IADVL

NEWSLETTER

TASK FORCE ON BIOLOGICS & SMALL MOLECULES

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Dear IADVLites,

Greetings from the “Taskforce on Biologics and Small Molecules”.

The role of biologics and small molecules has shown an exponential growth in various dermatological indications. The first newsletter penned by the members of the Task-force includes an update on newer biologics in psoriasis and JAKi, unconventional and innovative indications of existing biologics / small molecules available in the Indian scenario and an interesting quiz.

We hope you find these articles academically enriching and of value in your clinical practice.

Happy Reading !!

Dr. Vishalakshi Viswanath

NEWER BIOLOGICS IN PSORIASIS

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Introduction:

The advent of biologics has dramatically improved the treatment of psoriasis and, so has the therapeutic armamentarium been greatly enhanced. Also, over the last few years, our understanding of psoriasis pathophysiology has significantly expanded. With numerous latest discoveries and researches, the psoriatic disease is now best understood as an inflammation, i. e. mediated by the interleukin (IL)-23/T17 cell signalling axis which produces a patterned response leading to its chronic activation on the keratinocytes and infiltrating immune cells of the skin. This manuscript focuses on the useful facts about the FDA-approved newer biologic agents for psoriasis.

A. TUMOR NECROSIS FACTOR-ALPHA INHIBITORS:

i). Certolizumab:

Certolizumab is a PEGylated Fab fragment of humanized monoclonal TNF-α antibody. It is the first TNF-α inhibitor approved for use in women during pregnancy and breastfeeding by the European Union (EU) and FDA. [1] It has a longer half-life and is less immunogenic as it consists of PEGylation of the Fab fragment and lacks the Fc portion of the antibody, which makes it different from other TNF inhibitors.[2] Apart from moderate-to-severe chronic plaque psoriasis, it has been indicated in rheumatoid arthritis, Crohn's disease, and psoriatic arthritis (PSA). [2] It is administered in a dose of 200 mg or 400 mg subcutaneously once every 2 weeks.

ii). Golimumab

Golimumab is a fully human monoclonal TNF-α antibody. Although etanercept, adalimumab, and golimumab have all been used in relatively fewer psoriatic erythroderma patients,

they have shown good results. Atleast a 75% reduction in PASI (Psoriasis Area and Severity Index) score from baseline was observed in 67% of psoriatic erythroderma patients in the largest case series investigating etanercept, 50% of psoriatic erythroderma patients in the largest clinical study investigating adalimumab, and one psoriatic erythroderma patient who was treated with golimumab.[3]

It has also been evaluated in rheumatoid arthritis and PSA treatment. [2] It is administered 50 mg subcutaneously (SC) once every month.[2] It's once-a-month dosing schedule makes it advantageous over the other TNF-α antibodies.

B. INTERLEUKIN-BASED MOLECULES

a. Inhibitors of Interleukin-17

i) Ixekizumab:

Ixekizumab is a humanized immunoglobulin G4 (IgG4) monoclonal antibody. It acts by neutralizing IL-17A and is indicated commonly in moderate-to-severe plaque psoriasis and PSA patients.[4]

As a starting dose, in patients with moderate-to-severe plaque psoriasis, it is administered 160 mg SC, followed by every 2 weeks 80 mg SC for the next 12 weeks and later once per month only 80 mg is administered. In PSA patients, the first dose of 160 mg is administered followed by once-monthly doses of 80 mg.[5]

ii) Brodalumab:

Brodalumab is a humanized, anti-IL17RA monoclonal antibody that blocks the activity of IL17RA, 17A/F, and 17E.[4] It is most commonly administered in psoriasis and psoriatic arthritis (PSA) patients. It is administered 210 mg SC at weeks 0, 1, and 2 followed by the same dose every 2 weeks.[6]

These both are safe, effective, and tolerable biologics and are assumed to provide the highest clearance in psoriatic patients.[7]

However, they may cause adverse-effects that include headache, upper respiratory tract infections, nasopharyngitis, candida albicans mucocutaneous infections, diarrhoea, and mild neutropenia.[8] Few of the less commonly encountered side-effects include injection-site reactions, arthralgia, fatigue, inflammatory bowel disease, suicide, and

suicidal ideation.

iii) Other agents acting on the IL-17—Th17 pathway:

Currently, new anti-IL-17 antibodies are being investigated, such as bimekizumab, CNTO 6785, LY3074828, and SCH-900117.2 Anti-IL-17 nanoantibody and MSB0010841 are under study for the treatment of psoriasis.[4]

b. Inhibitors of P19 Subunit of IL-23

Biologics that inhibit the p19 subunit of IL-23, have revolutionized the treatment of psoriasis patients. Literature suggests that the genes for p19 and its receptor are linked to psoriasis development, wherein certain p19 alleles protect not only against psoriasis but also against inflammatory diseases (especially Crohn's). The examples include tildrakizumab, [approved in March 2018 by Food and Drug Administration (FDA)], and guselkumab, [approved in July 2017 by FDA and by European Medicines Agency (EMA) in November].[9,10] Another IL-23p19 inhibitor that has not yet been approved but applied for FDA and EMA approval is risankizumab.[11] Yet they have not been included in the international guidelines.

i) Guselkumab:

Guselkumab is a humanized monoclonal antibody that binds to the p19 subunit of IL-23, thus reducing IL-23p19 and IL-12/23p40 messenger RNA (mRNA) which are upregulated in the psoriatic lesions.[12] It is usually administered in patients with moderate-to-severe psoriasis as 100 mg subcutaneous injections at weeks 0, 4, and thereafter every 8 weeks.[12]

Two phase III clinical trials (VOYAGE 1 and 2) for treatment of moderate-to-severe plaque psoriasis patients with guselkumab has been recently published.[10,12] Both these trials compared guselkumab with adalimumab and placebo and were 48-week long studies. Both the VOYAGE 1 and 2 trials reported almost similar results at week 16, and the PASI90 response was observed in 73% and 70% of patients, respectively, as compared to 50% in adalimumab-treated patients.

In the phase III trials, most commonly the adverse events reported with guselkumab included non-serious infections (e.g., upper respiratory tract infections), nasopharyngitis, arthralgias, mild injection-site reactions, and headache. Some other rare adverse events encountered were nonmelanoma skin cancers and soft-tissue abscesses. The presence of

anti-guselkumab antibodies was observed in approximately 5% of the treated patients; however, no correlation between the antibody titre levels and loss of drug efficacy was noted.

ii) Tildrakizumab:

Tildrakizumab is a humanized monoclonal antibody that selectively targets the p19 subunit of IL-23. It is commonly administered in moderate-to-severe plaque psoriasis patients as 100 mg SC at weeks 0, 4, and thereafter every 12 weeks.[13]

iii) Risankizumab:

Risankizumab is another humanized IgG1 monoclonal antibody targeting the p19 subunit of IL-23.[9] A recent similar phase II clinical trial with risankizumab demonstrated the clinical superiority of selective p19 inhibition in comparison with ustekinumab.[11] It is commonly administered in psoriasis, PSA, ulcerative colitis, and Crohn's disease patients.

c. Inhibitors of IL-12/23

Briakinumab:

Briakinumab similar to ustekinumab is another fully human IgG1 monoclonal IL-12/23p40 antibody. For the treatment of psoriasis, rheumatoid arthritis, and inflammatory bowel disease It was being developed; however, in 2011, after the regulators wanted to see more data before approval its biological license application has been withdrawn.[14]

d. Inhibitor of IL 36

Spesolimab blocks the effects of interleukin-36. So far, it has been tried in patients with flares of generalized pustular psoriasis (GPP).[15] It is under review for approval by the US FDA. Effisayil 1, a phase 2 clinical trial investigated the safety and efficacy of spesolimab in patients with a GPP flare. It is administered as a single intravenous dose of 900 mg. A single dose cleared the skin lesions after a week and it not only continued to improve the skin lesions up to 12 weeks but it also reduced the pain and improved the quality of life of the patients.[15]

C. MISCELLANEOUS

· Prurisol, when taken orally causes inhibition of IL-20 and PRINS (psoriasis-associated nonprotein coding RNA induced by stress), thus reducing the proliferation rate of skin in patients with psoriasis.
· Gevokizumab and canakinumab, i.e. IL-1 β antagonists, have shown efficacy in the treatment of

generalized pustular psoriasis.[16]

Conclusion:

Biologics targeting Th1/Th17 cytokines and (IL)-23/T17 cell signalling axis have indeed revolutionised the psoriasis treatment in terms of both the safety and efficacy of these agents. Apart from the treatment effectiveness, it is important to understand and define the long-term risks of these biologic agents in order to minimise the risks for patients and guide their selection.

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NEWER JANUS KINASE INHIBITORS

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The Janus kinase inhibitors are a recent group of drugs used in dermatology. They mainly target and block the cytokine signaling which are mediated by the Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway, and thereby they regulate the immune response and cell growth. They are used for various indications like psoriasis, vitiligo, alopecia areata, GVHD, psoriatic arthritis and atopic dermatitis. The various JAK inhibitors in dermatology practice are Tofacitinib, Ruxolitinib and Baricitinib.

The following are the newer JAK inhibitors which are FDA approved for various dermatological conditions:

1. Abrocitinib
2. Upadacitinib
3. Delgocitinib
4. Ruxolitinib

ABROCITINIB: JAK1 inhibitor

FDA approved indication: Adults with refractory moderate to severe atopic dermatitis not responding to other systemic drugs including biologicals.[1]

Oral drug

Once a day dosage. Studies show significant efficacy in the form of improved Validated Investigator Global Assessment for Atopic Dermatitis (vIGA-AD) score, EASI75 compared to placebo.[2]
Available doses: 50 mg,100 mg (recommended) and 200 mg

Contraindications: Patients on antiplatelet therapies, lactating women, severe renal or liver impairment. Live vaccination immediately before or during treatment with upadacitinib is not recommended.

Adverse effects: Most common are naso-pharyngitis, nausea, headache, herpes simplex, increased blood creatinine phosphokinase, dizziness, urinary tract infection, fatigue, acne, vomiting, oropharyngeal pain, influenza, gastroenteritis, impetigo, hypertension, contact dermatitis, upper abdominal pain, abdominal discomfort, herpes zoster, and thrombocytopenia. Major adverse cardiac events have been noted.

UPADACITINIB: Second generation selective JAK1 inhibitor

FDA approved indication: Rheumatoid arthritis, Psoriatic arthritis (late 2021) and refractory, moderate to severe atopic dermatitis (Jan 2022) in adults and children ≥12 years.

Other indications: Oral erosive lichen planus,[3,4] alopecia areata5 and disseminated patch-type granuloma annulare.[6]

Oral drug

Once a day dosage. Studies have shown achievement of primary (EASI75, vIGA-AD) and secondary endpoints (improvement of EASI90 and also improvement of pruritus.[t]

Available doses:15 mg (recommended) and 30 mg.

Contraindications: Patients on DMARDS (infliximab, adalimumab, etanercept, abatacept), on other JAK inhibitors (tofacitinib) and immune-suppressants (azathioprine, tacrolimus, cyclosporine, intravenous (IV) corticosteroids, and 6-mercaptopurine). Live vaccination immediately before or during treatment with upadacitinib is not recommended.[9]

Adverse effects: Most common are upper respiratory tract infections (URTI) (14%), nausea (4%), elevated liver enzymes (2%), fever (1%), cough (2%), and herpes zoster. Malignancy, thrombosis and gastrointestinal (GI) perforations have been noted with concomitant use of

non-steroidal anti-inflammatory drugs (NSAID). One case report of molluscum contagiosum of an aged female in association with the use of upadacitinib.[10]

DELGOCITINIB: Pyrrolo-pyrimidine and a pan JAK inhibitor which inhibits JAK1, JAK2, JAK3 and tyrosine kinase 2.

Approved in Japan for treatment of atopic dermatitis in 2020. Fast Track Designation to delgocitinib cream (LEO Pharma) for the treatment of adult moderate-to-severe chronic hand eczema by the FDA in August 2020.[11]

Topical drug

Indications: Its use over a period of 24 weeks has shown improvement in pruritus in atopic dermatitis patients.12 Hand eczema cases showed improvement after use of topical cream for a period of 8 weeks.13 It is also reported to be effective in vitiligo14 and moderate-to-severe alopecia areata.[15]

Adverse effects: Systemic adverse effects are uncommon.

BARICITINIB: JAK 1 &2 inhibitor

Oral and topical drug

Dose: 4mg

FDA approved indications: The FDA granted baricitinib with priority review designation in February for severe alopecia areata as a potential first-in-disease medicine, with a regulatory decision expected in the United States in 2022. The drug has been approved in the United States and in more than 50 countries, including the European Union and Japan, for adults with moderate to severe atopic dermatitis who are candidates for systemic therapy.[16,17]

Other indication of oral: Anti-MDA5 antibody-positive dermatomyositis with alopecia areata.[18]

Topical bariticinib indications: Oral lichen planus,[19] lichen plano-pilaris,[20] severe nail lichen planus,[21] recalcitrant subacute cutaneous lupus erythematosus with concomitant frontal fibrosing alopecia22 and lichen sclerosus.[23]

Adverse effects: Upper respiratory tract infection, headache, acne, urinary tract infection, and increases in muscle-related blood markers.

TOFACITINIB: JAK 1& 3 inhibitor

Oral and topical drug
Newer indications: Extended-release tofacitinib (11 mg once-daily) for refractory Behçet disease,[24] resistant chronic actinic dermatitis,[25] primary cutaneous amyloidosis,[26] persistent erythema multiforme,[2]
androgenetic alopecia,[28,29] epidermolysis bullosa pruriginosa,[30]
granulomatous disorders – granuloma annulare, ulcerated necrobiosis lipoidica and sarcoidosis,[31] morphea and systemic sclerosis,[32] dermatitis herpetiformis,[33] and refractory dermatomyositis.[34]

Recently reported adverse effects: Lymphomatoid papulosis,[35] mild transient acne,[36] and multiple sclerosis.[37]

JAK INHIBITORS FOR HIDRADENITIS SUPPURATIVA: Upadacitinib, brepocitinib, Ropsacitinib,[38,39] and INCB054707.40

FUTURE JAK INHIBITORS: There are various other JAK inhibitors which are studied for uses in dermatology but yet to be approved by FDA/EMA.41-45 They include the following:

- Peficitinib
- Gusacitinib
- Fidancitinib
- Filgotinib
- Itacitinib
- Solcitinib
- Deucravacitinib
- Brepocitinib
- Ritlecitinib
- Pacritinib
- Dece3rnotinib
- Fedratinib
- CTP-543

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APREMILAST
Conventional and Unconventional uses

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Apremilast is an oral small molecule PDE-4 (phosphodiesterase-4) inhibitor, later is widely expressed in macrophages, lymphocytes, and natural killer cells, as well as non-hematopoietic cells such as keratinocytes and synovial fibroblasts. [1,2]

Mechanism of action

Cyclic adenosine monophosphate (cAMP) is a second messenger that has a key role in the regulation of many biologic responses in humans, including inflammation, apoptosis, and lipid metabolism and; Phosphodiesterase 4 (PDE4) is a key enzyme in the degradation of cAMP.(2) By inhibiting PDE-4, Apremilast increases cAMP levels in immune and non-immune cell types, which in turn decreases in the expression of inducible nitric oxide synthase and pro-inflammatory cytokines like TNF-α, interleukin (IL)-23,12 whereas increases the levels of anti-inflammatory cytokine such as IL-10.(3) Besides above-mentioned mechanism apremilast also binds to toll-like receptor 4 (TLR4) in peripheral blood mononuclear cells, further reducing the production of pro-inflammatory cytokines. (1)

FDA approved indication

1) Psoriatic arthritis – first approved for psoriatic arthritis in 2014.
2) Oral ulcers associated with Behçet's Disease - first and only approved treatment option for oral ulcers associated with Behçet's Disease in 2019.
3) Plaque psoriasis – In 2014 approved for moderate to severe plaque psoriasis although later in 2021, indication was revised for adult patients with plaque psoriasis who are candidates for phototherapy or systemic therapy across all severities, including mild, moderate and severe.

Off label indications / newer indications

As apremilast has a broad immunomodulatory effect and it is relatively safe drug, it has been used in various chronic inflammatory dermatoses where other therapies have failed. Other dermatological diseases where apremilast has been utilized as off label drug are aphthous stomatitis, other variants of psoriasis, atopic dermatitis, cutaneous sarcoidosis, hidradenitis suppurativa, lichen planus, alopecia areata, discoid lupus erythematosus, vitiligo, severe acne, rosacea, chronic actinic dermatitis [4], pityriasis rubra pilaris [5,6], prurigo nodularis, vulvodynia, chronic ENL. [7]

Dermatosis with open label study and/or RCT have been described in details below.

1) Nail and scalp psoriasis

Nail involvement can be seen in up to 40% patients of psoriasis and lifetime prevalence is significantly higher. [8] Nail psoriasis can lead to impaired quality of life, severe discomfort and even result in permanent disability. Scalp is the commonest and often first site to be affected in patients of plaque psoriasis. [8]
In ESTEEEM 1 and 2 study, 66.1% and 64.7% of patients had nail psoriasis; 66.7% and 65.5% had moderate to very severe scalp psoriasis at beginning. At week 16, apremilast produced greater improvements in Nail Area Psoriasis Severity Index score (NAPSI) versus placebo. A greater NAPSI-50 response (Nail Psoriasis Severity Index score) versus placebo and ScPGA response (Scalp Physician Global Assessment score 0 or 1) versus placebo were seen. [9]

2) Alopecia areata

Alopecia areata (AA) is a common, chronic and complex T-cell-mediated disease that leads to nonscarring alopecia. There is a lack of effective treatments for extensive AA, AT, and AU, with no universally proven therapy that induces remission. [10] PDE4 is increased in

human AA lesions; [11] thus apremilast may be a treatment option for AA. A RCT by Mikhaylov et al. for apremilast in moderate to severe alopecia areata showed a lack of efficacy in severe cases. [12] In a case series of nine patients with recalcitrant alopecia areata, including five patients who had also failed tofacitinib, all nine failed to benefit from apremilast treatment [13], While few case reports demonstrated considerable good responses. [14,15]

3) Atopic dermatitis

It is a chronic disease resulting from complex interaction between skin barrier defects and a dysregulated immune system. A patient of moderate to severe atopic dermatitis cannot be controlled on topical therapy solely as they usually require systemic immunosuppressive drug.

There have been numerous open labels and RCT on apremilast in atopic dermatitis, in which few patients exhibit improvement whereas others failed to respond. [16–18] To conclude, apremilast till now has a variable effect in atopic dermatitis.

4) Hidradenitis suppurative (HS)

HS is a chronic inflammatory recurrent follicular disease usually seen after puberty and commonly affects apocrine gland bearing areas like axilla, groin, perineal or parianal region, infra- and intermammary folds.

A clinically relevant improvement of inflammatory lesions was seen after 16 weeks of treatment with apremilast in 2 patients in whom apremilast was continued till 48 weeks.[19] A RCT of 20 patients (15 apremilast, 5 placebo) with moderate hidradenitis suppurativa (HS) reported a significant improvement with greater than 50% decrease in total abscess/nodule count in comparison to placebo over 16 weeks. [20] In case series of nine patients where 3 patients dropped out, 5 of 6 patients reported significant improvement in Sartorius score, pain and DLQI. [21]

5) Cutaneous sarcoidosis

Sarcoidosis is a multisystem granulomatous disease of unknown aetiology with the skin as second most commonly affected organ. An open label trial revealed effectiveness of apremilast in some patients of cutaneous sarcoidosis, though worsening of skin lesions were seen in 3 patients (20%) after 3 months of discontinuation of therapy. [22]

6) Lichen planus

A case series comprising of 10 patients of LP, refractory to topical steroids showed statically significant improvement in the lesions. [23] Apremilast has also been found effective in recalcitrant oral LP cases. [24]

7) Vitiligo

A successful use of oral apremilast therapy in controlling the progression of adult-onset vitiligo in 13 patients, while 8 patients showed some evidence of repigmentation in a study by majid et al. [25]

8) Recurrent aphthous stomatitis (RAS)

It is characterized by recurring episodes of ulcers, each episode lasting for 1 to 4 weeks and commonly seen in children or adolescent. [26] It often leads to significant impairment of quality of life. A single case report of RAS by Schibler et al showed complete clearance of the lesions within 6 weeks of initiation of apremilast after not responding to topical as well as systemic corticosteroids, antibiotics and colchicine. Patient was in remission after 12 months of treatment. [27]

9) Behcet's disease (BD)

BD is multisystem inflammatory disorder. Apremilast has shown promising results in oral ulcers in BD. In a phase-II RCT of 111 patients, significant reduction in number of oral and genital lesions was seen in 12 weeks of treatment. (28)

A single open label study has found apremilast to be effective in discoid lupus erythematosus [29] and moderate to severe erythematotelangiectatic as well as papulopustular rosacea. [30] Apremilast is also used in variety of other conditions like pityriasis rubra pilaris, Hailey-Hailey disease, generalized pustular psoriasis in isolated cases with variable success.

Table 1. Summarizes data of RCTs of apremilast in various dermatosis.

DISEASE	DURATION & DOSE OF DRUG	EFFICACY	STUDY, No. Of patients
AA	30mg BD 24-48 weeks	Mean change in SALT score at 24 weeks compared to baseline −1.45%±5.39 (SE) in apremilast vs −9.01%±6.37 (SE, p = .38) on placebo; 1/20 in apremilast group and 1/10 in placebo group reached 50% reduction in SALT score at week 24	Mikhaylov et al [12] 20 patients
AD	30/40mg BD 12-24 weeks	In 30 mg BID group at week 12, mean −26.0% (SD 40.1) change from baseline EASI score vs in placebo mean −11.0% change (SD 71.2), effect size −15.0% with 95% CI −34.5% to 4.5% (p>.05); in 40 mg BID group at week 12, −31.6% (SD 44.6) change in EASI score compared to −11.0% (SD 71.2) in placebo, effect size −20.6% with 95% CI −39.7 to −1.5 (p=.04)	Simpson et al. [18] 121 patients
Behcet's disease	30mg BD 12-24 weeks	Mean number oral ulcers at end of treatment (0.5 ± 1.0 vs. 2.1 ± 2.6a, p<.001); in apremilast group, median number oral ulcers at week 12 = 0 vs 2 in placebo group; pain via a visual	Hatemi et al [28] 111 patients

		analog scale -44.8 ± 29.8a compared to baseline on apremilast for 24 weeks (p<.001); 71% on apremilast achieved complete response in terms of oral ulcer resolution, compared to 29% in controls (p<.001);0 of 10 patients with baseline genital ulcers remained with ulcers at week 12 of apremilast, compared to 3 out of 6 on placebo (p=.04)	
HS	30mg BD 16 weeks	8 of 15 with >50% decrease in total abscess/nodule count, meeting criteria for HiSCR (0 out of 5 in placebo group achieved HiSCR); significant decreases in abscess/-nodule count vs baseline (mean difference -2.6; 95% CI -6.0 to -0.9, p=.011), in numerical rating scores for pain (-2.7; 95% CI -4.5 to -0.9; p=.009), and in scores for itch (-2.8; 95% CI -5.0 to -0.6; p=.015), but not in the DLQI (-3.4; 95% CI -9.0 to 2.3; p= .230)	Vossen et al [20] 15 patients
Nail psoriasis ESTEEM 1	30mg BD 52 weeks	NAPSI percentage change of -22.5% vs + 6.5% in placebo (p<.0001) at week 16, -43.6% vs baseline at week 32; 33.3% vs 14.9% (p<.0001) on placebo achieved a NAPSI-50 response at week 16 and 45.2% on apremilast achieved NAPSI-50 on apremilast at week 32	Rich et al [9] 363 patients
Nail psoriasis ESTEEM 2	30mg BD 52 weeks	NAPSI percentage change of -29.0% vs -7.1% in placebo (p<.0001) at week 16, -60.0% vs baseline at week 32; 44.6% vs 18.7% (p<.0001)	Rich et al [9] 175 patients

		on placebo achieved a NAPSI-50 response at week 16 and 55.4% achieved NAPSI-50 on apremilast at week 32	
Nail psoriasis UNVEIL	30mg BD 16-52 weeks	Mean percentage NAPSI score change in target nail: -10.5% in placebo vs -28.9% in apremilast group (p=.1215); percentage of NAP-SI-50 responders 18.5% in placebo vs 26.8% on apremilast (p=.5025); at week 52, for patients on apremilast for 52 weeks, -51.9% change in NAPSI score in index nail, 62.5% of patients achieved a NAPSI-50 response	Strober et al [31]
Scalp psoriasis ESTEEM 1	30mg BD 52weeks	46.5% on apremilast vs 17.5% on placebo with a baseline ScPGA of ≥ 3 achieved a ScPGA of 0 or 1 at week 16 (p<.001), at week 32, 37.4% of patients on week 32 of apremi-last achieved ScPGA of 0 or 1, 43.6% of patients switched from placebo to apremilast at week 16 achieved ScPGA of 0 or 1 at week 32	Rich et al [9] 374 patients
Scalp psoriasis ESTEEM 2	30mg BD 52 weeks	40.9% on apremilast vs 17.2% on placebo with a baseline ScPGA of ≥ 3 achieved a ScPGA of 0 or 1 at week 16 (p<.001), at week 32; 32.4% of patients at week 32 of apremilast achieved ScPGA of 0 or 1, 50.7% of patients who switched from place-bo to apremilast at week 16 achieved ScPGA of 0 or 1 at week 32	Rich et al [9] 176 patients

Scalp psoriasis UNVEIL	30mg BD 16-52	ScPGA of 0 or 1 with ≥2-point reduction from baseline: 20.0% on placebo vs 38.4% on apremilast (p=.0178); at week 52, 33.1% of patients on apremilast for 52 weeks with ScPGA of 0 or 1	Strober et al [31] 112 patients
Palmoplantar psoriasis	weeks 30mg BD 32 weeks	n patients with baseline PPPGA ≥ 3, at week 16, 14% of patients achieved PPPGA of 0 or 1 vs 4% on placebo (p=.1595); apremilast group PPPASI −7.4 ± 7.1 vs placebo −3.6 ± 5.9a (p=.0167) at week 16; 22% achieved PPPASI-75 at week 16 on apremilast vs 8% on placebo (p = 0.0499); at week 16, 36% on apremilast vs 22% on placebo achieved PPPASI-50 (p=.119); at week 32 of apremilast 38% achieved PPPASI-75 32 weeks	Bissonnette et al [32]

Pharmacokinetics [33]

Apremilast is rapidly absorbed by the body reaching its peak plasma concentration after 2-3 hours of oral intake.

t1/2 = 6-9 hours

Metabolism is mainly in liver by cytochrome P450 3A4 (CYP3A4), but also by CYP1A1 and CYP2A6.

Excretion is primarily through the urine and small proportion via the faeces.

Drug interaction

Strong CYP450 inducers such as rifampicin, phenobarbitone, carbamazepine, and phenytoin should not be simultaneously administered with apremilast as they could significantly reduce the levels of apremilast in the body. [34]

Contraindications

Hypersensitivity to drug or any ingredients of formulation. Apremilast is a Pregnancy Category C. [35] Women who are pregnant and breastfeeding are contraindicated to therapy. The administration of live vaccinations while being treated with apremilast is also contraindicated. [36]

Adverse effects

Most common AE reported are GI in nature includes diarrhoea, nausea and vomiting. Other AE are upper respiratory tract infection, nasopharyngitis, upper abdominal pain, hypersensitivity, dyspnea, cough, headache and skin rash. Depression and suicidal behaviour have been noted in various patients. (33)

Monitoring

Patients should be monitored for the development of adverse gastrointestinal manifestations perhaps dose reduction or treatment interruption should be prompted in the event of severe diarrhea, nausea, or vomiting. Patients with an underlying psychiatric history managed with apremilast should be monitored closely. Patients on treatment should also routinely have their weight monitored, as significant weight reductions may occur and require dose reduction or treatment interruption. (37)

Conclusion

As apremilast targets the central inflammatory pathways, it is devoid of any immunosuppression thus has an additional advantage above other conventional medicines. It has been found to be effective for many off label dermatosis but few case reports on miscellaneous condition have also showed ineffectiveness. For potential off-lable indication limited data are available so further clinical studies and RCTs in large number of patients are required to determine its promising roles in various dermatoses perhaps it could be safe and effective drug in dermatologist's armamentarium.

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Dupilumab- a game-changer in the management of atopic dermatitis

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Introduction

Atopic dermatitis (AD) is a common chronic inflammatory relapsing skin condition that has a significant impact on patients' and their families' quality of life. [1] Atopic dermatitis (AD) has a complex and multifaceted pathophysiology, and it presents clinically in a variety of ways. Existing topical or systemic medications are sufficient for the majority of AD patients, especially milder ones. Despite being a fairly common disease, there have not been many optionsfor treating moderate to severe atopic dermatitissystemically. The majority of the novel medications being developed as therapies for AD target a distorted immune response. Recent studies point to the effectiveness of small molecules that target the histamine-4-receptor (ZPL389) and Janus kinase inhibitors, as well as monoclonal α), antibodies against IL-4, IL-13, IL-31 receptor, and IL-22. [2]
Dupilumab (DUPIXENT®), the only biologic approved for AD treatment, is a fully human monoclonal antibody IgG4 directed to the α subunit of the interleukin-4 receptor (IL- 4R blocking IL-4 and IL-13, both crucial cytokines of the Th2 pathway. [2]

Mechanism of action

Dupilumab is a fully human IgG4 monoclonal antibody aimed against the α subunit of the interleukin-4 receptor (IL-4Rα). IL-4 receptors come in two different varieties: type I, which is a heterodimer of IL-4R and the common chain (C), and type II, which is a heterodimer of IL-4R and the IL-13 alpha chain (IL-13R1).
The Th2 pathway's essential cytokines, IL-4 and IL-13, which are involved in the development of dendritic cells (DCs), B cell activation, IgE class switching, and eosinophil recruitment, are inhibited by blocking IL-4R. [4]

Pharmacokinetics/pharmacodynamics

Dupilumab's maximal serum concentration is reached one week after a subcutaneous injection of 600 mg (64 percent bioavailability). Dupilumab is anticipated to be eliminated as endogenous IgGs that are catabolized into small peptides. [4]

Dosage and administration

The administration of dupilumab involves a subcutaneous injection. Adults: A 600 mg starting dose (two 300 mg injections at different injection sites) is advised, then 300 mg every other week (Q2W).
Pediatric Patients: Dupilumab is licensed for the treatment of patients with moderate-to-severe AD who are 6 years of age or older and whose illness is not sufficiently managed by topical prescription treatments or when those therapies are not recommended.

Body Weight	Initial Dose	Subsequent Doses
15 to less than 30 kg	600 mg (two 300 mg injections)	300 mg Q4W
30 to less than 60 kg	400 mg (two 200 mg injections	200 mg Q2W
60 kg or more	600 mg (two 300 mg injecions	300 mg Q2W

Efficacy: Clinical Trial

Two randomized Phase III trials, SOLO 1 and SOLO2, were conducted to evaluate the efficacy and safety of dupilumab. Adult patients with moderate-to-severe AD (671 in SOLO 1 and 708 in SOLO 2) were randomized and were given 300 mg dupilumab qw or q2w after a 600-mg loading dose or placebo. The primary objective (IGA score of 0 or 1, and a reduction of two points or more from baseline in week 16) was achieved by 38% and 36% in the groups that received biweekly injections and by 37% and 36% among the patients who received weekly injections in SOLO 1 and SOLO 2, respectively ($p < 0.001$ for all comparisons with placebo).
Similarly, the number of patients who achieved an EASI-75 in week 16 was significantly higher in patients who received dupilumab than in those who received a placebo (SOLO 1: 300mg qw 52%, 300 mg q2w 51%, placebo 15%; SOLO 2: 300 mg qw 48%, 300 mg q2w 44%, placebo 12%; $p < 0.001$ for all comparisons). Significant improvement in pruritus and quality of life scores was also reported by patients who received dupilumab.
Another phase III trial, LIBERTY AD CHRONOS, compared the concomitant use of dupilumab qw and q2w and medium-potency TCS therapy with placebo and TCS

treatment in 740 patients over 52 weeks. Overall, 39% of the patients in the active group achieved an IGA 0/1, in comparison with 12% of those who received a placebo (p <0.0001). In addition, an EASI-75 was achieved in 64% of patients who received dupilumab plus TCS qw and 69% of those who received dupilumab q2w compared with 23% in the placebo arm (p < 0.0001). [5]

Real-world efficacy in Indian patients: Our data

The data on severe AD patients treated with dupilumab by the author and colleagues was recently published. Retrospective chart analysis was done on patients from three Indian centers—two in Kolkata and one in Bangalore. A total of 25 patients who received dupilumab for at least 6 months were included in the study. At six months, the mean EASI score improved from 19.48 at baseline to 4.84. At the end of 6 months of treatment, 17 patients (68%) had an EASI 75 (75% improvement from baseline). All of these patients have previously received at least one systemic immunomodulator with little to no success.

With dupilumab therapy, the mean SCORAD score also improved, going from 37.32 at baseline to 8.04 after six months. It was determined that the improvement was statistically significant (P 0.001). Additionally, there was a considerable improvement in the quality of life,which went from a baseline mean of 17.08 to 6.52 after six months (P 0.001). In Indianindividuals with AD, Dupilumab showed comparable efficacy, acceptability, and safety in areal-world environment to that shown in clinical studies in western populations. [6]

Side effects

According to a meta-analysis of seven randomized, double-blinded, placebo-controlled clinical trials, dupilumab was more well-tolerated and had a higher safety profile than the majority of other systemic medications. Conjunctivitis, blepharitis, oral herpes, keratitis, eye pruritus, other herpes simplex virus infections, and dry eyes are the most frequent side effects. [5]

The use of dupilumab to treat allergic illnesses, particularly in children, may be constrained as a result of the rise in conjunctivitis, according to certain theories. A mechanism dependent on AD is suggested by the fact that additional trials with dupilumab in individuals with asthma, chronic sinusitis, and nasal polyposis did not demonstrate an increase in conjunctivitis compared with placebo.

Conclusion

Dupilumab's recent approval signals that the biologics revolution has now spread to treating AD. Dupilumab, either alone or in combination with TCS, exhibits a consistent efficacy and a positive safety profile, according to clinical trials and real-world research. It is recommended as a systemic treatment for people with moderate-to-severe AD who are not sufficiently controlled with topical treatments.

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INTRALESIONAL RITUXIMAB IN RECALCITRANT ORAL PEMPHIGUS : A CASE SERIES

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INTRODUCTION

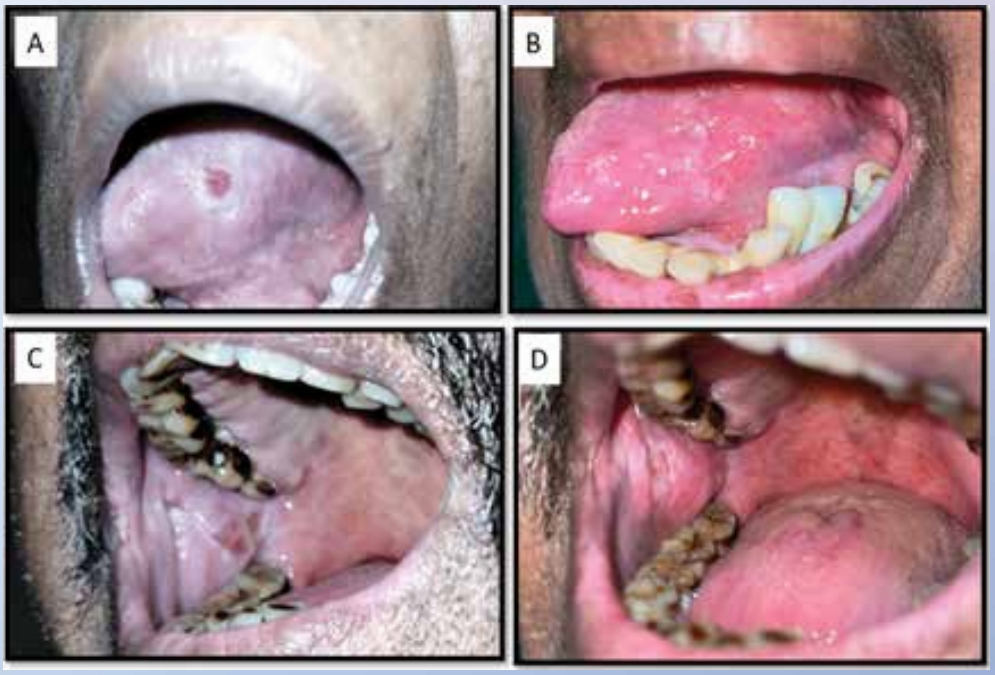
Oral lesions of pemphigus vulgaris (PV) are often recalcitrant to treatment and slower to heal than cutaneous lesions, thereby posing a therapeutic challenge to dermatologists. Gradual tapering of oral corticosteroids is often needed, thereby contributing to adverse effects. Rituximab is a chimeric monoclonal anti-CD20 antibody that has been approved by the US Food and Drug Administration to treat PV in 2018. Intralesional rituximab (IL RTX) has been successfully used in primary cutaneous B-cell lymphoma with and without systemic disease. However there are few studies in cases of recalcitrant mucocutaneous PV. The advantages and limitations of IL RTX in recalcitrant PV are discussed in this case series.

CASE SERIES

The case series included seven patients of PV with refractory oral lesions. The pemphigus severity score was used to determine the severity of PV based on the mucous membrane area and severity score [1] All patients had pre-treatment workup including baseline desmoglein levels.

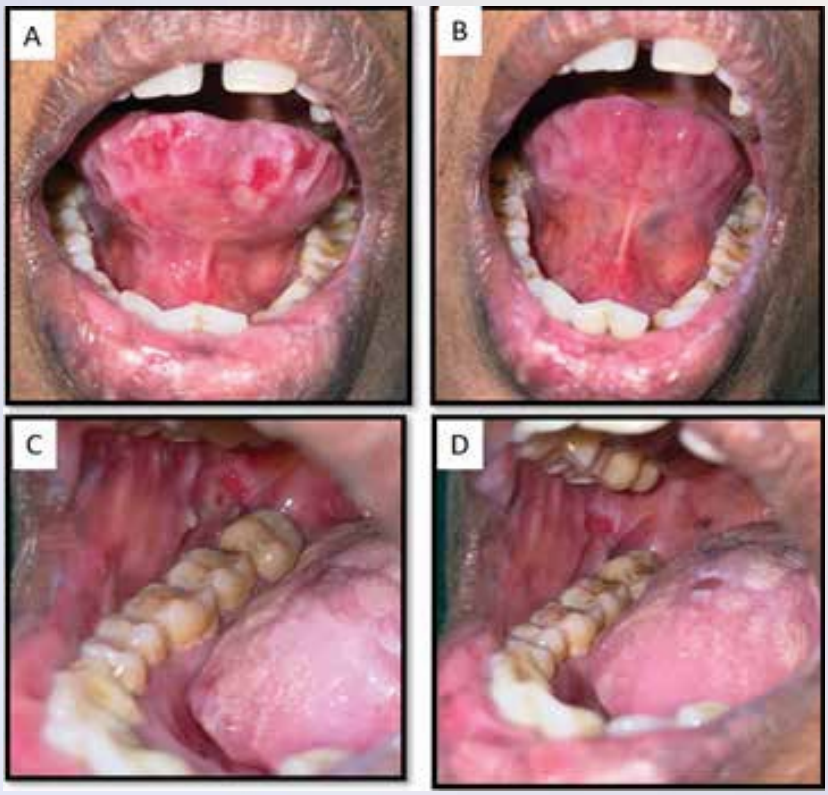
With written informed consent, IL RTX was administered after premedication with pheniramine maleate, and 500 mg of paracetamol. The size of the lesion and largest diameter was measured with the help of thermometer (for oral lesions) and ruler. After application of a topical anaesthetic spray, IL RTX was injected at a dosing of 5mg/cm2 with the help of insulin syringe. All patients were asked to follow up at 1st , 2nd and 3rd month after receiving IL RTX (100mg/10ml vial). Table1 shows the demographics, clinical characteristics, and response of patients to IL RTX. Five patients received only IL RTx at monthly interval, whereas two received concomitant IL RTX at fortnightly interval along with intravenous (IV) dosing as per rheumatoid arthritis (RA) protocol. None of the patients had received prior rituximab except Case 3, a case of paraneoplastic pemphigus with Castleman's tumor, who had received prior IV and IL RTX. Four patients achieved complete relief, whereas three showed partial improvement.

(Figure 1 and 2)



A, B – Case 1: Pre and post treatment photograph showing complete remission in refractory oral erosions on tongue
C, D – Case 2: Pre and post treatment photograph showing complete remission in refractory oral erosions on buccal mucosa

Figure 2. Partial remission (Case 3)



A, B: Pre and post treatment photograph showing complete healing of erosions on tongue
C, D : Pre and post treatment photograph showing partial healing of erosions on buccal mucosa

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Age/sex	49/F	65/M	45/F	40/M	59/M	41/M	49/M
Disease duration (months)	8	5	36	9	18	6	9
Duration of oral lesions (months)	8	5	1	9	2	6	9
Previous immuno-suppres-	Prednis-olone, cyclo-	Prednis-olone,cy-clophos-	(r e - lapse) Prednis-	Prednis-o - lone,aza-	(r e - lapse) Prednis-	Prednis-olone,cy-clophos-	Prednis-o - lone,aza-

santtherapy	phosphamide, DCP pulse	pha-mide, DCP pulse	olone, azathioprine, RTX (Lymphoma protocol) along with IL RTX three years ago	thioprine	o-lone,azathioprine	pha-mide	thioprine
Desmoglein levels (Dsg1 and 3)	43.65/>200	>200/>200	20/ >200	>200/>200	>200/>200	>200/>200	117.6/>200
Rituximab mg Day 1	20	20	12.5	20	10	5	15
Rituximab mg Day 15/30	5	10	12.5	10	-	5 (Day 15)	10 (Day 15)
Concurrent IV rituximab	-	-	Yes (2018)	-	-	yes	yes
Pemphigus severity score (pre-treatment)	4	6	6	5	5	3	6

Pemphigus severity score (posttreatment)	0	0	3	2	0	0	4
Adverse effects	Pain	-	-	-	Pain	-	Pain
Follow up (3rd-month)	CR	CR	PR	PR	CR	CR	PR

CR : Complete remission PR: Partial remission

DISCUSSION

IL RTX was first used in primary cutaneous B cell lymphoma by Heinzerling et al and it has also been successfully used for cutaneous manifestation of systemic B cell Lymphoma [2,3] The use of intralesional rituximab in refractory oral ulcers of pemphigus vulgaris was initially reported by Vinay et al.[4] It has also successfully been used in cases of paraneoplastic pemphigus with recalcitrant oral lesions. [5] The proposed mechanism of IL RTX is due to its local immunomodulatory effect and reversible reduction of CD 19 cells in peripheral blood. The rationale for IL RTX is based on the hypothesis that the dermal ectopic lymphoid structures may contain autoreactive lymphocytes with local auto antibody production. In recalcitrant scalp and oral lesions, the high vascularity permits absorption of rituximab and its local action. [4, 6] However, further research is needed to fully understand the mechanism of action of IL RTX

Oral PV is often resistant to treatment due to local contributory factors (poor dental hygiene, dentures, implants, smoking, tobacco addiction) [4] Vinay et al and Mazloom et al had used a dose of 5mg/cm2 IL RTX at fortnightly interval with good clinical outcomes. [4, 7] Both studies had measured the desmoglein levels and CD19 cell count. In this study IL RTX at 5mg/ cm2 dosing was repeated at monthly interval, however CD19 count was not evaluated due to financial constraints. Baseline desmoglein levels were high and repeat desmoglein levels is planned after six months in all patients. Gupta et al. observed a positive outcome in refractory scalp lesions with a lower dose of IL RTX per unit area (0.25mg/cm2) compared to the dose for oral mucosa. [8] Ahmed et al. however dispute

the efficacy of IL RTX because it is injected into the dermis or subcutaneous tissue. [6] It has been suggested that the syringe's beveled edge should be angled upwards for successful administration at epidermal level. Iraji et. al compared intralesional rituximab and steroid in recalcitrant mucosal and scalp lesions of pemphigus and found no statistically significant difference between both modalities. however intralesional therapy was considered more beneficial compared to increasing dosage of systemic therapy. [9]

In this case series, advantages of IL RTX over steroids include better tolerability, minimal pain at the injection site, and absence of atrophy or pigmentary changes. IL RTX eliminates the side effects of IV RTX and is a more cost-effective and economically feasible therapeutic approach. In patients with financial constraints and recalcitrant oral lesions, the patients can be pooled and given IL RTX with 100mg/ 10ml vial (cost of INR 2500). The limitations of this case series and other studies are the small sample size. Large-scale trials and further research are needed to determine recurrence predictors, pretreatment investigation protocol, and the dose of treatment with IL RTX.

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OMALIZUMAB IN THE MANAGEMENT OF MULTI-DRUG ALLERGY, POST DRUG HYPERSENSITIVITY SYNDROME: A CASE REPORT

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Introduction:

The cases of multi drug allergy is not very uncommon in clinical practices. It is equally frustrating to patients as well to the physician to manage such cases. Patients are scared of using any drug for danger of getting severe reactions while physician struggle to find suitable replacement of culprit drugs when situation arise to prescribe the drugs. In addition there are many confusing terms and obscure pathophysiology make this entity quite controversial. Multiple drug allergy syndrome (MDAS) term is used when patients has adverse reactions to two or more structurally unrelated drugs that appear to have an underlying immune-mediated mechanism[1]. In a large hospital based study multi-drug allergy reports varied from 1.7% to 8.7%[2]. Usually such patients when they are orally challenged with culprit drugs or tested with intradermal skin test under supervision, results are not proportionate to their history[3]. Traditionally, de-sensitisation is the recommended method along with course of oral antihistamines and oral corticosteroid to manage such cases of proven multi drug allergy[1]. But de-sensitisation of multiple drugs requires longer period of hospital admission. Injection omalizumab is a humanised, monoclonal anti IgE antibody, FDA approved for management of chronic moderate to severe persistent asthma, widely used and recommended as second line drug for management for chronic spontaneous urticaria[4] and various reports of its efficacy in idiopathic anaphylaxis[5,6]. We report two cases of multiple drug allergy in a patients with history of drug

hypersensitivity syndrome in past who were successfully managed by omalizumabFDA-approved newer biologic agents for psoriasis.

Case report

A 43 year old male, presented to our department with 15 years history of allergy to multiple drugs. He had history of drug induced hypersensitivity syndrome (DIHS) to dapsone during the treatment of Hansen's disease 15 years back for which he was managed by systemic steroid in tapering dose over six months. He developed diabetes following the long course of steroid. There was history of urticaria, generalised itching on various occasions when any drug was prescribed to him for trivial problem like upper respiratory infection, headache, loose motion etc. He was admitted at least five time for anaphylaxis during last 15 years following consumption of different groups of drugs. He was scared of taking any medication. One month ago he had developed furunculoses over right thigh for which he was administered intravenous amoxycillin and clavulinic acid combination along with tab paracetamol. Immediately, he developed anaphylaxis in the form of vomiting, loose motion, hypotension, tachycardia and tachyopnea. There was no history of fever, joint pains, oral ulcers, phtotosensitivity, chronic diarrhoea, unintentional weight loss or any features suggestive of underlying systemic illness. He denied dietary allergy or similar history in the family member. His complete blood count, liver function test, renal function test, blood sugar, serum electrolytes, blood sugar, serum electrolytes, (viral markers: HBS Ag, anti HCV, HIV 1&2 Ab), C3, C4 level, d-dimer, serum ferritin, CXR PA view, USG abdomen were essentially normal. His Serum IgE level (ImmunoCAP,FEIA) was 1235 kUA/l (Reference range < 64 kUA/L). Comprehensive allergy panel tests (ImmunoCAP,FEIA) revealed positivity for wheat, maize, hazel nut, black pepper, spinach, bitter guard (reference range < 0.35 kUA/L). Skin intradermal test with non irritating concentration revealed positivity to Inj ciprofloxcin, ampicillin, gentamycin and amoxycillinclavulinic acid combination and negative for inj ceftriaxone, metronidazole, paracetamol and diclofenac. Oral provocation tests were also conducted which shown positivity to similar group of drugs. Patch tests were also performed which shown positivity to doxycycline , trimethoprim-sulfamethoxazole (septran) , azithromycin and tab paracetamol but negative for cefixime , linezolid , diclofenac , naproxen, etoricoxib , ibuprofen and aspirin. A drug allergy profile for specific antibody was done and was found postitive for Penicillolyl V. The patient was diagnosed as a case of multi drug allergy syndrome. He was managed with Inj Omalizumab 300 mg subcutaneously to which he has responded very well. At the end of 08 months of therapy, he is now asymptomatic . He is not having any urticarial episodes or anaphylaxis since then even after provoked with proven allergic drug except trimethoprimsulfamethoxazole as this drug has not been rechallenged due to history of DIHS to dapsone.

Discussion

Traditionally, drug reaction is classified as predictable (type A) consisting of pharmacological expected effects like overdose, side effects, drug-drug interaction and secondary effects while unpredictable (type B) comprising of drug intolerance, drug idio-syncracy, drug pseudoallergy, and immune mediated drug reaction[7] . Immune mediated reaction is further classified into types I–IV hypersensitivity reaction by Gell and Coombs where type I: IgE mediated(e.g urticaria and anaphylaxis); type II: cytotoxic, IgG & IgM mediated(e.g haemolytic anaemia); type III: immune complex mediated (serum sickness); type IV: Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), drug rash with eosinophilia and systemic symptoms/druginduced hypersensitivity syndrome (DRESS/DIHS)[8]. Skin testing by prick test or intradermal test is recommended for type I hypersensitivity reaction. This is not recommended for other type of immunological drug reactions. Penicillin is the only drug for which skin testing is validated till now. Skin testing to other drugs, although not validated or standardized, can be considered using published non- irritating concentrations[9]. Oral drug challenge is the ultimate way to know the drug allergy but this can not be used in patients who had severe life threatening drug reaction in the recent past like SJS/TEN or DIHS/DRESS. The definitive way of management of multidrug allergy is not well studied in the literature. Desensitisation is the most common way to deal such patients. But this is very frustrating and time consuming for the patients as well as for the physician. Omalizumab binds to free IgE in the blood and interstitial space, forming biologically inactive IgE complexes that are unable to bind to Fc RI on the surface of mast cells and basophils, thereby reducing trigger to mast cell and basophil degranulation and the subsequent inflammatory cascade. By forming inactive complexes with IgE, omalizumab can also indirectly bind and sequester free allergens and possibly autoallergens such as thyroperoxidase and double-stranded DNA, which can bind to the sequestered IgE. There is also an important consequence of free IgE sequestration by omalizumab, which is the downregulation of Fc RI on the surface of mast cells and basophils, and a subsequently reduced sensitivity and/or responsiveness of these cells to allergens or activating autoantibodies[10,11] . Patients have been managed with omalizumab who had history allergy to aspirin, latex, insulin, carboplatin. There are reports of effectiveness in food allergy like allergy to peanut, milk and egg and multidrug allergy following drug hypersensitivity syndrome[12] . Our case had history of DIHS. The multi drug allergy could probably be explained by the consequences of dysregulated immunity which have altered the innate and cell mediated immunity leading to unusual recognition of drugs as allergens and manifesting as allergic reaction

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ALTERNATIVE USE OR OFF LABEL USES OF TNF-α INHIBITORS

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Tumour necrosis factor alpha (TNF-α) is involved in the pathogenesis of various autoimmune disease and key mediator involved in inflammatory response, various pharmaceutical agents which is acting against TNF-α successfully employed for treatment of various auto immune disease. Anti TNF- α agents include infliximab, etanercept, adalimumab, golimumab and certolizumab pegol.

TNF-α produced by monocytes and macrophage,[1] is a type of pro-inflammatory cytokines, having its role in inflammatory reactions and produces its effects mainly by apoptosis, antitumour and anti-viral activities[2] it exists in 2 forms: transmembrane protein (tmTNF) and soluble TNF (solTNF) form. solTNF is produced by cleavage of tmTNF by action of matrix metalloproteinase TNF converting enzyme (TACE, ADAM 17).[3] TNF-α action is mediated by its 2 types of receptors (TNFR). And majority of the effects is governed through type 1 receptor (TNFR1) which is activated by both solTNF as well as tmTNF, but mainly for solTNF. Whereas on the other side type 2 receptor (TNFR2) is preferentially activated by tmTNF.[4] TNFR1 produces inflammatory responses and mediate apoptosis,[5] whereas TNFR2 involve mainly with antiviral immune responses through generation of cytotoxic T-lymphocytes.[6]

Approved indication for TNF- α includes mainly psoriasis, psoriatic arthritis and hidradenitis suppurativa but several case reports and case series in the literature show that the TNF-α inhibitors can be used in the management of a growing number of inflammatory skin conditions as an off-label agents beyond approved indications.

Off label indication of TNF-α inhibitors

Sarcoidosis:

Sarcoidosis is a granulomatous disease having a role of TNF-α in its pathogenesis. Various case report of successful use of Infliximab[7-9] Etanercept10 and adalimumab[11,12] has been described.

Pyoderma gangrenosum:

The exact aetiology and pathogenesis of PG remains unclear, but there is a role of TNF-α in its pathogenesis.[13] Use of Infliximab,[14-16] Etanercept[17] and adalimumab,[18] are described in a number of reports in the treatment of PG.

Hidradenitis Suppurativa:

TNF-α is a key inflammatory marker in the disease's pathophysiology. Adalimumab is already an approved drug for the treatment for HS, but as an Off-label agent infliximab[19] is associated with moderate efficacy and as per another report 6 patient with refractory HS showed improvement with etanercept, 25 mg twice weekly.[20]

Sweets syndrome:

One published report with two patients with sweets syndrome and RA achieved complete skin clearance after etanercept administration.[21]

Vasculitis:

TNF-α is having an important role in ANCA-associated vasculitis by increasing expression of proteinase-3 or myeloperoxidase, which isrecognised by ANCA[22] case report showing efficacy of Infliximab provided remission in patients suffering from small vessel vasculitis with systemic complications.[23] whereas no remarkable benefit has been found with Etanercept.[24]

Giant cell arteritis (GCA):

The tissue concentration of TNF-α is found to be raised in giant cell arteritis leading to this belief that anti-TNF-α agents can be a promising option.[25] In a study of 44 patients with GCA, patient showed efficacy when treated with infliximab.[26]

Behcet's disease (BD):

TNF-α is a central inflammatory mediator in BD.[27] in a study trial of 40 patient of Behcet's disease treated with etanercept, most of them shown efficacy in oral and cutaneous lesions.[28] In another case study, infliximab and methotrexate shown efficacy in patients resistant to etanercept with RA and Behcet's disease.[29] Adalimumab also shown its efficacy in a prospective study of many patients in the treatment of BD.[30]

Atopic dermatitis:

There is more than 50 % improvement from baseline in a study of patient with AD getting treated with infliximab.[t] in another study where patient of AD getting treated with Etanercept showed efficacy and achieved remission after long term treatment.[32]

Pityriasis rubra pilaris (PRP):

Infliximab has shown significant improvement in patient with diagnosis of PRP,[33] Etanercept has also proved to be efficacious in both type I and type II PRP.[t] a study showed efficacy of adalimumab mono therapy as well in the successful treatment of PRP.[35]

Lichen planus (LP):

TNF-α is an inflammatory mediator involved in pathogenesis of AA. Severe erosive LP has improved with Etanercept.[36] Adalimumab also has been reported to be efficacious treatment of LP.[37]

Alopecia areata (AA):

TNF-α inhibitors have been shown to be double edged sword it can be both efficacious as well as it can induce also or worsen AA. [38] A patient with alopecia universalis which was unresponsive to multiple treatments shown improvement with adalimumab.[39]

Necrobiosis lipoidica diabeticorum:

NLD is associated with increased levels of TNF-α and promising result have been found with TNF-α inhibitors treatment,[40] case report showing efficacy with infliximab[41] and etanercept.[42] has been published.

Synovitis, acne, pustulosis, hyperostosis, and osteitis syndrome (SAPHO syndrome):

TNF-α is involved in the development of SAPHO syndrome. Report have been published showing efficacy of TNF-α inhibitors in management of SAPHO syndrome.[t] SAPHO syndrome associated with Palmoplantar pustulosis and HS have also been treated with TNF inhibitors.[44] a report has been published showing efficacy of a combined therapy of etanercept and isotretinoin for SAPHO syndrome associated with acne conglobata.[45] In a report, Adalimumab in combination with isotretinoin has been found to be efficacious for SAPHO syndrome.[46]

Toxic epidermal necrolysis (TEN):

TNF-α and IFN-gamma has a role in pathogenesis of TEN. In a published case series of TEN, Etanercept has shown complete healing.[47] in another case report Infliximab has been effective in treatment of TEN in one patient.[48]

Pruritus:

In a patient of Grover's disease with refractory pruritus who was non-responsive to conventional therapy, etanercept use has been associated with a reduction in pruritus by 98% and the response was maintained for four months.[49]

Keloid:

TNF-α along with fibro-genic factors has a role in the pathogenesis of keloids. A case report has been published showing therapeutic efficacy of Etanercept in Keloid.[50]

Erythema nodosum leprosum (ENL):

Both infliximab and etanercept has been found to have a good effect in ENL.[51] Infliximab (5 mg/kg) was used successfully in a case of refractory ENL not showing any benefit to conventional drugs including prednisone, pentoxifylline, and thalidomide, and no further episode of ENL were described in a follow up period of 1 year following two infliximab infusion at week 2 and 6.[52]

Other Dermatologic Diseases: [53]

Promising results have also been ascertained in the treatment of multicentric reticulohistiocytosis,[54] eosinophilic fasciitis,[55] panniculitis,[55] cicatricial pemphigoid,[56] aphthous stomatitis,[57] Sneddon–Wilkinson disease,[58] dermatomyositis,[59] and scleroderma[60]. These are largely limited to single case reports and small series.

Conclusion:

TNF has a unique role in the initiation and maintenance of inflammatory reactions, TNF inhibitors is an important weapon in the treatment armamentarium of a dermatologist because of its high efficacy TNF inhibitors are a promising group of modern drugs having a role in various diseases. there is growing evidence that TNF inhibitors may be effective in the treatment of numerous inflammatory disorders of the skin beyond their currently approved indications, but most of the evidences available in the form of case reports and uncontrolled case series. This depicts the need for future larger scale studies. Therefore, therapeutic efficacy of these drugs is still unknown. Further studies and trials are required to develop new therapeutics options We expect that the off-label use of biologics will continue to grow in the field of dermatology

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TOPICAL TOFACITINIB IN MANAGEMENT OF VITILIGO

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INTRODUCTION

Vitiligo is a common immune-mediated disorder. It is characterized by welldemarcated white macules and patches that develop due to melanocyte destruction. The condition is seen equally in both sexes. (1) Vitiligo patches can have a deep psychological impact on the patient, and they are often treated as social pariahs by the society.

Clinically, vitiligo is most commonly classified into segmental or nonsegmental vitiligo (2). Nonsegmental vitiligo is bilateral and crosses the midline. Segmental vitiligo (linear, band-like or blaschkoid distribution) is often unilateral, rarely crossing the midline. It has an earlier age of onset and is less responsive to medical therapy.

Diagnosis is usually made clinically but at times in case of a dilemma, a wood's lamp comes in handy, which accentuates amelanocytic tissue due to the autofluorescence of underlying dermal collagen. While rarely needed, skin biopsy can be used to confirm the diagnosis.

The pathology of Vitiligo is multifactorial and there is no one theory that holds the most merit over others (3). One of the theories involves the release of IFN from activated Tcells. This occurs through the JAK (Janus Kinase) pathway. This is also where tofaticinib comes

into play as it acts on inhibiting this very same pathway.

CXCL-9 and CXCL-10 recruit CD8+ Tcells to the skin, JAK signaling is activated in CD8 T cells. Thisresultsin increased INF□ release from CD8+ Tcells followed by keratinocyte production of CXCL9 and CXCL 10. These target the stressed melanocytes driving depigmentation.
As IFN signal transduction occurs through JAK1 and JAK2, blockade of JAK with tofaticinib inhibits IFN□ signaling, thereby downregulating CXCL 10 expression, leading to repigmentation.

Thus, JAK inhibitors are seen to be effective due to their blockade of INF-□ and CXCL-10 signaling.

Tofaticinib is a JAK-1 and JAK-3 inhibitor. Oral formulation is currently US FDA approved for use in Psoriatic Arthritis, Rheumatoid Arthritis, Ulcerative Colitis and Myeloproliferative disorders. Apart from these, many dermatological diseases have been seen to benefit patients such as Palmoplantar psoriasis, alopecia areata, atopic dermatitis and vitiligo. (4)

Topical tofaticinib is used as a 2% cream formulation initiated as twice a day therapy. It stands out particularly due to its efficacy being comparable to its counterparts such as topical corticosteroids (TC) and topical calcineurinin inhibitors (TCI). Added advantage being it does not share their side effects. Long term TC use leads to skin atrophy and surrounding hypopigmentation. Similarly, TCI come with its own set of black box warning from the US FDA for the risk of causing cancer, particularly lymphomas and localized burning at application site. (5)

Review of literature

Tofaticinib has been widely studied in oral formulation for various indications, but there have been very few studies in topical formulation, which have been mainly used in alopecia areata and atopic dermatitis, with very few case reports for use in vitiligo.

Mobasher et al evaluated 16 patients with vitiligo where they received 2% tofaticinib cream. All patients were from different ethnicities and therefore patients with varying Fitzpatrick skin type ranging from II-IV were studied at the same time. 3 patients had focal facial vitiligo, 2 had focal non-facial vitiligo and 11 patients had generalized vitiligo. All patients except 1 had previously received either topical corticosteroid, topical calcineurinin inhibitors and/or phototherapy. Thirteen of the sixteen patients showed repigmentation of varying degrees, 2 showed no change and 1 patient showed slow progression of the depigmented patches. Patients with facial lesions and Fitzpatrick type IV-VI showed better improvement. Only 1 patient reported acneiform eruption after onset of treatment

which resolved on discontinuation of the drug. One patient reported subtle skin contour changes on his chin which led to discontinuation of treatment after 2 weeks. (6)

In an institutional study by Mckesey et al, 11 patients with vitiligo were treated with 2% tofaticinib cream twice daily in combination with NBUVB thrice weekly over 4 months. All patients had been previously treated with TCI or TC along with either NBUVB or sun exposure. The mean facial VASI was 0.80 (range 0.1- 2.25) at baseline and 0.23 (range 0.03-0.75) at follow-up. There was a mean improvement of 70% (range 50% to 87%) among the 11 patients. The topical formulation also proved to be economical to the patients as compared to the oral drug. Facial lesions were chosen in this study because repigmentation is seen better for these patches with topical tofaticinib. (7)

A four-year-old boy showing segmental vitiligo over his right chin and anterior neck with an abrupt onset before 6 months was put on topical tofaticinib therapy. He had already used a TC twice daily for 6weeks without much relief. His parents were concerned mainly due to the lesions being on the face and the fact that he was about to start elementary school later that year. He was also put on tofaticinib 2% + NBUVB phototherapy thrice weekly. Freckling was observed within 4 weeks. At 6months, he showed complete repigmentation. He was then advised a taper which he discontinued in a month. There were no new patches for the following 6 months after which he showed some depigmented macules and was advised to restart the prior regimen. He did not show any adverse effects to the treatment. (8)

Another 17yr old boy with non-segmental acrofacial vitiligo since the last 15 yrs had reportedly exhausted all his treatment options. He was given oral and topical corticosteroids, topical tacrolimus, oral vitamin D and antioxidants. He was then given a combination therapy of topical 2% tofaticinib twice a day along with NBUVB thrice a week. The total dose for the face vitiligo was 1,000 mJ/cm2, starting with 200 mJ/cm2 and increasing by 50 mJ/cm2 each session. Considerable repigmentation was seen over facial lesions over a period of 9months. The patient had mild episodes of erythema and Acneiform eruptions during the course of treatment. (9)

Another study showed a 17-yr old girl with a history of hypopigmented patches over bilateral upper eyelids with associated leukotrichia since 4months. She had a past history of using topical tacrolimus 0.1% without much improvement. She was put on topical tofaticinib 2% twice a day therapy. There was no associated NBUVB as the treatment was ongoing in the summer months. She showed improvement with some repigmentation in 2 months and near complete repigmentation in 5months over both eyelids and eyelashes. (10)

DISCUSSION

It seems to be evident from the above-mentioned studies that long term use of topical tofaticinib is well tolerated over facial skin and shows good results. Some studies show efficacy of topical formulation to be comparable to the oral drug. This makes the treatment much easier considering the long list of investigations required before initiation of the oral drug. In developing countries, the cost of these investigations becomes a major hindrance for doctors as well as the patients in starting the drug. It also avoids the systemic side effects associated with the oral drug.

Topical tofaticinib does come with its set of drawbacks as seen from the few studies that have been performed on it. Itshows slower and unreliable results over non-facial skin. This is presumed to be due to a thicker epidermis and also inconsistent exposure to UV light of other bodily parts. (11) Also, as of now there are no US FDA approved formulations of topical tofaticinib and hence doctors have to rely on compounding pharmacies. Varying strengths may lead to differing results. Some studies also report transient acneiform eruptions, erythema, folliculitis, pruritis and surrounding hyperpigmentation (4,6).

Currently topical tofaticinib is only available from compounding pharmacies. In the Indian scenario, it is usually formulated in two concentrations- 1) 10 tablets of tofaticinib in 25gm of base 2) 30 tablets of tofaticinib in 10gm base. Base can either be white soft paraffin (cream/ointment) or alcohol (lotion). The more common 2% formulation costs around Rs 550 to 600/- for 1 ointment or lotion.

Best results are observed when using topical tofaticinib along with NBUVB. It is thought that tofaticinib helps in reducing the local inflammation while NBUVB trigger melanocyte activity inducing colour formation. Therefore, if studies are performed with larger sample sizes and also over non facial skin, topical tofaticinib can prove to be of value in managing vitiligo.

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QUIZ

Dr. Shekhar Neema
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1. Which of the following is a selective Tyk2 inhibitor?

a. Devucravacitinib
b. Abrocitinib
c. Filgotinib
d. Updacitinib

2. Which of the following is a selective JAK1 inhibitor?

a. Upadacitinib
b. Tofacitinib
c. Baricitinib
d. Ruxolitinib

3. Which of the following biologic inhibit IL17 A and F?

a. Secukinumab
b. Ixekizumab
c. Bimekizumab
d. Briakinumab

4. Which of the following biologic is safe for use in pregnant women?

a. Certolizumab
b. Infliximab
c. Rituximab
d. Adalimumab

5. Which biologic should not be used in patient of psoriasis with concomitant inflammatory bowel disease?

a. Secukinumab
b. Adalimumab
c. Infliximab
d. Ustekinumab

ANS : 1 A; 2 A; 3 – C; 4 – A; 5 -A

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