Trends-in-Medicine

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By Lynne Peterson

SUMMARY

Johnson & Johnson's Remicade may be the most effective biologic for psoriasis, but dermatologists are not interested in an infused drug, so Amgen's Enbrel is the big winner. There is little interest in either Biogen's Amevive or Genentech's Raptiva. Novartis' oral pimecrolimus could prove a spoiler for all the biologics; the Phase II data was good, but success hinges on the Phase III trial which doesn't begin until 2004. Allergan's oral tazarotene, a retinoid for psoriasis, may replace Roche's Soriatane because it appears equally efficacious but safer. A number of new cosmetic filler products have recently been approved by the FDA or are pending approval, with Medicis' Restylane getting the most attention.

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BIOLOGIC THERAPIES FOR PSORIASIS

Brand	Generic name	Identifier
Remicade	Infliximab	ximab=chimeric Mab
Raptiva	Efalizumab	zumab=humanized Mab
Humira	Adalimumb	umab=human Mab
Enbrel	Etanercept	cept=receptor-antibody fusion protein
Amevive	Alefacept	cept=receptor-antibody fusion protein

The top goals of biologic therapies for psoriasis:

1. Induce lasting disease remission
2. Downshift disease activity such that less "aggressive" and/or less costly therapies will work effectively
3. Prove to be efficacious for individual patients when no other systemic therapies are effective
4. Prove to be safe when other systemic therapies are not tolerated or are contraindicated
5. No major surprise adverse events in the future
6. Have sliding scale programs for indigent patients

Cost of Various Therapies for Psoriasis

Drug	Annual Cost	Dose
Methotrexate	$276	7.5 mg/week
Methotrexate	$468	15 mg/week
Cyclosporine	$5,016	100 mg TID
Johnson & Johnson's Remicade (infliximab)	$5,805	3 mg/kg/month x3
Amgen's Enbrel (etanercept)	$7,830	25 mg weekly
Roche's CellCept (mycophenolate mofetil)	$8,388	N/A
Johnson & Johnson's Remicade (infliximab)	$8,703	5 mg/kg/month x3
Biogen's Amevive (alefacept)	~$10,500	Weekly
Roche's Soriatane (acitretin)	$10,836	25 mg BID
Amgen's Enbrel (etanercept)	$15,660	25 mg BIW

Comparison of Biologic Therapies for Psoriasis

Drug	Amgen's Enbrel	Johnson & Johnson's Remicade	Biogen's Amevive	Genentech's Raptiva
PASI-75	14% 25 mg QW 34% 25 mg BIW 59% 50 mg BIW	83% at 10 weeks at 5 mg/kg	41% at 12 weeks, 52% at 24 weeks	26.6%
PASI-50	41% 25 mg QW 58% 25 mg BIW 74% 50 mg BIW	97% at 10 weeks at 5 mg/kg	N/A	58.8%
Most common side effects	Injection site reactions	Injection site reactions	Chills	Flu-like symptoms
Advantages	Subcutaneous, patient-administered, best safety profile, approved for pediatric JRA use, joints "feel better"	High efficacy, most rapid onset of action, most durable effect	Long duration of remission	Fast acting, short acting, efficacy comparable to Enbrel
Disadvantages	Rare cases of flare upon discontinuation	Infusion, antibody formation, infections/TB increase, worst safety profile	IM or IV push, takes a long time to work, weekly CD4 monitoring required	Rebound/flare upon discontinuation

During an interactive session at the AAD meeting, it was obvious that most dermatologists are aware of some of the basic facts about the biologic agents. Before the lecture:

- 76% knew that the average remission following 12 weekly injections of Amevive is seven months, and this improved to 92% after the lecture.
- 61% knew that the only biologic approved to treat psoriatic arthritis is Enbrel, but this improved to 79% after the lecture.
- 70% knew that Remicade is approved to treat Crohn's Disease and is effective for psoriasis and pyoderma gangrenosum, and this improved to 88% after the lecture.
- However, only 28% knew that a statistically significant improvement in psoriasis could be detected after two weeks of treatment with Raptiva, and this actually worsened to 26% after the lecture. Most thought it took six weeks to see significant improvement.

The attitude towards psoriasis is changing as well as the treatment of the disease. An expert said, "As recently as 2002, we thought clearance was not a realistic expectation for psoriasis treatment, and we are on the verge of changing that thinking forever…We also are trying to get away from classifying psoriasis as mild vs. moderate to severe…We are trying to say there are patients appropriate for topical therapies, and patients who need everything else. Many of us feel that after topicals fail, all therapies should be able to be tried." Another expert said he doesn't use a step-wise approach to treatment of psoriasis: "I don't have patients fail topicals or orals first. The FDA said Amevive is approved for first-line use, and I use that."

Amgen's Enbrel (etanercept)

Enbrel appears to be the big winner in psoriasis. Almost every doctor prescribing biologics is using it – and most are using it exclusively or predominantly. Enbrel is being prescribed mostly for psoriatic arthritis (PsA) but also off-label for psoriasis. Reimbursement seems to be pretty good, though there have been a few cases of push-back from carriers who are limiting use to psoriatic arthritis and requiring documentation of radiographic evidence of the arthritis plus a rheumatology consult.

Dermatologists really like Enbrel because it is well-known and because patients can give it to themselves. Most of the doctors interviewed don't want to get involved with prescribing any biologic except Enbrel. Some also reported that psoriasis patients said their joints "feel better with Enbrel. One commented, "Every day I hear that, and it is more than with the other products."

In psoriasis, more appears to be better with Enbrel; 50 mg twice a week is more efficacious than the 25 mg twice a week that is used in rheumatoid arthritis, and some researchers said they thought 100 mg twice a week might be even better. An expert said, "With Enbrel, I don't think there is any difference between once and twice a week dosing from the patient perspective. It is quite speedy, and has a more durable effect than Raptiva. The efficacy is about equal to Raptiva, except that the 50 mg BIW has an edge over Raptiva. Enbrel has a good safety record and can be used in juvenile RA, and (they) are starting a pediatric psoriasis trial. And no monitoring is required with Enbrel."

There were a few reports that there is some flare (rebound) when Enbrel is discontinued. However, this appears to be mostly mild and relatively uncommon.

New Phase III data on Enbrel in psoriasis was presented at the meeting, and it looked very good.

Enbrel Phase III Results From Study 0016.039 in Psoriasis

Measurement	Placebo (for 12 weeks followed by 12 weeks of Enbrel 25 mg BIW)	Enbrel 25 mg QW	Enbrel 25 mg BIW	Enbrel 50 mg BIW
Completers – 24 weeks	87%	85%	87%	92%
Any infection	48%	46%	54%	44%
Serious Adverse Events	1%	1%	1%	1%
Week 12				
PASI-50	14%	41%	58%	74%
PASI-75 (Primary endpoint)	4%	14%	34%	59%
PASI-90	1%	3%	12%	22%
Physicians Global Assessment: Clear or Almost Clear	5%	23%	34%	49%
DLQI total score	11	47	51	61
Patient's Global Assessment	6%	17%	35%	50%
Injection site reactions	7%	11%	17%	13%
Week 24				
PASI-50	59%	58%	70%	77%
PASI-75	33%	25%	44%	59%
PASI-90	14%	6%	20%	30%
% PASI score improvement	53%	50%	62%	71%
Physicians Global Assessment of Clear or Almost Clear	37%	26%	39%	55%
DLQI Total Score	53%	54%	60%	74%
Patient's Global Assessment	35%	31%	46%	66%

The question some doctors had was: Will managed care pay for the higher dose of 50 mg twice a week (BIW)? So far, insurance carriers have not given dermatologists much of a problem with reimbursement for Enbrel. A doctor said he has seen little push-back from carriers, "One insurance plan actually asked for a rheumatology consult, and that turned out to be a faculty member with the university health plan…I haven't seen any evidence of increased restrictions on the drug, and I'm writing 50 mg BIW in private practice. One time an insurer queried me, and then I cut back to 25 mg BIW…I'm sending patients to the pharmacy with a prescription, and 25% of the time they are handed the drug right then; 75% of the time, they have to have prior authorization, so I had to write letters but it was a smooth experience…In contrast, I had to write 15 letters for Amevive patients."

An Amgen official discussed how well Enbrel is doing in dermatology. She said that 1,400 dermatologists – mostly medical dermatologists -- are now prescribing Enbrel, with many of them starting in the last three months. She said Amgen surveyed 200 dermatologists and found:

- 57% use biologics.
- 96% of doctors using biologics are Enbrel users.
- When asked which of the four biologics they prefer, 72% said Enbrel.
- The top reasons for choosing Enbrel were: 84% route of administration, 82% efficacy, 70% safety, 14% frequently of dosing, 14% no rebound, 11% no TB black box, and 26% other.

Asked if Amgen needs to do more tests to file Enbrel in Europe, an Amgen official said, "That is a Wyeth decision. We have no interest in the European market."

BIOGEN'S AMEVIVE (alefacept)

Amevive attracted surprisingly little interest at this meeting. The CD-4 testing, the potential danger of the low CD-4 count, the reimbursement issues, the slow onset of action, and the lower efficacy are dulling interest in the first biologic to be FDA-approved to treat psoriasis.

Some of the doctors are dabbling with Amevive, but reimbursement approvals so far have been rare. Biogen sales reps at the Biogen booth were telling doctors it only takes four days for approval, but doctors indicated approvals are taking a month or longer. One expert said he finally has gotten approval for five patients to get Amevive, but he doesn't know what he'll get reimbursed, so he said he's taking a chance and could wind up losing money. Another doctor said he is reserving Amevive for Enbrel failures, and third said he chose Amevive over Enbrel for ***one*** patient because the patient co-pay was significantly less with Amevive – but his other patients are all on Enbrel. Even doctors at several major academic centers said they aren't using Amevive.

Asked what route of administration for Amevive he would prefer if he had psoriasis, one expert said, "I would choose IV because it hurts less, but you need to look at each patient…In the best of all worlds, I would choose IV." IV administration appeared to be preferred mode of Amevive administration for other doctors as well.

GENENTECH'S Raptiva (efalizumab)

There was no interest in Raptiva for psoriasis among doctors who are not investigators. There was no buzz, no excitement about it whatsoever.

The BLA for Raptiva was filed with the FDA in December 2002. Genentech officials said they will be making one additional submission to the package to update the safety data with information they have, per discussions with the FDA, and they said it is not uncommon to add data more than 90-days after the BLA filing. Genentech is also pursuing trials of Raptiva in RA, psoriatic arthritis, and other unnamed areas. The psoriatic arthritis trial has completed enrollment, and the data should be available later this year.

Phase III data on Raptiva in psoriasis was presented at the AAD meeting, and a researcher concluded that it is effective at 12 weeks. At four weeks, Raptiva was 12% better than placebo, which he said was statistically – but not clinically – significant: "But you know something is going on by four weeks, which is important in the real world."

Raptiva Phase III Trial Results at 12 Weeks

Measurement	Placebo	Raptiva (1 mg/kg QW subQ)
PASI75	4.3	26.6
PASI50	N/A	58.8
PASI thickness score	16.8	50.7
PSA frequency score	18.4	47.6
Most Common Side Effects		
Headache	21%	33%
Chills	5%	12%
Myalgia	4%	10%
Pain	5%	10%
Fever	2%	7%

Asked how the company will position Raptiva in the market, a Genentech official said, "Raptiva has a good safety and efficacy profile. I don't think there are any drugs with better efficacy or safety. We also have a convenient dosing formulation – subQ. Many patients were dosed at home, and we didn't see any difficulty with that. Also, the size of our database, though smaller than Enbrel, is the largest psoriasis database, with more than 2,100 patients." Asked how Genentech can compete with the Enbrel data in psoriatic arthritis, the official said, "We will emphasize the advantages of Raptiva rather than pointing out deficiencies in the competitors." Another official said, "We talked to a lot of practicing dermatologists, and it is interesting about the differences in what will drive usage for each...There is a large unmet medical need (in psoriasis) and we don't feel the number of biologics is a detriment. It will help patients to have a lot of options."

European regulators have demanded a comparator trial before approving Biogen's Amevive, but Genentech officials do not believe they will be required to do a comparator trial for Raptiva. A Genentech official said, "That is not a requirement of the EU. It is based on an interpretation of the clinical data presented. They look at the overall risk:benefit profile. We believe Raptiva has a very respectable risk:benefit profile, and one that should be more acceptable to them. It is not our expectation that an active comparator trial will be required." Another official said, "It comes down to the magnitude of treatment effect and the safety database…but we are having ongoing discussions (with European regulators)." However, non-company sources believe that Raptiva will face the same European regulatory problem as Amevive. In fact, one source said the EMEA is going to issue new guidelines soon that may require head-to-head (comparator) studies before approval of most drugs.

Genentech officials did not specify how many additional sales people are being hired to sell Raptiva, but they said the Raptiva sales force "will probably be a little smaller than Xolair." Raptiva will be distributed through specialty distributors.

Some of the issues with Raptiva include:

Rebound. The reported rate of rebound ranges from 3% to 9%. Researchers downplayed "flares" with Raptiva, saying that rebound occurs in about 3%-4% of patients, which they said is comparable to methotrexate or cyclosporine, though no rebound trials have yet been done with those drugs. Other sources put the rebound/flare rate at 9%. A researcher said, "Raptiva has a hard landing for a subset of patients (maybe 3% have a hard landing by National Psoriasis Foundation criteria)…Almost all Raptiva rebound occurs when the drug is withdrawn, but no one treats patients that way...There have been one or two patients who have had rebound while on the drug, but that is very rare out of 2,100 patients."

Genentech is conducting tapering or transition studies to determine the best way to handle stopping Raptiva. A researcher said, "In the tapering study, after 24 weeks, patients moved to a section of the trial where they are going to every-other-week dosing or stepping down by .25 mg/kg each week…The transition study is designed to take patients from methotrexate to Raptiva and then off Raptiva again. Xoma is running that trial, and it has started. I'm not involved in that."

Malignancy. "There is no major signal that leads us to believe there is a malignancy issue…there is no imbalance in the data."

Response. There is nothing to suggest that responders can be pre-identified, but a speaker said response is "pretty quick – two to four weeks."

JOHNSON & JOHNSON'S REMICADE (infliximab)

Remicade is considered the most effective biologic for psoriasis, but almost no dermatologists are interested in using it. Not one non-academic doctor plans to add an infusion capability. The lack of enthusiasm for the drug was surprising, given its efficacy and speed of action, especially since doctors said rapid onset is important to patients. There was awareness of dose creep with Remicade, but several experts said the neutralizing antibodies are a non-issue if the drug is dosed with a maintenance schedule rather than intermittently.

The off-label status of the drug in psoriasis is not the barrier; it's the need to infuse it. Asked if dermatologists will set up infusion centers to administer Remicade, an expert said, "They will refer patients to rheumatologists. Cosmetic dermatologists won't set up infusion centers, but I don't know what medical dermatologists will do." Another expert said, "IV infusion (with Remicade) is a huge hurdle for dermatologists to deal with…There is no question that Remicade has an unparalleled speed of onset and durability of onset...but there is a huge safety signal in terms of infections…This is a treatment of last resort. I really like the two subcutaneous drugs (Enbrel and Raptiva), when you go through those options, you can go to Remicade and have something good happen."

A researcher presented 10-week data from the induction regimen of a 26-week study of Remicade as monotherapy in psoriasis patients previously treated with PUVA or systemic medications. He said, "I thought it wouldn't be as good (as Enbrel), and I was wrong…Rapid onset of efficacy was noted by week four, and the results were numerically superior at all time points in the 5 mg/kg group than in the 3 mg/kg group."

Remicade Phase III Trial Results – Induction Regimen

Results	Placebo	Remicade 3 mg/kg	Remicade 5 mg/kg
PASI-75 at week 4	0	35.4%	47.4%
PASI-75 at week 8	4.0%	58.3%	70.1%
PASI-75 at week 10	5.9%	71.7% (p<.001)	87.9% (p<.001)
PASI50	23.6%	83.8%	97%
PASI90	2.0%	45.5%	57.6%
Side Effects			
Headache	5.9%	9.2%	13.1%
Infusion reactions	0.7%	4.4%	5.2%
Patients with 1 or more infusion reactions	2.0%	14.3%	17.2%
Patients retreated	51	98	99
Discontinuation	41.2%	7.1%	6.1%
Discontinuation for lack of efficacy	33.3%	3.1%	1.0%
Discontinuation for adverse events	0	2.0%	1.0%

NOVARTIS' Oral Pimecrolimus

This agent continues to look very promising, but the data is still early and the trials small. All of the opinion leaders are aware of this agent, but they want to see long-term toxicity data. Other dermatologists were less familiar with this agent, and many were not aware it was even in development.

Data from two trials of oral pimecrolimus were presented at AAD: one a single-center safety study comparing the oral to the cream version and a larger Phase II study. In the safety study, the PK data looks good, showing no renal toxicity (the main problem with cyclosporine), no effect on serum creatinine or renal plasma flow, even though the drug is cleared renally. With Novartis' Neoral (cyclosporine), 17% of patients get renal signs, a Novartis official said. There also was no hepatotoxicity. This study found 60% decrease in PASI at day 28 with 20 mg BID, and 75% decrease in PASI at 28 days with 30 mg BID. Mean time to recurrence was 8 weeks, and there was no rebound. There was no effect on blood pressure or blood glucose.

Phase II Results with Oral Pimecrolimus

PASI Improvement	% Patients			
	Placebo	10 mg bid	20 mg bid	30 mg bid
Week 7 *				
≥90%	0	0	9.4	28.6
≥75%	0	7.9	21.9	40
≥50%	8.1	15.8	53.2	60
Week 13 **				
≥90%	0	5.3	25	40
≥75%	0	7.9	31.3	51.4
≥50%	2.7	26.3	56.3	68.5

* After 6 weeks of treatment
**After 12 weeks of treatment

Oral pimecrolimus has the same molecular mode of action as cyclosporine, but its pharmacological profile is different from both cyclosporine and Fujisawa's tacrolimus (Prograf, FK-506), according to Novartis researchers. It reportedly has more affinity for the skin and less affinity to the lymph nodes than tacrolimus, as shown by distribution studies. Compared to tacrolimus, oral pimecrolimus was found to be as effective in reducing skin inflammation but was about 60 times less effective in suppressing localized GVHD, an animal model for the assessment of immunosuppression. Additional animal studies confirmed these findings. This is why oral pimecrolimus is not a transplant drug; it is not a strong immunosuppressant.

From the preclinical data, researchers concluded that oral pimecrolimus has a broader therapeutic window than cyclosporine, tacrolimus, and corticosteroids and therefore has the potential to be effective without the side effects known for these drugs. A researcher explained, "In the clinic in psoriasis patients, cyclosporine at 1 mg/kg would be safe, but you need to increase the dose to 3-5 mg/kg to get a therapeutic effect.

Oral pimecrolimus is like the safety of low-dose cyclosporine with the efficacy of higher dose cyclosporine."

The final dose may be 30 mg BID for clearance and 20 mg BID for maintenance. A 20 mg QD dose reportedly doesn't produce much visible improvement in psoriasis, but biopsies show the drug is inducing a lymphocyte response even at that dose, suggesting that perhaps longer treatment with lower doses also would work – or that lower doses would work for maintenance.

For patients who fail oral pimecrolimus, a researcher suggested a topical may be added, but he was not sure that combining methotrexate or a biologic with oral pimecrolimus would be safe until that is tested. He would be particularly concerned about the safety of combining oral pimecrolimus and Amevive.

Novartis has its End-of-Phase-II meeting with the FDA in the next couple of weeks and will be discussing the Phase III requirements then.

The positives:

➢ **Efficacy and onset of action.** Experts all agree that if the efficacy continues to be comparable to cyclosporine and the safety is better, this drug will be a blockbuster. So far, both efficacy and onset of action are comparable to cyclosporine.

➢ **No apparent renal or hepatic toxicity.** There is no evidence of renal toxicity and no hepatotoxicity, though the drug has not been studied long enough to be certain renal toxicity will not be a problem.

➢ **Quick response.** There is a "dramatic response" in four to five weeks.

➢ **Possibly intermittent therapy.** This drug may be able to be used with repeat courses, rather than continuously, a Novartis official suggested.

The negatives:

➢ **Patient selection.** The Phase II trial patients were carefully selected and not real-world. They were ***not*** followed after the trial, so there will not be additional data coming on these patients. A researcher described these patients as "perfect patients" – no diabetics, no hypertension – saying, "It was like a normal volunteer study except they had psoriasis."

➢ **Lack of long-term data.** There is no long-term data. The patients in the safety study who were given the drug for 12 weeks were followed out to a year with no adverse events appearing, but patients on drug for a year need to be studied for safety. Safety issues with cyclosporine take time to show up; there is a cumulative toxicity issue with cyclosporine.

➢ **Slow Development**. Novartis researchers said this was due to "priorities at Novartis right now" and a desire to "do it right." The Phase III trial will not start until 2004, and the drug probably will not be on the U.S. market until early 2006.

➢ **Safety issues.** In the Phase II trial, there were three cases of a creatinine increase in the 30 mg arm, none in the 20 mg arm, and one in the placebo arm. In all cases, the increase was about 30% but still within the normal range, and the patients on drug all continued on the drug with no problems and no dose reduction, and the creatinine decreased. There was one patient in the 30 mg arm who discontinued treatment for abnormal lab values, but these were not specified except that the issue was not creatinine. An expert who has worked with oral pimecrolimus warned that safety is the real concern with this calcineurin inhibitor and pointed to several side effects that may prove problematic:

- "Headache is a common side effect, but it occurs across all dose groups equally."
- "The hot feeling has a clear relationship to dose."
- "GI disorders appear to increase with dose – with up to a 38.3% incidence in the 30 mg BID group."
- "Nausea is the most common side effect."
- "There is a small signal of a creatinine problem in this perfect population. Five percent of patients had a 30%-50% increase in serum creatinine over a 12 week treatment period. The historical control is 20% with cyclosporine…but this data came from long-term use in patients with co-morbid conditions, so it can't be compared to the pimecrolimus patients who were pre-selected."

Researchers still want to see:

- Phase III trials in more representative patients.
- Treatment for one year or more.
- Combination therapy looking at efficacy and safety.
- Pediatric trials.
- Psoriatic arthritis trials.
- Trials in other inflammatory diseases.

Phase III Trial Details

There will be comparator arms (plural) in this trial -- one will be cyclosporine and probably a biologic as well (which one has not been decided). The trial will have "real world" patients and will be conducted in both atopic dermatitis and psoriasis, and the company will seek approval in both. This is a double-blind, 12-week efficacy but one-year safety trial. After the treatment period, all patients will be rolled into the active arm for long-term follow-up. All patients (including all drop-outs) will be followed for five years. The trial will start in 2004 and will be large ("thousands" of patients). Both the 20 mg BID and the 30 mg BID doses will be tested. There will be QT testing as part of the trial; the Novartis researchers were well aware of the new FDA attitude on QT.

OTHER PSORIASIS TREATMENTS

ALLERGAN'S oral tazarotene

Allergan already markets Tazorac, a topical tazarotene, for psoriasis, but the company is exploring an oral version as well. Oral tazarotene poses a significant threat to Roche's Soriatane (acitretin). Dermatologists generally agreed they would prefer oral tazarotene to Soriatane if the efficacy data is similar but the safety data better. Patients (especially male patients) doing well on Soriatane may not be switched to oral tazarotene, but oral tazarotene is likely to be the No. 1 choice for new patients.

Tazarotene could expand the market as well as cut into Soriatane's market share. It won't replace the biologics, but it might be tried before doctors turn to a biologic. An expert said, "If dermatologists pick up on this, it will expand the market…I think the retinoids are great for pustular psoriasis, either as monotherapy or in combination and for palms and soles, the retinoids are my first line for patients who require a systemic medication, but again often in combination with something else." Another expert said, "I want to see more than 12 weeks safety data on (oral) pimecrolimus. That is not as important with tazarotene. We did tazarotene in our office, and it worked fine, but I am not a super fan of retinoids…If my patients have access to biologics, that's where I'll take them -- if they have insurance for them – because of the side effects of retinoids. Retinoids change the mucus membranes, and there's a lot of dryness. Patients are tolerating (oral tazarotene) better in the trials then they tolerate Soriatane, but there's still a lot of baggage."

Allergan has completed two Phase III trials (048P and 049P) of oral tazarotene. Sources did not consider the efficacy results as dramatic, and it is not possible to directly compare the efficacy to Soriatane, but sources generally considered the efficacy similar.

An investigator said there was no statistically significant difference between placebo and the drug in terms of alopecia, dry mouth, dry nose, or dry eyes. He said, "Dry lips (cheilitis) is the only one of the mucous membranes that showed a statistically significant increase over placebo, and only about 20% of patients (on tazarotene) developed dry skin. Our concern was ocular problems and dry eye because that can increase the risk of corneal opacities, but there was no statistically significant difference from placebo. If I had to rate the problems we worry about with retinoids, it is dry lips, eyes, nose (bleeding), and skin, and hair thinning that are most significant, and tazarotene only showed a high incidence of cheilitis…which was mostly mild to moderate and can be handled fairly well with standard lip balms."

The biggest advantage of tazarotene over Soriatane may be the length of time that women of child bearing age are affected. With Soriatane, women are supposed to avoid pregnancy for three years, but with tazarotene the time frame may only be 30 days, as with Accutane. An investigator said, "This is a critical difference. Bearing in mind that psoriasis is a disease of young patients; the majority of patients get it before age 35. Excretion of tazarotene is far shorter; the half life is about 7-12 hours, compared to 49 hours for Soriatane, which also has an alcohol conversion issue…Looking at the PK and elimination data on tazarotene, it looks as if this will be similar to Accutane, which is 30 days instead of three years. So, even if the efficacy data is the same, you have less mucotoxicity outside of cheilitis and the teratogenicity is less…Tazarotene won't be first line like the biologics,

Pooled Analysis of Two Phase III Trials of Oral Tazarotene at Week 12

Measurement	Placebo	4.5 – 5.0 mg QD	p-value
Number	350	340	---
Baseline OLA (on a scale of 1-6)	3.4	3.4	---
Mean body Surface Area (BSA)	30%	29%	---
Primary Endpoint: OLA complete or nearly complete response (none or minimal psoriasis)	3%	17%	p<.001
Secondary Endpoint 1: Global Treatment Success >50%	14.9%	53.8%	p<.001
Secondary Endpoint 2: Global Treatment Success >75%	7.4%	29.7%	p<.001
Adverse Events			p<.05
Cheilitis	17%	66%	
Dry Skin	15%	24%	
Headache	12%	19%	
Arthralgia	8%	17%	
Myalgia	8%	14%	
Back Pain	3%	7%	

Several questions were raised about this data, including:

- **Pooling.** Only a pooled analysis of the two trials was presented at the meeting, but the FDA likely will require the individual trials be positive as well as the pooled analysis. However, the pooled groups were well-matched.
- **Dropouts.** Unlike the Phase II trial, which had a drop out rate of 33%, an investigator said the number of patients who dropped out of the Phase III trials was less than 10%, but the company has not released official dropout figures yet.
- **Trial endpoints.** All of the biologics for psoriasis have used PASI scores, but Allergan used OLA for the primary endpoint and Global Treatment Success for secondary endpoints. Since oral tazarotene will be reviewed by CDER instead of CBER (which reviewed the biologics), the endpoints Allergan used appear appropriate; other oral drugs for psoriasis have been approved on non-PASI endpoints. For example, Soriatane was approved on Global Assessment.

Sources agreed that OLA and the Global Score cannot be compared to PASI scores, "PASI is a score that stands by itself. Unfortunately, the current gold stand for psoriasis is PASI, but bear in mind that this is something no dermatologists do in clinical practice; they just eyeball it. No one uses PASI except in a clinical study. Allergan was one of the first companies to take OLA and use a different standard than PASI…In meetings with the FDA (about tazarotene), it became obvious the Agency wanted a defined primary endpoint, and that typically was PASI-75 improvement, but the FDA is now telling industry and the National Psoriasis Foundation that there are other possible options and that PSAI-50, OLA and Global Response are all secondary endpoints."

ACNE

Very few dermatologists questioned are prescribing generic isotretinoin. All prefer the brand (Hoffman-La Roche's Accutane), though many doctors acknowledged that the pharmacy may be substituting a generic without their knowledge. Among the reasons for the loyalty to brand Accutane: (a) desire to deal with only one product in the office, to avoid having to sort through different plans and formularies, (b) brand considered more "reliable," (c) experience with brand, (d) perception that there is not a big cost savings with the generics, and (e) allegiance to Roche for "working hard to keep Accutane on the market and available for patients."

Sources all said they use Roche's S.M.A.R.T. (System to Manage Accutane Related Teratogenicity) pregnancy prevention program when prescribing Accutane – or a generic. With SMART, doctors apply yellow self-adhesive warning stickers to all Accutane prescriptions. The stickers alert the pharmacist that the patient has met the pregnancy protection requirements and can be given Accutane. The generic manufacturers (Bertex and Genpharm, which sells isotretinoin as Amnesteem) have similar programs.

Dermatologists said they consider the programs totally interchangeable. All are giving out the SMART program, regardless of what the patient is taking. Some assume the pharmacy will provide the generic company's equivalent program information if a generic is substituted, but none were concerned if this did not happen since they consider the information equivalent. A Texas doctor said, "The programs are interchangeable." A Pennsylvania doctor said, "The booklets are almost identical, and it doesn't matter what sticker is used." A Midwest doctor said, "I tell patients about the generic and the brand, and let them choose. But I tell them to ask the pharmacy how much they are actually saving with the generic because a lot of pharmacies don't pass on the savings to the patients. I also tell them the brand is sometimes more reliable. When cost is not a big issue for the patients, they choose the brand. But I use the SMART program for everyone."

ATOPIC DERMATITIS

Doctors questioned at the meeting said the two key topical agents they are using for atopic dermatitis are Novartis' Elidel (topical pimecrolimus) and Fujisawa's Protopic (tacrolimus). Most said they use more Elidel than Protopic because there is less stinging with Elidel. A Florida dermatologist said, "If I had more pediatric patients, I would use even more Elidel." A Utah dermatologist said, "I use mostly Elidel." A Minnesota dermatologist said, "I usually use Elidel because it burns a little less than Protopic." Sources were unaware of any new products close to market that would be likely to affect sales of either Elidel or Protopic.

BOTULINUM TOXIN

Comparison of Botulinum Toxin Products

	Allergan's Botox	Elan's Myobloc	Inamed's Dysport
Type	Type A	Type B	Type A
How sold	100 unit vials	2500, 5000 and 10,000 vials	500 unit vials
Equivalence to Botox	N/A	---	2-5 units Dysport per 1 unit of Botox
Formulation	Lyophilized	Liquid	Vacuum dried
Reconstitution	Yes, stable 24 hours	No, very stable	Yes, no need to refrigerate
Refrigeration	Yes	No, can be stored up to 30 months	No
Side Effects	Nothing significant	Stings on administration, some dry mouth	Nothing significant
Advantage	Long duration	Rapid onset, greater area of diffusion, more even effect	Longer duration than Botox

ELAN'S Myobloc (botulinum toxin-B)

A researcher pointed out that Myobloc works in a totally different manner – at the intracellular level – from Allergan's Botox. He said, "Surprising, Myobloc has rather different effects when you inject it. Most importantly, it doesn't last as long, so we've not been impressed that it is real competition for Botox." Another speaker said, "The problem with Myobloc is that once you get a dose that works and that lasts, you see a problem with dry mouth and dry eyes, but the effect only lasts 10-11 weeks…Myobloc won't be a serious competitor."

INAMED'S Dysport (botulinum toxin-A)

Dysport is very similar to Botox and may be a serious competitor for Botox A researcher said, "Dysport is essentially identical to Botox, and it works in the same manner. There are minor differences in production. And it looks as if they are responding the same way." Asked how he would choose between Botox and Dysport, he said, "Price! It will be fascinating to have some real competition in this area."

Dysport is in Phase II trials in North America. That trial will be completed this year and analyzed by the end of the year. A Phase III will start later in 2003.

COSMETIC PROCEDURES: SKIN FILLERS

A number of new filler products have recently been approved by the FDA or are pending approval to cosmetically remove wrinkles and lines. Among these are:

Collagen

- **INAMED'S CosmoDerm**, a collagen made from human foreskin that is used to treat fine lines and wrinkles. It was approved in March 2003 week. The advantages are that no skin test is required before using it, and it has lidocaine mixed in to reduce the pain of the injection. Acts like collagen, lasts as long but doesn't need to have skin test. A Utah dermatologist said, "It will have a place because it is not cow collagen, but it doesn't last as long (about three months) as Restylane, which last six to 12 months."

- **INAMED'S Cosmoplast**. This also was just approved by the FDA. Like CosmoDerm, it contains lidocaine, but it is used for deeper furrows.

- **ARTES MEDICAL'S Artecoll**, plastic beads of bovine collagen. It is not yet FDA approved, but it is used in Europe. It is longer lasting (> 6 months) than collagen, but sources said there is no room for error because it is not easily removed, and there have been cases of granulomas reported in Europe.

Hyaluronic Acid

These are not approved yet in the U.S. for cosmetic purposes, but they are approved in 51 other countries. They are relatively long-lasting (six to 12 months, depending upon the volume used). And they reportedly give smooth, natural results. The disadvantage is that the injections are more painful than collagen injections because there is no lidocaine mixed in, so a topical, local or block anesthesia must be used. In addition, they are associated with erythema, ecchymoses and swelling in 10%-15% of people one to five days post treatment.

- **GENZYME BIOSCIENCE'S Hylaform**, which will be sold by Inamed. This is waiting for FDA approval. It is a hylan gel made from rooster combs. Data will be published in the Journal of Dermatologic Surgery in June 2003, and the PDUFA date is in June 2003.

- **GENZYME'S Synvisc**, which is used off-label by some doctors. None of the dermatologists questioned at the meeting are using it, but many knew of other doctors who were.

- **MEDICIS'S Restylane**, a cross-linked hylan gel. This product is not yet FDA-approved, but it garnered the most interest of the new fillers at the meeting. A Florida doctor said, "Restylane is interesting as an alternative to collagen, and it doesn't require a skin test. The lidocaine (in the Inamed products) is a minimal advantage." A Utah doctor said, "I've been using Restylane for a year, with great results. I like the way it feels. It's not permanent, and the pain is a little more (than the Inamed products) but that is not a huge issue)." A Minnesota dermatologist said, "I haven't used fillers yet, but I plan to start. I'm interested in Restylane. It's easy to use, doesn't require pre-testing, and is synthetic."

Liquid Silicone

Liquid silicone (silicone oil) is approved for use in the eye, but sources were dubious about the outlook for them in skin. The FDA considers liquid silicone to be a device, not a drug. Doctors can tell patients about these products, and they can use them off-label, but they can't advertise them. Another problem is that unknown, adulterated products have been used by non-physicians, giving liquid silicone a bad reputation. There also can be minor complications, such as bumps from over-correction. An expert said, "These should not be used in large areas like the breasts or areas that easily over-correct like forehead wrinkles or the line above the chin, but they are safe. Diabetics on insulin routinely get about 5 cc of (silicone) because it is a lubricant for needles and syringes." A Utah dermatologist said, "I'm not impressed with the new liquid silicones. In the past there were nightmares with liquid silicone due to contaminants, and it can drift a little, so you have to watch out." Another dermatologist said, "I think the liquid silicone is the most iffy of the new fillers, but I think it's safe."

- **BAUSCH & LOMB'S Adatosil.**

- **ALCON'S Silikon,** which is much less viscous than Adatosil. Reportedly, this is the most popular of the two agents. It is usually administered in serial injections, with multiple treatments at four-to-six week intervals, using a 27-gauge needle. An expert said, "Often there is no improvement until two or three treatments have been given, but then the improvement is permanent."

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