Review Article

Intralesional Agents in Dermatology: Pros and Cons

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Abstract

Since introduced in 1961, intralesional (IL) agent has become an essential part of the dermatological practice. The term IL referred to the direct delivery of agent percutaneously into skin lesions. This therapeutic approach is relatively safe, easy to perform and applicable for a broad range of dermatological conditions. On the other hand, immediate side effects, including pain during administration, bleeding, high risk of infection and allergic reaction, and subsequent side effects involving skin changes such as atrophy, telangiectasia, pigmentary changes, and striae are usually associated with this modality. This review paper highlights the pros and cons of IL agents in modern dermatology practice.

Keywords: 5-Fluorouracil, bleomycin, botulinum toxin-A and hyaluronic acid fillers, corticosteroids, cryotherapy, immunotherapy, intralesional agents, mesotherapy, platelet-rich plasma

Key message: Because intralesional agents are relatively safe, easy to implement, and effective in a broad spectrum of dermatological indication with excellent success rate and minimum systemic side effects, the trends in its use have been emerging nowadays. Pros over the cons make it a preferred choice in the dermatology field.

Review

Intralesional (IL) agent therapy is the injection of a higher concentration of a agents directly into skin lesions without significant systemic absorption.[1] Historically, in 1961, it was first introduced by Hollander *et al.* and, with the advent of time, has become a crucial part of dermatological therapy.[2] The main principle behind this method is the formation of an intradermal depot and sometimes subcutis depot which bypass the superficial barrier zone.[1] In this review paper, we have gathered evidence of associated pros and cons of various agents that are used via IL route. Patients having an active or herpetic infection at the injection site and the previous history of hypersensitivity are contraindicated for IL drug therapy. Supp I enlists the level of evidence (LoE) that is used in this review paper.

Pros Associated with Treatment of IL Agents

Faster action, extended duration of action due to depot/reservoir effect, reduction in the need for long-term topical therapy, less side effects of systemic treatment, improvement in patient compliance, and deeper penetrance than topical therapy are the major advantages of IL agent therapy. Furthermore, synergistic action can be obtained while combined with other treatment modalities, e.g., IL drugs with cryotherapy for keloids.

Most commonly used IL agents

Corticosteroids

Since the early 1950s, cortisone and hydrocortisone acetate suspensions have been widely accepted, before low-solubility formulations such as triamcinolone acetonide (2.5–10 mg/mL;1 mg/cm^2) have been developed, which is the most preferred agent to date.[3] As per existing data reported by Verbov *et al.*[3] revealed 0.1–0.2 mL/cm dose per session with an interval of 3–6 weeks between two consecutive injections is most commonly used. The

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maximum dosage of triamcinolone acetonide should not exceed 40 mg/mL/session. Table 1 illustrates the suggested strength of IL triamcinolone acetonide injections in various dermatological conditions.[4-15] IL corticosteroid injection may be a beneficial therapeutic approach in cases where the topical formulation is not appropriate for use, mainly due to low potency and inefficient epidermal barrier penetration, or under clinical circumstances consistent with epidermal atrophy. This is a cost-effective, globally accessible and highly effective technique. This mode of therapy may be helpful to the dermatologist to avoid the notable and sometimes fatal side effects of systemic corticosteroid. When an additional local high dose of a corticosteroid is required to treat cutaneous disease, they can be used as a supplement to systemic therapy.[16] In agreement with United States Food and Drug Administration (USFDA), IL triamcinolone (10 mg/mL) is on-label drug. As per stated, a 10 mg/mL dose is indicated for alopecia areata; discoid lupus erythematosus; keloids; localized hypertrophic, infiltrated inflammatory lesions of granuloma annulare, lichen planus, lichen simplex chronicus (neurodermatitis), psoriatic plaques, necrobiosis lipoidica diabeticorum and occasionally useful in cystic tumors of an aponeurosis or tendon.[17]

5-Fluorouracil

Table 2 outlines the possible use of IL 5-fluorouracil (available as 50 mg/mL ampoule) in various dermatological condition.[18-24] In each reported study, the interval between each session was 1 week. The upside of IL 5-fluorouracil is that it allows higher drug concentration in the lesion for a longer duration compared to topical formulation. It is used as "off label" drug for IL application.

Botulinum toxin-A and hyaluronic acid fillers

In 2002, the USFDA-approved therapeutic botulinum toxin-A for various aesthetic uses. Evidence of beneficial effects of botulinum toxin-A in various aesthetic conditions are as follows: hypertrophic scars (2.5 U/cm^3; LoE-Ib),[25] keloid scars (100 U diluted with 5 mL of preservative-free saline; LoE-V),[26] upper facial rejuvenation (10–40 IU with 4–6 months duration, for periorbital area 10–30 IU up to 3–4 months and forehead 6–15 IU used for 3–6 months; LoE-V),[27] and multiple hidrocystomas (concentration of 7.5 U/0.1 mL; LoE-IV).[28] This therapeutic approach is a simple and well tolerated. Compared to corticosteroid, IL botulinum toxin type A has minimal discomfort and other adverse events as well as no risk of scarring. USFDA-approved the three botox for cosmetic use: onabotulinum,

Table 1: Suggested strength of IL triamcinolone acetonide injections from existing literature

Author, year	Indications	Dosage/session (mg/mL)	Level of evidence
Drugs.com, 2019[4]	Sarcoidosis, localized psoriasis, hypertrophic lichen planus, nail lichen planus, and granuloma faciale	5–10	V
Marks *et al.*, 2019,[5] Riis *et al.*, 2016,[6] Drugs.com, 2019,[4] Sar-Pomian *et al.*, 2012[7]	Necrobiosis lipoidica, hidradenitis suppurativa, lichen simplex chronicus, Pemphigus	10	V, IV, V, V
LeCourt *et al.*, 2019[8]	Prurigo nodularis (more scarred pruriginous lesions may require higher concentrations)	2.5	V
Bolduc *et al.*, 2018[9]	Alopecia areata	2.5–10	V
Tkachenko *et al.*, 2018,[10] Wang *et al.*, 2014[11]	Discoid lupus erythematosus and vitiligo	3	V, V
Ahm *et al.*, 2012[12]	Hemangiomas	10–40	IV
Coppola *et al.*, 2018[13]	Keloids (thick or moderate/hypertrophic scars)	40 or 10	IIIa
Cyr *et al.*, 2006[14]	Granuloma annulare	2.5–5.0	V
Leeming *et al.*, 1965[15]	Cystic acne	2–3 (not on face) 1–2 (face)	V

Table 2: Evidence of use of IL 5-fluorouracil along with dosage strength in the listed dermatological indication

Author, year	Indications	Dose/total injections	Level of evidence
Mahajan *et al.*, 2014[18]	Resistant localized plaque psoriasis	0.1 mL/cm^2/3 injection	Ib
Yazdanfar *et al.*, 2008[19]	Warts	4 mL of 50 mg/mL 5-fluorouracil and 1 mL of a mixture of 20 mg/mL [2%] lidocaine and 0.0125 mg/mL epinephrine/4–5 injections	Ib
Oh *et al.*, 2005[20]	Infantile digital fibromatosis	10 mg (0.2 mL)/5 injections	V
Morse *et al.*, 2003, Kirby *et al.*, 2010[21,22]	Squamous cell carcinoma, basal cell carcinoma and nonmelanoma skin cancer	0.8 to 2.4 mL/8 injections	V, IIa
Gupta *et al.* 2002, Fitzpatrick, 1999[23,24]	Keloids	50–150 mg/16 injections	Ia
		0.9 mL of 5-FU+0.1 mL triamcinolone acetonide (10 mg/mL)/average 5–9 injections	V

abobotulinum, and incobotulinum. Mentioned all are based on botulinum toxin A.

Platelet-rich plasma

Treatment details of platelet-rich plasma (PRP) in various dermatological conditions are enlisted in Table 3.[29-36] PRP was prepared using a double centrifugation technique. PRP is a safe, simple, inexpensive, and biocompatible procedure. Its ability to facilitate wound healing and no probabilities of allergic reactions have attracted attention in diverse medical fields. Both the PRP treatment and the device used to prepare it are "cleared" by the FDA, rather than "approved" as PRP is not a drug and in FDA, D stands for Drug.

Mesotherapy

It is an "intra-dermotherapy" rather than an "IL therapy." In IL therapy, the injection is targeted inside the skin condition to be treated regardless of whether the skin lesion is in dermis or subcutis, whereas, in mesotherapy, the depth of needle penetration exceed more than 4 mm into the skin and injections are regularly spaced.[37] As per the literature review, mesotherapy has shown promising outcomes in the treatment of androgenic alopecia(LoE-Ib),[38] telogen effluvium (LoE-V), cellulite lipolysis (LoE-V), and localized fat dissolution (phosphatidylcholine, vitamin complex, trace elements, collagenases, hyaluronidases, etc.) (LoE-V and acute cutaneous leishmaniasis (LoE-Ib).[39] It is a nonsurgical, minimally invasive method having a rapid rate of onset, due to the short time necessary to reach the site of action, as well as a prolonged local action. It is not FDA approved.

Cryotherapy

It is an "off label" therapy. IL cryotherapy with liquid nitrogen has been used, along with steroids, for the treatment of keloids and hypertrophic scars (LoE-IV).[40] IL cryotherapy allows for focused destruction of keloid scar tissue with minimal surface damage to the epidermis. Also, it claims to enhance volume reduction and decrease recurrences while minimizing the risk of hypopigmentation.

Bleomycin

Bleomycin is not USFDA-approved drug for IL therapy despite it is used in the treatment of the various conditions. It is marketed as bleomycin sulfate powder lyophilized 15 U/vial (reconstituted with 1–5 mL sterile water for injection or 0.9% normal saline) or 30 U/vial (2–10 mL water/normal saline). It penetrates poorly through cell membranes. Interestingly, penetration can be enhanced by disrupting cell membranes when reconstituting with local anesthetic (lignocaine).[41] As shown in Table 4, with varying dose, it is beneficial in the field of dermatology.[42-53] IL bleomycin offers the advantage of low dose than the usual systemic dose (30 mg twice weekly), no significant systemic adverse effects and high patient satisfaction. It does not require special puncture needles or technical expertise and there is a minimal drug wastage from spills. Compared to cryotherapy, it was also proved to be efficient in the treatment of plantar warts in terms of cure rate, less number of session, and low recurrence rate.[54]

Immunotherapy

This therapeutic modality utilizes the ability of the immune system to mount a delayed-type hypersensitivity response to various antigens and also the wart or tumor tissue. In today's practice, measles, mumps, and rubella vaccine (MMR) (0.1 mL/lesion, 1–3 weekly, up to 3–6 weeks/till complete resolution) (LoE-IIb),[55] mycobacterium indicus pranii (LoE-IV) [(0.1 mL/lesion weekly till 10 weeks or complete resolution),[56] bacillus Calmette–guérin (*BCG*) vaccine (0.1 mL/lesion every 2 weeks, till 5 doses or complete resolution of warts) (LoE-V),[57] candida antigen (0.1–0.3 mL (1:1000), repeated after 3 weeks until complete resolution/4 weeks) (LoE-IV),[58] purified protein derivative (PPD) or tuberculin test antigen (0.1/lesion injected 1–3 weekly till complete resolution/12 weeks) (LoE-IIb)[59] are the most commonly used IL immunomodulator agents. Apart from this, other antigens such as trichophyton skin test antigen have also shown satisfactory results with varied success in the therapy of warts. Notably, no scarring or pigmentation has been observed unlike other destructive warts therapies, and lower recurrence rate is further benefits. At present, cryosurgery, laser surgery, electrosurgery, bleomycin, curettage, and topical keratolytic applications are available alternatives for the treatment of warts. These modalities are associated with pain, unsightly, and recurrences. In new research era, talimogene laherparepvec, a herpes-based oncolytic viral injectable therapy, is the first USFDA-approved IL therapy for advanced melanoma. Apart from this, other IL therapies including PV-10 (Rose Bengal), IL-12

Table 3: The recommended dose of PRP in various dermatological conditions

Author, year	Indication	Treatment	Level of evidence
Gopinath *et al.*, 2019[29]	Chronic nonhealing cutaneous ulcers	6 injections/1 week interval	IV
Tuknayat *et al.*, 2018[30]	Melasma	3 injections/1 month interval	C
Mahajan *et al.*, 2018[31]	Chronic localized vitiligo	6 injections/2-week intervals	C
Gamil *et al.*, 2017[32]	Striae distensae	3 injections/1 month interval	Ib
Goyal *et al.*, 2017[33]	Male pattern baldness	6 injections (0.1 mL per cm^2)/ 21 days interval	Ib
Behnia-Willison *et al.*, 2016[34]	Lichen sclerosus	3 injections/4 to 6 weeks apart and again at 12 months	IV
Shumez *et al.*, 2015[35]	Alopecia areata	3 injections/3 weeks interval	IIIb
Jeong *et al.*, 2011[36]	Refractory lipodermatosclerosis	5 injections/2-week interval	V

plasmid electroporation, and Coxsackievirus A21 have shown favorable clinical outcomes.[60]

Rarely Used IL Drug Therapy

Tranexamic acid

It is off-label treatment for melasma. Published report by *Veggalam and Perumalla* (LoE-IIb) and Pazyar *et al.* (LoE-IIb) suggested its potential role in the treatment of melasma (0.05 mL of 4 mg/mL—1 cm apart, once a week ×12 weeks).[61,62] The use of oral and intravenous dosage forms is limited due to its adverse effects and contraindications resulted by its thrombolytic property. Its IL administration was reported to be an effective way of treatment for melasma with minimum risk of adverse effects.

Table 4: With varying dose, the beneficial effect of bleomycin in the field of dermatology

Author, year	Indication	Dose	Level of evidence
Dinh Huu Nghi *et al.*, 2019[42]	Keloids	0.2–0.4 mL/cm^2 (maximum volume per session 3.5 mL, the interval between each session: 4 weeks and the total number of session depend on the cosmetic outcome)	IV
Unni *et al.*, 2017[43]	Common warts	Concentration: 1 unit/1 mL. Maximum 2 injection was given	Ib
Aziz-Jalali *et al.*, 2014[44]	Resistant warts	1 mg/mL IL/1–3 doses/every 4 weeks	IV
Kumar *et al.*, 2012[45]	Lymphangioma	0.5 mg/kg body weight, not exceeding 10 units at a time	IIa
Soni *et al.*, 2011[46]	Palmo-plantar and periungual warts	0.1–2 mL/session, monthly, up to 4 injections/wart	Ib
Dhar *et al.*, 2009[47]	Cutaneous warts	Concentration: 1 mg/1 mL (0.1% or 1 unit/mL). Less than 2 mL of 0.1% bleomycin solution was given in a single visit.	Ib
Gyurova *et al.*, 2006[48]	Multiple basal cell carcinomas	3 IU bleomycin solution every 48 h (bleomycin was dissolved in normal saline solution to a concentration of 2 IU/mL and further diluted with an equal amount 1% lidocaine hydrochloride); approximately 0.375 mL of the solution was injected into each lesion. In total, seven injections were given.	V
Pienaar *et al.*, 2006[49]	Hemangiomas and vascular malformation	0.3–1 mg/kg, up to a maximum of 15 mg/month	IIb
Heller *et al.*, 1998[50]	Cutaneous and subcutaneous tumors	The dose of IL bleomycin (electrochemotherapy) was based on tumor volume. It was administered at a concentration of 5 Units/mL. The dosage was as follows: 0.5 Units for tumors up to 100 mm^3, 0.75 Units for tumors 100–150 mm^3, 1.0 units for tumors 150–500 mm^3, 1.5 units for tumors 500–1000 mm^3, 2.0 units for tumors 1000–2000 mm^3, 2.5 units for tumors 2000–3000 mm^3, 3.0 units for tumors 3000–4000 mm^3, 3.5 Units for tumors 4000–5000 mm^3, and 4 Units for tumors larger than 5000 mm^3.	IIb
Soyuer, 1988[51]	Leishmaniasis cutis	1% Solution of bleomycin sulfate in normal saline solution/1.5 mg of bleomycin/ one injection	V
Sayama *et al.*, 1983[52]	Keratoacanthoma	0.2 to 0.4 mg according to the size of the lesions	IV
Figueroa *et al.*, 1980[53]	Condyloma acuminatum	1 mg of bleomycin diluted in 1 cc of sterile water injected. 0.5 and 5 mg per session/ at intervals of 2 to 3 weeks/total injection range 1–4	IV

Table 5: Describes the indications of IL interferons in dermatology

Author, year	Indication	Interferon	Dose/duration	Level of evidence
Mahajan *et al.*, 2020,[63] Cornell *et al.*, 1990,[64] Tourani *et al.*, 1989,[65] Kütting *et al.*, 1997,[66] Wollina *et al.*, 1998,[67] and Wollina *et al.*, 1999,[68] Cozzio *et al.*, 2006[69]	Leishmaniasis	IFN-γ	1–30 μg/m^2	V
	Basal cell carcinoma	IFNα-2b	1.5 million IU on 3 alternate days per week for 3 consecutive weeks*	Ib
	Cutaneous B-cell lymphoma	IFNα-2a	3 to 9 million/units/session and the sessions were repeated three times a week for several months	V
Oh *et al.*, 2004[70]	Keratoacanthoma	IFNα-2b	3MIU per week for 4–6 week	
Lacy *et al.*, 2002[71]	Peyronie's disease	IFNα-2b	1–2 MIU weekly for 3–5 weeks	
Welander *et al.*, 1990[72]	Genital warts	IFNα-2b	1 MIU three times a week on alternative day for a total of nine injections	Ib
Wolff *et al.*, 1985[73]	Mycosis fungoides	IFNα-2	2 × 10^6 units three times weekly for 4 weeks in one lesion	Ib

IFN = interferon; MIU = Million International Unit

*For larger tumor size, more doses have been given

Interferons

Interferons (IFNs) are glycoproteins belonging to the family of cytokines with antiviral, antitumor, and immunomodulatory activities. Table 5 describes the indications of IL interferons in dermatology.[63-73] IL interferon may be worked as a beneficiary in some situations such as patients for whom surgery would not suitable due to the presence of hemostasis, increased risk of infection or an inability to tolerate the rigors of surgery or some cases in which malignancy occurring in particular locations (anatomic regions tricky to operate on or where scarring might result in functional impairment). Only IFN-α-2b is "on-label" for hairy cell leukaemia, malignant melanoma, follicular lymphoma, follicular non-Hodgkin's lymphoma, AIDS-related Kaposi's sarcoma chronic, and hepatitis C.[74]

Sclerosants

These are "off-label" used agents. Various studies reported a favorable outcome of sodium tetradecyl sulfate in the mentioned indication: intraoral hemangiomas(LoE-V),[75] late-onset eccrine angiomatous hamartoma (IL sclerosant-polidocanol with 2 mL of 3% ethoxysclerol, total five sessions; the 2-week interval between each session; LoE-V),[76] vascular malformation (30 mg/mL of sodium tetradecyl sulfate; LoE -V),[77] pyogenic granuloma and mucocele [0.5–1 mL of 3% polidocanol (Asklerol); LoE-IV],[78] cystic hygromas (0.5 mg/kg, at intervals of 2 weeks; LoE-V),[79] wrist ganglion cysts (sodium tetradecyl sulphate; 1–2 cc of inj.; LoE-IV)[80] and pseudocyst (3% sodium tetradecyl sulfate; LoE-V).[81] This mode of treatment with a variety of sclerotic also has shown beneficial effects in telangiectasias, venulectasias of lower extremities, lymphangioma, and circumscriptum in a dose of 0.1 to 0.5 mL/site at weekly intervals (LoE-V).[1] IL sclerotherapy is a noninvasive, economic technique, and there is a low risk of hemorrhaging. The reported advantages of sodium tetradecyl sulphate as a sclerosing agent are the absence of pain, no hemolysis, less hyperpigmentation, complete regression of low vascular lesions and very low incidence of allergic reactions.

Amphotericin B

It is not USFDA approved. Mushtaq *et al.*[82] and Nikandish *et al.*[83] have been promisingly attempted in lesions of cutaneous leishmaniasis (case series: the dose of 2.5 mg/mL/week, the total number of dose 3 to 10 depending severity of disease) (LoE-IV) and ocular leishmaniasis (1.5 mg per injection/week till 6 weeks) (LoE-V), respectively. Since 1950, antimoniate compounds has recognized as first-line treatment for cutaneous leishmaniasis. At the current time, growing antimonial tolerance and increasing prevalence of the disease worldwide; leads to the development of other better alternatives. With advance research, IL amphotericin comes out an as good option for this condition. IL amphotericin B is a feasible and less expensive alternative to antimoniate and especially, useful in patients who were resistant or allergic to meglumine antimoniate. The mechanism of leishmanicidal action is believed to be drug-binding to parasite ergosterol precursors, such as lanosterol, causing disruption of the parasite membrane.

Methotrexate

However, it is a off-label drug, various studies have been reported the potential role of methotrexate in keratoacanthomas (0.4 to 1.5 mL of 12.5 or 25 mg/mL/total 1–2 injections) (LoE-IV),[84] nail psoriasis (25 mg/mL) (LoE-IV),[85] cutaneous malignancy (~0.3-2.0 mL of 12.5 or 25 mg/mL, two injections ~2 weeks apart) (LoE-IV),[86] recurrent squamous cell carcinoma (3 IL injections:1.0 mL of 25 mg/mL at week 0, 1.0 mL of 25 mg/mL at week 2, 0.6 mL of 25 mg/mL at week 7 (LoE-V).[87] It is a good alternative for surgical excision in the treatment of keratoacanthoma. IL methotrexate is an inexpensive and noninvasive procedure, and cosmetic outcomes are very satisfactory compared with surgical excision. Furthermore, hospitalization or general anesthesia is not needed. The cost of a 2 mL vial (25 mg/2 mL) of methotrexate is less than 200 INR. Each vial can be used multiple times.

Vincristine and vinblastine

Vincristine, not USFDA approved for IL application, a universally known vinca alkaloid antiblastic drug that disrupts microtubular function which is used in haematological neoplasms and nephroblastomas. Thus, its usage in epithelial neoplasms is a mainstay for the activity in Kaposi sarcoma (0.03–0.08 mL of vincristine sulphate at a concentration of 1 μg/mL) (LoE-IIIb).[88] Besides, another vinca alkaloid agent, such as vinblastine, is also recommended for systemic therapy because of its reduced neurotoxicity.[89] Vinblastine is marked in 10 mL vials and used in a dosage of 1 mg/mL. Approximately 0.03–0.1 mL of the drug is injected, after diluting with 0.9% normal saline (LoE-IV). IL vincristine gives excellent therapeutic response in Kaposi sarcoma with full healing and recovery of function, low cutaneous reactions, and no systemic toxicity.

Verapamil

It is "off-label" drug. Levine *et al.*[90] have demonstrated the beneficial effect of IL injection of calcium antagonist verapamil in the therapy of Peyronie's disease (5 mg/2 cc diluted to 10 cc total volume with injectable saline) (LoE–IV). According to Margaret Shanthi *et al.*,[91] IL verapamil combined with triamcinolone is preferred choice in the treatment of keloids and hypertrophic scars when given in a dose of 2.5 mg/mL every 3 weeks for 6 months (LoE–Ib). This outcome was supported by the verdicts of Ahuja *et al.*,[92] concluded previously mentioned combination is nearly similarly efficient with very few adverse effects

and provides a remedial alternative for treating larger and recalcitrant scars (LoE-Ib). Clinically, this drug is safe for patients with Peyronie's disease if precautions are taken to prevent injury to the dorsal neurovascular bundle. Compared to other modes of therapy, it appears to induce a rapid, beneficial effect in some patients (those with angulation of less than 30°) for reduction of plaque size. Patients with localized plaque are the most qualified for IL injection of verapamil. IL verapamil may be a proper choice compared to triamcinolone in the treatment of hypertrophic scars and keloids, as patient acceptability is good for IL verapamil and lower adverse drug reactions reported with its use.

Photodynamic therapy

IL photodynamic therapy is off-label and its uses continue to increase. IL photodynamic therapy is a modality in which photosensitizers such as aminolevulinic acid have been inserted intralesionally and then photosensitizers are exposed to a specific wavelength of light, creating a form of oxygen that destroys surrounding cells. Various published literature documented the use of IL photodynamic therapy with a considerable improvement in hidradenitis suppurativa [Photosensitizer: 5% 5-aminolevulinic acid (ALA); radiation: multidiode (630 nm) 1.2 watts (W), fluence 180 Joules (J/cm^2); Follow-up 5–7 week interval] (LoE-IV),[93] myxoid cysts [Photosensitizer: 5% 5-ALA; radiation: multidiode (630 nm) 1 Watts (W), fluence 240 Joules (J/cm^2); Follow-up 2 months] (LoE-IV),[94] pyogenic granuloma [Photosensitizer: Nearly 0.3 mL/cm^3 of 5-ALA, 20% solution; radiation: Waldmann photodynamic therapy 1,200 L (600–720 nm), light dose of 100 J/cm^2, 1 W, fluence 100 mW/cm^2; follow-up after 2 week] (LoE-IV),[95] cutaneous malignancies (nodular basal cell carcinoma, squamous cell carcinoma) [Photosensitizer: nearly 0.3 mL/cm^3 of 0.5% 5-ALA under 2% mepivacaine hydrochloride anesthesia; radiation: a red light at 100 J/cm^2 (LoE-IV)[96] and acne [Photosensitizer: 0.1–0.15 cm^3 of 5-ALA; radiation: long-pulsed dye laser, passes 2-3, 7.5 J/cm^2 fluence, 10 ms pulse duration, 10 mm spot size, a dynamic cooling spray of 30 ms with a 30 ms delay, interval between each session 1 month, total session 3] (LoE-IV).[97] In comparison with systemic photosensitizer administration, there are minimum skin phototoxicity and maximum local tissue destruction. It is prophesied that the preceding will result in less circumferential damage predisposing the formation of strictures. The upside of IL photodynamic therapy includes as following mentioned features:

- Safe, minimally invasive, and effective treatment
- Selective destruction of the tumors
- No pain
- Does not alter adjacent tissue and organs
- Proven clinical effectiveness
- Effectiveness in dermal tumors with great depth and thickness, impossible to obtain with other noninvasive techniques
- Fast, comfortable procedures with nor downtime neither side effects
- Accurate control of energy
- No hospital stay

Rituximab

It is off labelly used drug. This anti-CD20 monoclonal antibody was attempted favorably in oral pemphigus vulgaris (5 mg/cm^2, total two injections on days 1 and 15) (LoE-IV)[98] and primary cutaneous B-cell lymphomas (10 mg/mL [3 mL], total nine injections, 3 times/week followed by a 3-week treatment-free period) (LoE-IV).[99] IL administration allows local delivery of the drug, lacks the adverse effects of intravenous administration, reduces the amount of drug administered (<10% of the intravenous dose), and therefore is less expensive. Being an outpatient procedure also offers an advantage. No reported cutaneous atrophy and scars.

Cyclosporine

Many authors describe their experience in managing psoriasis with great success by using IL cyclosporine at a dose of 17 mg/mL/3 times weekly/up to 4 weeks. LoE-IV however, it is not FDA approved drug.[100,101]

Mistletoe extract

Traditionally, it is a whole remedy originating from *Viscum album* L., used in treatment of primary cutaneous B-cell lymphoma at a dose of 20 mL/month [20 mg/mL/ampoule] (LoE-V).[102] It is not FDA approved for the treatment of cancer.

Placental extract

The placental extract comprises of growth factors, anti-inflammatory agents, and antiplatelet activation and used as off-label agents. It is mainly reported as adjuvant therapy with IL injections dexamethasone has shown promising result in the mouth opening in patients with oral submucous fibrosis (LoE -IIb).[103]

Vitamin D3

It is not approved by USFDA for IL application. Existing data postulated the efficacy and safety of IL vitamin D3 in recalcitrant warts (0.2 to 0.5 mL, 600,000 IU, 15 mg/mL; a maximum of 5 warts were injected per session at 3-week intervals until resolution or for a maximum of four treatments) (LoE-IV),[104] multiple cutaneous warts [0.2 mL, 15 mg/mL; the interval between each session is 2 week, maximum of four sessions or until complete clearance] (LoE-IV),[105] common warts (0.2 mL, 300,000 IU, multiple sessions up to complete clearance or maximum four sessions) (LoE-IIb)[106] and plantar warts (0.3 mL,100,000 IU, 2.5 mg/mL) (LoE-IIIa).[107] IL vitamin D3 is an inexpensive, safe modality to treat multiple warts in developing countries.

Sodium thiosulfate

IL sodium thiosulfate in the concentration of 250 mg/mL may effectively treat patients with a localized cutaneous disease like calciphylaxis (LoE-V)[108] and calcinosis cutis (LoE-V).[109] This is off-label, usually well-tolerated, and inexpensive treatment. Direct targeted action with minimal systemic side effects is the main advantages of this therapy over systemic treatment. The time required for progressive healing of the wound is usually less. It may be used in both nonuremic and uremic calciphylaxis, and it is of special interest in bedridden elderly patients. Furthermore, it does not require any hospitalization and can be done in the outpatient clinic setting. The procedure is easy to learn, and any physician or resident can perform it after learning the injection techniques properly.

2% Zinc sulfate

This therapeutic approach has been shown encouraging result in plane warts (LoE-V),[110] common warts (LoE-IIb),[111] cutaneous leishmaniasis (LoE-IIIb),[112] and basal cell carcinoma (LoE-V).[48] It is used as an off-label drug.

Pentavalent antimony compound

It is not USFDA approved. Meglumine antimoniate (20 mg/kg/day) and sodium stibogluconate (SSG) are the main compounds belong to this category. Effectiveness of pentavalent IL antimoniate infiltration therapy for cutaneous leishmaniasis was studied and promising results have been obtained from gathered evidence (LoE-Ia).[113] With this therapy, we can achieve lower total doses of antimony (and thus less toxic effects) and a more flexible schedule without the requirement of daily drug administration. Also, this modality does not require investment in equipment, which makes it feasible to implement in the short term.

Cons Associated with Various IL Drug Therapy

Like other medication therapy, IL drug treatment also has some drawbacks, which have made it a matter of debate. Corticosteroids tend to disrupt collagen and elastic fibers and cannot be utilized in the circumstances, in which destruction is contraindicated like acne, necrobiosis lipoidica, and discoid lupus erythematosus. The risk of infection is higher, but there is no risk of hepatitis virus or HIV transmission. In some cases, a significant accidental damage to the eyes has been reported. The Dermo-Jet is not appropriate for injection to the proximal nail fold, as permanent dystrophy of the nail has been reported.[114] With the use of IL 5-fluorouracil, fewer instances of recurrences were elicited.[115] Usually, botulinum toxin type A was more expensive and was more difficult to procure. PRP is also more expensive and the process to obtain the PRP requires more time for the patient and the physician. In IL mesotherapy, cryotherapy and vitamin D3 multiple sittings are required. Principal disadvantages of the IL interferon-α-2b are high cost, multiple visits and prolonged follow-up. Hence, interferon could be now prescribed only for cases in which the cosmetic outcome is of predominant concern. Pulmonary fibrosis is associated with a high dosage of bleomycin.[116] Also multiple treatment sessions are required with this modality. Apart from reported side effects, there is no significant disadvantage associated with IL sclerosants therapy. The downfall with IL immunotherapy is pain associated with the injection, so children who prefer the nonpainful topical application and for patients with warts in extremely painful sites, such as those with periungual warts, it is futile.[58] Immunotherapy using diphenylcyclopropenone and squaric acid dibutyl ester is limited by allergic contact dermatitis, urticarial reactions, and pigmentary disturbances. Autologous vaccine therapy is limited by the oncogenic potential of the virus. The risk of cutaneous TB is associated with intralesional BCG vaccine. IL methotrexate contraindicated under various conditions includes pregnancy or breastfeeding, and individuals with an active infection, blood dyscrasias, drug interactions, hepatic disease, or renal disease. In IL methotrexate, treated patients with renal insufficiency, the rare incidence of pancytopenia has been documented.[117] Hence, a baseline and follow-up laboratory monitoring is recommended for patients treated with IL methotrexate.[118] There is a major drawback associated with the use of IL vinca alkaloids is: it requires the physician to perform the injection. IL photodynamic therapy is contraindicated in various conditions includes a nonresponsive tumor, a history of porphyria, systemic lupus erythematosus, photosensitive dermatoses, and allergy to the active ingredients in the photosensitizer, which is considerably rare. The main drawback of IL rituximab in secondary cutaneous B-cell lymphomas is the risk of relapse by not treating the systemic disease.[119] The main drawback of IL sodium thiosulfate was the pain during injections. To address this issue, before injecting sodium thiosulfate, local anesthesia with lidocaine 1% was given. This procedure probably is enhanced tolerability of formulation. On rare occasion, Hoigne phenomenon is associated with the use of more than 200 pharmacological agents including meglumine antimonite, and mainly occurs due to infusion of the drug. This reaction having psychiatric symptoms, disturbances of perceptions and intense anxiety as main clinical features. Furthermore, neurological signs and symptoms including panic, fear of death, alteration of consciousness, hallucinations, accompanied by tachycardia, tachypnea, hypertension, and numbness in the extremities may also be observed. In this situation, the withdrawal of the offending drug is a good way to rapidly attenuate clinical symptoms. Specific side effect for individual drugs belongs to this category is summarized in Supp II.

Conclusion

To sum up, IL therapy is a simple, safe office procedure when used carefully and judiciously. It is integral part for doing good dermatologic practice in modern time.

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Conflicts of interest

There are no conflicts of interest.

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Supplementary Material

Supp I: Level of evidence (LoE)
Level Ia: Systemic review of randomized control trials
Level Ib: Individual randomized control trials
Level IIa: Systemic review of the cohort study
Level IIb: Individual cohort study
Level IIIa: Systemic review of a case-control study
Level IIIb: Individual case-control study
Level IV: Case series
Level V: Expert opinion without explicit critical appraisal and/or reports of expert committees. Based on physiology and bench research, text book, literature review.

Supp II: Specific side effect for various IL drug therapy

IL drugs	Associated side effects
Corticosteroid injections	Atrophy, pain, hemorrhage, ulceration, hyper- or hypopigmentation, perilesional linear atrophy and hypo pigmentation, calcification, secondary infection, granuloma formation, allergic reaction, hypothalamus–pituitary–adrenal axis suppression, endocrine changes like hirsutism, striae, moon faces, and buffalo hump, growth retardation in young children, syncope, blindness
5-Fluorouracil	Pain, necrosis, hyperpigmentation, pruritus, partial wound dehiscence, local infection, ulceration, and atrophic scarring
Botulinum toxin and fillers	Edema, pain, erythema, temporary hypesthesia and over- or under-correction
Platelet-rich plasma (PRP)	Relatively safe with no risk of hypersensitivity
Mesotherapy	Pain, edema, erythema, local infection or abscess, lichenoid eruptions, hyperpigmentation and hypersensitivity reactions
Cryotherapy	Pain, erythema, hypo- or hyperpigmentation at the site of injections
Interferons	Flu-like symptoms, pancytopenia, hypocalcemia, hyperlipidemia, depression, cardiac arrhythmias, gastrointestinal upset, renal toxicity, alopecia, xerosis, injection site reactions, and menstrual irregularities
Bleomycin	Redness, swelling, pain and burning subside. Rare side effects are Raynaud's phenomenon, narrowing of fingertips, restricted nail growth, scarring, lymphangitis, paresthesias, and hematoma formation
Immunotherapy	Pain, pruritus, chills, transient erythema, edema, induration at the injection site, burning sensation, pruritus, myalgia, infection, wounding, ulcers, scarring, and hypo- or hyper pigmentation, autism in case of vaccines controversial granulomatous hepatitis and arthralgia
Sclerosants	Nicolau syndrome, which manifests with tissue necrosis, in a single case of pyogenic granuloma. Other complications include pain, ecchymosis, hyperpigmentation, necrosis, ulceration, and thrombophlebitis
Amphotricin–B	Local pain, fibrosis, local allergic reaction, transient erythema and pain at the injection site, mild burning sensation, and transient chemosis
Methotrexate	Ulceration, necrosis, and pancytopenia
Vincrisine and Vinblastine	Pain, erythema, and pruritus
Verapamil	No major side effects have been noted except for rare injection site reactions.
Photodynatimc therapy	Injection site reactions
Rituximab	Injection site reactions
Cyclosporine	Injection site reactions
Mistletoe extract	Injection site reactions, occasionally, mild uterine contractions may occur starting about 6 h after application and lasting about 1 h and mild headache
Placental extract	Mild local pain following the injections
Vitamin D3	Transient mild to moderate pain, itching, edema at the site of injection, mild erythema. Rare side effect like dyspigmentation. No signs of hypervitaminosis D or systemic side effects
Sodium thiosulfate	Transient local pain during injection
2% zinc sulfate	Early complications (pain, tenderness, or swelling) and late complications (postinflammatory hyperpigmentation, scaring, ulceration)