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Immunological Strategies to Fight Skin Cancer

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ABSTRACT

Skin cancer is the most common human cancer, and is currently considered a global epidemic. Recently, there has been a growing interest in immunomodulators, or up-regulators of the immune response, for the treatment and cure of various forms of skin cancer, including melanoma and nonmelanoma skin cancers, cutaneous T-cell lymphoma, Kaposi's sarcoma, cutaneous extramammary Paget's disease, and vulvar intraepithelial carcinoma neoplasia. Strategies to augment the host's immune response against cancer cells and/or cancer cell antigenicity have been investigated, including recombinant cytokines, immunomodulators, dendritic cell immunization, tumor antigen vaccination, T-cell-based immunotherapy, and gene therapy. Although the current standard of care for most of these cancers includes Mohs micrographic surgery, curettage, and cryo-, laser-, or radiotherapy, immunomodulators are becoming essential in the treatment of patients who are poor surgical candidates and/or require noninvasive therapy.

Key Words: *skin cancer, melanoma, squamous cell carcinoma, immunomodulators, interferon, imiquimod*

Recently, there has been a growing interest in immunomodulators for the treatment and cure of skin cancers. The therapeutic effect of immunomodulators on melanoma and nonmelanoma skin cancers, cutaneous T-cell lymphoma (CTCL), Kaposi's sarcoma (KS), cutaneous extramammary Paget's disease, and vulvar intraepithelial carcinoma neoplasia (VIN) is currently being investigated. Today, immunomodulators are essential in the treatment of patients who are poor surgical candidates and/or require noninvasive therapy, and there is a growing interest in understanding the safety, mechanisms, and therapeutic effect of immunomodulators on skin cancers.

Interferon

Cutaneous Melanoma

In the United States, adjuvant high-dose interferon (IFN) therapy has become the standard of care for melanomas with a high risk of recurrence, and the FDA has approved the use of IFN-α-2b for the treatment of patients with melanomas thicker than 4mm and patients with lymph node metastasis. An early randomized prospective trial by Creagan, et al. did not find a significant difference between IFN-α-2b treated melanoma Stage I and II subjects vs. untreated controls. Although the experimental group had a longer disease-free survival (median, 17 months for the IFN-α-2b group vs. 10 months for the control group), the difference was not

significant (p=0.09).[1] However, when Rusciani, et al. evaluated Stage II melanoma IFN-α-2b treated subjects vs. Stage II untreated controls, they found a metastasis rate of 19.6% (10 of 51 treated subjects) vs. 60% (18 of 30 untreated controls) at 3 years follow-up (p<0.0001), and a metastasis rate of 25% (4 of 16 treated subjects) vs. 63% (12 of 19 untreated controls) at 5 years follow-up (p<0.005). The Stage I melanoma IFN-α-2b treated subjects did not have a significantly different disease progression than the untreated Stage I controls at 3 and 5 years follow-up.[2]

IFN-α-2b therapy appears to be more effective in patients with lesions that have a poor prognosis. A recent study examined the combination of IFN-α-2b and surgery in high-risk melanoma patients. In this retrospective study of 150 patients, adjuvant high-dose IFN was an effective treatment option for patients with high-risk melanoma (Stage IIC, III) after definitive surgery. The 2-year and 5-year relapse-free survival rates were estimated at 48% and 36%, respectively.[3]

Basal Cell Carcinoma

The antiproliferative property of IFNs has also been employed in the treatment of patients with low-risk nodular basal cell carcinoma (nBCC) or superficial basal cell carcinoma (sBCC). Basal cell carcinoma (BCC) cells have been shown to express the CD95 ligand (FasL) and CD95 receptor (FasR), whereas the surrounding CD4+ T cells predominantly express FasR. Thus, in IFN treated patients, BCC may regress by FasR–FasL mediated apoptosis.[4] Intralesional IFN-α-2b at a concentration of 1.5 million international units (IU) used over a 3 to 4-week period has been shown to have an overall success rate of up to 100%.[5,6] However, when used for aggressive forms of BCC, this protocol has resulted in a cure rate of only 27% of treated patients.[7] Therefore, IFN treatment of BCC remains an alternative only for patients with low-risk nodular or superficial BCC.

Squamous Cell Carcinoma/ Actinic Keratosis

Intralesional recombinant IFN-α-2b has been shown to be effective in the treatment of squamous cell carcinoma (SCC) and actinic keratosis (AK). When IFN-α-2b was administered at a dose of 1.5 million IU three times/ week for 3 weeks to SCC lesions, 33 of 34 (97.1%) lesions showed an absence of SCC histologically.[8] However, when compared to other treatments for AK, the use of IFN is limited by the pain of injections and the multiple follow-up visits necessary.

Cutaneous T-cell Lymphoma

IFN-α is one of the most effective single-therapy agents for the treatment of CTCL.[9] Low-grade, nonHodgkin, T-cell lymphomas are always associated with cutaneous involvement and include mycosis fungoides (MF) and the Sézary syndrome (SS).[10] A literature review by Bunn, et al. of 207 MF and SS cases treated with IFN-α-2a revealed an overall response rate of 55%, with 17% of cases being complete responders to IFN-α-2a

Interferon-α-2b/ Study	Melanome	Design	Number of Treated Patients	Dose/ Route	Frequency/ Duration	Length of Treatment	Partial Clearance Rate	Complete Clearance Rate
Creagan et al.[1]	Stages I, II	Ra, Pr	131	20 MU/m^2/ IM	t.i.w. x 12 wk	6.1 yrs	41 (Stage I) 12 (Stage II)	72
Fluck et al.[3]	Stages IIC, III	Ra, Re	150	20 MU/m^2/ IM 10 MU/m^2/ SC	5 d/wk x 4 wks t.i.w. x 48 wks	2.9 yrs	17 (Stage IIC) N/R (Stage IIIA) 40 (Stage IIIB) 9 (Stage IIIC)	73
Kirkwood et al.[42]	Stages IIB, III	Ra, Pr	146	20 MU/m^2/ IM 10 MU/m^2/ SC	5 d/wk x 4 wks t.i.w. x 48 wks	6.9 yrs	17	38
Kirkwood et al.[43]	Stages IIB, III	Ra, Pr	215	20 MU/m^2/ IM 10 MU/m^2/ SC	5 d/wk x 4 wks t.i.w. x 48 wks	4.3 yrs	28	84
Kirkwood et al.[44]	Stages IIB, III	Ra, Pr	438	20 MU/m^2/ IM 10 MU/m^2/ SC	5 d/wk x 4 wks t.i.w. x 48 wks	1.3 yrs	37	46

Table 1: Summary of key published studies assessing the efficacy of interferon-α-2b for skin cancer treatment

Abbreviations: CTCL–cutaneous T-cell lymphoma; d–day; IM–intramuscular; MU–million international units; N/R–Not Reported; Pr–prospective; Ra–randomized; Re–retrospective; SC–subcutaneous; t.i.w.–three times/week; wk–week; yrs–years

therapy. These authors concluded that recombinant IFN-α-2a monotherapy has greater benefit in patients with early-stage disease, with 3 million IU of IFN-α-2a given subcutaneously three times/week being the optimal treatment regimen. In this study, no therapeutic differences were observed between IFN-α-2a and -2b.[11] A study by Vonderheid, et al. has revealed that intralesional injections of MF plaques with IFN-α-2b at a dose of 1 million IU given three times/week for 4 weeks produces substantial localized clinical and histological improvement with 10 of 12 plaques demonstrating complete regression localized to the IFN-α-2b injected sites.[12]

Kaposi's Sarcoma

The use of IFN-α-2a and -2b in the treatment of KS in patients with acquired immune deficiency syndrome due to the human immunodeficiency virus has been approved by the US FDA. The recommended dosages for IFN-α-2a and -2b are 36 and 30 million IU subcutaneously three times/week, respectively. The average response rate of KS to high-dose IFN-α therapy has been approximately 30%. In many cases, tumor recurrence has been observed within 6 months after discontinuation of treatment, and response to subsequent treatments has not been reliable. This has led to indefinite treatment regimens until side-effects become intolerable.[13]

Imiquimod

Cutaneous Melanoma

As an immune response modifier, imiquimod induces IFN-α, tumor necrosis factor (TNF)-α, IL-1, IL-6, IL-8, and IL-12 production by monocytes, macrophages and toll-like receptor (TLR)-7-bearing plasmacytoid dendritic cells. TLR-7 is an essential receptor for imiquimod-induced immune responses.[14] Imiquimod also generates production of IFN-α after CD4 cells are stimulated by IL-12. IFN-α stimulates cytotoxic T lymphocytes responsible for killing virus-infected and tumor cells.

Topical imiquimod 5% cream has been found to be effective in the treatment of lentigo maligna (LM, *in situ* melanoma). In a pilot, open-label, nonrandomized study evaluating the effectiveness of imiquimod 5% cream once daily for a maximum of 13 weeks on five patients with LM, a 100% response rate was observed without reoccurrence during a 3–18 month follow-up interval.[15] Case reports describing multiple metastatic melanoma skin lesions clearing after topical imiquimod 5% cream application have also been published. The two patients studied applied imiquimod 5% cream three times/week to the metastatic skin lesions with a 1cm surrounding margin.[16]

Basal Cell Carcinoma

Imiquimod 5% cream has been shown to induce the expression of FasR on BCC cells, and FasR mediated apoptosis may contribute to the effectiveness of imiquimod in BCC treatment.[17] An initial 16-week, dose-ranging, vehicle-controlled trial examining the effect of 5% imiquimod cream on nBCC and sBCC found an overall histological response rate of 83% (20/24) in the 5% imiquimod cream treatment group vs. 9% (1/11) in the vehicle treatment group.[18] Subsequent sBCC randomized, multicenter studies have reported 100% efficacy with twice daily application vs. 73–88% efficacy with once daily application of 5% imiquimod cream.[19–21]

Squamous Cell Carcinoma/ Actinic Keratosis

Imiquimod studies in SCC patients are restricted to AK and *in situ* SCC clinical presentations. A 16-week, twice weekly, imiquimod 5% cream treatment regimen has been approved by the FDA for patients with AK lesions on the face or scalp. This treatment regimen has achieved a 45.1% (97/215) complete clearance and a 59.1% (127/215) partial clearance rate. These clearance rates are significantly higher than the complete and partial clearance rates found in the vehicle group ($p< 0.001$).[22]

Bowen's Disease

Current therapies for Bowen's disease, or intraepidermal SCC, include 5-Fluorouracil, surgical excision, curettage, electrocautery, cryo-, laser-, photo-, and radiotherapy.[23] In a Phase II open-label study, 16 biopsy-proven plaques of Bowen's disease, with diameters ranging between 1–5.4 cm, were treated once daily for 16 weeks with imiquimod 5% cream. Of the 16 lesions treated, 15 were on the lower extremities and 1 was on the shoulder. Fourteen of 15 patients (93%) had no residual tumor present in the 6-week post-treatment follow-up biopsy. Thirteen patients were followed to 6 months without disease recurrence.[24]

Extramammary Paget's Disease

Extramammary Paget's disease (EMPD) is an infrequent epidermal malignancy most commonly occurring in the anogenital and vulvar regions. Therapeutic modalities include wide local excision and Mohs micrographic surgery. A case report of two patients with primary limited cutaneous perineal and genital EMPD describes successful treatment of EMPD with imiquimod 5% cream, with confirmation of cure after 7.5–12 weeks of monotherapy. The treatment-associated morbidity

Imiquimod/ Study	Skin Cancer	Design	Number of Treated Patients	Dose/ Route	Frequency/ Duration	Length of Treatment	Partial Clearance Rate (%)	Complete Clearance Rate
Wolf, et al.[15]	Melanoma - Lentigo Maligna	Pi, OL, NR	5	5% cream /Top	q.h.s. x 5–13 wks	10 wks (median)	100 (5/5)	0 (0/5) (at median follow-up of 13 months)
Marks, et al.[19]	BCC - Superficial	Ra, OL, DR	3 33 30 33	5% cream/ Top	b.i.d. x 7 d/wk q.d. x 7 d/wk b.i.d. x t.i.w q.d. x t.i.w.	6 wks	100 (3/3) 87.9 (29/33) 73.3 (22/30) 69.7 (23/33)	N/R
Geisse, et al.[20]	BCC - Superficial	Ra, DB, VC	185 179 179 181	5% cream/ Top 5% cream/ Top Vehicle/ Top Vehicle/ Top	5 d/wk q.d. x 7 d/wk q.d. x 5 d/wk q.d. x 7 d/wk	6 wks	82 (152/185) 79 142/179) * 3 (11/360)*	N/R
Schulze, et al.[21]	BCC - Superficial	Ra, DB, VC	84 82	5% cream/ Top Vehicle/ Top	q.d. x 7 d/wk q.d. x 7 d/wk	6 wks	80 (67/84) 6 (5/82)	N/R
Mackenzie-Wood[24]	Bowen's Disease - Leg/Shoulder	Pr, OL	16	5% cream/ Top	q.d. x 7 d/wk	16 wks	93 (14/15)	0 (0/13) (at 6 month follow-up)
Lebwohl, et al.[22]	Actinic Keratosis - Face/Scalp	Ra, DB, VC 2 phase 3 trials	215 221	5% cream/ Top Vehicle/ Top	q.d. x 2 d/wk q.d. x 2 d/wk	16 wks	45.1 (97/215) 3.2 (7/221)	83.3% 0% (at 8 wk follow-up)
Korman, et al.[45]	Actinic Keratosis - Face/Scalp	Ra, DB, VC 2 phase 3 trials	242 250	5% cream/ Top Vehicle/ Top	q.d. x 3 d/wk q.d. x 3 d/wk	16 wks	48.3 (117/242) 7.2 (7.2/250)	86.6% 14.3% (at 8 wk follow-up)

Table 2: Summary of key published studies assessing the efficacy of imiquimod for skin cancer treatment

Abbreviations: BCC–basal cell carcinoma; b.i.d.–twice/day; d–day; DB–double blind; DR–dose response; N/R–not reported; NR–non-randomized; OL–open label; Pi–pilot study; Pr–prospective; Ra–randomized; Top–topically; VC–vehicle controlled; wk–week; q.d.–once/day; q.h.s.–every night; t.i.w.–three times/week; *–combined

was minimal when compared with other more invasive therapies.[25] Another case study has documented the eradication of EMPD of the scrotum in a 68-year-old male with nightly application of imiquimod 5% cream for 6 weeks, with no signs of reoccurrence at 6 months after discontinuation of therapy.[26]

VIN

Imiquimod was preconceived as possibly beneficial in the treatment of VIN of human papilloma virus etiology, due to its antiviral and antineoplastic properties; however, the literature shows mixed results. In a prospective, observational study examining the effects of imiquimod 5% cream three times/week for 16 weeks in 15 patients with high-grade VIN, 3 demonstrated local side-effects, including soreness, burning, erythema, ulceration, and blistering. One patient required hospitalization, catheterization, and analgesia. Of the 13 patients who completed the study, four demonstrated clinical improvement. Of these four patients, only one had a negative VIN biopsy. All four patients who responded clinically relapsed 4 months after treatment.[27] However, in a recent study examining the effect of imiquimod 5% cream applied three times/week for a maximum of 16 weeks in eight patients with biopsy-proven bowenoid and basaloid, VIN 2/3 had better results. Total clearance and partial clearance was observed in six patients and two patients, respectively, and the post-treatment biopsy showed an absence of precancerous lesions in seven of eight patients (87.5%).[28]

Dendritic Cell-based Therapy

The use of autologous dendritic cells (DCs) loaded with tumor-associated antigens as a natural adjuvant to actively prime an effective immune response against tumor cells is also being investigated.[29–35] A Phase I clinical trial by Escobar, et al. designed to address the

IL-12 Study	Skin Cancer CTCL	Design	Number of Treated Patients	Dose/ Route	Frequency/ Duration	Length of Treatment	Partial Clearance Rate	Complete Clearance Rate
Rook et al.[41]	T1/2 T3 T4	Pr, OL	5 2 3	50–300ng/kg/SC	q.d. x 2 d/wk q.d. x 2 d/wk q.d. x 2 d/wk	up to 24 wks	40% (2/5) 0% (0/2)* 50% (1/2) *Observed regression of injected tumor	40% (2/5) 0% (0/2) 0% (0/2)

Table 3: Summary of key published studies assessing the efficacy of IL-2 for skin cancer treatment

Abbreviations: CTCL: cutaneous T-cell lymphoma; d: day; IL: Interleukin; OL: open label; Pr: prospective; q.d.: once per day; SC: subcutaneous; wk: week;

safety and efficacy of immunizations with tumor lysate-loaded DCs in Stage III–IV metastatic melanoma patients found a significantly longer post-vaccination survival in patients with a delayed type IV hypersensitivity reaction against the melanoma cell lysate (17.25 months) than in nonresponders (8.625 months), (p=0.0261).[36] This study demonstrated that the vaccination procedure used was safe and could induce a clinical and immunologic response in patients with advanced melanoma, like other studies with comparable protocols.[35,37] However, a recent randomized Phase III clinical trial studying the effect of dacarbazine monochemotherapy vs. vaccination with autologous peptide-pulsed DCs in patients with metastatic melanoma found Grade 3/4 toxicities in seven patients in each treatment arm, and a total of 75 deaths at median follow up of 22.2 months. No significant differences were found in overall or progression-free survival between the two treatment arms.[29]

Interleukin-2

Cutaneous Melanoma

Dose-related serious toxicities have limited IL-2 studies in melanoma patients, and low-dose IL-2 therapy has produced disappointing clinical response rates.[38] When high-dose, 100,000 units/kg, intravenous, recombinant IL-2 was examined in 47 patients with metastatic malignant melanoma, up to 20% achieved objective responses; however, three patients developed myocardial infarction and one patient died during therapy.[39] IL-2-based biochemotherapy (IL-2, IFN-α-2b, cisplatin, dacarbazine, and vinblastine) has shown a response rate of 48%. It appears that this combination is statistically superior to either IL-2 or chemotherapy alone.[40] Results of ongoing trials may clarify the true value of IL-2 in combination chemotherapy.

IL-12

Cutaneous T-cell Lymphoma

CTCL presents with marked defects in IL-12 production, and progression of CTCL has been associated with profound defects in cell-mediated immunity and cytokine production. A Phase I dose-escalation trial examined the effect of recombinant human IL-12 (rhIL-12) at a concentration of 50ng/kg, 100ng/kg, or 300ng/kg, given two times/week subcutaneously for up to 24 weeks in 10 patients with CTCL. A complete clinical response (CR) was defined as complete disappearance of all measurable CTCL lesions for at least 1 month. A partial response (PR) was defined as at least 50% disappearance of all CTCL skin lesions for at least 1 month. Only patients with plaque stage disease (n=2) presented a CR. Two plaque stage patients and one Sézary syndrome patient had a PR. None of the T3 stage patients responded to the rhIL-12 treatment. The authors announced the development of future Phase II/III clinical trials based on the high response rate of plaque stage CTCL patients to rhIL-12.[41]

Future clinical trials on immunomodulators will continue to change the approach, management, and follow-up of skin cancer patients. These skin cancer therapies will continue to be based on principles governing the immune system. As our knowledge of the immune system continues to grow, the application of safe and efficacious immunomodulators to treat skin cancer will continue to change the practice of dermatology.

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The Use of Lasers for Decorative Tattoo Removal

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ABSTRACT

As the incidence of tattoo placement continues to increase, so does the demand for tattoo removal, with more than 10 million people in the US alone with a tattoo. Used in an appropriate clinical setting, Q-switched lasers provide relatively efficacious clearance of decorative tattoo pigment with minimal side-effects. We present our clinical experience along with literature findings on decorative tattoo removal and the important issues practitioners should consider in the management of tattoos.

Key Words: *tattoo, laser*

In the United States, an estimated 7–20 million people carry at least one tattoo.[1] Recently, Laumann and Farmer conducted a random survey of 500 men and women and found a prevalence of tattooing in 26% of males and 22% of females. Of those with tattoos, 17% considered tattoo removal.[2] The top reasons for tattoo removal are to improve self-esteem, to remove a disliked design, and to increase credibility with friends.[3]

Prior to laser technology, tattoos were removed via techniques with a high likelihood of scarring, such as surgical excision and cryosurgery. Unfortunately, no one laser system can remove all available tattoo inks. This review provides our clinical experience and recommendations for decorative tattoo removal.

The Tattoo

Essentially, tattoos are exogenously placed chromophores. Amateur tattoos are less dense, placed at variable depths, and composed of carbon-based ink. Professional tattoos contain a variety of densely packed, colored pigments at a uniform depth. Once implanted, the ink particles are phagocytosed by resident dermal fibroblasts, where they permanently remain in the superficial dermis.[4]

Laser Removal

In order to selectively remove tattoo pigments placed in the dermis, pulsed lasers must meet the following criteria:

a) The laser wavelength must be well absorbed by the targeted ink.

b) The heat generated should be spatially confined to the target.

c) The energy delivered must be sufficient to cause the desired effects.[5]

Quality-switched (Q-switched) lasers (lasers with ultrashort energy pulses in the nsec domain) with wavelengths in the visible-to-near infrared range (532–1064nm), enable the deposit of energy very quickly, producing a "photoacoustic" effect. The intense heat transients cause some particles to shatter and kill the cells in which the pigment resides. The rupture of pigment-containing cells eventually triggers phagocytosis and the packaging of tattoo fragments for lymphatic drainage.[6]

Several issues are important when evaluating a tattoo for removal (Table 1).[7] Amateur tattoos generally require fewer treatment sessions than professional tattoos. Distally located tattoos are more difficult to remove, and older tattoos may or may not be easier to remove than newer ones.[8] Lastly, bright-colored inks may necessitate more treatment sessions.

Q-switched Laser Systems

The use of Q-switching laser pulses was first explored with the Q-switched ruby laser (QSRL) (694nm), and expanded to include the Q-switched neodymium: yttrium-aluminum-garnet (Nd:YAG) laser (532nm and 1064nm) and the Q-switched alexandrite laser

Risks	Potential Solutions
Textural changes	Can be minimized with larger laser spot sizes and spacing the treatments 6–8 weeks apart.
Scarring (~ 5%)	Is highest on the chest, outer upper arm, and ankle.
Pruritus	Can be significant in the healing phase and minimized with topical corticosteroids.
Cobblestone texture	Seen within 2 weeks of treatment, is a sign of incipient scarring, and is frequently reversed with b.i.d. application of Class I topical steroids.
Hyperpigmentation and hypopigmentation	Can vary depending on skin phototype and is usually minimized with the 1064nm wavelength. If hyperpigmentation occurs, postoperative use of hydroquinone-containing compounds and UVA/UVB sun block can be beneficial, as can the avoidance of sun exposure.
Pre-existing local allergic reaction	Can worsen after laser treatment resulting in urticaria, or a systemic allergic reaction. In these cases, Q-switched laser treatment should be used with extreme caution. It is best to either use an ablative CO_2 laser or Nd:YAG to vaporize the tattoo or proceed with caution, cover with systemic corticosteroids, and consult an allergist before embarking on treatment.
Immediate pigment darkening	Frequently occurs in white, pink or skin-toned tattoos. Appropriate patient education should be provided prior to treatment of any at-risk tattoo. If and when darkening occurs, two treatment options remain: The tattoo can be excised or ablated, or multiple additional Q-switched laser treatments can be performed to eliminate the darker pigment. The best way to anticipate such darkening is to treat a test spot and evaluate after initial skin whitening has faded.

Table 1: Risks of laser removal of decorative tattoos and potential solutions

(755nm). The absorption spectrum of tattoos is unknown, with some colors responding better than others. As a result, a combination of laser systems may be used in stages for a single tattoo (Table 2).

Laser	Black	Blue	Green	Red
Alexandrite 755nm	XX	XX	XX	
Ruby 694nm	XX	XX	XX	
Nd:YAG 1064nm	XX	XX		
Nd:YAG 532nm				XX

Table 2: Choice of Laser for Removal of Tattoo Ink by Ink Color

Q-switched Ruby Laser (694nm)

The QSRL is effective for the removal of black, blue, and green inks. The laser penetrates to a depth of approximately 1mm and has spot sizes up to 6.5mm. Because this wavelength is well absorbed by melanin, caution should be used, as injury to melanocytes can lead to transient hypopigmentation and even depigmentation as well as textural change. The goal of treatment should be immediate tissue whitening (corresponding to water vapor in the skin) with minimal or no bleeding, and as with all laser treatments, no more than 10%–20% spot overlap should be employed. When compared to the other Q-switched lasers, the QSRL was shown to have the highest clearing rate after four and six treatments of blue-black tattoos. However >95% clearance was only obtained in 38% of the tattoos.[9] For amateur tattoos, it has been reported that a mean of 4.92 treatments are needed to achieve clearance of > 90% of pigment.[10] Other studies suggest only 11%–28% of professional tattoos achieve >75% clearance after more than six treatments.[11,12]

Q-switched Nd:YAG Lasers (532nm and 1064nm)

The Q-switched Nd:YAG laser system overcomes the obstacle of excessive melanin absorption and is used to remove blue and black ink and tattoos in darker skin types (1064nm), or red pigment (532nm). The clinical endpoint following laser treatment is whitening of the skin with occasional mild pinpoint bleeding. Current models offer a spot size range of 1.5–8mm, which may be more appropriate for eyeliner tattoos.

532nm

The 532nm wavelength (green light) is absorbed by hemoglobin, and as a result, purpura lasting 1 week to 10 days frequently occurs after treatment. This

wavelength is also effective for red, orange, and occasionally yellow ink. In 63% of red tattoos, > 75% clearance was achieved after one to five treatments at 2.5 J/cm^2. In this same study, only two of eight yellow tattoos faded.[13]

Some reports have detailed the paradoxical darkening of red tattoo pigment as well as other skin-toned, yellow, and pink tattoos.[14,15] This occurs as the laser pulse reduces ink from rust-colored ferric oxide (Fe_2O_3) to jet black ferrous oxide (FeO).[16] Similarly, bright colors may contain white ink made up of titanium dioxide (TiO_2, T4+) that is reduced to TiO_2 or blue Ti3+ upon laser treatment.

1064nm

The long 1064nm wavelength has the deepest penetration and carries the least risk of hypopigmentation; however, it is also the least effective in removing brightly colored pigments. Of all the laser systems, it is the one we recommend for use in darker skin types. This wavelength may also be useful when residual, more deeply placed ink particles are all that remain, as well as in the treatment of eyeliner tattoos, because it is less likely to damage the hair follicle.

Ferguson and August found that 79% of amateur black tattoos were >75% clear after one to five treatments at 1064nm, and 74% of professional tattoos achieved similar clearance but required up to 11 treatments (average 6.3).[13]

Q-switched Alexandrite Laser (755nm)

Although this laser system has the least amount of tissue splatter owing to its slightly longer pulse duration of approximately 50nsec (compared to 5–15nsec for the Nd:YAG and 15–40nsec for the ruby laser) it is not as successful as the other models. Similar to the QSRL, the alexandrite is most effective for removing black, blue, and green inks. As with the other lasers, the clinical endpoint is tissue whitening. In a study by Stafford, et al., an average of 11.6 treatments was required to completely remove professional blue-black tattoos, compared with 10.3 treatments for the same results in subjects with amateur tattoos. Hypopigmentation occurred in 80% of treated subjects, which resolved within 3–4 months of treatment.[17]

Further Research

As noted, the data available for solid colors have been mixed and may not be adequate for patient satisfaction. As a result, picosecond lasers such as the titanium:sapphire (795nm) laser are being compared to current Q-switched technology. It is theorized that by confining thermal and photomechanical damage to the target particle more effectively, these lasers may optimize tattoo removal either by increased phagocytosis or through transepidermal elimination. Initial animal studies[18] have been promising, as was a study in human subjects that showed a higher success rate of tattoo clearing with fewer laser treatments.[19] To date, however, only prototypes of this laser are available.

Conclusion

While no single laser system holds the answer for tattoo removal, Q-switched lasers can successfully fade most tattoos with minimal adverse effects. In understanding the capabilities and limits of current laser technology, practitioners can set realistic goals with their patients. Complete clearance of all treated tattoos is rare. At best, depending on the color, practitioners can expect 75% clearance in half the cases they treat. As the demand for tattoo placement increases, research continues to perfect tattoo removal with the development of picosecond and femtosecond laser systems.

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Class	Name/Company	Approval Dates and Comments
Antibacterial Agent	**Minocycline HCl** *SOLODYN™ Extended Release Tablets* Medicis	The US FDA approved this once-daily oral antibiotic in May 2006 for the treatment of inflammatory lesions of non-nodular moderate-to-severe acne vulgaris in patients 12 years of age and older. SOLODYN™ is not bioequivalent to any other minocycline product.
Antibacterial Agent	**Linezolid** *ZYVOX® 600mg* Pfizer Japan	Japan's Ministry of Health, Labor and Welfare approved a new indication in April 2006 for this antibacterial agent. It is now available for the treatment of infections associated with methicillin-resistant *Staphylococcus aureus* (MRSA).
Antibacterial Agent	**Tigecycline** *Tygacil®* Wyeth Pharmaceuticals	The EMEA's Committee for Medicinal Products for Human Use approved this antibiotic in May 2006 for use in complicated infections of the skin and soft tissue that were hospital or community acquired. This product is in a new class of antibiotics called glycylcyclines and has *in vitro* activity against many Gram-positive and Gram-negative bacteria, including MRSA.
Antiviral Agent	**CF-1743** FermaVir Pharmaceuticals	The US FDA accepted an Investigational New Drug application in May 2006 for preclinical and clinical studies related to a novel antiviral drug candidate for the treatment of shingles.

Drug News

Antipsoriatic Agent	In April 2006, Taclonex® (calcipotriene 0.005% and betamethasone dipropionate 0.064%) became available by prescription in the US. The US FDA approved this once-daily topical ointment in January 2006 for the treatment of psoriasis vulgaris in adults 18 years of age and older for up to 4 weeks.
Research News	A new meta-analysis of previous studies of tumor necrosis factor (TNF)-blocking antibodies, recently published in the *Journal of the American Medical Association**, found an increased risk of serious infections and a dose-dependent increased risk of malignancies in patients with rheumatoid arthritis. Collectively, using various types of analyses, the researchers found that those treated with TNF-blocking antibodies had 3.3 times the risk of developing cancer than those given placebo, and 2.0 times the risk of serious infection. Cancers were much more common in those patients treated with high doses of TNF-blocking antibodies. These drugs are also used to treat psoriasis, psoriatic arthritis, and Crohn's disease. *Bongartz T, et al. *JAMA* 295(19):2275-85 (2006 May 17).
Research News	According to a study published in the February issue of the *International Journal of Dermatology**, using makeup to cover a severe facial blemish may not improve the quality of a woman's life. Using the Skindex-16 and the Fear of Negative Evaluation assessment tools, the investigators found that severe facial blemishes of any cause have a significant impact on women's quality of life, and the effect of these lesions is mediated in part by psychological characteristics related to self-perception and self-presentation. They also found that women who did not use foundation, while they represented only 10% of the study population, had better health-related quality of life than those who did. *Balkrishnan R, et al. *Int J Dermatol* 45(2):111 (2006 Feb).

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