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Mycophenolate Mofetil: A Dermatologic Perspective

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ABSTRACT

Introduced in the 1970s as a treatment for psoriasis, mycophenolic acid has since been reformulated as mycophenolate mofetil (MMF). With an improved side-effect profile and enhanced bioavailability, MMF is a promising drug for immune-mediated skin disease. Currently approved for the prevention of organ rejection, its list of "off-label" dermatologic indications continues to grow. As a noncompetitive inhibitor of inosine monophosphate dehydrogenase (IMPDH), MMF inhibits de novo purine synthesis. Its relative lack of hepatonephrotoxicity and seemingly low risk of carcinogenicity offer important therapeutic advantages. While case reports and case series dominate the dermatologic literature, preliminary results are sufficiently promising to warrant larger, randomized clinical trials with this emerging therapy.

Key Words: *mycophenolate mofetil, CellCept®, inflammatory skin disease, dermatology*

In the past two decades, an increasing number of immunosuppressive agents have been developed to prevent allograft rejection in organ transplantation. A number of these medications have shown therapeutic efficacy in inflammatory skin disease; however, patients and physicians must be mindful of their toxicities. Originally isolated from cultures of *Penicillium stoloniferum*, mycophenolic acid (MPA) was first recognized as a lipid-soluble, weak organic acid.[1] It was later shown to have antibacterial, antiviral, antifungal, antitumoral and immunosuppressive properties.[2-6] In 1975, MPA demonstrated therapeutic efficacy in psoriasis.[7] However, it soon fell into disrepute with growing concerns about its long-term risk of carcinogenicity. Moreover, tolerability of MPA was limited by gastrointestinal upset. Subsequent investigations led to the development of mycophenolate mofetil (MMF) (CellCept®, Roche Pharmaceuticals), the semi-synthetic 2-morpholinoethyl ester of MPA.[8] This new formulation showed enhanced bioavailability, tolerability and efficacy.[8] By 1995, MMF received US FDA approval for the prevention of acute renal allograft rejection and soon became recognized as an effective treatment option for immune-mediated skin disease.

Mechanism of Action

Mycophenolate mofetil selectively and noncompetitively inhibits inosine monophosphate dehydrogenase (IMPDH) in the *de novo* purine synthesis pathway. This enzyme facilitates the conversion of inosine monophosphate to

xanthine monophosphate, an intermediate metabolite in the production of guanosine triphosphate. As MMF results in the depletion of guanosine nucleotides, it impairs RNA, DNA and protein synthesis.[9]

The purine bases, adenosine and guanosine, may be synthesized through two pathways: the *de novo* purine synthesis pathway, and the hypoxanthine-guanine phosphoribosyl transferase salvage pathway. As lymphocytes lack the salvage pathway, MMF selectively inhibits lymphocyte proliferation and antibody formation. Moreover, MMF preferentially blocks the type II isoform of IMPDH, predominantly located on lymphocytes; thus, it also holds potent cytostatic effects on T and B cells.[9] Herein lies the selective advantage of this immunosuppressive agent.

Mycophenolate also prevents the glycosylation of lymphocyte and monocyte glycoproteins that are involved in adhesion to endothelial cells. It may further inhibit the recruitment of leukocytes to sites of inflammation and impair antigen presentation.[10] While it does not inhibit early events in the activation of human peripheral blood mononuclear cells (i.e., IL-1 and IL-2 production), MMF blocks the coupling of these events to DNA synthesis and proliferation.[9]

Pharmacokinetics

After ingestion, MMF is hydrolyzed to its parent compound, MPA, by plasma esterases. Predominantly bound to albumin, MPA has a bioavailability that approaches 94%.[11] The peak concentration of the active metabolite is obtained within 60-90 minutes after oral administration. Upon systemic absorption, MPA undergoes hepatic conjugation to its inactive glucuronide form (MPAG). Approximately 87% of the drug is excreted through the kidneys, 6% in the feces and the remainder undergoes enterohepatic recirculation. Beta-glucuronidase, found within the epidermis and gastrointestinal tract, can convert MPAG to the active MPA form.[11]

Safety

At usual doses, MMF is generally well tolerated. Compared to other immunosuppressants, such as methotrexate, azathioprine and cyclosporine, the lack of hepatonephrotoxicity with MMF offers an important therapeutic advantage. The most common side-effects are gastrointestinal (i.e., nausea, diarrhea, abdominal cramps, constipation, vomiting and anorexia) and genitourinary (i.e., urgency, frequency, dysuria, hematuria and, occasionally, sterile pyuria). These occur in up to 36% and 40% of patients, respectively. Other reported adverse events include neurologic (i.e., headache, tinnitus and insomnia), cutaneous (i.e., exanthematous eruptions, acne and pedal edema), cardiorespiratory (i.e., dyspnea, cough, chest pain, palpitations and hypertension) and metabolic (i.e., hypercholesterolemia, hyperglycemia, hypophosphatemia and hypo/hyperkalemia) reactions. Severe leukopenia has been reported to occur in less than 3% of MMF-treated patients. However, unlike treatment with azathioprine, use of MMF does not put patients with an inherited deficiency of thiopurine methyltransferase at risk.[12]

Infection rates with MMF therapy are difficult to quantify in the dermatologic literature. Opportunistic infections occur in up to 40% of transplant patients treated with MMF; however, the majority of these patients are also treated with other immunosuppressive agents.[13] In addition to standard bacterial and viral infections, patients are at increased risk for herpes simplex, herpes zoster, cytomegalovirus, candidiasis, cryptococcosis, aspergillosis, mucormycosis and *Pneumocystis carinii* pneumonia.[13] When compared to renal transplant patients treated with azathiprine, those treated with MMF have a higher incidence of herpes simplex and tissue invasive CMV infections.[13]

The long-term risk of carcinogenicity with MMF remains controversial. In the dermatologic literature, few malignancies have been reported in patients receiving MMF or its pro-drug, MPA. Lymphoproliferative disease or lymphoma developed in 0.4%-1% of patients receiving MMF with other immunosuppressive agents for renal, cardiac and hepatic transplantation.[13] As part of controlled clinical trials, these patients were followed for ≥1 year. Non-melanoma skin cancer occurred in 1.6%-4.2% of patients, while other types of malignancy appeared in 0.7%-2.1% of patients.[13] Three-year safety data in renal and cardiac transplant patients failed to reveal any changes in the incidence of malignancy.[13]

The risk of malignancy may be related to the intensity and duration of immunosuppression rather than the use of any specific agent. However, certain immunosuppressants are known to be mutagenic and carcinogenic. For instance, urinary, myeloproliferative, lymphoproliferative and cutaneous malignancies occur in a significant number of patients treated with cyclophosphamide.[13] Moreover, the active metabolite of azathioprine, 6-thioguanine, is a purine analogue that becomes incorporated into DNA. This process may cause chromosomal breakage with resultant mutagenesis.[14] As a noncompetitive inhibitor of purine synthesis, MMF fails to initiate chromosomal breaks. Potentially less mutagenic than azathioprine, MMF

may have a lower risk of carcinogenicity; however, it will take several years for this advantage to be substantiated.

While there are no adequate studies on MMF in pregnant women, the drug has been shown to be teratogenic in animals. Therefore, MMF should be avoided during pregnancy unless the potential benefit justifies the potential risk to the fetus (pregnancy risk C).

Possible drug interactions with MMF are listed in Table 1.

Dosage

In adults, the usual dose of MMF ranges from 2-3g/day.[15] In the pediatric population, MMF should be administered as 600mg/m^2 per dose every 12 hours.[15] While renal insufficiency has no consistent effect on the pharmacokinetics of MPA, dose reductions should be considered in patients with severe renal impairment.[15] In order to prevent a disease flare, many clinicians would consider tapering MMF slowly.

Mycophenolate mofetil is currently available as 250mg capsules, 500mg tablets, a powder for oral suspension (200mg/ml), and a lyophilized, sterile powder for intravenous administration. In many countries, an enteric-coated formulation may also be accessible. While a topical formulation may yield promising results, one has yet to be made commercially available.

The average cost for a 1-month course of MMF in Canada, administered at a dose of 1g twice daily, amounts to $560 CDN.

Clinical Uses

Approved for the prevention of organ rejection, the list of "off-label" indications for MMF continues to grow. Case reports and open-label clinical trials document its use in the dermatologic literature. Potential indications are listed in Table 2, and select dermatoses are reviewed below.

Psoriasis

Multiple case reports suggest that MMF is an effective treatment option for psoriasis.[16-20] In a study of 11 patients with stable plaque-type psoriasis, the efficacy of MMF was measured using the Psoriasis Area and Severity Index (PASI) score.[21] Patients initially received MMF 1g twice daily for 3 weeks followed by 0.5g twice daily. Within 3 weeks of therapy, there was a reduction in PASI of between 40% and 70% in seven of the 11 patients. Only one patient achieved a reduction in PASI of <25% from baseline. After 6 weeks, there was further improvement in six patients. However, PASI worsened in four patients when MMF was tapered to the lower dosage.

In a two-center, prospective, open-label clinical trial, 23 patients with moderate to severe psoriasis were treated with MMF 2-3g/day for 12 weeks.[22] In the 18 patients who completed the study, the PASI was reduced by 24% ($p<0.001$) at 6 weeks and by 47% ($p<0.001$) at 12 weeks. Moreover, MMF appeared to have a beneficial effect on patients suffering from psoriatic arthritis. The treatment was well tolerated: five patients developed nausea, one patient experienced periorbital edema and

Drug	Mechanism of Drug Interaction	Effect on MP Levels
Cholestyramine	Inhibit enterohepatic recirculation of MP	Decrease
Antacids (Al, Mg)	Decrease absorption of MP	Decrease
Divalent Cations (Ca, Fe)	Decrease absorption of MP	Decrease
Metronidazole	Decrease bioavailability of MP	Decrease
Fluoroquinolones	Decrease bioavailability of MP	Decrease
Probenecid	Inhibit tubular secretion of MP	Increase
Acyclovir	Inhibit tubular secretion of MP	Increase
Ganciclovir	Inhibit tubular secretion of MP	Increase
Salicylates	Increase free fraction	Increase
Azathioprine	Not studied	Not Studied

Table 1: Drug interactions with mycophenolate mofetil.
MP=mycophenolate; Al=aluminum; Mg=magnesium; Ca=calcium; and Fe=iron.

Dermatologic Disease
Psoriasis
Lichen planus
Dermatitis -Atopic dermatitis -Dyshidrotic dermatitis -Chronic actinic dermatitis
Immunobullous disease -Pemphigus vulgaris -Pemphigus foliaceus -Paraneoplastic pemphigus -Bullous pemphigoid -Mucous membrane pemphigoid -Linear IgA disease -Epidermolysis bullosa acquisita
Connective tissue disease -Systemic lupus erythematosus -Subacute cutaneous lupus -Chronic discoid lupus -Chilblains/lupus perniosis -Dermatomyositis -Scleroderma -Urticarial vasculitis -Takayasu's arteritis -Microscopic polyangiitis -Polyarteritis nodosa -Behçet's disease -Wegener's granulomatosis
Pyoderma gangrenosum
Graft-versus-host disease
Recurrent erythema multiforme
Cutaneous Crohn's disease
Sarcoidosis

Table 2: Potential dermatologic uses of mycophenolate mofetil

pruritus, and one patient had a transient leukopenia. Thus, MMF monotherapy appears to be an effective treatment for patients with moderate-to-severe, plaque-type psoriasis.

Dermatitis

In a pilot study of 10 patients with severe refractory atopic dermatitis, MMF was increased to a dose of 2g/day.[23] After 12 weeks of therapy, the median scores for disease severity (SCORAD index) improved by 68%. These findings were associated with a significant decrease in serum IgE and a shift in the T-helper (Th)-1 to Th2 cytokine ratio.

In another study of 10 patients with moderate-to-severe atopic dermatitis, MMF was administered at 2g/day for a month and tapered to 1g/day.[24] In a 20 week follow-up period, there was a 74% reduction in the SCORAD index as compared with baseline ($p<0.01$). Dyshidrotic eczema and chronic actinic dermatitis have also responded to MMF therapy.

Immunobullous Disease

Multiple case series have documented the efficacy of MMF as a steroid-sparing agent in the autoimmune mucocutaneous blistering diseases. In a historical, prospective study, Mimouni, et al. studied 42 consecutive patients with pemphigus who were recalcitrant to standard therapies.[25] Of these patients, 31 were diagnosed with pemphigus vulgaris (PV) and 11 with pemphigus foliaceus (PF). A complete remission was obtained in 22 (71%) and 5 (45%) of PV and PF patients, respectively. The treatment was administered for an average of 22 months, and the median time to achieve remission was 9 months. In two patients, MMF was discontinued for nausea and symptomatic, reversible neutropenia. Others have demonstrated similar success with MMF in treating patients with PV, PF, paraneoplastic pemphigus, bullous pemphigoid, mucous membrane pemphigoid, linear IgA disease and epidermolysis bullosa acquisita.[26-32]

Connective Tissue Disease

The efficacy of MMF in systemic lupus erythematosus has been clearly validated. Moreover, the cutaneous lesions of subacute cutaneous lupus, chronic discoid lupus and lupus perniosis have shown response to MMF therapy. Clinical improvement has also been demonstrated in other connective tissue diseases such as dermatomyositis, scleroderma, urticarial vasculitis, Takayasu's arteritis, microscopic polyangiitis, Wegener's granulomatosis, polyarteritis nodosa and Behçet's disease.[6,15]

Other Dermatologic Disease

Mycophenolate mofetil has been shown to benefit other dermatologic conditions including lichen planus, pyoderma gangrenosum, graft-versus-host disease, recurrent erythema multiforme, Steven-Johnson syndrome, sarcoidosis, and cutaneous Crohn's disease.[6,15]

Conclusion

In a variety of inflammatory skin disorders, MMF has been successfully used both in combination with

systemic steroids and as monotherapy. Early reports on efficacy and tolerability suggest that MMF offers hope to patients with immune-mediated skin disease. As gleaned from transplant data, its safety profile appears reassuring. However, randomized clinical trials with long surveillance periods are warranted to validate the efficacy and safety of MMF in the treatment of dermatologic disease.

References

1. Alsberg CL, Black OF. Contribution to the study of maize deterioration; biochemical and toxicological investigations of *Penicillium puberulum* and *Penicillium stoloniferum. Bull Burl Anim Ind.* US Dept Agr 270:1-47 (1913).
2. Abraham EP. The effect of mycophenolic acid on the growth of *Staphylococcus aureus* in heart broth. *Biochem J* 39:398-404 (1945).
3. Abrams R, Bentley M. Biosynthesis of nucleic acid purines. I. Formation of guanine from adenine compounds in bone marrow extracts. *Arch Biochem* 56(1):184-95 (1955 May).
4. Cline JC, Nelson JD, Gerzon K, Williams RH, Delong DC. *In vitro* antiviral activity of mycophenolic acid and its reversal by guanine-type compounds. *Appl Microbiol* 18(1):14-20 (1969 Jul).
5. Kosugi Y, Saito Y, Mori S. Antiviral activities of mizoribine and other inosine monophosphate dehydrogenase inhibitors against several ortho- and paramyxoviruses. *Antiviral Chem Chemother* 5:366-71 (1994).
6. Liu V, Mackool BT. Mycophenolate in dermatology. *J Dermatolog Treat* 14(4):203-11 (2003 Dec).
7. Jones EL, Epinette WW, Hackney VC, Menendez L, Frost P. Treatment of psoriasis with oral mycophenolic acid. *J Invest Dermatol* 65(6):537-42 (1975 Dec).
8. Lee WA, Gu L, Miksztal AR, Chu N, Leung K, Nelson PH. Bioavailability improvement of mycophenolic acid through amino ester derivatization. *Pharm Res* 7(2):161-6 (1990 Feb).
9. Allison AC, Eugui EM. Purine metabolism and immunosuppressive effects of mycophenolate mofetil (MMF). *Clin Transplant* 10(1 Pt 2):77-84 (1996 Feb).
10. Mehling A, Grabbe S, Voskort M, Schwarz T, Luger TA, Beissert S. Mycophenolate mofetil impairs the maturation and function of murine dendritic cells. *J Immunol* 165(5):2374-81 (2000 Sep 1).
11. Bullingham RE, Nicholls AJ, Kamm BR. Clinical pharmacokinetics of mycophenolate mofetil. *Clin Pharmacokinet* 34(6):429-55 (1998 Jun).
12. Sievers TM, Rossi SJ, Ghobrial RM, et al. Mycophenolate mofetil. *Pharmacotherapy* 17(6):1178-97 (1997 Nov-Dec).
13. Repchinsky C, editor. Compendium of pharmaceuticals and specialties: the Canadian drug reference for health professionals. *Ottawa: Canadian Pharmacists Association* (2004).
14. Kitchin JE, Pomeranz MK, Pak G, Washenik K, Shupack JL. Rediscovering mycophenolic acid: a review of its mechanism, side effects, and potential uses. *J Am Acad Dermatol* 37(3 Pt 1):445-9 (1997 Sep).
15. Assmann T, Ruzicka T. New immunosuppressive drugs in dermatology (mycophenolate mofetil, tacrolimus): unapproved uses, dosages, or indications. *Clin Dermatol* 20(5):505-14 (2002 Sep-Oct).
16. Nousari HC, Sragovich A, Kimyai-Asadi A, Orlinsky D, Anhalt GJ. Mycophenolate mofetil in autoimmune and inflammatory skin disorders. *J Am Acad Dermatol* 40(2 Pt 1):265-8 (1999 Feb).
17. Geilen CC, Tebbe B, Garcia Bartels C, Krengel S, Orfanos CE. Successful treatment of erythrodermic psoriasis with mycophenolate mofetil. *Br J Dermatol* 138(6):1101-2 (1998 Jun).
18. Haufs MG, Beissert S, Grabbe S, Schutte B, Luger TA. Psoriasis vulgaris treated successfully with mycophenolate mofetil. *Br J Dermatol* 138(1):179-81 (1998 Jan).
19. Tong DW, Walder BK. Widespread plaque psoriasis responsive to mycophenolate mofetil. *Australas J Dermatol* 40(3):135-7 (1999 Aug).
20. Grundmann-Kollmann M, Mooser G, Schraeder P, et al. Treatment of chronic plaque-stage psoriasis and psoriatic arthritis with mycophenolate mofetil. *J Am Acad Dermatol* 42(5 Pt 1):835-7 (2000 May).
21. Geilen CC, Arnold M, Orfanos CE. Mycophenolate mofetil as a systemic antipsoriatic agent: positive experience in 11 patients. *Br J Dermatol* 144(3):583-6 (2001 Mar).
22. Zhou Y, Rosenthal D, Dutz J, Ho V. Mycophenolate Mofetil (CellCept(R)) for Psoriasis: A Two-Center, Prospective, Open-Label Clinical Trial. *J Cutan Med Surg* 7:193-7 (2003 Apr).

23. Neuber K, Schwartz I, Itschert G, Dieck AT. Treatment of atopic eczema with oral mycophenolate mofetil. *Br J Dermatol* 143(2):385-91 (2000 Aug).

24. Grundmann-Kollmann M, Kaufmann R, Zollner TM. Treatment of atopic dermatitis with mycophenolate mofetil. *Br J Dermatol* 145(2):351-2 (2001 Aug).

25. Mimouni D, Anhalt GJ, Cummins DL, Kouba DJ, Thorne JE, Nousary HC. Treatment of pemphigus vulgaris and pemphigus foliaceus with mycophenolate mofetil. *Arch Dermatol* 139(6):739-42 (2003 Jun).

26. Enk AH, Knop J. Mycophenolate is effective in the treatment of pemphigus vulgaris. *Arch Dermatol* 135(1):54-6 (1999 Jan).

27. Farley-Li J, Mancini AJ. Treatment of linear IgA bullous dermatosis of childhood with mycophenolate mofetil. *Arch Dermatol* 139(9):1121-4 (2003 Sep).

28. Nousari HC, Griffin WA, Anhalt GJ. Successful therapy for bullous pemphigoid with mycophenolate mofetil. *J Am Acad Dermatol* 39(3):497-8 (1998 Sep).

29. Katz KH, Marks JG Jr, Helm KF. Pemphigus foliaceus successfully treated with mycophenolate mofetil as a steroid-sparing agent. *J Am Acad Dermatol* 42(3):514-5 (2000 Mar).

30. Megahed M, Schmiedeberg S, Becker J, Ruzicka T. Treatment of cicatricial pemphigoid with mycophenolate mofetil as a steroid-sparing agent. *J Am Acad Dermatol* 45(2):256-9 (2001 Aug).

31. Williams JV, Marks JG Jr, Billingsley EM. Use of mycophenolate mofetil in the treatment of paraneoplastic pemphigus. *Br J Dermatol* 142(3):506-8 (2000 Mar).

32. Schattenkirchner S, Eming S, Hunzelmann N, Krieg T, Smola H. Treatment of epidermolysis bullosa acquisita with mycophenolate mofetil and autologous keratinocyte grafting. *Br J Dermatol* 141(5):932-3 (1999 Nov).

~ Conference News ~

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Drug Treatments for Skin Disease Introduced in 2004

Drug Class	Generic/Trade Company Names	Indication	Approving Regulatory Agency
Antiacne Agent	**Clindamycin Foam 1%** *Evoclin®* Connetics	Approved for topical application in the treatment of acne vulgaris	US FDA
Antibacterial Agent	**Cefdinir Oral Suspension** *Omnicef®* Abbott Laboratories	A new 250mg/5ml dosing option approved for use in pediatric patients 6 months to 12 years of age. This more concentrated form allows parents to administer fewer teaspoons/dose to their children.	US FDA
	Clindamycin *Evoclin® Foam 1%* Connetics	Approved for the treatment of mild-to-moderate acne vulgaris. Evoclin® was formerly referred to as Actiza™.	US FDA
Antihistamine	**Desloratadine Syrup** *CLARINEX®* Schering-Plough	Approved for the relief of symptoms associated with seasonal allergic rhinitis in children >2 years of age, and perennial allergic rhinitis and chronic idiopathic urticaria, or hives of unknown cause in children as young as 6 months of age.	US FDA
Antipruritic Agent	**Cetirizine HCl** *Zyrtec®* Pfizer/UCB Pharma	A new chewable formulation approved for the treatment of seasonal and perennial allergic rhinitis and chronic idiopathic urticaria in children ≥2 years of age.	US FDA
Antipsoriatic Agent	**Alefacept** *Amevive®* Biogen Idec	Approved for the treatment of adult patients with moderate-to-severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy.	Israeli Ministry of Health Therapeutic Goods Administration—Australia TPP Canada
	Efalizumab *Raptiva®* Serono	Approved for the treatment of adult patients with moderate-to-severe chronic plaque psoriasis.	Swissmedic CHMP Europe
	Etanercept *Enbrel®* Amgen/Wyeth Pharmaceuticals	Approved for the treatment of moderate-to-severe plaque psoriasis who failed to respond to, or have a contraindication to, or are intolerant of other systemic therapy.	US FDA CHMP Europe
Dermal Filler	**Hyaluronic Acid Filler** *Hyalite™* Mentor	Approved for soft tissue augmentation in the correction of wrinkles and folds and for lip enhancement.	CHMP Europe
	Hyaluronic Acid Filler *RESTYLANE®* Medicis	Approved for the correction of moderate-to-severe facial wrinkles and folds.	US FDA
	Hylan-B Gel *Hylaform* Inamed/Genzyme	Approved for injection into the mid-to-deep dermis for correction of moderate-to-severe facial wrinkles and folds.	US FDA
	Injectable Poly-L-Lactic Acid *Sculptra* Dermik Laboratories	Approved for the correction of lipoatrophy in people with HIV infection.	US FDA

Drug Class	Generic/Trade Company Names	Indication	Approving Regulatory Agency
Enzyme Replacement Therapy	**Agalsidase Alfa** *Replegal™* Transkaryotic Therapies	Approved for the treatment of Fabry disease under its Notice of Compliance with Conditions Policy, under which Transkaryotic Therapies can market this product while conducting post-marketing studies	TPP Canada
Immunomodulatory Agent	**Imiquimod Cream 5%** *Aldara®* 3M Pharmaceuticals	Approved for clinically typical, nonhyperkeratotic, nonhypertrophic actinic keratoses on the face or scalp in immunocompetent adults.	US FDA TPP Canada
	Imiquimod Cream 5% *Aldara®* 3M Pharmaceuticals	Approved for the treatment of biopsy-confirmed, primary superficial basal cell carcinoma in adults with normal immune systems.	US FDA TPP Canada
Medical Device	**Clinical Phototherapy System** *ClearTouch™ Light Unit Assembly* Radiancy	Approved for the treatment of pustular inflammatory acne.	US FDA
	Ultrasonic Skin Permeation Device *SonoPrep®* Sontra Medical	Approved for use with topical lidocaine.	US FDA
Monoclonal Antibody	**SGN-30** Seattle Genetics	Granted Orphan Drug Designation for the treatment of T-cell lymphomas.	US FDA
Neurotoxin	**Botulinum Toxin – Type A** *BOTOX®* Allergan	Additional indication approved for the treatment of severe primary axillary hyperhidrosis that is inadequately managed with topical agents.	US FDA
Oncologic Agent	**MDX-010** Medarex	Granted Orphan Drug Designation for the treatment of high-risk Stage II, Stage III, and Stage IV melanoma.	US FDA
Psoriatic Arthritis Agent	**Leflunomide** *Arava®* Aventis	A new indication approved for the treatment of adult patients with active psoriatic arthritis.	CHMP Europe
	Etanercept *Enbrel®* Amgen/Wyeth Pharmaceuticals	Approved for the treatment of psoriatic arthritis.	TPP Canada US FDA
	Etanercept *Enbrel®* Amgen/Wyeth Pharmaceuticals	New dosing formula approved for the treatment of psoriatic arthritis and moderate-to-severe plaque psoriasis – a prefilled syringe that will eliminate the need to mix the drug prior to injecting and will allow most patients receiving this drug to take only one injection/week instead of the two 25mg injections currently used weekly by patients.	US FDA
	Infliximab *REMICADE®* Schering-Plough/Centocor	Approved for use in combination with methotrexate for the treatment of active and progressive psoriatic arthritis in patients who have responded inadequately to disease-modifying antirheumatic drugs.	CHMP Europe

Twelve Technical Strategies to the Perfect Surgical Scar

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In an age where our patients are becoming much more cosmetically sensitive, patients often express significant concern over scars that will be left in visible anatomic locations. With the progressive aging of our "baby boomers", Canadian dermatologists, family physicians and surgeons are being faced with increased demands for skin biopsies and surgical procedures to treat skin malignancy and disease. Achieving an excellent surgical result while managing disease can be a daunting task when the basic surgical principles we were all taught have been lost to time and the perpetuation of poor surgical habits that were adopted from others. Here are a few strategies that can help to improve your scar outcomes.

First, place incisions parallel to relaxed skin tension lines or in existing facial rhytids. These "lines of election" are found perpendicular to the long axis of the underlying facial muscles. Observing the patient in states of facial animation and repose will help exaggerate these lines for easier identification.

Second, convert all circular defects to ellipses prior to primary closure. Observe the 4:1 rule where the length of the ellipse should be four times the diameter of the initial defect to achieve a primary closure without unnecessary skin redundancy.

Third, incise tissues at right angles. This helps ensure perfect wound edge approximation and avoids one skin edge riding over the other. If you can't correct beveled edges then take a deep bite on the thick skin side and a shallow bite on the thin side to correct the difference.

Fourth, minimize tissue trauma by handling the tissue only with appropriate forceps and by limiting the pressure you use to hold the tissue. Increased amounts of skin edge trauma will reduce the result of the final scar. Holding the skin at the dermal level avoids surface marks made by the instruments.

Fifth, observe meticulous hemostasis. Unwanted hematomas increase the local inflammation and scarring in a given area as well as serving as a focus for infection. Hyfercators, designed for office use, are an affordable way to add this technical control to your practice.

Sixth, obliterate all dead spaces and use layered closure. Dead space obliteration can occur while placing your absorbing inverted dermal stitches. Although they take time to place, the use of interrupted dermal stitches will almost eliminate the complication of wound dehiscence and allow you the confidence to remove the skin stitches early. Remember that for the first few weeks, all of the strength of the closure is provided by your stitches.

Seventh, design a tension-free closure. This is achieved by appropriate design of the excision or flap, by adequate tissue undermining, and through the use of dermal sutures. More intricate techniques are used to achieve this end in advanced closures.

Eighth, ensure perfect wound edge approximation and skin edge eversion. Limited undermining of the margin allows greater control and easier eversion. Depth of suture bites and distance from the skin edge to the suture entry and exit points should be the same on each side of the wound closure. Fine bites with little tissue actually held by the suture will give less eversion than more substantial bites.

Ninth, use nonabsorbable stitches for surface closure. Absorbing stitches are more reactive, thereby increasing local inflammation and scarring.

Tenth, use interrupted stitches. Although running stitches are faster, they have been shown to strangulate the wound edge and it can be harder to control the level of the wound edge particularly for less experienced hands.

Eleventh, use small skin stitches and remove them early. You must practice a layered closure method in order to do this or you will get a wide-stretched scar or wound dehiscence.

Twelfth, instruct your patients in proper post-operative wound care techniques.

Class	Name/Company	Approval Dates and Comments
Medical Device	**Clinical Phototherapy System** *ClearTouch™ Light Unit Assembly* Radiancy	The US FDA granted marketing approval in December 2004, for this light-based therapy for the treatment of pustular inflammatory acne.
Antiarthritic Agent	**Adalimumab** *HUMIRA®* Abbott Laboratories	The US FDA received a supplemental Biologics License Application in December 2004, for the additional indication of psoriatic arthritis. Also in December 2004, the EMEA received a Marketing Authorization Application for this human monoclonal antibody for the same additional indication. It is currently approved in the US and the European Union for the treatment of rheumatoid arthritis in adult patients when the response to disease-modifying antirheumatic drugs has been inadequate.
Antibacterial Agent	**Dalbavancin** Vicuron Pharmaceuticals	The US FDA received a New Drug Application in December 2004, for this novel antibiotic for the treatment of complicated skin and soft tissue infections caused by Gram-positive bacteria, including the most difficult-to-treat strains of *Staphylococcus*-methicillin-resistant *Staphylococcus aureus*.
Oncologic Agent	**MDX-010** Medarex	The US FDA granted Fast Track Designation in October 2004, for this fully human antibody in combination with MDX-1379, a melanoma vaccine, for the treatment of previously treated, unresectable Stage III and Stage IV metastatic melanoma.
Antibacterial Agent	**Clindamycin** *Evoclin® Foam 1%* Connetics	The US FDA approved this antibiotic foam in October 2004, for the treatment of acne vulgaris. Evoclin® was formerly referred to as Actiza™.

Drug News

Drug Warning	The US FDA issued a public health advisory directing health care providers to prescribe pimecrolimus (Elidel®, Novartis) and tacrolimus (Protopic®, Fujisawa) only as directed and only after other eczema treatments have failed to work because of a potential cancer risk associated with their use. In addition, they added a black box warning to the health professional label for both products and are developing a Medication Guide for patients. The move was based on animal studies that have shown that three different species of animals have developed cancer following exposure to these drugs applied topically or orally and at doses higher than generally used by patients. The risk of cancer appeared to be dose-dependent increasing with increasing drug dose and duration. The products' manufacturers have agreed to conduct research to determine whether there is an actual risk of cancer in humans, and if so, its extent. The President of the American Academy of Dermatology, Dr. Clay J. Cockerell, stated that they are very disappointed that the US FDA has taken this action, despite the fact that there is no data that proves proper topical use of these products is dangerous in humans.

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