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Updates and new medical treatments for vitiligo

- Vitiligo is the most common disorder of depigmentation, and in 2012 its worldwide prevalence ranged from 0.06-2.28%

- Melanogenesis is determined genetically but is influenced by several intrinsic and extrinsic factors :

  - The intrinsic factors are released by surrounding cells, including *keratinocytes, fibroblasts, inflammatory, neural and endocrine cells*

  - extrinsic factors include *ultraviolet radiation and drugs*

- positive regulators of melanogenesis: **L-tyrosine and L-DOPA** (pigment precursors), **ultraviolet radiation and the melanocortin 1 receptor**

pathogenesis of vitiligo

- **Autoimmune hypothesis** :
- association with other autoimmune diseases
- the high level of *antibodies against melanocytes* found in **10%** of patients with vitiligo
- Inflammatory infiltrate that is observed at the margin of active lesions

- **Biochemical theory :**

  - *damage to melanocytes is due to an imbalance in oxidative stress; a higher level of hydrogen peroxide in patients with vitiligo and increased superoxide dismutase activity reinforce this theory*

- **Melanocytorrhagy theory :**

  - *defective cell adhesion leads to detachment and transepidermal loss of melanocytes with exposure of autoantigens and activation of the immune system leading to melanocyte injury*

- **convergence theory :**

  - *Combination of genetic background, susceptibility to environmental changes, altered epidermal microenvironment, an intrinsic melanocyte defect and an autoimmune response*

Pharmacological treatment

- ***Topical treatment***
- ***Corticosteroids***

- modulation and inhibition of inflammation
- **potent** (betamethasone valerate) or **very potent** (clobetasol propionate), are considered first-line therapy for vitiligo
- The sun-exposed areas have a better response to treatment
- In face, neck, genitals or intertriginous regions where absorption may be higher and more side effects may present, *topical calcineurin inhibitors (TCI) or lower potency steroids are preferred*
- The application of daily TCS for up to **3 months** is recommended . After that, an intermittent regimen can be used for **up to 6 months**, and if no response is seen after **3-4** months, the application should be discontinued

- In a meta-analysis, Njoo *et al* reported the effectiveness of TCS in localized vitiligo, measured as the percentage achieving ≥75% repigmentation, which was comparable with potent (56%) and very potent (55%) TCS.(*To increase the probability of a therapeutic response when TCS is used as monotherapy, very potent TCS may be preferred*)
- The side effects of TCS include ***atrophy, striae, telangiectasias, hypertrichosis and acneiform reactions***. The most frequent local side effect is atrophy, which depends on diverse factors, including age, site of application, the potency of the TCS and the presence of occlusion
  - **SO** → *Corticosteroid holidays and tapering from high to mild potency* can be used to minimize side effects

- Kwinter *et al* performed a retrospective study in pediatric patients with vitiligo treated with moderate to high potency TCS:

cortisol levels were abnormal in 29% of patients, and the potential risks associated were lesions located in the head and neck

mometasone furoate and methylprednisolone acetonate are preferred

Calcineurin inhibitors

- They function by inhibiting calcineurin, a pro-inflammatory protein in lymphocytes and dendritic cells that induces the transcription of **IL-2 and TNF-α**
- recommended for the ***head and neck*** areas as they have less side effects, mainly the lack of atrophy risk
- *Moderate daily sun exposure is recommended during treatment*
- The side effects of TCI include burning sensation, pruritus and increased susceptibility to infection (herpes simplex and molluscum contagiosum)

- The efficacy of TCI as monotherapy in a systemic review and meta-analysis by Lee *et al (2019)*, demonstrated ≥25% repigmentation in 55%, ≥50% repigmentation in 38.5%, **and ≥75% repigmentation in 18.1% of patients**. The results in children were ≥25% repigmentation in 66.4% and **≥75% repigmentation in 31.7% patients.**
- A better response was achieved on the face and neck followed by the trunk and extremities and *the least response was observed in the hands and feet*

- Ebrahim *et al (2020)* performed a study comparing the application of *tacrolimus 0.1% alone or in combination with microneedling* in patients with localized stable vitiligo.
- Both groups applied tacrolimus daily, but the combination group also received microneedling and tacrolimus application every 2 weeks for up to 12 sessions.
- The results exhibited earlier pigmentation and *≥75% pigmentation in 50.00% of patients in the combination group* compared with 29.92% in the monotherapy group

- Abd-Elazim(2020) *et al* studied a randomized placebo-controlled trial in patients with stable generalized vitiligo. In each patient, three lesions of similar size were chosen. *One lesion was treated with tacrolimus 0.03% daily, another with a combination of monthly microdermabrasion and daily tacrolimus 0.03%, and the last was treated with placebo.*
- The **combination group achieved moderate to excellent response (≥50% repigmentation) in 65.7%** of lesions compared with monotherapy with tacrolimus in 25.8% of lesions

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Vitamin D3 analogs

- Useful as **adjuvants** to other therapies due to their immunomodulatory effects inhibiting T-cell activity, enhancement of melanocyte development and induction of melanogenesis
- The maximum recommended dose is *100 g weekly on 30% of the body surface* with the combination of calcipotriol 0.005% and betamethasone 0.05% for 4 weeks using the ointment and 8 weeks for the cream

- **The transdermal delivery of drugs may be increased using microneedling.**
- Ibrahim *et al (2019)* studied the combination of microneedling with calcipotriol 0.05 mg/g and betamethasone 0.5 mg, compared with microneedling with tacrolimus 0.03%.
- The patients received both therapies in two different lesions. The creams were applied daily and **microneedling was performed every 2 weeks for a maximum of 12 sessions.**
- The combination with calcipotriol and betamethasone exhibited 76-100% repigmentation in 60% of patients compared with 32% in the combination with tacrolimus

combination of calcipotriol and betamethasone with microneedling was superior and also effective in sites resistant to therapy (elbow, knees, extremities and acral area)

Pseudocatalase/superoxide dismutase

- Oxidative stress and H2O2 are believed to play roles in vitiligo. These are ***toxic to melanocytes, inhibit tyrosinase, and cause the deactivation of catalase***
- In a study performed in a pediatric population by Schallreuter *et al*, patients were treated with twice daily application of **pseudocatalase PC-KUS** activated with low-dose nb-UVB.
- The results demonstrated a halt of disease progression in 70/71 patients; >75% repigmentation was achieved in 92.9% of children with lesions located on the face/neck, 78.6% on the trunk, 72.7% on the extremities and 9.4% on the hands/feet

- Information on side effects and safety of pseudocatalase is lacking . **Current data are not in favor of an additional effect of topical catalase compared with UVB alone**

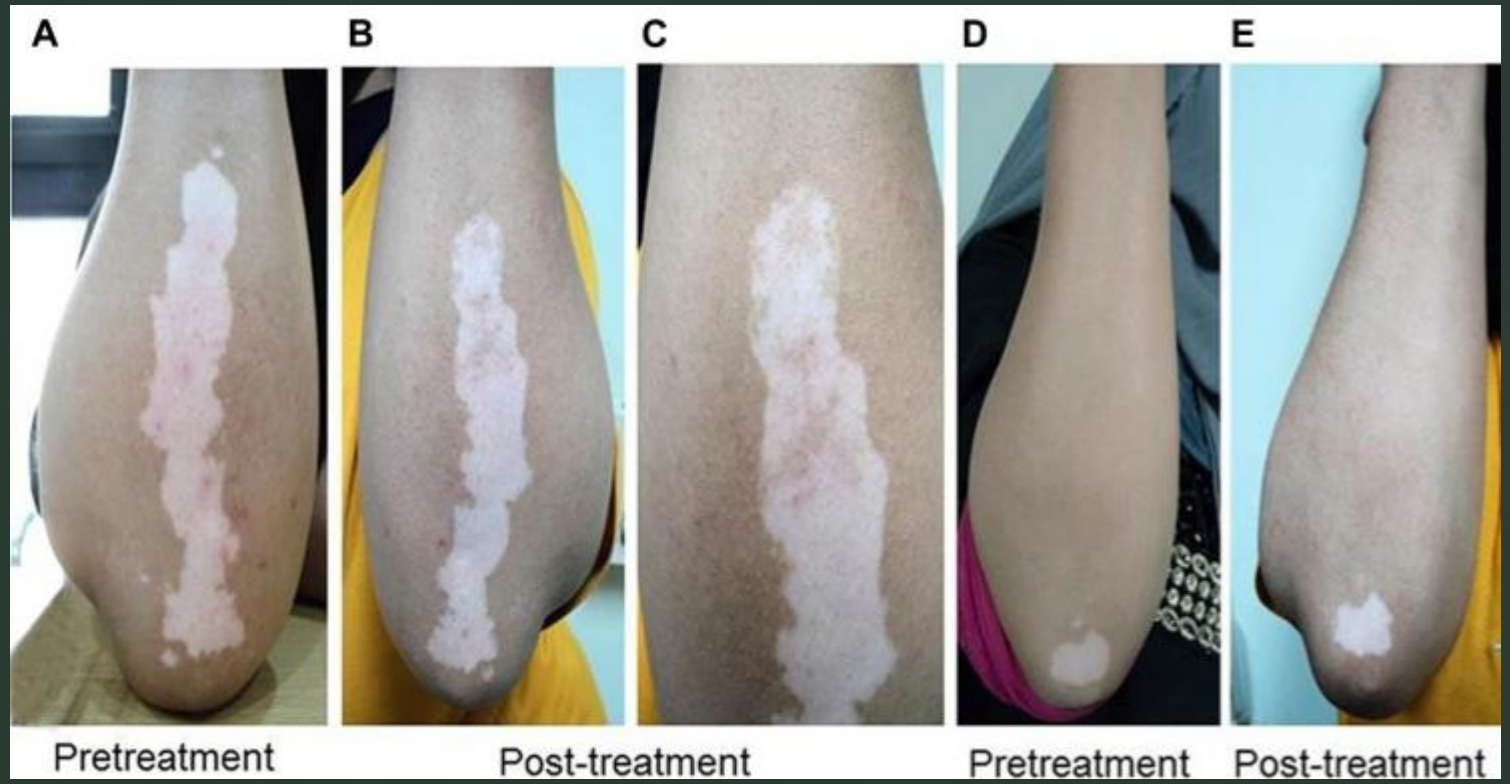
Topical 5-FU

- The observation of hyperpigmentation following therapy with this drug led to its use in vitiligo

- stimulation of follicular melanocytes with **migration** during epithelization and by increasing the number of melanosomes in keratinocytes

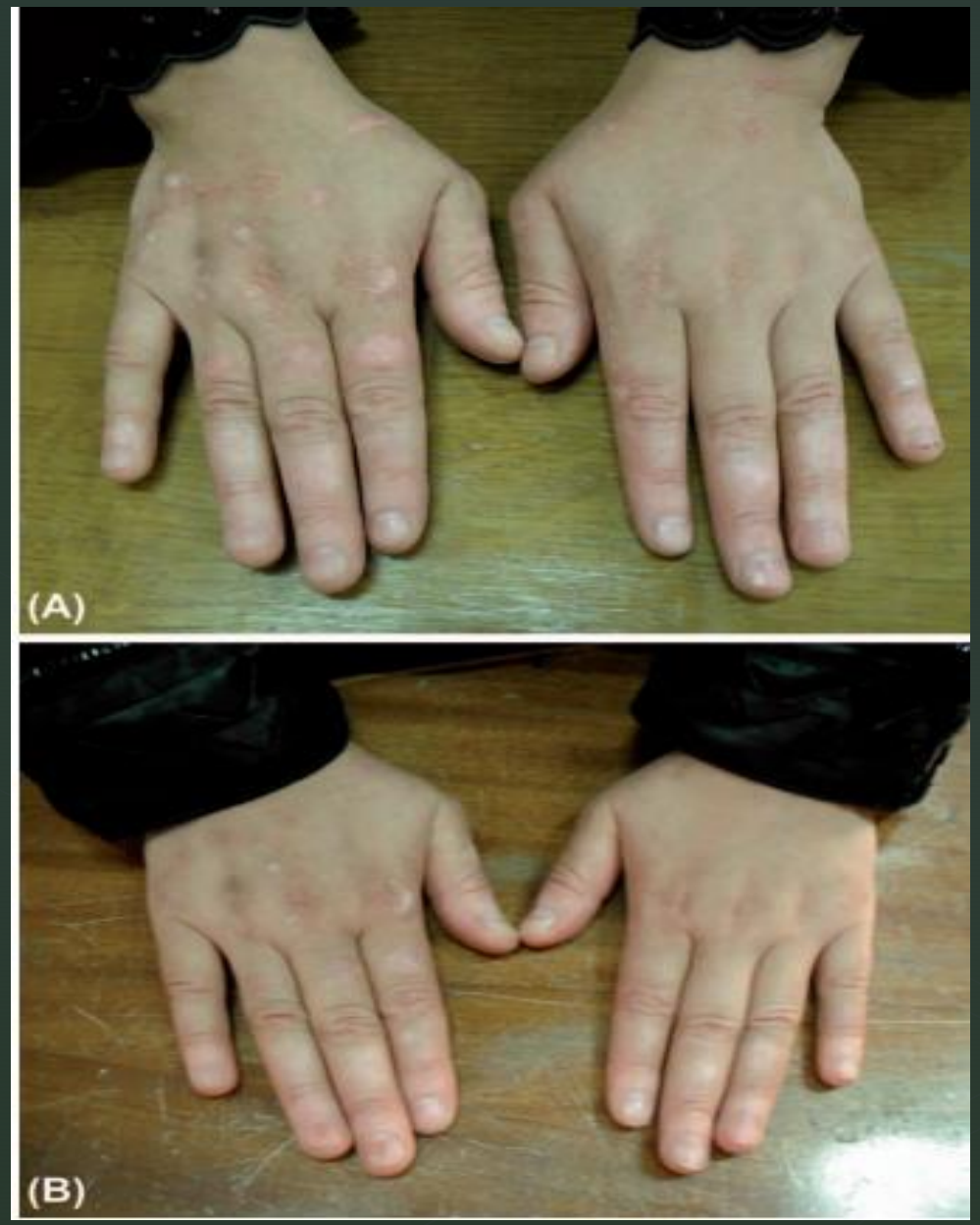
- **The efficacy of monotherapy with 5-FU** has been reported by Tsuji-Takuo and Hamada . A 5-FU cream was applied following epidermal abrasion, once daily for 7-10 days and >75% repigmentation was observed in 64% of patients
- Abdelwahab *et al(2020)* assess the effect of **5-FU in monotherapy compared with its combination with ablative erbium: YAG** (2,940 nm) laser in non-segmental vitiligo. Erbium: YAG laser was applied using the surgical handpiece with a spot size of 4 mm and a fluence of 60 J/cm2. A total of two to three passes were given with an endpoint of pinpoint bleeding, receiving three treatment sessions every 4-6 weeks.
- 5-FU cream was used daily for 2 weeks after each session. *The range of repigmentation in the combined treatment was 0-70%, with <25% repigmentation in 73.3 and 50-75% repigmentation in 10% of patients*

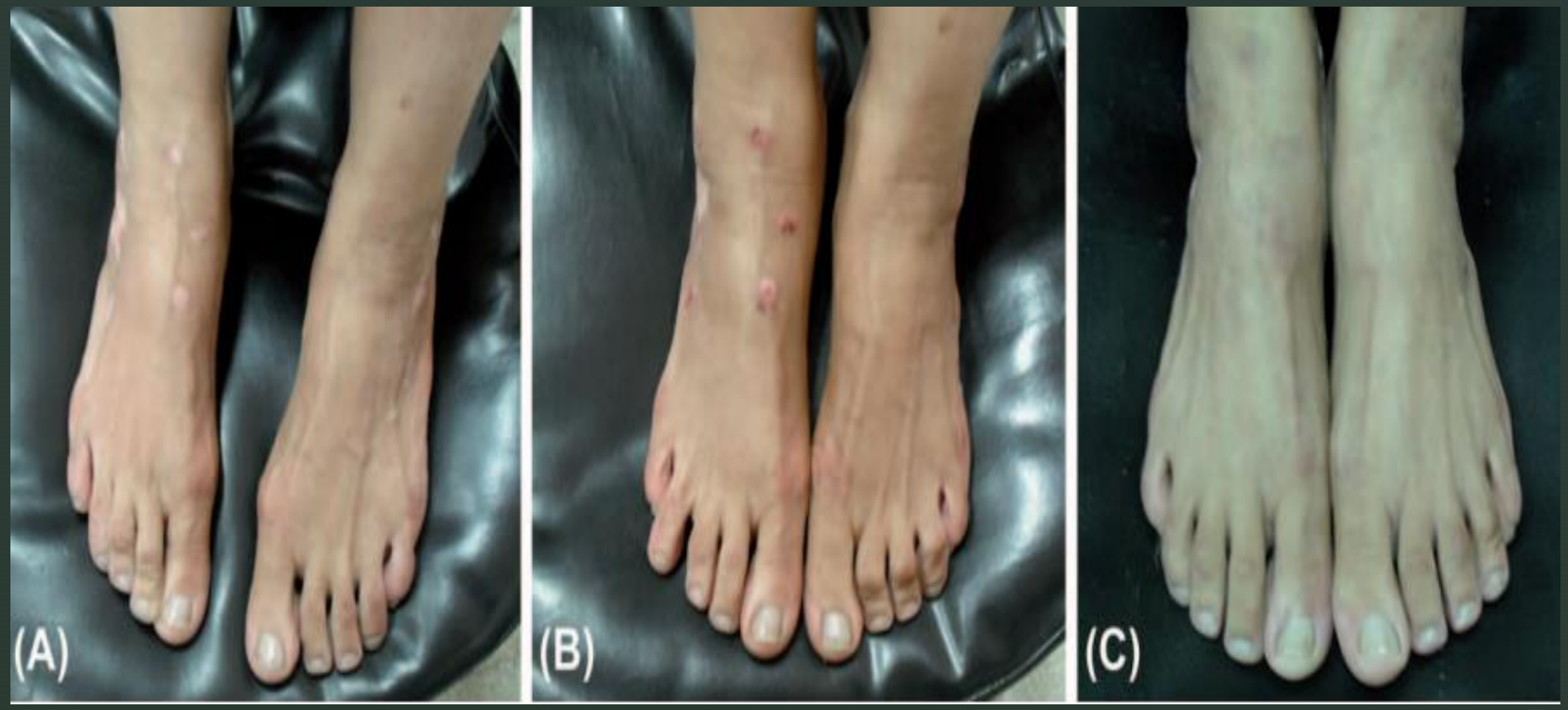
treatment with Er:YAG laser and 5-FU cream



- **CO2 laser with topical 5-FU** was studied in acral vitiligo by Mohamed *et al .* The laser was employed at a rate of 1-2 Hz in level 2 pulse control and a power of 0.9 W to deliver single pulses using the single-spot handpiece. In the abraded area, 5-FU was applied daily for **7 days**, and CO2 laser sessions were repeated monthly until healing or a **maximum of 5 sessions**.
- ***The results demonstrated >75% repigmentation in 49.8% of the lesions and 50-75% repigmentation in 6.1% of the lesions***

after 5 sessions of CO 2 laser plus 5FU. The response was complete re-pigmentation of the lesions on the dorsum of hands and good, excellent to complete re-pigmentation of some lesions on the fingers. The periungual lesions of fi ngers showed no response.

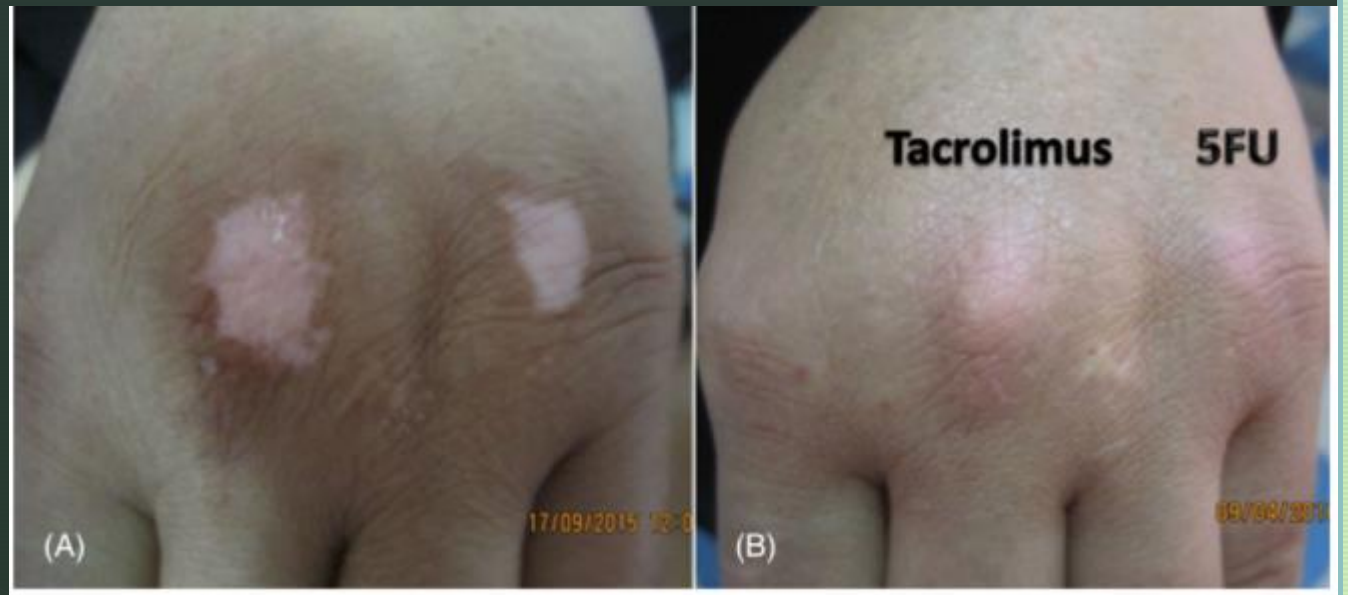


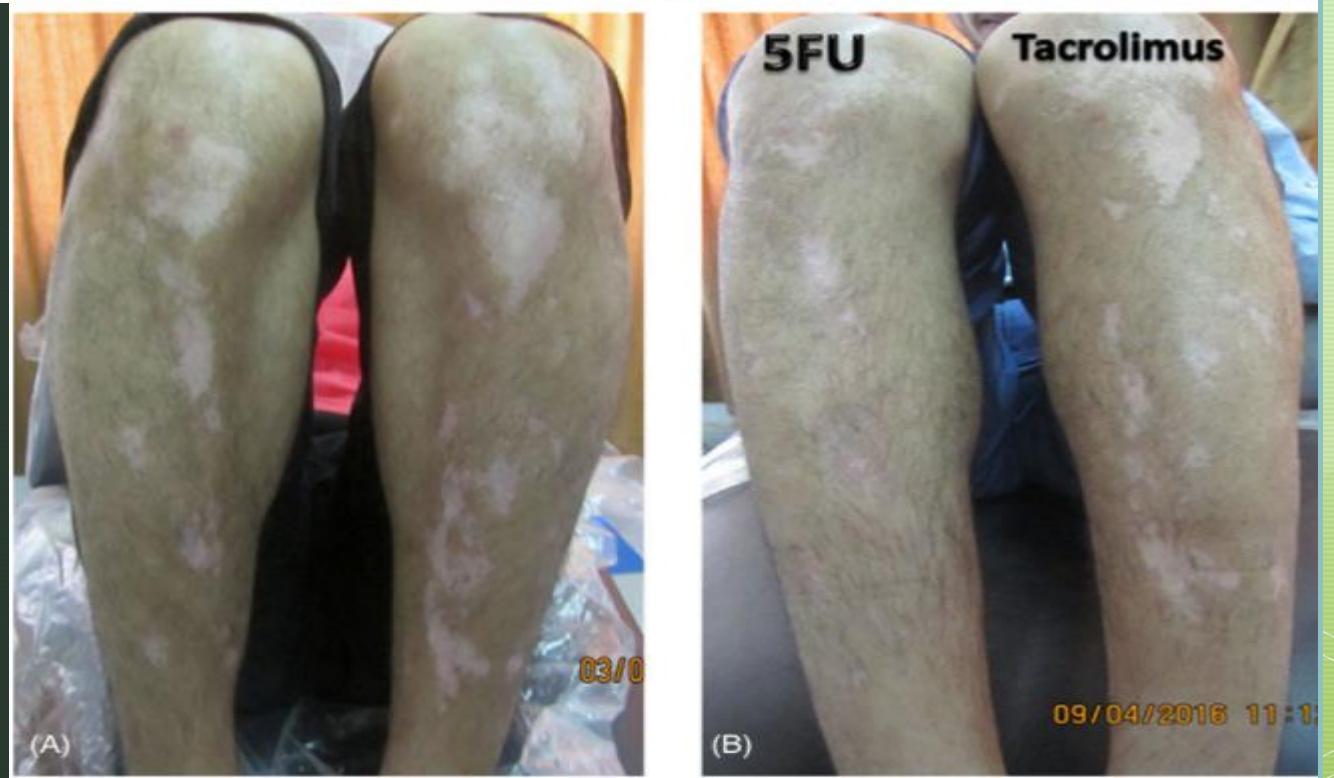


[B] the lesions of the same patient after 5 days of 5FU cream application following one pass of CO 2 laser superficial ablation. [C] Good response of the same lesions after 5 sessions of treatment.

- Mina *et al* performed a study **comparing microneedling with either topical tacrolimus or topical 5-FU**.
- In each patient, two patches of vitiligo were treated. First, microneedling with a Dermapen at the lowest speed and a depth of 0.25-0.50 mm according to the area was performed, then one patch was treated with a solution of 5-FU (50 mg/ml) and the other with tacrolimus 0.03% ointment.
- Daily application of either 5-FU or tacrolimus for 2 weeks was continued. Microneedling was repeated every 2 weeks for a maximum of 12 sessions.
    - **The reported efficacy with the combination of 5-FU was >75% repigmentation in 48% of patients** compared with 16% in the tacrolimus group

Microneedling+ 5FU or Tacrolimus





Methotrexate (MTX)

- Decreasing the number of T cells producing TNF-α, consequently having *anti-inflammatory, immunomodulatory and antiproliferative effects*
- In a recent **case report** in a patient with stable vitiligo, significant repigmentation was observed following treatment with topical **MTX 1% gel** applied twice daily for 12 weeks, along with folic acid supplementation

Prostaglandin F2 alpha analogs

- Hyperpigmentation seems to be due to an **increase in melanogenesis**
- Kanokrungsee *et al (2021)*: the efficacy of **Bimatoprost 0.03%** (2015). **Bimatoprost ophthalmic solution 0.03% can be used as one drop for 2 cm2 body surface area twice a day).**solution was assessed in patients with non-segmental facial vitiligo compared with **tacrolimus 0.1% ointment**.
- Both topical drugs were applied twice daily for 12 weeks.
  - **Repigmentation was observed in 60 and 50% of the patients in the bimatoprost and tacrolimus groups, respectively.**
  - In addition, >50% repigmentation was achieved in 20% of patients in the bimatoprost group compared with 10% in the tacrolimus group, although no statistically significant differences were observed between the two groups

Basic fibroblast growth factor (bFGF)-derived peptide

- Through melanocyte migration
- Kamala Subhashini *et al (2015)* in a comparative study in patients receiving monotherapy with either **bFGF 0.1% solution** or betamethasone valerate 0.1% ointment. Both groups applied their respective drug daily for 16 weeks.
- **The bFGF group reported >75% repigmentation in 45% of patients**, 50-75% repigmentation in 35 compared with 0, 7 respectively, in the betamethasone group.

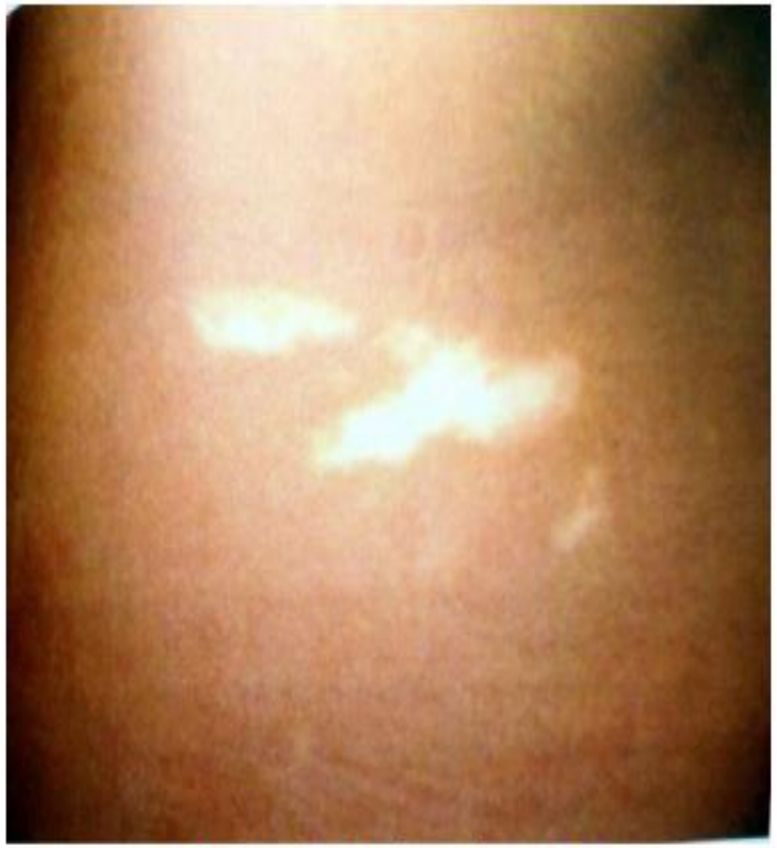


Fig no.2: Before bFGF treatment

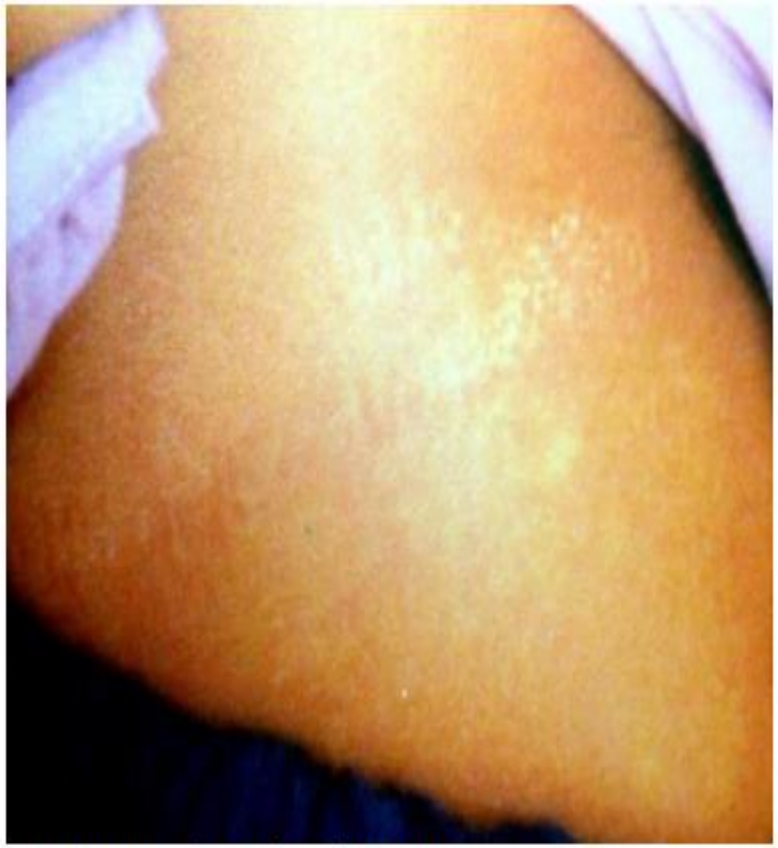


Fig no .3: After bFGF treatment

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Trichloroacetic Acid

Original Article

Trichloroacetic Acid in Different Concentrations: A Promising Treatment Modality for Vitiligo

Ahmad Nofal, MD,* Mohamed M. Fawzy, MD,† and Rania Alakad, MD*

BACKGROUND Despite the recent advances in the treatment of vitiligo, results are still largely unsatisfactory and many patients show either weak or no response to treatment. Few clinical trials have investigated the use of trichloroacetic acid (TCA) to induce repigmentation in stable vitiligo.

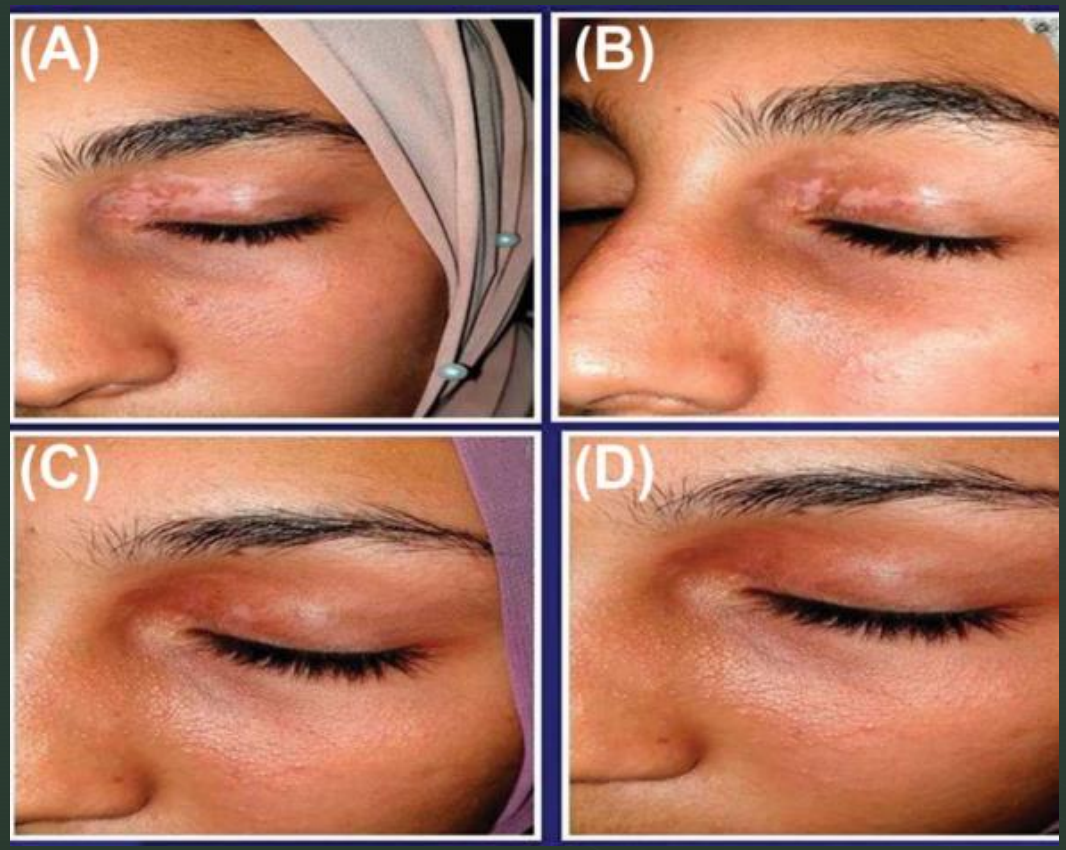
OBJECTIVE To evaluate the efficacy and safety of TCA, in different concentrations, for the treatment of stable localized vitiligo.

METHODS The study included 100 patients with acral/nonacral stable vitiligo. Trichloroacetic acid was applied, as a monotherapy, to the vitiliginous patches at different concentrations according to the treated site every 2 weeks until complete repigmentation or for a maximum of 6 treatment sessions. Follow-up was done every month for 6 months to detect any recurrence.

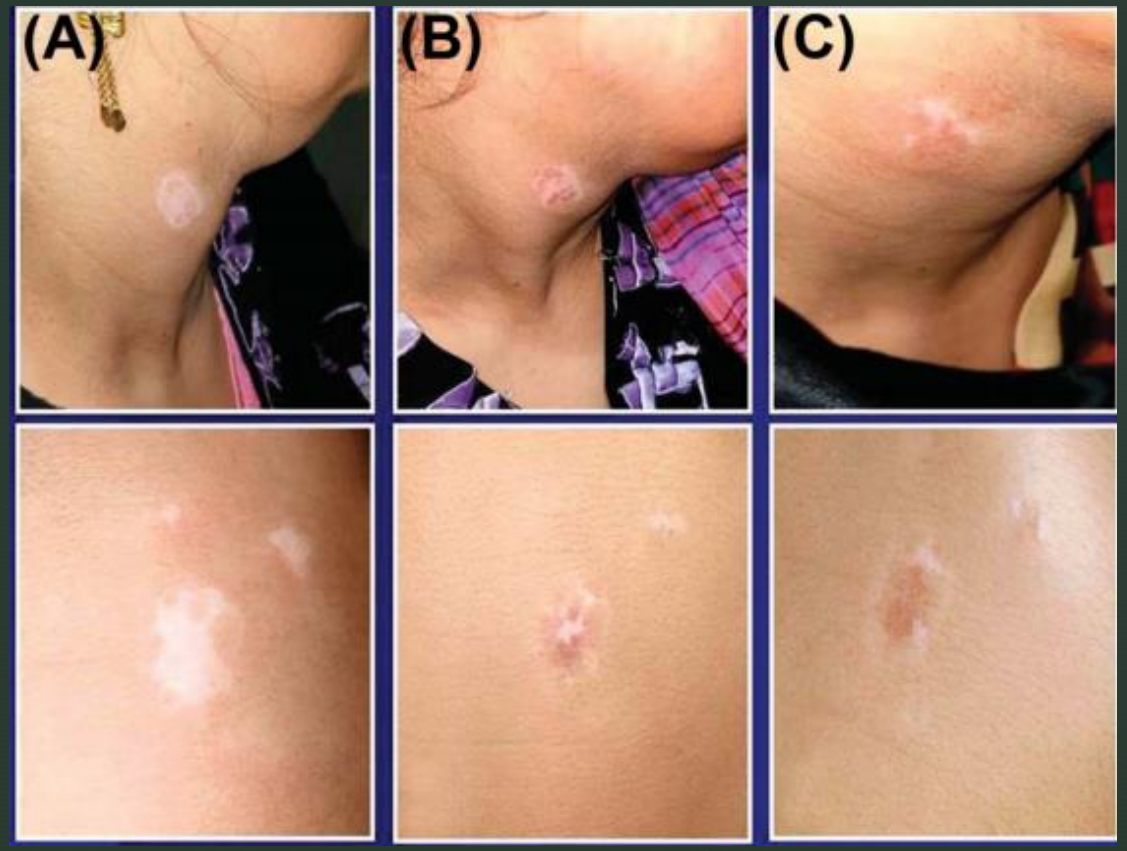
RESULTS Eyelid vitiligo showed the highest response to TCA treatment (excellent response in 80% of cases), followed by the face, trunk, and extremities. Lower response rates were noticed in the hands and feet vitiligo. Adverse effects were transient and insignificant in few patients.

CONCLUSION Trichloroacetic acid seems to be a potential, cost-effective, well-tolerated therapeutic option for the treatment of vitiligo in the adults and pediatric populations.

(A) Before therapy with TCA 30%. (B) After 2 sessions. (C) After 3 sessions. (D) Excellent response after 4 sessions.



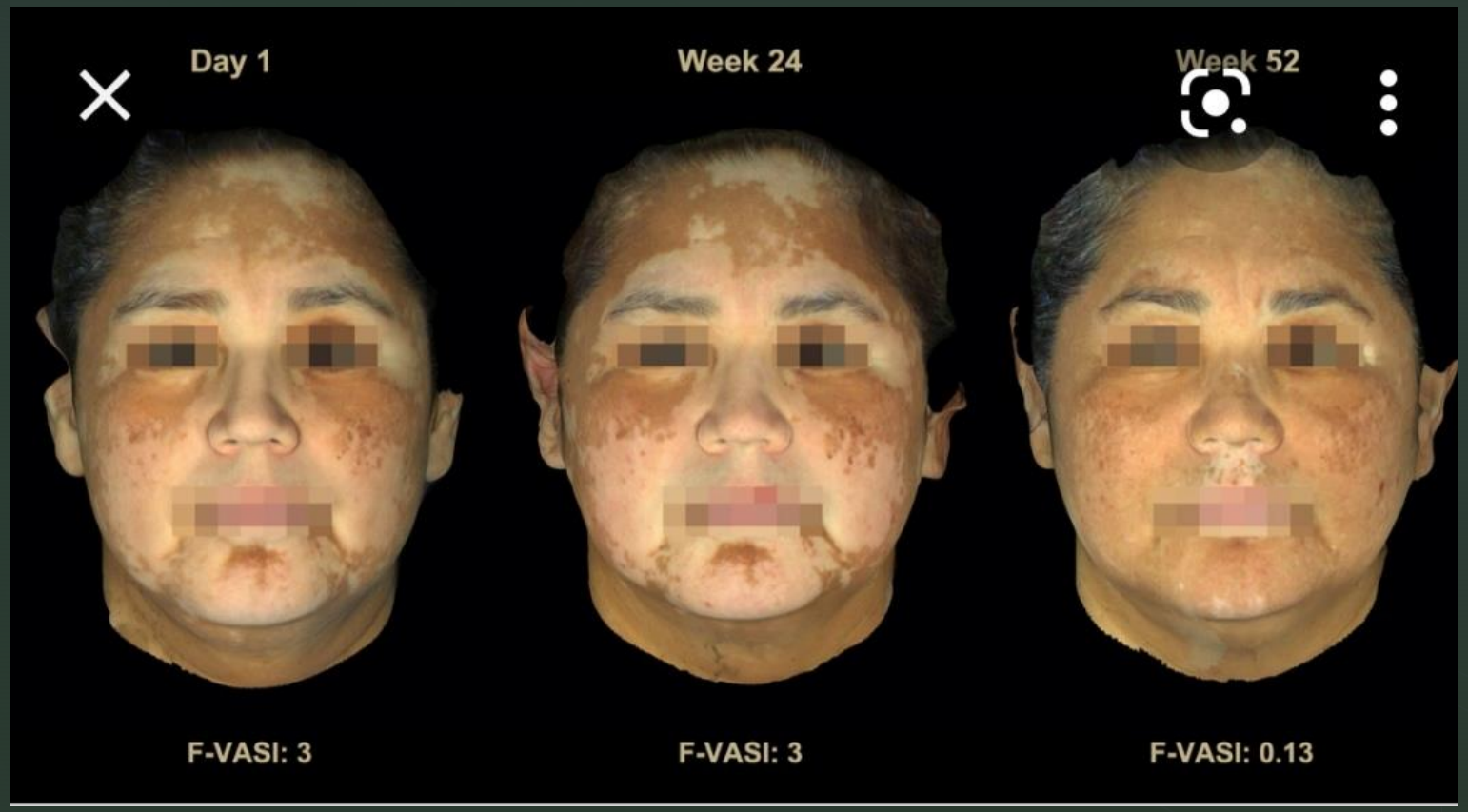
(A) Before therapy with TCA 50%. (B) After 2 sessions. (C) Excellent response after 3 sessions.



Janus kinase (JAK) inhibitors
Tofacitinib and Ruxolitinib

- downregulation of the JAK-STAT pathway, which **decreases IFN-γ**
- A recent phase 2 study by Rosmarin *et al* (2020) evaluated the efficacy and safety of ruxolitinib cream **at three different concentrations (0.15, 0.5 and 1.5%)** compared with placebo, for up to 52 weeks.

- Patients were classified into four different groups of ruxolitinib: 1.5% twice daily, 1.5% once daily, 0.5% once daily and 0.15% once daily. Efficacy was evaluated using the percentage of patients achieving **≥50% improvement in the baseline facial VASI** (F-VASI50). **The ruxolitinib 1.5% once and twice daily** groups achieved a F-VASI50 in 50 and 45% of patients, respectively



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- Mobasher *et al (2020)* performed an open-label study with **Tofacitinib 2% cream twice daily in 16 patients with vitiligo**. Notably, patients were allowed concomitant use of TCS, TCI, supplements, or phototherapy during the study.
- Repigmentation was observed in 81.2% of patients. In addition, >90% repigmentation was observed in four patients
- The side effects of JAK inhibitors include erythema, pruritus, hyperpigmentation and transient acne

Systemic treatment Corticosteroids

- SCS is administrated to treat ***rapidly progressive active vitiligo***. **Pulse therapy** with SCS is preferred to decrease the potential side-effects.
- Patients undergoing therapy with SCS should be monitored for blood pressure, glucose levels, weight, waist circumference and infections, as well as an ophthalmic examination every 6-12 months
- The side effects of SCS are weight gain, transient weakness, fatigue, insomnia, acne, agitation, menstrual disturbances, hypertension, headache, flush symptoms and hypertrichosis

- Kim *et al* also performed a study with **continuous use of SCS** in patients with active vitiligo. Oral prednisolone was given the **first 2 months at 0.3 mg/kg of body weight, the third month at half of the initial dose, and the fourth month at half of the previous dose.**
  - *The results exhibited arrest of vitiligo progression in 87.7% of patients and repigmentation in 70.4% of patients*
- Pasricha and Khaitan used a therapy based on **pulses of either betamethasone or dexamethasone at 5 mg orally for 2 consecutive days every week**; treatments were continued until complete repigmentation or 4 months of continuous treatment with no further improvement.
  - *The results were halt in active disease in 89% of patients with 5 mg dose after 1-3 months and repigmentation was observed in 80% of patients after 2-4 months of treatment*

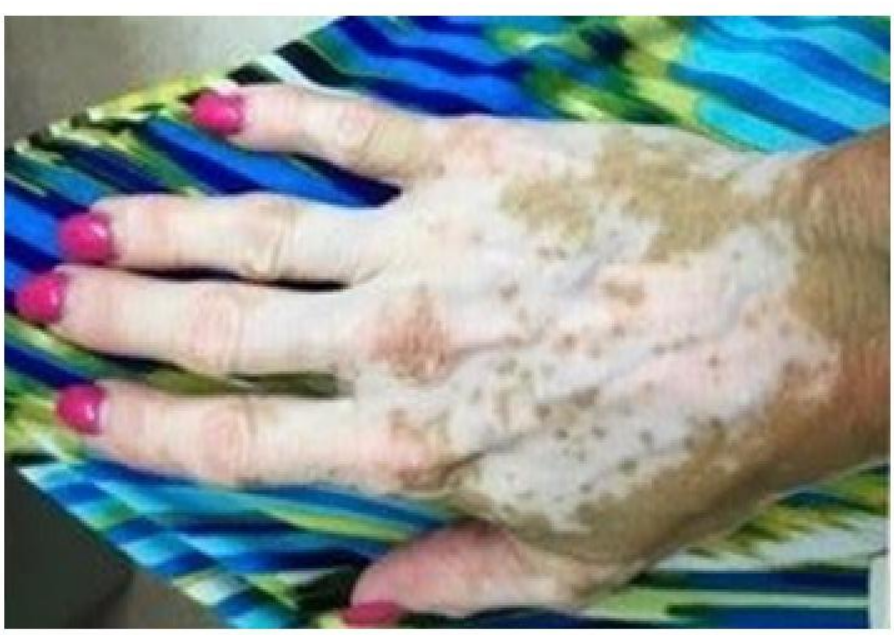
- Kanwar *et al (2013)* reported a retrospective study with a cohort of 444 patients with active vitiligo, using a **low-dose oral mini-pulse therapy with a dose of 2.5 mg/day on 2 consecutive days every week**.
- *Arrest in disease activity was achieved in 91.8% of patients, during follow up 12.25% of these patients experienced one or two relapses in activity*
- Radakovic-Fijan *et al* administering **10 mg of dexamethasone 2 consecutive days for 24 weeks**.
- *The arrest of vitiligo activity was achieved in 88% of patients with active vitiligo*

- Seiter *et al* also implemented a therapy based on pulses but with an intravenous route.
- **Methylprednisolone was intravenously administered for 3 consecutive days at a dose of 8 mg/kg of body weight**. The treatment was repeated at 4 and 8 weeks if tolerated.
  - *Active vitiligo progression was halted in 85% of patients and repigmentation in 71% of patients. Patients with stable vitiligo had no change in pigmentation*

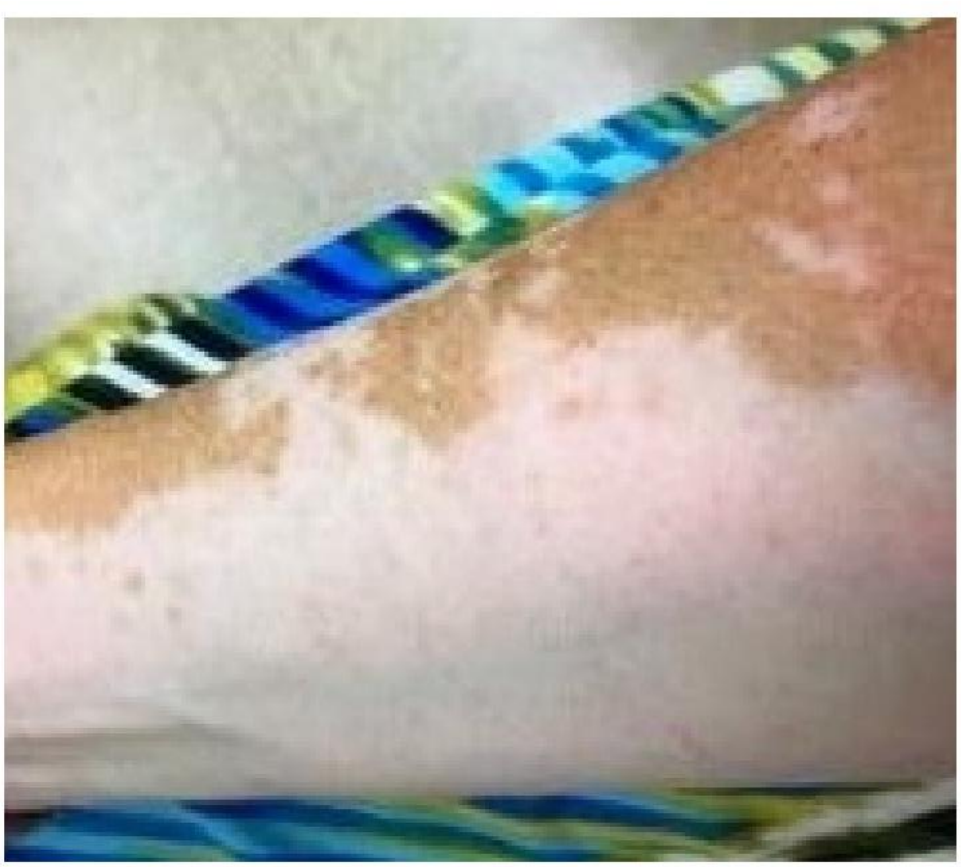
Apremilast

- **A phosphodiesterase 4 inhibitor** that acts by increasing intracellular cAMP
- Apremilast application in vitiligo is due to its immunomodulation properties, increasing cAMP concentration results in the decreased production of pro-inflammatory mediators **(IL-23, IL-17, TNF-α and IFN-γ) and an increase in anti-inflammatory mediators, such as IL-10**
- Huff and Gottwald(2017) used Apremilast **(30 mg twice daily)** in a resistant case for 13 months, and two intramuscular injections of 60 mg of triamcinolone acetonide were simultaneously applied. The results were **repigmentation in 60-70% of the chest and extremities**


L-S-h




LI-S-h

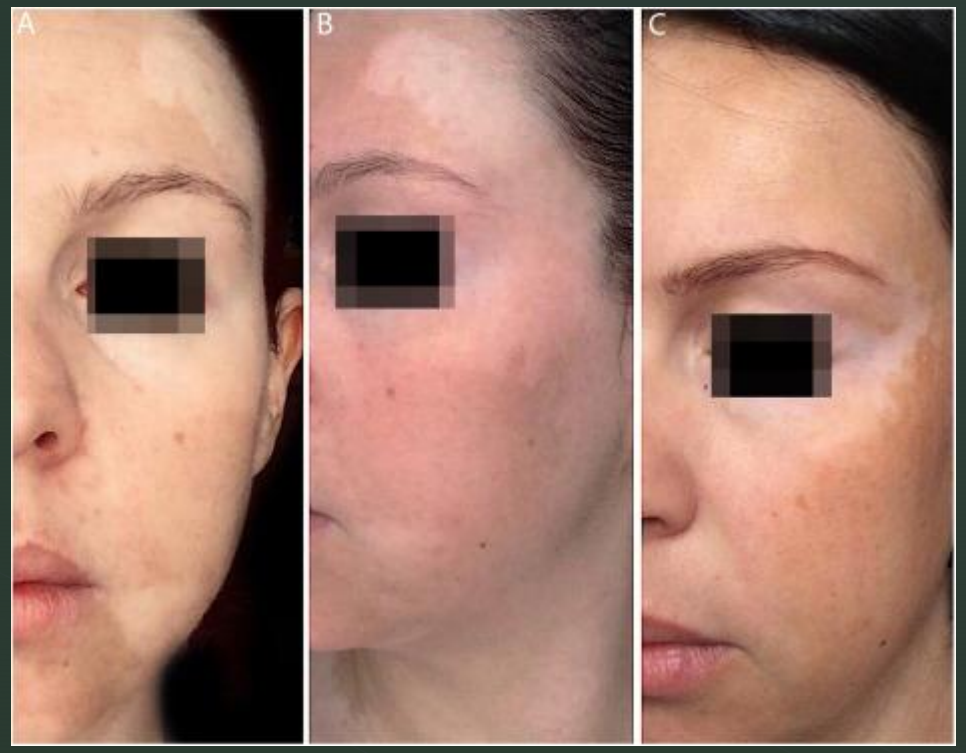


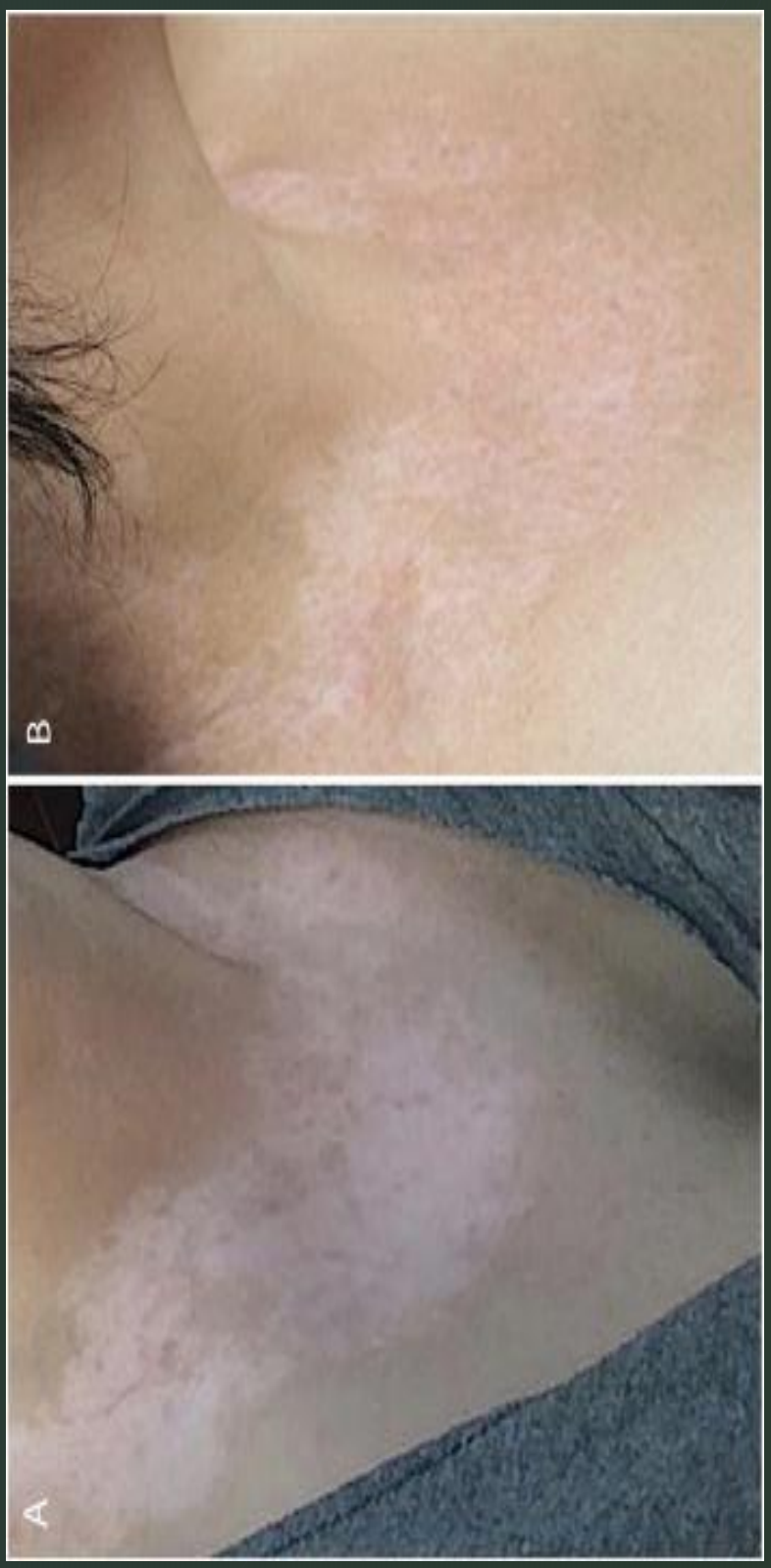
- More recently, a pilot study performed by Majid *et al* (2019) reported a case series of 13 patients with rapidly progressing non-segmental vitiligo treated with apremilast 30 mg twice daily for 3 months after initial titration.The patients could use topical tacrolimus on the exposed parts of the body.
  - **The results were stabilization in all patients and partial repigmentation in 61.5% of patients**
- The side effects of apremilast include headache, nausea, vomiting, weight loss, depression and abdominal pain

JAK inhibitors

- Craiglow and King (2015) reported the case of a 50-year-old female with widespread and progressive vitiligo treated with oral tofacitinib citrate **5 mg daily for 5 months**, with nearly complete repigmentation of the forehead and hands, while other areas exhibited partial repigmentation
- Liu *et al(2017)* reported a case series of **10 patients treated with tofacitinib 5-10 mg, once or twice daily for at least 3 months**
- Repigmentation was observed in 50% of patients at sites of **low-dose nb-UVB phototherapy** or sun-exposed areas;
  - **the authors suggest that low-level light may be required for melanocyte regeneration and repigmentation during treatment with JAK inhibitors**

A and B) Prior to treatment, white macules all over the face. (C) After two years of treatment




B
A

- The side effects were upper respiratory infections, weight gain, arthralgia and mild **elevation of lipid levels**

Minocycline

- Minocycline **protects melanocytes from oxidative stress** and prevents their loss in the early stages of the disease
- Parsad and Kanwar (2010) performed a study on 32 patients with gradually progressive vitiligo. Patients were treated with **100 mg of minocycline daily for 3 months**, the arrest of activity was achieved in 90.6% of patients, and moderate to marked repigmentation was observed in **21.8%** of patients

- Siadat *et al (2014)* **compared minocycline 100 mg daily to nb-UVB** phototherapy in patients with unstable vitiligo during 3 months of treatment. Vitiligo was active in 100% of patients at the beginning of the trial; however, this decreased to **66.1** and 23.8% in the **minocycline** and nb-UVB groups, respectively, following treatment
- The side effects of minocycline are nausea, gastrointestinal complaint, headache, and hyperpigmentation of the nails, oral mucosa or skin

MTX

- Most of the initial reports of improvement in vitiligo treated with MTX were in patients *using it for concomitant rheumatoid arthritis or psoriatic arthritis*.
- The dosage of MTX varied from ***7.5-25.0 mg weekly***
- The side effects of MTX are hepatotoxicity, idiosyncratic pulmonary toxicity, pancytopenia, nausea, vomiting and diarrhea
- In a prospective study performed by Nageswaramma *et al (2018)*, 20 patients with unstable vitiligo were treated with MTX 15 mg weekly and folic acid supplementation. The results were **moderate repigmentation in 70% of patients** and arrest in progression in 90% of patients.

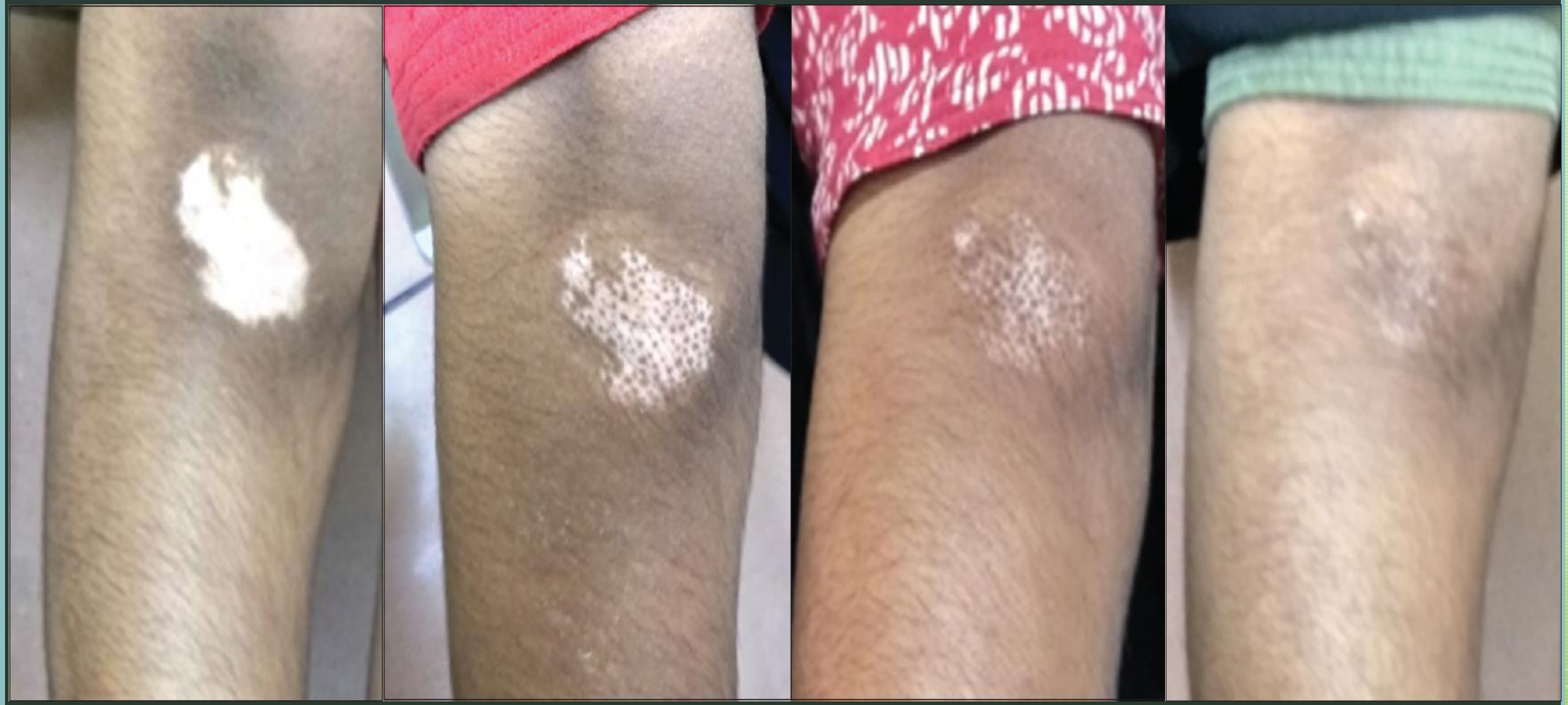
- In an uncontrolled pilot study by Alghamdi and Khurrum (2013), **no clinical improvement** was observed with MTX 25 mg weekly for 6 months.
- A randomized comparative study performed by Singh *et al* (2017) compared MTX 10 mg weekly to oral corticosteroid mini pulses with 2.5 mg of dexamethasone on 2 consecutive days for 24 weeks. **Both groups had a similar reduction in the VIDA score** at the end of the study

- ElGhareeb *et al (2020)* performed a study with 42 patients to assess the efficacy and safety of oral MTX and oral mini pulse of dexamethasone, used either alone or in combination. Patients were randomly divided into three groups.
- Group A received **15 mg of MTX** divided into three doses, with a 12 h weekly interval. Group B received **5 mg of dexamethasone daily on 2 successive days** every week. Group C received a **combination of both protocols**. All groups received the treatment for 3 months. The results demonstrated a *significant decrease in disease extension in group C* compared with the other groups

Azathioprine

- There is a study of its use in vitiligo performed by Madarkar *et al (2019)*,comparing azathioprine *50 mg twice daily to betamethasone 5 mg on 2 consecutive days every week for 6 months*
- Remarkable improvements were observed in both groups, and the authors suggest that both therapies are equally effective in vitiligo .
- The side effects of azathioprine include myelosuppression, hepatotoxicity, gastric irritation, increased susceptibility to infections (herpes simplex and human papillomavirus) and hypersensitivity syndrome

1-3-6 months follow up..



- Radmanesh and Saedi(2006) performed a study on 60 patients into two groups. The first group received *azathioprine calculated at 0.60-0.75 mg/kg per day (maximum dosage 50 mg) combined with twice-weekly oral psoralen (methoxypsoralen 0.3-0.4 mg/kg) plus UVA.*
- The second group only received *oral psoralen plus UVA* (PUVA). Both groups were followed for 4 months. The results exhibited earlier repigmentation at 5 oral PUVA sessions and greater repigmentation (58.4%) in the **combination group** compared with the oral PUVA monotherapy group at 8 sessions with 24.8% repigmentation

Cyclosporine

- Taneja *et al(2019)* performed an open-label, single-arm study in 18 patients with progressive vitiligo using ***cyclosporine at a dose of 3 mg/kg/day, divided into two doses for 12 weeks***. Progression of vitiligo was arrested in 61% of the patients and repigmentation was observed in 81% of the patients

- The side effects of cyclosporine are renal dysfunction, hypertension, gingival hyperplasia, hypercalcemia, hyperuricemia, nausea, abdominal discomfort, tremor, headache, arthralgias and hypertrichosis

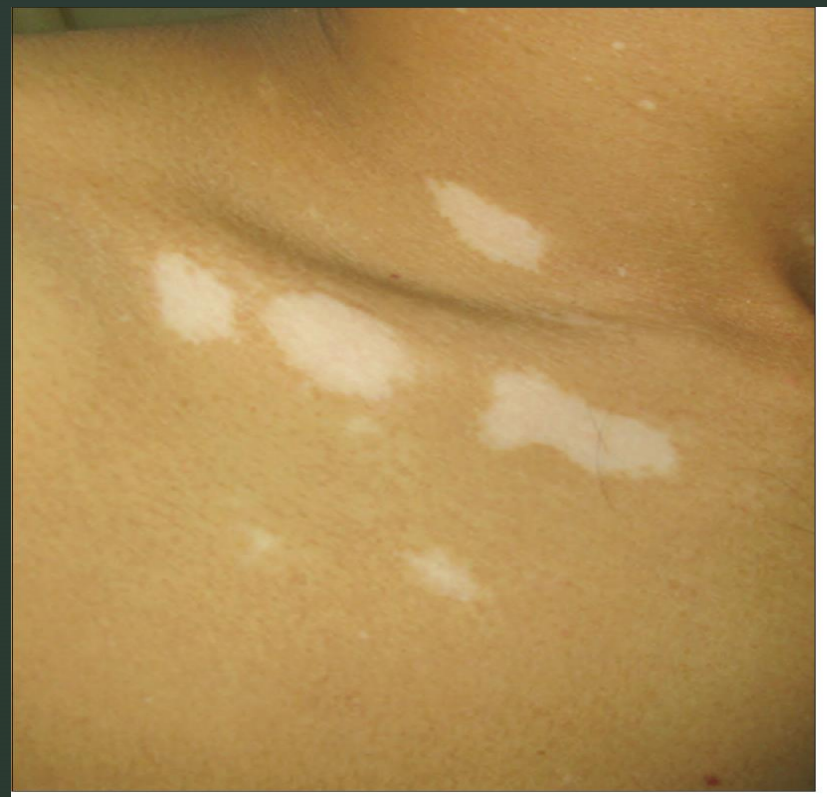


Figure 2a: Pretreatment vitiliginous lesion in the supra and infraclavicular areas

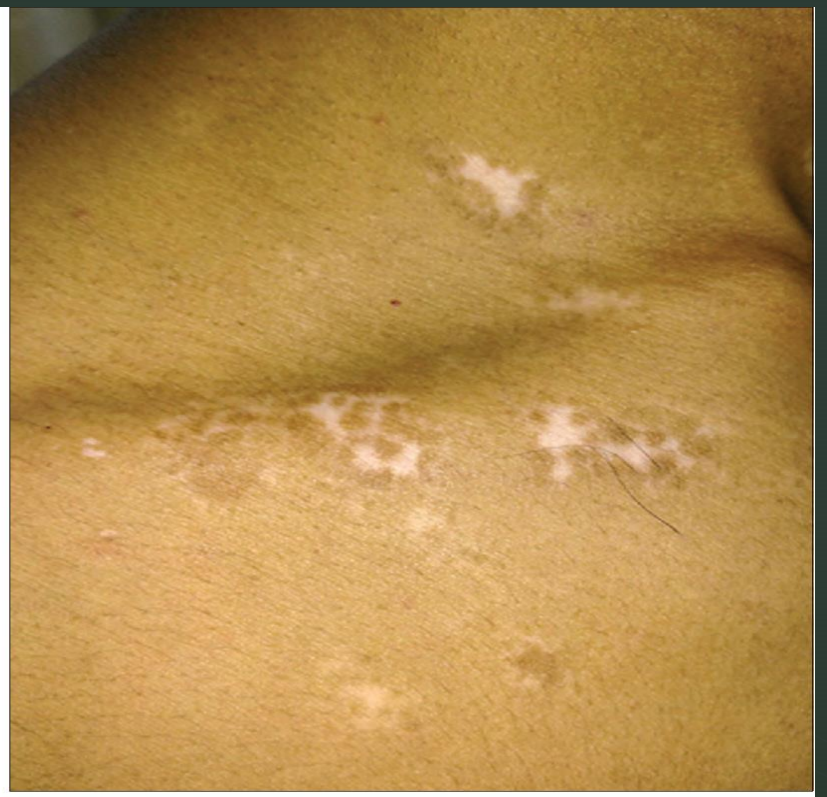
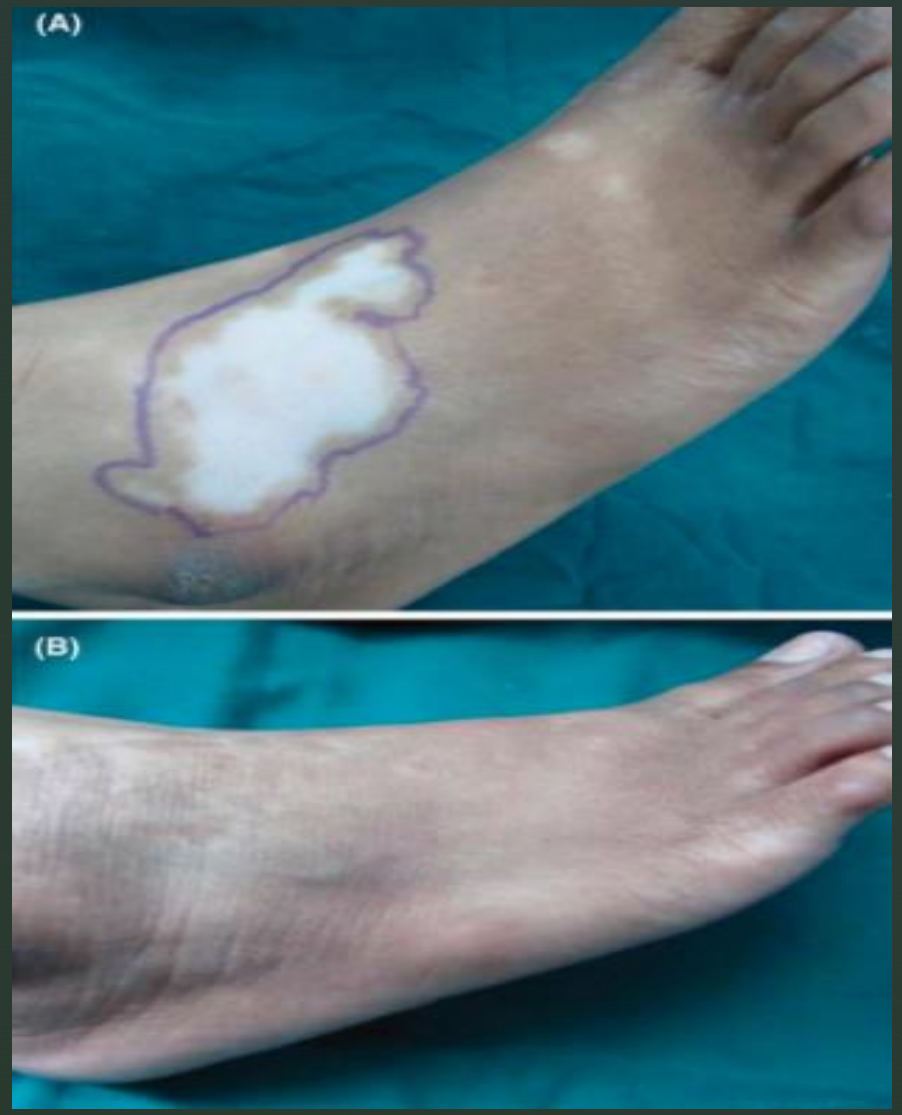


Figure 2b: Posttreatment repigmentation of the lesions in supra and infraclavicular areas after 3 months of therapy with oral cyclosporine

- A pilot study was performed by Mutalik *et al (2017)* in patients with localized stable vitiligo treated **with autologous nonculture melanocyte-keratinocyte cell transplant (NCMKT)**.
- The objective was to assess the efficacy of cyclosporine to prevent the perilesional depigmentation halo seen after NCMKT surgery. The treatment group received cyclosporine postoperatively for 3 weeks at 3 mg/kg/day followed by cyclosporine for 6 weeks at 1.5 mg/kg/day.
- The results were >75% repigmentation in 100% of patients in the cyclosporine group compared with 28% of patients in the group without treatment. In the latter group, most patients (52%) achieved 25-50% repigmentation. ***The authors concluded that postoperative cyclosporine allowed a uniform and complete repigmentation following NCMKT***

(B) Six months after noncultured melanocyte–keratinocyte cell transplant and cyclosporine



Mycophenolate mofetil (MM)

- Bishnoi *et al (2020)* evaluated MM efficacy in stabilizing non-segmental vitiligo. *Mofetil mycophenolate up to 1 g twice daily was compared with dexamethasone 2.5 mg on 2 successive days weekly* for 180 days. The arrest of disease activity was achieved in 80% of patients in the **corticosteroid group** compared with 72% of patients in the MM group.
- The most common side effects in the MM group were nausea and diarrhea. Treatment was discontinued in two patients in the MM group due to leucopenia and transaminitis, respectively

Physical therapy
Phototherapy

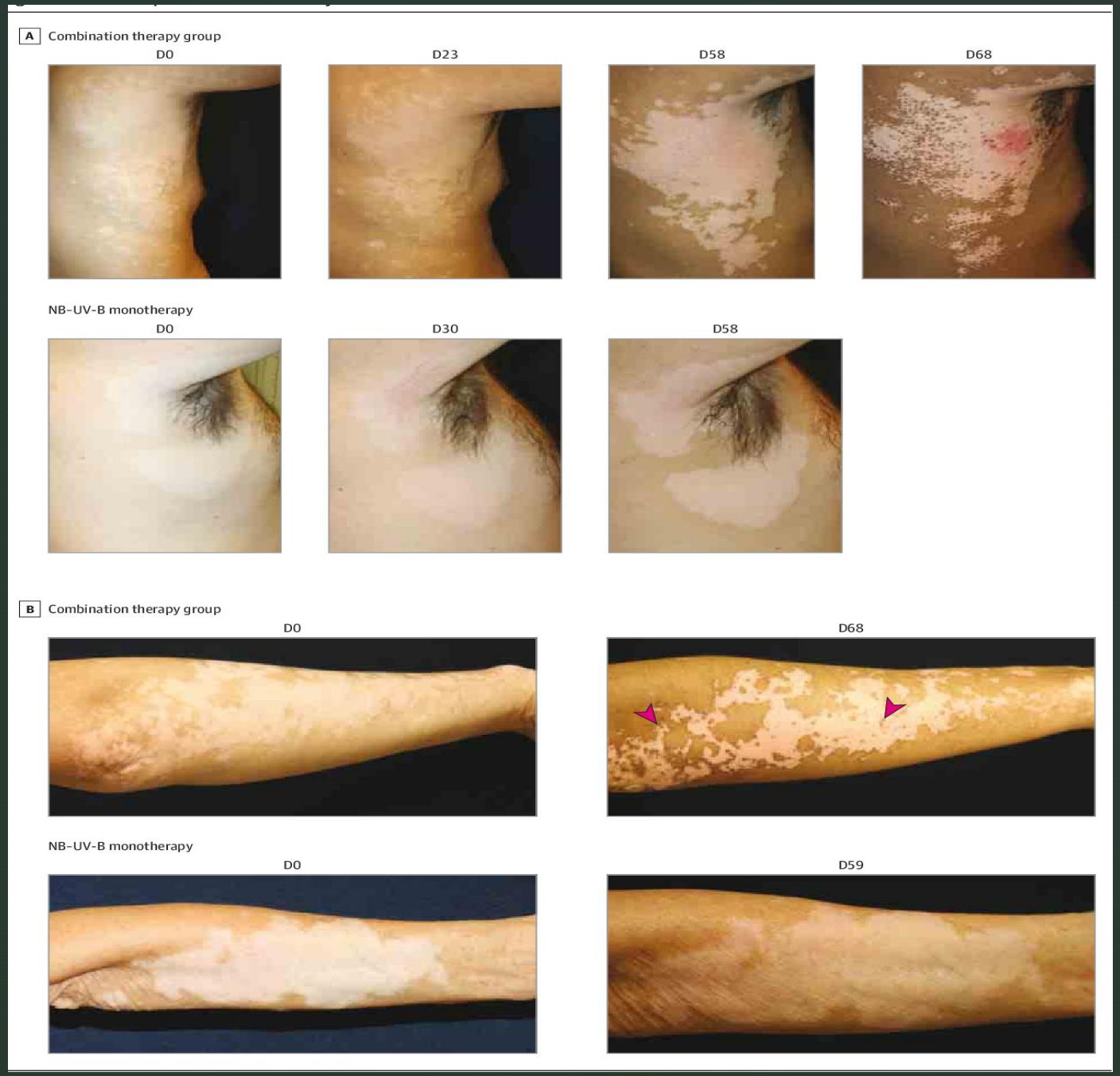
- ***Narrow-band UVB***
- UVB & UVA have several systemic effects, such as activation of the central HPA axis, activation of the proopiomelanocortin pathway in the hypothalamus, immunosuppressor and opioidogenic effects
- The mechanism of action of nb-UVB (311 nm) phototherapy in vitiligo is through **immunosuppression**, induction of melanocyte differentiation, melanin production and migration of melanocytes from perilesional skin
- Total body nb-UVB is recommended for widespread vitiligo **>15-20%** of the BSA

- **Recommendations**: **3** sessions every week , the initial dose is **200 mJ/cm2 ,** pink erythema lasting less than 24 h is desired
- The dose can be increased by **10-20%** each session until pink erythema is achieved
- The response to treatment should be assessed after **18-36 sessions**
- At least **72 sessions** are recommended before discontinuing therapy
- There is **no maximum number of sessions** in patients with phototypes IV-VI, and no recommendation was made for other phototypes
- The maximum acceptable dose is **1,500 mJ/cm2 for the face and 3,000 mJ/cm2 for the body**

- Treatment response to **monotherapy with nb-UVB** phototherapy was evaluated in a systematic review and meta-analysis by Bae *et al (2017)*,where ≥25% repigmentation was achieved in 62.1% of patients at 3 months, 74.2% of patients at 6 months and 75% of patients at 12 months.
- According to the site, the best response was observed on the **face and neck**, followed by the trunk, extremities, and lastly the hands and feet

- **combinations with nb-UVB:**
- **TCI** :TCI and nb-UVB may improve the clinical response in the face and neck
- **oral mini-pulse of dexamethasone** 4 mg on 2 consecutive days weekly with nb-UVB
- **JAK inhibitors**
- **Afamelanotide 16 mg subcutaneously** **(injectable controlled release implant)** applied monthly for 4 months along with nb-UVB

afamelatonide



- ***PUVA***. PUVA radiation (320-340 nm) induces melanogenesis by *immunosuppression and promoting growth of melanocytes*
- The oral psoralens are given **1-3 h before the UVA radiation**, some examples are **8-methoxypsoralen** (0.6-0.8 mg/kg), 5-methoxypsoralen (1.2-1.8 mg/kg) and trimethylpsoralen (0.6 mg/kg)
- Topical PUVA uses the psoralen as a cream or ointment (8-methoxypsoralen 0.001%) and is applied **30 min** before UVA radiation

- The advantages of **Topical PUVA** include fewer treatments, smaller cumulative UVA doses, less systemic and ocular phototoxicity
- PUVA therapy should be given for **at least 6 months** before considering the patient non-responsive and for a maximal response, **continuous therapy is required for up to 1-2 years**
- Parsad *et al* compared treatment with nb-UVB to PUVA and marked to complete repigmentation was observed **in 41.9% of patients with nb-UVB** compared with 23.6% of patients with PUVA.

- Bhatnagar *et al* compared treatment for induction of stability with nb-UVB or PUVA; **vitiligo was arrested in 80% of patients using nb-UVB** and only 40% of patients with PUVA.
- The side effects of PUVA are phototoxicity, headache, dizziness, depression, insomnia, hyperactivity, bronchoconstriction, tachycardia, ankle edema, nausea, vomiting, pruritus, xerosis, photoaging, hyperpigmentation, hypertrichosis, increased risk of non-melanoma skin cancer, and liver and eye toxicity

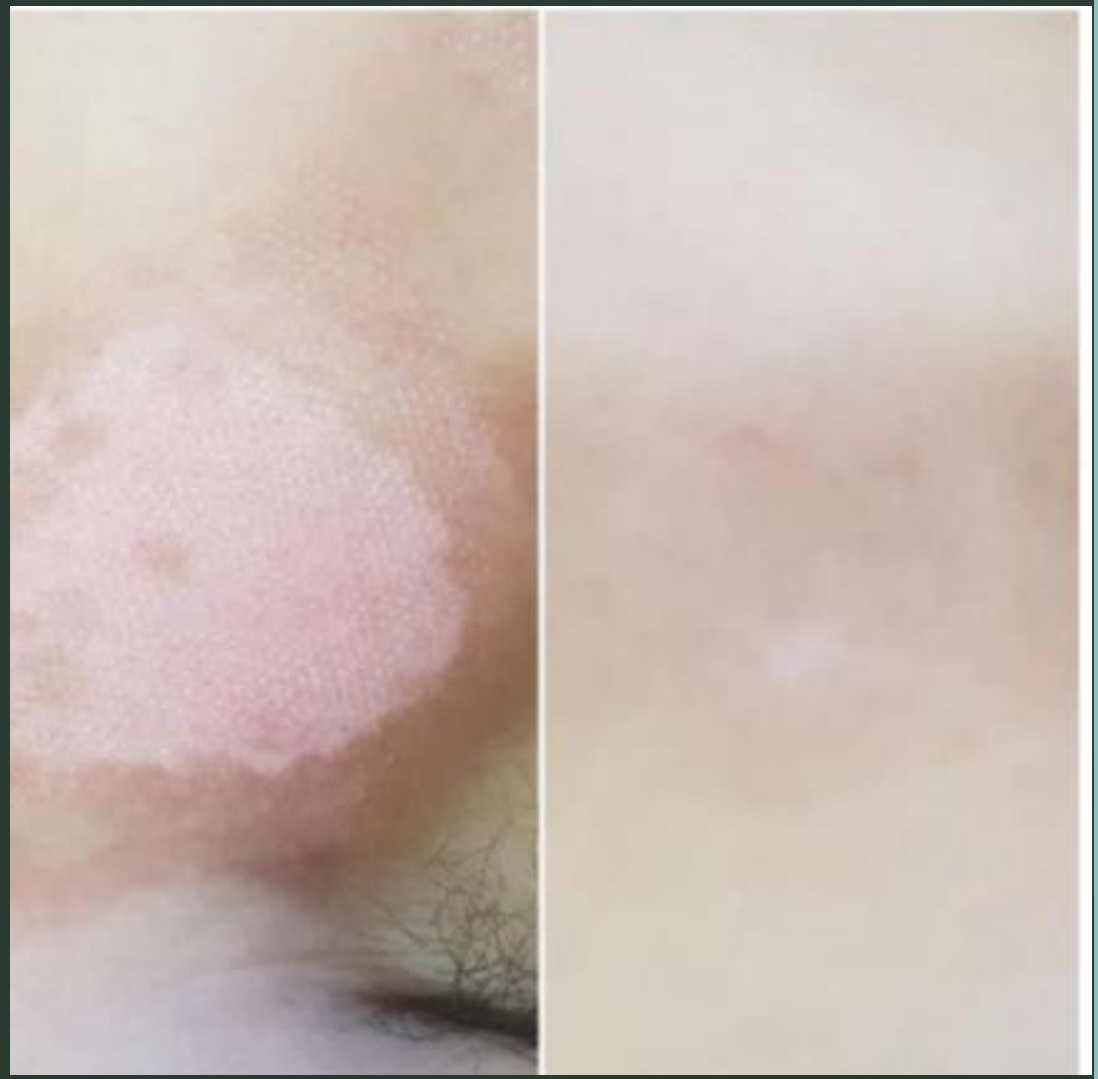
Laser therapy
EL. Excimer light

- Useful for **targeted phototherapy** (308 nm)
- The mechanism of action is a *direct cytotoxic effect on T cells, and stimulation of melanocyte migration and proliferation in hair follicles*
- In a systematic review and meta-analysis by Lopes *et al* (2016) **NO** significant difference in efficacy was observed between excimer lamps, EL and nb-UVB in achieving ≥50 and ≥75% repigmentation
- The treatment failure rate was reduced with the combination therapy
- The side effects of EL are pruritus, burning sensation and dryness

Combined Fraxel Erbium and UVA1 laser

- Lotti *et al (2018)* investigated a combined **laser and topical latanoprost approach in 30 adults with vitiligo**, with active or stable localized disease.
- Initially, the vitiliginous lesions were treated with a single passage of Fraxel erbium laser, with a wavelength of 1,540 nm and an energy level of 1,800 mJ/P.
- Immediately after obtaining columnar areas of epidermal ablation, they applied latanoprost 0.005% solution onto each skin lesion. **After 24 h, the skin lesions were irradiated with a UVA1 laser (355 nm) for 20 min**.
- *The treatment was repeated every 21 days, for 9 months. A total of 27 patients (90%) obtained >75% repigmentation, while three patients (10%) achieved 50-75% repigmentation* .

Progressive rapid repigmentation of Vitiligo patches after treatment with Laser Fraxel Herbium, local application of Latanoprost solution and UVA1 irradiation



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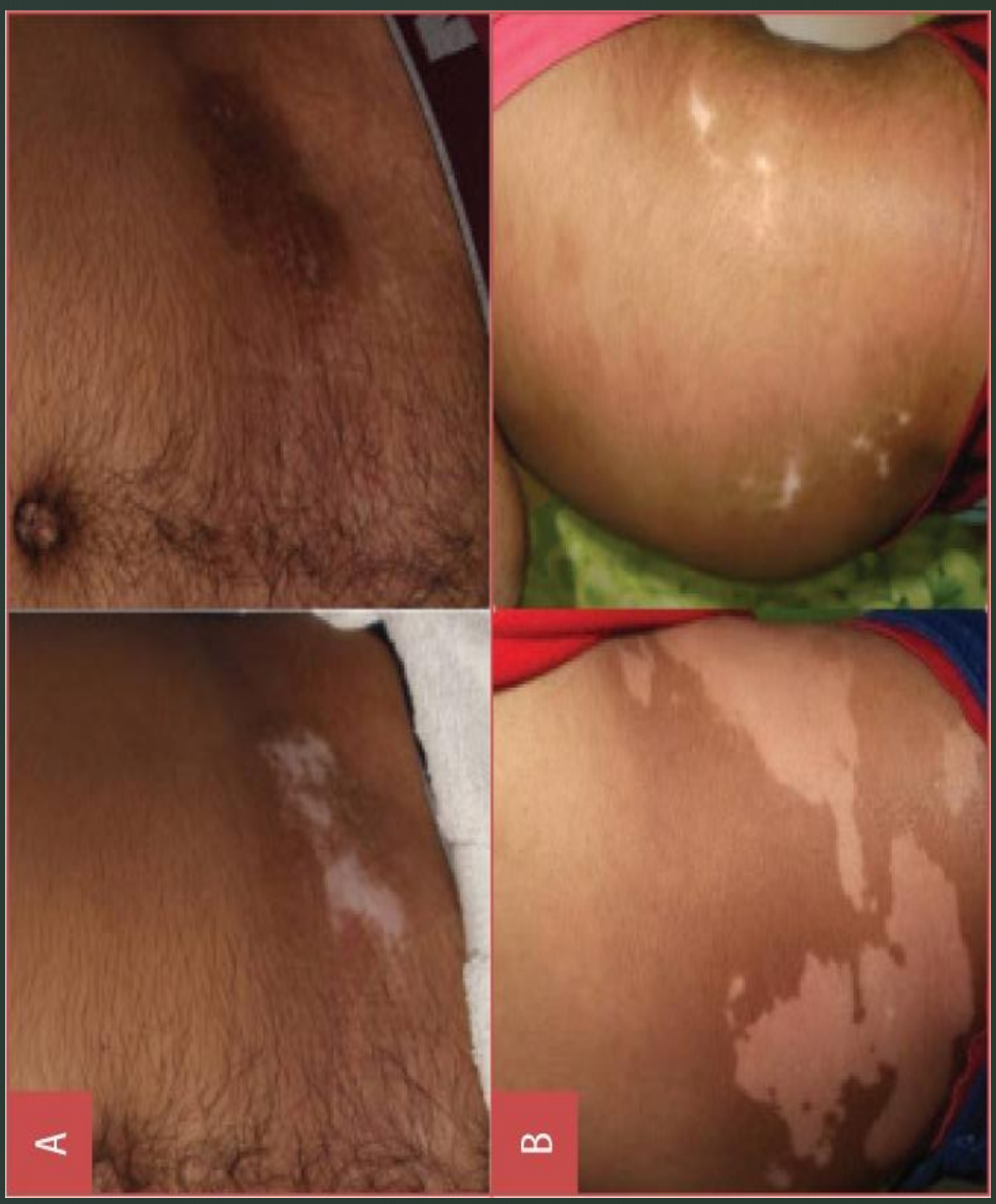
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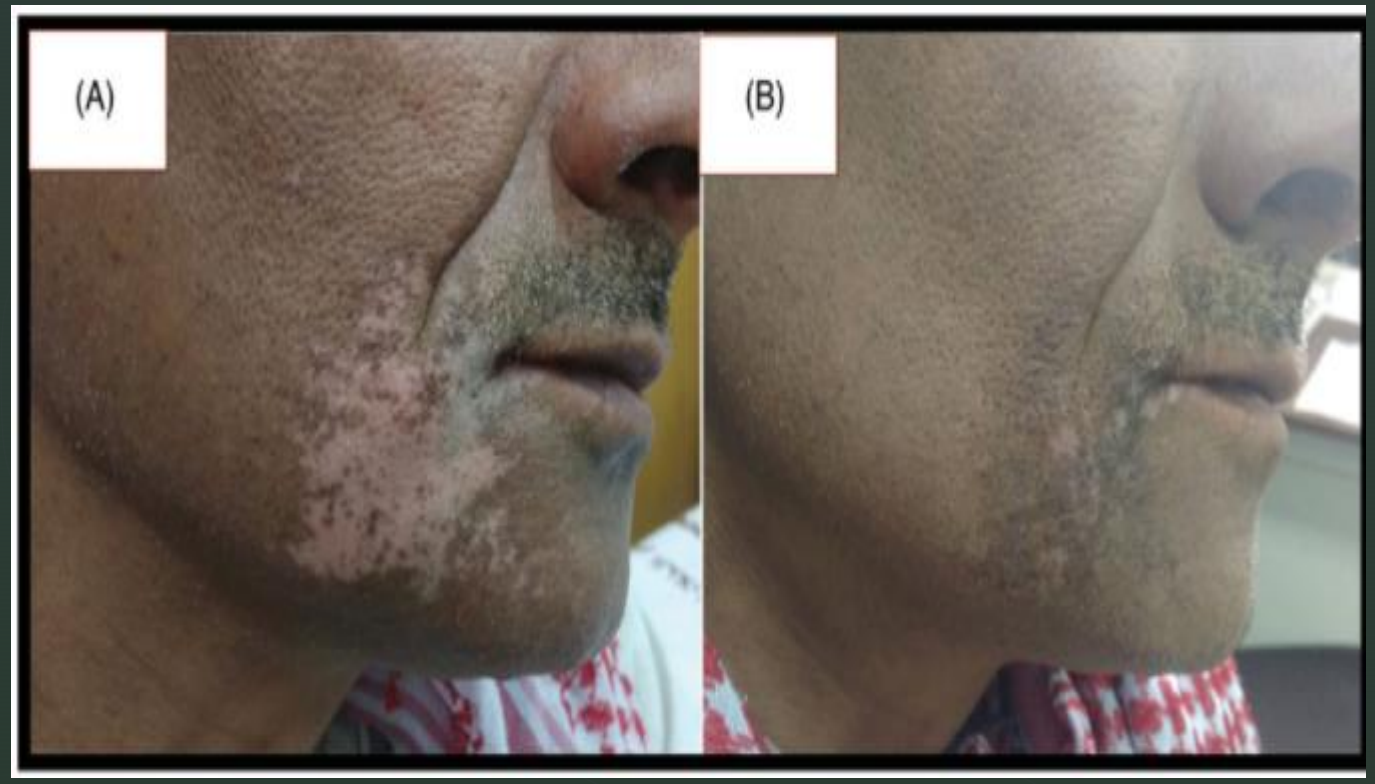

A prostaglandin F2a analog, latanoprost 0.005%, was used for intradermal injection in the next day of NB-UVB sessions.The injection was done using insulin syringe at a depth of 3–4 mm with 1 cm distance between each point of injection. The procedure was repeated once weekly for each patient until improvement for maximum 3 months (12 sessions NBUVB).

Depigmentation therapies

- recommended for extensive and refractory vitiligo, **when >50% of the body surface is affected or if cosmetically sensitive areas are the major component involved**
- Monobenzyl ether of hydroquinone (MBEH) **10%** is applied topically **daily the first month**, then MBEH **20%** is applied daily for 1 month, and after that twice daily.
- The concentration can be increased to **30-40%**
- patients present depigmentation after 3-6 months in areas distal to the application.
- Other treatment options are 4-methoxyphenol, 88% phenol solution, laser and cryotherapy

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