ISO; the optimal recommended starting dose of isotretinoin is 0.5 mg/kg/day, which is continued for 4 weeks, following which the dose is escalated to 1 mg/kg/day, which is maintained over the ensuing treatment course unless laboratory values and adverse clinical effects warrant dose adjustments. Treatment with ISO is continued till the cumulative dose of 120–150 mg/kg is attained. The FDA-approved dosing frequency is twice daily **(25).**

Indications:

The FDA did not approve oral isotretinoin until 1982 as a treatment for severe, resistant nodular acne that did not respond to systemic antibiotics or other conventional therapies. Despite having only an acne indication, isotretinoin has been reported to be used off-label for various dermatoses. These include gram-negative folliculitis, inflammatory rosacea, and pyoderma faciale ,rosacea fulminans . Its efficacy has also been described in disorders of keratinization such as psoriasis, pityriasis rubra pilaris, Darier's disease, ichthyoses, and keratodermas. Isotretinoin has also been evaluated as chemoprevention for cutaneous neoplasms and as adjuvant therapy in various genodermatoses like xeroderma pigmentosum and epidermodysplasia verruciformis . Isotretinoin suppresses growth of malignancies only while actively used, the malignancy may return after the drug is discontinued. **(23).**

- **Psoriasis:**

Isotretinoin in psoriasis can be considered a therapeutic option in women with childbearing potential who wish to avoid long-term use of contraceptives following acitretin for almost 2–3 years, in view of its shorter half-life. As isotretinoin modulates inflammatory cells and keratinocyte hyperproliferation and differentiation, it has been shown to be of value in psoriasis. isotretinoin probably has been shown to be most effective in managing pustular psoriasis with dose 1.5 mg/kg/day **(26).**

Contraindication:

Pregnancy and lactating women:

All women of childbearing potential are required to use two effective forms of contraception simultaneously because major fetal abnormalities have been documented related to isotretinoin administration. Pregnancy, planning pregnancy, and breast-feeding are absolute contraindications to therapy. **(23).**

Moreover, patients should not donate blood during the course of therapy or 1 month after discontinuation, because of the risk of exposing pregnant women or women planning pregnancy to excessive isotretinoin levels during a blood transfusion **(23).** To prescribe and receive isotretinoin, FDA requires prescribers and patients to register with the iPLEDGE program **(27).**

Psychiatric disorder:

Caution should be exercised if considering isotretinoin in patients with psychiatric disorders and suicidal ideation, as there are conflicting reports on exacerbation of psychiatric disorders associated with isotretinoin. **(23).**

Monitoring:

Isotretinoin is often associated with moderate increases in serum levels in alanine aminotransferase (ALT), aspartate aminotransferase (AST), and very low-density lipoproteins (VLDL), triglycerides (TGs). Assuming that isotretinoin-induced hepatocyte apoptosis explains raised serum transaminase concentrations, and Isotretinoin-mediated FoxO1 signaling may explain isotretinoin-induced hypertriglyceridemia **(28).**

Oral isotretinoin use can lead to various abnormalities in hematological parameters with, such as leukopenia, neutropenia, agranulocytosis, thrombocytopenia, and thrombocytosis. The incidence and severity of alterations in hematological parameters are usually not significant. Routine monitoring of white blood cell count, hemoglobin level, and platelet count during isotretinoin therapy has been recommended for patients with a clinical suspicion of an abnormality **(29).**

Advirse Effects:

- **Skin:**

Mucocutaneous adverse events are common and usually dose dependent. Chelitis is common, developing in up to 98% of patients. In fact, the lack of chelitis may be a marker for noncompliance with therapy. The higher the dose of isotretinoin, the higher the prevalence of chelitis.

Xerosis, with occasional accompanied pruritus, occurs in up to 50% of patients and may be especially prevalent in patients with an atopic diathesis. Other mucocutaneous side effects included but are not limited to: acral desquamation, facial erythema, eczema (which may require topical corticosteroid therapy), skin fragility, paronychia, pyogenic granulomas, bruising, eruptive xanthomas, photosensitivity (due to thinning of the stratum corneum), paronychia, onycholysis, nail plate fragility, and alopecia **(23).**

Sun sensitivity is also very common adverse effects seen in patients taking isotretinoin. Sun protection and skin moisturizers and barriers are important patient education topics before starting the medication. Patients should also avoid all skin resurfacing procedures (waxing, dermabrasion, laser therapy) during treatment and at least six months after treatment to prevent skin irritation and scarring **(27).**

- **Ocular:**

Isotretinoin and other retinoids are well known to affect the eyes. Dry eyes are very common during treatment and is caused by isotretinoin's apoptotic effect on the meibomian glands. Some people develop contact lens intolerance as a result. In some people, these changes are long-lasting or irreversible and represent. Meibomian Gland Dysfunction (MGD) that lead to other common effects on the eyes include inflammation of the eyelid (blepharitis), red eye caused by conjunctivitis and irritation of the eye. More rare ocular side effects include blurred vision, decreased night vision (which may be permanent), colour blindness, development of corneal opacities, inflammation of the cornea (keratitis), photophobia and other visual disturbances **(30).**

- **Gastrointestinal:**

Isotretinoin may cause mild, non-specific and common gastrointestinal symptoms including nausea, constipation, diarrhea, and abdominal pain. The drug is associated with inflammatory bowel disease (IBD) ulcerative colitis, but not Crohn's disease. More recently, large case control and cohort studies showed no association between isotretinoin use and the occurrence of either Crohn's or ulcerative colitis **(31).**

- **Musculoskeletal:**

Isotretinoin has a number of muscoloskeletal effects. Myalgia (muscular pain) and arthralgia (joint pain). Although sacroiliitis is a rare complication of isotretinoin, inflammatory back pain without sacroiliitis can be seen frequently. Musculoskeletal complaints are dose-related can improve within month of anti-inflammatory drug **(32).**

- **Teratogenicity:**

Isotretinoin is a teratogen highly likely to cause birth defects if taken by women during pregnancy. The more common birth defects this drug can cause are CNS abnormalities (hydrocephalus and microcephaly), cardiac septal defects, microophthalmia, thymus gland abnormalities, hearing and visual impairment, missing or malformed earlobes, facial dysmorphism, and abnormalities in brain function **(31).**

- **Central Nervous System (CNS):**

CNS side effects are rare. Although individual signs of increased intracranial pressure, such as headache, nausea and vomiting, are occasionally observed, the complete syndrome with papilledema and blurred vision is rare. Concomitant use of other drugs associated with intracranial hypertension (e.g., tetracycline, doxycycline or minocycline) is a major risk factor for developing pseudotumor cerebri and should be avoided **(33).**

- **Menstrual irregularities:**

Several instances of amenorrhea in women of childbearing age taking isotretinoin who are not taking oral contraceptive pills(OCPs) have been reported. a menstruation-related side effect (oligomenorrhea, amenorrhea, or dysmenorrhea). In each documented instance, the amenorrhea spontaneously resolved once the medication was discontinued. Additionally, evidence suggests that such cases of amenorrhea are underreported due to the encouraged use of concurrent OCPs while on isotretinoin **(34).**

- **Toxicity:**

There is no commonly used antidote for isotretinoin intoxication. Reports of acute intoxication indicate exacerbations of common, well known isotretinoin side effects, including cutaneous xerosis and cheilitis **(27).**

Drug interaction:

Isotretinoin therapy should not be started without first doing an accurate medication review and risk assessment.Tetracycline class antibiotics should not be administered with isotretinoin because of an amplified risk of pseudotumor cerebri from both drugs. Vitamin A supplements should be avoided due to additive toxic effects of isotretinoin.

Metabolized by the liver's cytochrome P450 system, caution should be taken when prescribing isotretinoin with other similarly metabolized medications. For example, isotretinoin has been shown to reduce carbamazepine levels. Moreover, ketoconazole has been shown to increase isotretinoin plasma levels **(23).**

Isotretinoin is 99.9% bound to albumin in plasma. Medications such as salicylic acid and indomethacin have a high affinity for albumin may displace isotretinoin from albumin and can increase the unbound fraction and activity of the drug

Patients with known hypersensitivity to isotretinoin or any of its components (e.g., parabens, soy, or other retinoids) should not be treated with isotretinoin . Finally, heavy alcohol intake should be avoided, as it has been shown to reduce efficacy of the drug **(23).**

References

1. Paul S., Das A., and Ghosh C. (2022): Efficacy and safety of isotretinoin in comparison to methotrexate in the patients suffering from moderate-to-severe plaque psoriasis: A prospective cohort study. Asian Journal of Medical Sciences, 13(4), 66-7.
2. Nicole M, Golbari BA, Martina L et al., (2018): Current guidelines for psoriasis treatment Cutis; 101(3s):10-12.
3. Kaushik SB and Lebwohl MG (2019): Review of safety and efficacy of approved systemic psoriasis therapies. International journal of dermatology, 58(6), 649-658.
4. Singh, S.K. and Singnarpi, S.R. (2021): Safety and efficacy of methotrexate (0.3 mg/kg/week) versus a combination of methotrexate (0.15 mg/kg/week) with cyclosporine (2.5 mg/kg/day) in chronic plaque psoriasis: A randomized non-blinded controlled trial. IJDVL; 87(2) 214-222.
5. Parisi R, Symmons DP, and Griffiths CE, et al. (2013): Global epidemiology of psoriasis: a systematic review of incidence and prevalence. J Invest Dermatol ; 133(2):377–385.
6. Boehncke, W. H. (2015): Etiology and pathogenesis of psoriasis. Rheumatic Disease Clinics; 41(4), 665-675.
7. Alcusky M, Lee S, Lau, G, et al (2017): Dermatologist and patient preferences in choosing treatments for moderate to severe psoriasis. Dermatol Ther; 7(4):463–483.
8. Brandon A, Mufti A and Sibbald RG (2019): Diagnosis and management of cutaneous psoriasis: a review. Advances in skin & wound care, 32(2), 58-69.
9. Chiricozzi A, Pimpinelli N and Ricceri F (2017): Treatment of psoriasis with topical agents: recommendations from a Tuscany Consensus. Dermatol Ther; 30(6):e12549.
10. Mehta D and Lim HW (2016): Ultraviolet B phototherapy for psoriasis: review of practical guidelines. Am J Clin Dermatol; 17(2):125-33.
11. Ladizinski B , Lee KC , Wilmer E , et al (2013): A review of the clinical variants and the management of psoriasis. Adv Skin Wound Care;26(6):271-84.
12. Menter A, Korman NJ, Elmets CA, et al (2009): Guidelines of care for the management of psoriasis and psoriatic arthritis: section 4. Guidelines of care for the management and treatment of psoriasis with traditional systemic agents. J Am Acad Dermatol; 61(3):451- 85.
13. Nast A, Amelunxen L, Augustin M, et al (2018): S3 Guideline for the treatment of psoriasis vulgaris, update–Short version part 2– Special patient populations and treatment situations. JDDG: Journal der Deutschen Dermatologischen Gesellschaft, 16(6), 806-813.
14. Ortiz NEG, Nijhawan RI and Weinberg JM (2013): Acitretin.Dermatologic therapy, 26(5), 390-399.

15. Armstrong AW and Read C (2020): Pathophysiology, clinical presentation, and treatment of psoriasis: a review. Jama, 323(19), 1945-1960.
16. Abdelmaksoud, A., Lotti, T., Anadolu, R. et al. (2020): Low dose of isotretinoin: a comprehensive review. Dermatologic Therapy, 33(2), e13251.
17. Chu S., Michelle L., Ekelem C. et al. (2021): Oral isotretinoin for the treatment of dermatologic conditions other than acne: a systematic review and discussion of future directions. Arch Dermatol Res 313, 391–430.
18. Samuel, A., Julie John, Riya Alex. et al. (2020): Psychiatric Adverse Events in Patients Taking Isotretinoin - A Review International Journal of Pharmaceutical Sciences Review and Research., 60(1): 105-108.
19. Kovács D, Hegyi K, Szegedi A et al. (2019): Isotretinoin is indirectly effective in sebocytes. The British Journal of Dermatology.182(4),1052-1054.
20. De Vita V and Melnik C (2017). The magnitude of mTORC1 Signalling may predict the response to Isotretinoin treatment in patients with Hidradenitis Suppurativa. Dermatology ,(5): 233-399– 400.
21. Al-Sudany K, Mohammed H, Alrifai B (2019): Down-regulation of S100a7a antimicrobial peptide in acne vulgaris patients after isotretinoin therapy. Dermatologic Therapy , 32(6): e13136.
22. Sardana K and Verma G (2017): Propionibacterium acnes and the Th1/Th17 Axis, implications in acne pathogenesis and treatment. Indian J Dermatol; 62(4): 392–394.
23. On, S. C. J., & Zeichner, J. (2013): Isotretinoin updates. Dermatologic Therapy, 26(5), 377-389.
24. Yurdakok B, Filazi A and Ince S. (2017): Retinoids. In Reproductive and Developmental Toxicology .Academic Press. (pp. 481-492).
25. Bubna, A. K. (2020): Isotretinoin: In acne and beyond–An overview. Indian Journal of Drugs in Dermatology, 6(2), 59.
26. Abhinav, C., Mahajan, V. K., Mehta, K. S. et al. (2015): Weekly methotrexate versus daily isotretinoin to treat moderate-to-severe chronic plaque psoriasis: A comparative study. Our Dermatology Online/Nasza Dermatologia Online, 6(4).
27. Pile HD, Sadiq NM. (2022): Isotretinoin. [Updated 2022 May 8]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-.
28. Melnik, B. C. (2017): Apoptosis May Explain the Pharmacological Mode of Action and Adverse Effects of Isotretinoin, Including Teratogenicity. Acta Dermato-Venereologica, 97(2),*173-181* .
29. Tamer F, Yuksel ME, Avcı E. (2019): Is mean platelet volume an inflammatory marker in acne patients treated with isotretinoin? Acta Dermatovenerol Alp Pannonica Adriat.,28(2),65-69.
30. Neudorfer M, Goldshtein I, Shamai-Lubovitz O, et al. (2012): Ocular adverse effects of systemic treatment with isotretinoin. Archives of dermatology, 148(7), 803-808.
31. Marson, J. W., & Baldwin, H E. (2021): Isotretinoin update. Dermatological Reviews, 2(6), 331-342.
32. Karaosmanoğlu, N., & Mülkoğlu, C. (2020): Analysis of musculoskeletal side effects of oral Isotretinoin treatment: a cross-sectional study. BMC Musculoskeletal Disorders, 21(1), 1-10.
33. Ganceviciene R, Zouboulis CC.(2010): Isotretinoin: state of the art treatment for acne vulgaris. JDDG: Journal der Deutschen Dermatologischen Gesellschaft, 8, S47-S59.
34. Priya Chelliah, Donald Glass. (2020): Comprehensive review of reports of menstrual irregularities associated with isotretinoin. International Journal of Women's Dermatology, 6(5), 365-367.