**Artecoll® – an injectable micro-implant for longlasting soft tissue augmentation**

Never before have so many people sought our assistance to help get get rid of their wrinkles. Until recently, most biological materials presented shortcomings – resorption within months, allergic reaction, and on occasion, foreign body or granuloma formation at the site of injection.

Our demand for a “filler” that can be injected easily, and which is biologically inert and permanent, has been a major target. Artecoll® is a novel formulation of polymethylmethacrylate (PMMA) microspheres suspended in bovine collagen which would appear to provide such an advance, in terms of permanency.

Dr. Alastair Carruthers

Artecoll® consists of homogenous polymethylmethacrylate (PMMA) microspheres evenly suspended 1:3 in a solution of partially denatured 3.5% collagen. All microspheres have a uniform size of 32–40 microns in diameter and have a smooth, round surface. Artecoll® contains an average concentration of 0.3% lidocaine.

Artecoll® is presently available for use in Western Europe, has been granted clearance by the HPB in Canada, but is still awaiting approval by the US FDA.

PMMA has been in common use since 1945, and is used in dental prostheses, hip implants, bone cement, intra-ocular lenses, repair material used in cranio-facial surgery as well as many other medical devices. Many studies have found it to be chemically inert and biocompatible. PMMA microspheres have been used for tissue augmentation since 1989, and in more than 100,000 patients worldwide, Artecoll® has shown a high degree of safety and an extremely low complication rate.

**Mode of action**

Artecoll® exploits the body’s natural disposition to encapsulate foreign bodies with connective tissue. The size of the microspheres hinders macrophagal phagocytosis, or dislocation within the connective tissue. In the first weeks following subdermal injection, the microspheres of PMMA are individually enclosed in connective tissue, as is the case with implants such as cardiac pacemakers. The amount of connective tissue generated often corresponds to the quantity of injected collagen previously suspending the PMMA spheres. The collagen vehicle will be degraded by the body within 1–3 months. The microspheres are expected to remain reaction-free and in place for the rest of the patients life.

During injection, large deposits of Artecoll® should be avoided to minimize any possibility of granuloma formation.

**Indications**

The main indication for Artecoll® implantation is the naturally occurring folds and wrinkles in the face. The ideal patient is between 40 and 50 years old, when the excess of skin does not yet justify a facelift. Artecoll® is not an alternative to a facelift but rather is an adjunct to it. Conversely, it does not interfere with later facelifting.

**Dermatologic Indications for Artecoll® Implantation**

<table>
<thead>
<tr>
<th>Possible indication</th>
<th>Limiting indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glabellar frowns</td>
<td>Firm scars and acne scars</td>
</tr>
<tr>
<td>Perioral lines</td>
<td>Single crow’s feet</td>
</tr>
<tr>
<td>Nasolabial folds</td>
<td>Dark shadowed eyelids</td>
</tr>
<tr>
<td>Depressed corners of the mouth</td>
<td></td>
</tr>
</tbody>
</table>

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**Glabellar frowns (22.5%) Perioral lines (15%) Nasolabial folds**

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**Depressed corners of the mouth (13%)**

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**Possible indication**

- Winkle augmentation
- Lip augmentation
- Depressions after rhinoplasty

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**Limiting indication**

- Firm scars and acne scars
- Single crow’s feet
- Dark shadowed eyelids

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**Contraindications**

Contraindications are a known allergy to collagen or lidocaine, and prospective patients should undergo a test implantation of Artecoll®. Thin and flaccid skin, susceptibility to keloids, and atrophic skin diseases are other contraindications. Do not use Artecoll® for atrophy or defects in subcutaneous fat, or rubberlike nodules might result and be felt for the rest of the patient’s life.4

**Directions for use**

A degree of expertise is required for successful use of Artecoll®. It is essential that the operator be given proper instruction, ensuring subdermal placement and the best possible cosmetic result.

It is critical to inject strictly subdermally – this avoids the possibility of blanching due to microspheres being visible through the skin. Staying in the correct plane, the gray of the needle should never shine through the skin.

**Cost of Therapy**

<table>
<thead>
<tr>
<th>Product</th>
<th>Volume</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Artecoll®</td>
<td>0.5 ml</td>
<td>$350 Canadian</td>
</tr>
<tr>
<td></td>
<td>The box as delivered contains 4 syringes (0.5 ml)</td>
<td>$1400 Canadian (equivalent to $900 U.S.)</td>
</tr>
</tbody>
</table>

The volume required depends on the extent and number of wrinkles, but 1 ml is sufficient for most uses.4 The cost to the patient depends on the overall treatment and services provided by the physician.

Although Zyplast® is cheaper than Artecoll® initially, after one year’s treatment, because Artecoll® lasts longer, the costs become more equivalent.

Dr. Alastair Carruthers.1

**Results**

In studies to date, the effects of Artecoll® are long-lasting, being still visible after 3, 4 or more years of follow-up. In two studies, ninety per cent of patients surveyed anonymously were pleased or satisfied with the results after as long as three years4, and in one study, 91% of patients would repeat the treatment.5,6

**Side effects**

Some local discomfort may occur at the site of injection, along with transient itching which subsides within a matter of weeks. Two reports have been published concerning side effects of PMMA microsphere implants. Dr W.L. Mang of Lindau, Germany has written a critical review7, but the lack of specific details makes this report difficult to assess. The second publication by McCleland and others8, suggests that Artecoll® has the potential to elicit an immune response in humans, and that the microspheres of PMMA are susceptible to phagocytosis and elimination. Prior to 1994, Arteplast® was the PMMA microsphere product trialled. In this product, the microspheres were not uniform in size and not free of irregular particles, and injection was intradermal in some cases. With Artecoll®, the PMMA spheres are uniform in size and free of fragments, injection is sub-dermal rather than intradermal and side effects are much reduced.

**Summary**

When used for the proper indications, and when injected at the proper subdermal level, Artecoll® implantation provides cosmetically acceptable results for as long as four to five years. As a precaution against collagen sensitivity, an intradermal challenge should be performed. Prior instruction is advised in order to acquire a satisfactory technique.

Remember that if the plexiglass beads are wrongly placed, the patient has to live with the results. No matter what training is offered, this technique will be widely used and abused by some.

Arnold Klein9

Artecoll® is not suitable for treating fine lines. Sheri Feldman10

Some precision is required in using Artecoll®, but the relative permanence of the results makes it worthwhile in properly selected patients.

Alastair Carruthers1

**References**

5. Summary of Artecoll clinical studies and articles. From sub-groups of patients from ref4, studied for the Ethics Committee of the University of Frankfurt.
Unanswered Questions in Antifungal Therapy for Onychomycosis

Onychomycosis affects about 7–8% of the North American population and having significant social, psychologic, health, and occupational effects, is more than a cosmetic issue; it is a clinical and economic problem. However, with three new, orally effective, antifungal agents, we have for the first time effective treatment that can provide benefit for a high percentage of patients. This review examines some of the areas of uncertainty and controversy.

Recurrence and relapse in onychomycosis

There is a difference between “re-infection” and “relapse”. Relapse, or “delayed failure” refers to recurrence of the original infection that was clinically and mycologically cured at one time-point following therapy. Reinfection is a new infection resulting from exposure to a fungus in shoes, floors or fomites. In many cases when there is a recurrence of infection, it may be difficult to distinguish between relapse and reinfection. Some have suggested that the recurrence of toenail onychomycosis, once complete clinical and mycological cure has occurred, is more likely to be due to relapse if it has developed within 18 months of starting oral antifungal therapy, and reinfection when toenail onychomycosis recurs 18 months or more beyond the start of therapy. The time-point of 18 months is an arbitrary choice; others have suggested 24 months from the start of therapy. The terms relapse and recurrence have been used interchangeably in the literature.

Dermatophytoma complications may be a leading cause of treatment failure

In a significant number of cases of dermatophyte onychomycosis, a dense white linear area or a round white area is seen. When the overlying nail is cut back, a densely packed clump of thick walled, somewhat abnormal looking dermatophyte hyphae is revealed. It is probable that antifungal drug penetration into such lesions does not achieve adequate concentrations and nail removal is necessary in order for antifungal drugs to prove effective. The dermatophytoma is not particularly adherent and can be readily removed.

What roles do increasing age, disease duration or ethnic origin play in re-infection or relapse?

Older people have a higher prevalence of nail disease. They also respond less well to treatment, as do patients with more severe nail involvement. Since nail growth slows with increasing age, and local trauma increases, the elderly are more likely to develop nail infections and more likely to have reinfections. The decrease in T cell function associated with aging may be the primary reason for the increased recurrence rates, although patients with long-standing onychomycosis may have nails that grow relatively more slowly compared to the usual growth rates of nails in those of a similar age and gender. Because the newer antifungal drugs require new growth of nail to replace the old infected portions, growth of nail is a necessary feature to effect a cure. Therefore, a long disease duration and a slow rate of nail outgrowth are associated with a poorer response to treatment with the new oral antifungal agents.

Another reason that disease duration and increasing age may impede cure rates, is the fact that the infections may become more complicated and other non-dermatophyte moulds and/or yeasts and/or bacteria may become secondary pathogens. There is no evidence for ethnic differences in re-infection or relapse rates.

In onychomycoses, what is the incidence of recurrence and relapse following treatment with itraconazole or terbinafine?

Currently, it is not possible to distinguish between relapse and reinfection. Used in their currently recommended regimen, until recently there was thought to be no clear difference between the drugs. However, in the L.I.ON. double-blind, double-dummy study, continuous terbinafine for 12 weeks and 16 weeks resulted in statistically significantly superior mycological and clinical cure rates as compared to intermittent itraconazole given for one in every four weeks for 12 and 16 weeks. Estimated rates of recurrence/relapse following treatment with itraconazole or terbinafine range from 15–30%.

We’re on the Net!

http://www.derm.ubc.ca
depending on the patient population under study.\textsuperscript{2,7,10,12}
Following pulse therapy with itraconazole for toenail onychomycosis, after 1 year, the incidence of relapse/recurrences is on average 10\% based on a number of clinical trials, including more than 1300 patients treated with 3 pulses for toenail onychomycosis.\textsuperscript{7} There is relatively little information on the rate of recurrence/relapse of toenail onychomycosis in special populations treated with the newer antifungal agents.\textsuperscript{4}

**Is there evidence of resistance emerging to itraconazole, terbinafine, fluconazole or griseofulvin?**

- For superficial fungal skin/nail or hair infections there is as yet no evidence for dermatophyte resistance emerging to itraconazole, terbinafine or fluconazole.\textsuperscript{2,6,7,9} Usually, failures can be attributed to a wrong diagnosis, poor compliance and less than optimal absorption with itraconazole capsules not being taken with a fatty meal.\textsuperscript{7} Why some patients under optimal conditions still fail to respond to treatment with itraconazole or terbinafine is not fully understood. It seems that some of the fungal elements (e.g. with dermatophytes) are present as arthrospores in the nail unit. These arthrospores have thicker cell walls than hyphal elements and are encapsulated in such a way that drug penetration becomes difficult or perhaps impossible.\textsuperscript{7}

In onychomycosis, especially in those patients with long-standing disease, fungal organisms protect themselves in this way so that they can better survive in their environment. Surviving arthrospores may also be the reason for more frequent relapses in patients with long standing disease. This should not be termed resistance as there is some evidence that when these fungi are transformed to a hyphal phase, they are once again very sensitive to treatment. In fact, we might consider stimulating the conversion of their arthrospore phase into a hyphal phase before commencing with antifungal agents.\textsuperscript{4,7}

- For superficial Candida infections in the immunocompetent host/healthy patient, again there is no evidence supporting the emergence of resistance.\textsuperscript{6,7,9}

- In the immunocompromised host, induced resistance to fluconazole has been identified in Candida. Recently, Candida albicans isolates resistant to fluconazole have been reported with increasing frequency in oral infections in HIV-positive patients. This was mostly observed during long-term treatment. So far, ketoconazole resistance has only been described in Candida albicans following chronic use in chronic mucocutaneous candidiasis patients. Even though the use of ketoconazole in HIV infected patients has increased, acquired resistance has not been reported. Acquired and intrinsic resistance to Candida spp has not been documented.\textsuperscript{7}

“*In vitro*” cross resistance between different azoles has been documented by some laboratories but not by others. Cross-resistance evidenced by some labs, has not been confirmed by other laboratories studying these same strains.

**What is the importance or significance of agents being fungicidal rather than fungistatic?**

Clinically, the difference is not important.\textsuperscript{7,9} It is more important to get the appropriate concentration of oral antifungal agent at the site of the infection (e.g. nail unit, hair or the skin).

**Are moulds increasing?**

Dermatophytes are the prime pathogens in onychomycosis.\textsuperscript{4} Non-dermatophyte moulds may occur from time to time, but are generally not a problem and their appearance is generally an incidental finding as a laboratory contaminant.\textsuperscript{9} In young adults and adults up to 65 years of age, non-dermatophyte moulds may be more likely to be saprophytes than true invaders, although in some cases they do cause an invasive toenail infection. In patients older than 65, nail growth declines further and non-dermatophytic moulds may find it easier to penetrate the nail unit and cause invasive nailplate infection.\textsuperscript{7} If this hypothesis is correct, we will see more non-dermatophyte infections as the average age of the population increases.\textsuperscript{7} The incidence of moulds is significantly higher in the tropics and moulds are more likely in patients returned from the tropics.\textsuperscript{8}

**Do some individuals have an “inherited predisposition” to severe forms of fungal infections?**

Fungal infections of the feet and toenails are transmitted via infected fungal elements or arthrocondidia. People who are at highest risk include those who have sweaty feet, and individuals such as army recruits, athletes, etc. who walk over surfaces which are heavily contaminated with fungus, such as in gyms and locker rooms. A genetic predisposition may explain why some people who are exposed get an infection and others don’t.\textsuperscript{7,9} There is some evidence to suggest that atopic patients may have a more chronic form of fungal infection.\textsuperscript{7} However, this observation has not been substantiated.
### Treatment of Onychomycoses of the toenails

<table>
<thead>
<tr>
<th></th>
<th>Itraconazole Sporanox®</th>
<th>Terbinafine Lamisil®</th>
<th>Fluconazole Diflucan®</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Action</strong></td>
<td>Fungistatic</td>
<td>Fungicidal</td>
<td>Fungistatic</td>
</tr>
<tr>
<td><strong>Dosage</strong></td>
<td>200 mg daily for 12 weeks**</td>
<td>250 mg daily for 12 weeks</td>
<td>150 mg once weekly until a normal appearing nail is present, typically 9–12 months.4</td>
</tr>
<tr>
<td><strong>Approximate cost</strong></td>
<td>US$1,089 for 12 weeks CAN$670 for 12 weeks</td>
<td>US$587 for 12 weeks CAN$322 for 12 weeks</td>
<td>US$540 for 48 weeks CAN$720 for 48 weeks</td>
</tr>
<tr>
<td><strong>Take with food</strong></td>
<td>Ensures maximal absorption when the capsules are used.</td>
<td>Not clinically important</td>
<td>Does not affect absorption</td>
</tr>
<tr>
<td><strong>Monitoring</strong></td>
<td>In patients with pre-existing renal or hepatic dysfunction – monitor closely. Refer to the insert.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Affects cytochrome P450 Drug interactions</strong></td>
<td>yes with a number of drugs</td>
<td>no less of a problem</td>
<td>yes with a number of drugs</td>
</tr>
<tr>
<td><strong>Dosage forms available</strong></td>
<td>Capsule</td>
<td>Tablet</td>
<td>Tablets</td>
</tr>
<tr>
<td><strong>Regulatory approval</strong></td>
<td>US (FDA) Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Canada (HPB) Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Major European Agencies Yes</td>
<td>Yes</td>
<td>Not applied for</td>
</tr>
</tbody>
</table>

* Based on the Average US Wholesale Price (Red Book, January, 1999) and Average Canadian Wholesale Price to Pharmacies, January 1999.

**Itraconazole pulse therapy for onychomycoses of the fingernails, but not the toenails, has been approved by the US FDA. The pulse regimen is approved in Canada.

Now that we have improved means of treating toenail onychomycosis, it is even more important to pay attention to ways of reducing the recurrence (relapse and reinfection) of toenail onychomycosis. Patient education is one way in which we can reduce the potential for reinfection. Some strategies include avoidance of facilities with a high level of dermatophyte contamination (communal swimming pools, showers, changing facilities) discarding old shoes that may have a high density of fungal spores, and the judicious use of topical antifungal agents. This is especially important in at risk populations, for example, those with a genetic predisposition and immunocompromised individuals.4

Dr. Aditya Gupta4

### References

7. De Doncker PGR Personal communication December, 1996.
10. Scher RK. Personal communication October, 1996.
## Update on Drugs

<table>
<thead>
<tr>
<th>Class</th>
<th>Name/Company</th>
<th>Approval Dates and Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anesthetic – topical</strong></td>
<td>Lidocaine 2.5%, prilocaine 2.5% Emla® patch Astra</td>
<td>Emla® patches, previously approved by the FDA, are now launched in the US for the reduction of pain associated with injections in children aged over one month.</td>
</tr>
<tr>
<td><strong>Psoriasis – severe recalcitrant plaque</strong></td>
<td>Cyclosporin SangCya® Sangstat</td>
<td>Approved by the US FDA in October, 1998, SangCya® is the first generic formulation of cyclosporin to reach the market. Like Neoral®, it is approved for use in adult, non-immunocompromised patients who have failed to respond to at least one other systemic therapy.</td>
</tr>
<tr>
<td><strong>Psoriasis – severe recalcitrant plaque</strong></td>
<td>Metronidazole lotion 0.75% Metrolotion® Galderma</td>
<td>Lotion dosage form was approved by the US FDA November, 1998 for the treatment of the inflammatory papules and pustules of rosacea.</td>
</tr>
<tr>
<td><strong>Warts – External genital &amp; perianal</strong></td>
<td>Imiquimod Aldara® 3M Pharmaceuticals</td>
<td>Aldara® is now available in the UK (its first European market), following approval by the UK Regulatory Agency in late 1998. It is already available in the US, Australia and New Zealand.</td>
</tr>
<tr>
<td><strong>Wound closure</strong></td>
<td>2-octylcyanoacrylate Dermabond Topical Skin Adhesive® Ethicon</td>
<td>Approved by the US FDA for closing lacerations and incisions that otherwise would require sutures, staples or skin strips.</td>
</tr>
</tbody>
</table>

## Drug News

<table>
<thead>
<tr>
<th>Class</th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Aids-related Kaposi’s sarcoma</strong></td>
<td>Alitretinoin gel 0.1% Panretin® Ligand</td>
<td>The FDA has issued Ligand Pharmaceuticals with a letter stating that Panretin® is approvable for the topical treatment of cutaneous lesions in patients with AIDS-related Kaposi’s sarcoma.</td>
</tr>
<tr>
<td><strong>Antihistamines</strong></td>
<td>Loratidine Claritin® Schering-Plough</td>
<td>Schering-Plough is taking action against Pfizer and UCB Pharma for the alleged breach of a 1996 settlement relating to marketing claims for cetirizine. Schering-Plough can claim that loratidine is non-sedating. Cetirizine’s labelling includes a warning about drowsiness, but Schering-Plough allege that Pfizer and UCB are promoting the drug as being non-sedating and less sedating than loratidine. (Scrip 2378, October 14, 1998)</td>
</tr>
<tr>
<td><strong>Herpes labialis</strong></td>
<td>Penciclovir Denavir® SmithKline Beecham</td>
<td>A joint meeting of the US FDA’s Non-prescription Drugs and Antiviral Drugs Advisory Committees (NDAC and ADAC) voted against Denavir® being switched from prescription only to OTC.</td>
</tr>
<tr>
<td><strong>Lyme disease</strong></td>
<td>Lyme disease vaccine LYMErix® SmithKline Beecham</td>
<td>Awaiting approval by the FDA. Results from a pivotal study show that this vaccine is as effective in a six-month dosing schedule as in a 12-month schedule.</td>
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</tbody>
</table>