

Current Best Evidence

Current best evidence from dermatology literature - Part II

Calabrò G, De Vita V, Patalano A, Mazzella C, Lo Conte V, Antropoli C. Confirmed efficacy of topical nifedipine in the treatment of facial wrinkles. J Dermatolog Treat 2013; Early Online: 1-7.

There has been an ever-increasing demand for aesthetic procedures to reverse the effects of aging, particularly in the facial area. Recently, topical nifedipine has been found to have anti-wrinkle effects. The aim of this study was to confirm the anti-wrinkle efficacy and tolerability of a 0.5% nifedipine-based topical formulation.

A randomized study was conducted in 20 healthy female volunteers aged between 45-60 years with moderate to moderately severe facial wrinkles and Fitzpatrick's skin phototypes II-IV. Ten volunteers (group A) applied a cream containing nifedipine at a concentration of 0.5%, hyaluronic acid, collagen, and vitamin A and E, and the other 10 (group B) applied a good moisturizer, containing hyaluronic acid, collagen, and vitamin A and E. Patients in both groups were instructed to apply measured amounts (0.1 g) of topical formulations on forehead, nose-geniene, periocular and perilabial wrinkles, twice daily for 3 months after washing the face with the same mild facial cleanser. All parameters were evaluated at baseline (T0), and then 30 (T1), 60 (T2), and 90 (T3) days later. The aesthetic improvement was evaluated by a blinded investigator using the Wrinkle Severity Rating Scale (WSRS) with grade 1 indicating minimum severity and grade 5 indicating maximum severity. In group A, mean WSRS scores at T1 (2.79), T2 (1.99), T3 (1.84) were approximately 1.38, 1.93, and 2.09 times lower than mean WSRS score at T0 (3.85), respectively. In group B, the mean WSRS score at T0 was 3.78, at T1 3.41, at T2 3.42, and at T3 3.36. Post-treatment WSRS score was significantly lower than the baseline WSRS score only in the nifedipine group.

Improvement in skin hydration was found to be more in group A than in group B at the end of the study period of 90 days. Also, the use of nifedipine cream in

group A resulted in significant overall lightening of the skin compared with baseline and the control group. The absence of de-pigmenting agents in the tested product suggests a possible role of nifedipine in skin lightening. No significant change in blood pressure and heart rate were recorded during this study.

Comment: Both intrinsic and extrinsic factors influence the aging process. Extrinsic factors include sun exposure, repetitive or exaggerated mimic expressions, gravity, and smoking. Reactive oxygen species (ROS), a byproduct of both environmentally induced and intrinsic aging, lead to a cascade of biochemical reactions within the skin, resulting in the production of matrix metalloproteinases (MMPs) and proinflammatory cytokines. Reduction in collagen and elastin and a loss in hydration are the main structural changes in skin resulting from aging leading to wrinkling. Wrinkles can be divided into four main types: Atrophic crinkling rhytids, permanent elastotic creases, dynamic expression lines, and gravitational folds. Each type usually develops on specific skin regions exhibiting distinct micro-anatomical characteristics. However, the most important pathogenic mechanism is the chronic contraction of mimic muscles.

Nifedipine is a dihydropyridine-type calcium channel blocker that blocks the transmembrane influx of calcium ions into muscle cells inhibiting their contraction, thus accounting for its efficacy in the treatment of facial wrinkles. In nifedipine group, there was a greater improvement in viscoelastic properties of skin, and another significant effect observed was skin lightening. Authors have not provided explanation for the observed skin lightening effect. Its poor percutaneous penetration combined with its rapid metabolism in the skin limits its systemic absorption and side-effects. So, topical nifedipine preparations can prove to be an economical, effective, and convenient means of anti-wrinkle treatment.

How to cite this article: Citation will be included before issue gets online***

Received: July, 2013. **Accepted:** July, 2013. **Sources of Support:** Nil. **Conflict of Interest:** None declared.

Further in-depth studies are needed to evaluate the anti-aging effects of topical nifedipine over longer treatment period and its possible role not only in skin rejuvenation, but also in the prevention of cutaneous aging by increasing skin hydration and elasticity.

Amerio P, Amoruso G, Bardazzi F, Campanati A, Cassano N, Conti A, et al. Detection and management of latent tuberculosis infections before biologic therapy for psoriasis. *J Dermatolog Treat* 2013;24:305-11.

The biologic agents are highly efficacious in the treatment of psoriasis and psoriatic arthritis. However, their use is associated with an increased risk of developing active tuberculosis (TB). All patients should be screened for latent tuberculosis infection (LTBI) prior to initiating therapy. This article reviews the current recommendations for screening and chemoprophylaxis of LTBI in Italian psoriasis patients treated with biologics.

LTBI is defined by the presence of *Mycobacterium tuberculosis* without clinical symptoms, and bacteriological and radiographic signs of disease. Only about 10% of these patients develop active TB, immunosuppression being a major risk factor for activation. Among the anti-TNF- α agents, the risk of LTBI activation is three to four times higher with the monoclonal antibodies (adalimumab, infliximab, and certolizumab) as compared to etanercept. There are no reports of LTBI reactivation with alefacept. The risk of LTBI with ustekinumab is lower than that observed with anti-TNF- α therapy. However, screening for LTBI is recommended before starting any biologic therapy for psoriasis.

According to the recommendations of an expert working group of Italian dermatologists, screening process for LTBI includes taking complete medical history, chest X-ray (CXR), purified protein derivative skin test (PPD), and interferon γ release assays (IGRAs). History pertaining to age, TB vaccination, previous TB infections, family history of TB, exposure to possible sources of infection, and any recent immunosuppressive or long-term antibiotic therapy should be taken. CXR should be performed in two projections and interpreted by a radiologist (although US National Psoriasis Foundation consensus statement recommends an X-ray only if immunologic tests are positive). Indurations larger than 5 mm are considered positive in the PPD test. Although having good sensitivity, false negatives can result from immunosuppression as a consequence of an autoimmune disease, medication, and age. False positives test can result from vaccination with

bacillus-calmette-guérin (BCG) and exposure to non-tuberculous mycobacteria. A two-step test, also known as a booster PPD, has been suggested, in which a second PPD is administered 1-3 weeks after the first to provoke an anamnestic response to reinforce weakened immune memory. This is useful in older patients or in patients who are at high risk of infection but show a negative result on the first PPD test. *In vitro* immunological tests for LTBI include QuantiFERON and T-SPOT.TB, collectively referred to as IGRAs. These assays correlate better with TB exposure, and they are not influenced by vaccination with BCG or previous exposure to non-tuberculous mycobacteria. They also have a higher specificity. IGRAs employing a cocktail of antigens may be more sensitive than PPD in immunosuppressed patients.

A positive IGRA test is an indication for prophylactic treatment, independent from the results of other tests. The situation is less clear when the IGRA and radiology results are negative, but the PPD is positive. In this case, it is necessary to carefully evaluate the individual situation. If the medical history does not suggest a risk, the PPD result is generally considered a probable false-positive, especially if there is a history of BCG vaccination. However, chemoprophylaxis may still be initiated if a false-negative IGRA result is suspected. If the X-ray results are positive while the other tests are negative, the patient should be referred to a pulmonologist for further evaluation.

For prophylactic treatment, in most cases, isoniazid at a dose of 300 mg/day for 9 months is recommended. The combination of rifampicin/pyrazinamide is not recommended due to the risk of hepatotoxicity. Anti-TNF- α therapy can be started at least 1 month after initiating prophylactic therapy.

Comment: The advent of TNF- α inhibitors as a treatment modality in psoriasis is a significant step forward in its management. However, a significant roadblock still remains due to the risk of developing TB in patients with LTBI preventing the optimal utilization of this modality. Animal studies have shown that TNF- α inhibition impairs inflammatory cell trafficking and granuloma formation. Currently recommended screening for LTBI, typically, risk assessment, tuberculin skin testing (TST), and CXR used prior to anti-TNF- α treatment can significantly reduce TB activation rates, but newer screening tests like IGRAs may enhance screening efficacy further.

Patients positive on screening who are treated with isoniazid and subsequently receive anti-TNF- α treatment still have approximately 19% risk for TB.

IGRA test has a better sensitivity and specificity than TST in detection of LTBI and is superior for predicting TB infection, especially in immunosuppressed patients. In a country like India where BCG vaccination is routinely administered to all in infancy, IGRA test has still higher utility, and the requirement for TB chemoprophylaxis can be significantly reduced. A strategy of simultaneous testing to optimize diagnostic sensitivity is suggested in the clinical use of biological drugs. IGRAs performed post-TST was elevated since day 3. So, it is advisable that when using a two-step screening strategy, it is better to perform an IGRA within 3 days after performing the TST.

A higher rate of TST positivity is found in patients of psoriasis being screened for LTBI than the corresponding inflammatory bowel disease (IBD) patients, which may be due to the priming of their clinically healthy skin to overreact to a broad-spectrum of antigenic triggers, including *M. tuberculosis* derived antigens and also there is a higher degree of drug-induced immunosuppression in patients of IBD. It seems reasonable to propose that injection of tuberculin antigens into the unaffected skin of patients with overt plaque psoriasis triggers augmented inflammatory reactions resulting in stronger TST, and adherence to the widely accepted TST-based recommendations for the diagnosis of TB leads to overdiagnosis of LTBI in patients with plaque psoriasis.

In countries, where TB prevalence is very high, the criterion of LTBI diagnosis may be less valuable and the guiding principle for LTBI treatment may not be as strict as in the western countries. Unlike active disease, monotherapy is often used in treating LTBI. The lower bacillary load in LTBI reduces the chances of developing resistant mutants, although this possibility cannot be fully excluded. Isoniazid at a dose of 5 mg/kg (upto 300 mg/day) is used for chemoprophylaxis for a period of 9 months, and the anti-TNF α therapy can be given at least 1 month after initiating prophylactic therapy.

The screening protocols for LTBI need to be applied in a way that there are less false positives so as to avoid denial of treatment to candidates who are eligible for anti-TNF- α therapy. It should also be sensitive enough to identify patients at risk of LTBI activation. The tendency of patients with psoriasis to have higher

number of false-positive TST results and the reduced diagnostic specificity of the TST in BCG-vaccinated populations may greatly diminish the value of traditional screening method of TST in psoriatic patients in India. TST needs to be combined with clinical history and supportive evidence from CXR and IGRA's to help decision-making while screening for LTBI in psoriasis patients being considered for anti-TNF α therapy.

Wolosker N, Campos JR, Kauffman P, Yazbek G, Neves S, Puech-Leao P. Use of oxybutynin for treating plantar hyperhidrosis. *Int J Dermatol* 2013;52:620-3.

Plantar hyperhidrosis (PLH) is an emotionally distressing condition. Several anti-cholinergic drugs have been tried for its treatment in past, but their use is limited by their adverse effects. Oxybutynin is an anti-cholinergic drug, which is primarily used for treating urinary disorders and diminished sudoresis is one of its side-effects. The aim of this study was to evaluate the effectiveness and patient satisfaction with the use of oxybutynin when given at low doses for treating PLH. Thirty-five patients (aged between 18-71 years) with PLH were treated with oxybutynin, of these 30 (female-26, male-4) completed the study. They also had hyperhidrosis at other sites on the body, palmar in 25 (83.3%), axillary in 13 (43.3%), craniofacial in 5 (16.6%), and thoracic and abdominal in 5 (16.6%). During the first week, patients received 2.5 mg of oxybutynin once a day, 2.5 mg twice a day from the eighth to the 42nd day, and from the 43rd day till the end of 12 weeks, 5 mg twice a day.

At the completion of 12 weeks of treatment, 70% of patients had moderate or great improvement in PLH and more than 60% of patients showed improvement at all of the hyperhidrosis sites. Two-third of patients presented improvement in quality of life (QOL). QOL was much better in 9 (30.0%), a little better in 11 (36.6%), and the same in 10 patients (33.3%). Dry mouth was the most common side-effect (76.6%). Using 5 mg of oxybutynin per day, 66.6% of patients either did not present dry mouth or only presented it mildly, which encouraged the patients to continue with the treatment. Using 10 mg/d, this symptom increased but was tolerated well. Other side-effects reported were headache (10%) and urinary retention (6.6%); however, they were not significant enough to lead to discontinuation of treatment.

Comment: Hyperhidrosis is a disorder of excessive sweating beyond what is expected for thermoregulatory needs and environmental conditions. Hyperhidrosis

may be primary or secondary to medications or general medical conditions. Primary hyperhidrosis has an estimated prevalence of nearly 3% of the population. Topical therapy (20% aluminum chloride solution, 15% aluminum chloride in 2-4% salicylic acid gel, and 0.5%, 1%, 2% glycopyrrolate) is generally considered first-line treatment for most cases of focal hyperhidrosis. Other topical agents such as glutaraldehyde, formaldehyde, and tannic acid are seldom used today due to irritancy, skin discoloration, and the availability of better alternatives. For those who fail such treatment, other options available are iontophoresis, botulinum toxin A (BTX-A) injections and surgical or video-assisted endoscopic thoracic sympathectomy. But all these modalities have their limitations.

Only limited data are available regarding the use of oral medications in the management of hyperhidrosis. The various drugs tried include anti-cholinergic drugs: glycopyrrolate (1-2 mg, once/twice daily), oxybutynin (5-15 mg/day) and tolterodine (4 mg/day), and alpha-2-agonists: clonidine (0.6-1.2 mg/d).

Oxybutynin is primarily indicated for urge incontinence where it is used in higher dosage (15 mg/d) and hence leading to a greater incidence of side-effects in these patients. When used in low and progressively increasing doses, it is found to be highly effective for hyperhidrosis with minimum side-effects. There was improvement in hyperhidrosis at all the sites in two-third of the patients. Potential side-effects of oral anti-cholinergics include dry mouth, constipation, nausea, blurred vision, urinary retention, drowsiness, and dizziness. The side effects of oxybutynin are mild as compared to other anti-cholinergics. In this study also, the side-effects were mild and well tolerated by the patients. Because of its rapid resorption ($T_{max} < 1$ hour), oxybutynin would also be suitable for use 'on demand,' for example, in specific social situations that provoke hyperhidrosis. It is contraindicated in patients with urinary retention, partial or complete obstruction of the gastrointestinal tract, paralytic ileus, gastroesophageal reflux disease, uncontrolled narrow-angle glaucoma and also in those with hypersensitivity to the drug substance. Limitation of the study is that there was no follow up of the patients after the drug was stopped. Treatment of plantar hyperhidrosis is challenging with each therapeutic modality having its own merits and demerits. Treatment of PLH with oxybutynin is a good alternative in patients failing on topical treatment and

not willing for iontophoresis or BTX-A. It has been found to be effective with a minimum of side-effects.

Tran KD, Wolverton JE, Soter NA. Methotrexate in the treatment of pemphigus vulgaris: Experience in 23 patients. *Br J Dermatol* 2013. [In press]

Pemphigus vulgaris (PV) is an autoimmune mucocutaneous blistering disorder. The first-line treatment for patients with PV consists of high-dose glucocorticoids, which have greatly reduced the mortality associated with this disease. This is a retrospective chart review of 23 patients of PV who were treated with methotrexate (MTX) between 2001 and 2012. The primary objective was to evaluate the efficacy of MTX in inducing clinical improvement in PV patients, as indicated by the drug's steroid-sparing effect and also to determine if it could be effective as a monotherapy in maintaining symptom control.

All the 23 patients included in the study (before the initiation of methotrexate) were treated with prednisone at a mean maximum dose of 71 mg/day (range 20 to 140 mg/day). Thirteen (56.5%) patients had received non-steroidal immunomodulators other than MTX before. The mean dose of prednisone at the time of initiation of MTX was 35 mg/day (range 10 to 70 mg/day). The initial dose of MTX was 7.5 mg weekly, with increases of 5 to 7.5 mg weekly every 2 to 8 weeks depending on the therapeutic response, until a maximum dose of 15 to 25 mg weekly. Folic acid at a dose of 1 mg/day was prescribed. Concomitant treatment with topical glucocorticoids such as clobetasol propionate ointment, dexamethasone oral rinses and intralesional injections of triamcinolone acetonide 20 mg/mL was continued. Symptom control was defined as either complete clearance of skin lesions, or as "minimal disease activity" exemplified by 1 to 2 new lesions every month that could be controlled with topical therapy and that were not considered to cause considerable distress by the patient. In patients achieving symptom control after addition of MTX, prednisone was tapered. Patients who were successfully weaned from prednisone were then put on tapering doses of MTX.

Of the 23 patients included in this study, 2 (8.6%) developed adverse events after initiation of MTX requiring cessation of the drug, while 21 (91.3%) had improvement in blistering and were able to reduce their dose of systemic corticosteroids. Sixteen (69.6%) patients were eventually weaned completely off prednisone, with a mean time from

initiation of MTX to discontinuation of prednisone of 18 months (range 7-30 months). Five (21.7%) patients experienced a partial steroid-sparing effect requiring a mean maintenance dose of prednisone of 6.75 mg/day. One patient experienced no therapeutic benefit after 2 months of MTX reaching a maximum dose of 25 mg/week. In the 16 patients who were successfully weaned from prednisone, tapering of MTX dose was attempted in 14. Of these 14 patients, the weekly dose of MTX could not be reduced without resulting in a flare of disease in 3 patients, MTX was reduced to 8.75 mg/week (range 5 to 15 mg/week) in 8 patients, and 3 patients were eventually completely tapered from MTX. Of the 3 patients who were completely tapered off MTX, 2 remained in remission for a duration of 3 and 7 months, and the third was in remission lasting for 26 months.

These results were largely unchanged when compared with the subgroup of patients who had previously received other systemic immunomodulators.

Comment: High-dose systemic steroids are considered the first-line of treatment for PV. However, the appreciable morbidity associated with systemic glucocorticoids has resulted in the use of other immunosuppressive drugs like azathioprine, cyclophosphamide, mycophenolate mofetil, cyclosporine, and methotrexate. In addition, dapsone, tetracyclines, plasmapheresis, intravenous immunoglobulin (IVIg), and rituximab have been used successfully. Although good results have been reported with biological agents, their high cost is a major limiting factor.

In this study, steroid dose could be reduced in 91% patients and in 69.6%, prednisone was completely tapered. MTX is a safe and efficacious treatment for patients with PV and should be included in the adjuvant therapy armamentarium. Another advantage is that it is a relatively cheap and easily accessible drug with which dermatologists have a vast experience. MTX generally has a delayed beneficial effect on oral lesions, whereas the cutaneous lesions usually respond more rapidly. In patients with severe to moderately severe PV, once the initial disease has been brought under control using high doses of systemic corticosteroids, MTX may be useful in maintaining that control, while allowing a lowering of the corticosteroid dose. It may even be successful in controlling the disease as a monotherapy, but it usually does not lead to complete prolonged remission of the disease.

Most of the studies showing efficacy of MTX in PV have been retrospective case series. Previous studies also suggest that a significant number of patients show clinical improvement with MTX and the drug has steroid-sparing effects. Further prolonged, placebo-controlled or multiple-arm prospective clinical trials are needed in order to further assess the role of MTX in the treatment of PV.

Tse TW, Hui E. Tranexamic acid: An important adjuvant in the treatment of melasma. *J Cosmet Dermatol* 2013;12:57-66.

Melasma is a highly prevalent, chronic pigmentary disorder. Tranexamic acid (TA) is a plasmin inhibitor used to prevent abnormal fibrinolysis to reduce blood loss. This article reviews the rationale use and safety profile of TA as an adjuvant treatment in melasma.

TA has been tried in the treatment of melasma in the oral, topical, and intradermal injection formulation. Eight studies using oral TA (0.5-1.5 g/day) in the treatment of melasma were reviewed. The response to therapy was evaluated after 4-10 weeks of starting the drug. It was concluded that the usual effective dose of TA in melasma can be 250 mg 2-3 times daily, which is much lower than the dose used to reduce excessive bleeding. Clinical response was observed after a period of at least 1 month. Side-effects in the form of gastrointestinal upset and a decrease in the amount of menses were found in a minority of patients (3-4%). No change was found in the coagulation parameters. Recurrence of melasma was seen after stopping treatment in a few patients. It was also found that the duration of the therapy and not the higher dose made the treatment regime more effective.

Since systemic TA has potential side-effects, topical TA has been tried in melasma. Available data in literature on the efficacy of topical TA is scarce, and results are conflicting. Some studies suggest that melasma improves in significant number of patients with topical 2% TA emulsion when applied for 5-18 weeks and no side-effects were observed. While another study showed that topical 5% TA when used for a 12-week period caused more irritation to the applied area without any extra benefit. Recently, topical TA in liposome formulation has been developed to reduce irritation.

One study has reported on the efficacy of intradermal injections of TA. The study showed that 85 patients who completed weekly intradermal injections of TA, 0.05 ml TA (4 mg/mL) in the melasma lesion at

1 cm intervals for 12 weeks had significant decrease in the melasma area and severity index (MASI) from 8 weeks onward (8 rated good, 65 rated fair results). No significant side-effect was noted.

Comment: The pathogenesis of melasma is multifactorial; genetic predisposition, UV light exposure and hormonal influences being the major etiologic factors.

TA is a plasmin inhibitor used to prevent abnormal fibrinolysis to reduce blood loss. It acts by attaching to the lysine-binding sites of plasmin and plasminogen. It inhibits UV-induced plasmin activity in keratinocytes by preventing the binding of plasminogen to the keratinocytes, thus suppresses the production of prostaglandins (PGs) and UV-induced melanogenesis, through the suppression of the epidermal plasmin activity. Lesser free arachidonic acids and depleted production of PGs reduces the melanocyte tyrosinase activity. This might be the mechanism for the effect of TA on melasma and improvement of post-inflammatory hyperpigmentation. Besides, it also reverses melasma-related dermal changes, such as vessel proliferation and increased number of mast cell.

In the majority of studies showing the efficacy of TA in melasma, the drug has been given orally. Although systemic TA has been reported to be safe for the treatment of melasma, the risk-benefit study must be done on a larger scale. The primary side-effects noted with its use are gastrointestinal complaints (nausea, diarrhea, and abdominal pain). There are also reports of serious complications such as deep venous thrombosis, pulmonary embolism, cerebral artery thrombosis and embolism, and coronary artery thromboembolism.

There is limited published literature on the role of topical TA and intradermal TA injections in melasma. Topical TA may cause irritation and allergy. Therefore, novel topical TA liposome formulations have been developed, but they are not yet commercially available. By injecting TA intradermally, it may be possible to treat the dermal and mixed-type melasma. Intralesional microinjection of TA appears to be a potentially new and promising therapeutic tool that can be easily performed in outpatient settings, with relatively rapid results and without significant side-effects.

Although many agents are available in the therapeutic options of melasma, its management is still challenging and recurrences are common. TA can prove to be a useful adjunct in the treatment of this

difficult to manage disorder of hyperpigmentation. It may also have some synergistic activity when used in combination with the other treatment modalities. But, like other available treatment options, it is not uniformly effective in all the cases. It leads to improvement in pigmentation in many patients, complete clearance in few, and recurrences can occur on stopping the treatment.

Carbo MA, Pastor MV, Nicolas BR, Sanjuan VP, Estebanez EQ, Carpio EG. Omalizumab in chronic urticaria: A retrospective series of 15 cases. *Dermatol Ther* 2013;26:257-9.

Chronic idiopathic or spontaneous urticaria (CU) affects around 0.1% of the population and can be highly distressing. It is defined by the presence of daily or almost daily symptoms for more than 6 weeks. Omalizumab is a monoclonal anti-IgE antibody approved for the treatment of severe allergic asthma and is also being tried in CU. This is a retrospective case series of 15 patients with CU treated with omalizumab. Omalizumab was administered at a dose of 150-300 mg subcutaneously every 2-4 weeks; the dosage used was adjusted according to total weight and serum IgE levels. Improvement was assessed after 3 and 6 months of treatment. Complete response was defined as symptom disappearance that could be followed by discontinuation of anti-histamines, and partial response as symptom improvement, but with symptom worsening when attempting to discontinue anti-histamines. After 3 months of treatment, 12 patients responded, with partial response in 9 and complete response in 3. At 6 months, 8 of 10 patients continuing on omalizumab had a complete response and 2 had a partial response. In patients discontinuing the drug, symptoms recurred after 5 weeks without treatment. Only 2 patients reported dizziness or nausea after the injections.

Comments: The chronic types of urticaria are divided into physical urticaria (cold, delayed pressure, vibratory urticaria, and urticaria factitia), other urticaria types (aquagenic, cholinergic, contact urticaria, and exercise-induced urticaria/anaphylaxis), and spontaneous urticaria. Chronic spontaneous urticarias may be idiopathic (55%) or autoimmune (45%) as defined by the presence of the immunoglobulin IgG against the alpha subunit of the high affinity IgE receptor, or IgG anti-IgE antibodies.

The first-line drugs for the treatment of CU are second generation H1 anti-histamines. In non-responders,

the dose of the anti-histamine can be increased upto four-fold of the recommended dose or sedating H1 anti-histamine/H2 anti-histamine may be added. The second-line therapies are doxepin, leukotriene receptor antagonist, corticosteroid (short-term only), dapsone, chloroquine, hydroxychloroquine, and sulfasalazine. The third-line treatments include methotrexate, cyclosporine, mycophenolate mofetil, omalizumab, autologous serum therapy, intravenous immunoglobulin, and plasmapheresis.

Omalizumab is a recombinant humanized anti-IgE-IgG monoclonal antibody approved for the treatment of moderate to severe allergic asthma. It blocks the high-affinity Fc receptor of IgE and also reduces the expression of FcεRI on circulating basophils and mast cells, thus reducing their activation and histamine release. In addition to the anti-IgE mechanisms, it also induces eosinophil apoptosis, downregulates inflammatory cytokines IL-2, IL-4, IL-13, and TNF-alpha. This explains the successful results of omalizumab in CU patients even with low levels of serum IgE.

Omalizumab has been shown to be effective in chronic autoimmune urticaria, chronic idiopathic urticaria and various urticaria subtypes such as cholinergic, heat, cold, solar, and delayed pressure urticaria. It is used in doses of 150 mg or 300 mg subcutaneously every second or fourth week, depending on the weight and serum IgE levels. It has been found to be effective in restoring the patient's quality of life and in reducing the

urticaria activity score. Few or no side-effects have been reported with omalizumab therapy. The most frequent adverse events noted are nausea, flu-like symptoms, diarrhea, nasopharyngitis, upper respiratory infection, and headache. Anaphylaxis has very rarely been reported (<0.1%). Omalizumab is an excellent treatment choice for severe treatment-refractory urticaria. It allows for a significant reduction in the dose of anti-histamines, systemic steroids, and other immunosuppressives in patients with CU, thus minimizing their side-effects. The drawbacks with this therapy are the high cost, not uniformly effective in all patients, prolonged treatment, and risk of recurrence on stopping the treatment. Further studies should be performed to confirm its efficacy in urticaria refractory to the conventional treatment.

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