Trends-in-Medicine

February 2004
By Lynne Peterson

SUMMARY
Biologic agents to treat psoriasis generated a lot of interest at this meeting. There were numerous sessions every day on biologics, and each was packed. Dermatologists clearly wanted to know more about all of these agents, but it is Amgen's Enbrel that is taking off strongest. ♦ The data on Allergan's oral tazarotene (page 8) looked good, and when it is FDA-approved, this agent will cause some doctors to delay use of biologics. ♦ There was no significant new data on Novartis's oral pimecrolimus (page 11), but the drug will start Phase III trials later this year. ♦ There also was new information presented in several other areas of dermatology, including topical agents for psoriasis and other conditions (page 11), dermal fillers (page 12), botulinum toxin (page 14), and melanoma (page 15).

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AMERICAN ACADEMY OF DERMATOLOGY

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Dermatologists were interested in a variety of topics at this meeting, but psoriasis – oral agents as well as biologics – appeared to dominate the meeting. On the cosmetic side, new dermal fillers and botulinum toxin attracted attention.

BIOLOGICS FOR PSORIASIS

The high level of interest in biologics at this meeting might indicate that usage is likely to increase substantially over the next year. A speaker said, "Will dermatologists embrace this? I hope in five years time the answer is definitely yes. Less than 25% of (psoriasis) patients are treated now with systemics…It is not just the train wrecks that need to be treated." Another speaker said, "To dermatologists new to the biologic era, I want to point out that we must and should become familiar with these agents…I encourage all dermatologists to get on a par with doctors in other specialties."

However, most community doctors are much less enthusiastic about the biologics than their academic colleagues. Many of them have not started prescribing biologics yet, others are just getting started, and a few do not intend to use biologics at all over the next year. Over and over, community doctors complained that the lecturers and "opinion leaders" are "in the employ of the pharmaceutical companies." As a result, they are approaching the biologics cautiously, and they are not sure what to believe about individual agents. A Pennsylvania doctor said, "I have psoriasis myself, but I don't use biologics. I will use them when the safety is there. The side effects listed are scary. I think the FDA approves things too quickly…And Enbrel (Amgen, etanercept) doesn't work on palms and soles." An Ohio doctor said, "I haven't used any biologics yet because I haven't had a patient who was a reasonable candidate, but if I get an appropriate patient I would use Enbrel because it is a known commodity."

More than 20 doctors were interviewed about their biologic use. On average, community doctors estimated that 13% of their psoriasis patients are currently on a biologic. In a year, they expect that to increase on average to 17%.

Doctors were seeking more information and guidance on how to choose among the biologics and how to use them in combination therapy. A speaker said, "In my opinion, not all biologics are created equal." He listed the worst to the best in this

order (worst first). Several speakers also offered lists, and they were remarkably similar:

1. Biogen's Amevive
2. Genentech's Raptiva
3. Roche's Soriatane
4. Amgen's Enbrel
5. Narrow Band -UVB therapy
6. Methotrexate
7. PUVA
8. Cyclosporine
9. Goeckerman therapy (generally not available in the U.S.)

Although speakers placed Soriatane above Raptiva and Amevive in terms of efficacy, a leading expert said that this is just not true. However, most community doctors predicted that Allergan's oral tazarotene – if it has less side effects than Soriatane and a more favorable pregnancy warning – will delay their use of biologics. However, a better pregnancy label was deemed critical. With that, these doctors said they would probably try oral tazarotene before they would go to a biologic. A source said, "Oral tazarotene could delay my use of biologics. Some patients won't want to inject, and the cost of biologics is high, but it varies by patient."

Other interesting comments made by a psoriasis speaker included:

- "One surprising finding is that most biologics don't work as well as older therapies, but they don't have some of the organ toxicity."
- "Many U.S. dermatologists don't feel comfortable using biologics; 87% prescribe only topicals for psoriasis."
- "There is a fighting chance that most, if not all, dermatologists will feel comfortable using safer biologics even if they are still afraid of other systemic agents."
- "33% of dermatologists account for 95% of systemic agents used."
- "33% of dermatologists don't use any biologics."
- "Biologics and pre-biologics don't have to be mutually exclusive…They can be used together. When starting safer biologics, it is often not necessary and may even be inadvisable to abruptly stop the existing pre-biologic therapies. If a patient is doing well on methotrexate or Soriatane, and you abruptly stop that to start Enbrel, etc., then the patient may have a flare before the biologic kicks in…So, many times I continue the pre-biologic when starting the biologic. And if biologic monotherapy is not adequate, then you can add a pre-biologic…Initially, it is better to overlap the two…I would double up for many months before moving to a biologic alone…A biologic plus methotrexate or an oral retinoid might be used for ongoing maintenance. A biologic plus UVB plus a retinoid is my favorite stacking."

Amgen presented some interesting results from its surveys about the attitudes of dermatologists to psoriasis treatment and biologics. Amgen also analyzed dermatology practices and concluded that psoriasis is not a large revenue generating procedure. An Amgen official said, "The point is that where dermatologists want to operate is cosmetics because psoriasis takes time…They want efficiency and to have the procedure very straightforward…That is really important."

Total systemic prescriptions written by dermatologists	Current treatments patients are on for psoriasis	Willingness to use biologics
36% methotrexate (34,000 patients)*	42% topicals	59% of discontinued patients
28% Enbrel (11,000 patients)	22% phototherapy	71% of topical users
26% Soriatane (17,000 patients)	10% systemics (87,000 patients)*	67% of phototherapy users
10% cyclosporine	6% other	91% of systemic users
~5% Amevive (2,000 patients)	10% none	N/A

*Adds to more than 100% due to combination use

Condition	% of a dermatologist's workload
Pre-cancer/cancer	28%
Warts/moles	17%
Acne	14%
Cosmetic Treatments	10%
Dermatitis	9%
Psoriasis/psoriatic arthritis	6.5% (75-100 moderate/severe psoriasis patients per dermatologist)
Rosacea	6%

Biologic	Cost per PASI-75 responder
Amevive	~$60,000
Raptiva	~$48,000
Enbrel (either 25 mg BIW or step-down)	~$25,000
Enbrel 50 mg BIW	~$38,000

Condition	% of dermatologist's practice revenue
Destruction/ excision	76%
Cosmetic	17%
Light therapy	3.5%
Other	3%

Condition	Average revenue per minute
Consultations (including psoriasis)	$5.70
Medical procedures	$13.73
Cosmetic procedures	$20.15

The speakers did a good job of presenting the various agents fairly, emphasizing the positives and negatives of each. One said, "The failure of one drug does not predict failure of others."

Experts emphasized that it is difficult to compare the different biologic agents by looking at the PASI scores in their clinical trials because the entry criteria and other factors were different. However, such a comparison may still be useful.

With respect to combination psoriasis therapy, a speaker said, "Topicals used in stubborn areas may allow a decrease in the dose/duration of biologics…For the majority of patients, systemics are probably not a good idea. The data on combinations are starting to be accumulated, but what we need that we don't have…is a test where you get buccal DNA and then say which agent to use…We don't have that…Right now we are just guessing, and the choice of one of these biologics over the other is based on convenience to patients and insurance, not necessarily the pathophysiology of the patient's disease." Another speaker commented, "I think combination therapy means adding a topical to a biologic…The routine addition of a systemic should be regarded as drug failure…If you have to add methotrexate to Enbrel, that is an inadequate response…I have plenty of patients on high dose Enbrel and methotrexate…Some did well, but plenty of patients with both had no response…As a routine matter, combining therapies with systemics is an indication the biologic is not getting the job done."

Measurement	Amevive	Raptiva	Remicade	Enbrel	Humira
Durability	+++ 85 days	++ 67 days	++++	++	N/A
Efficacy	++	+++	++++	++/+++	+++/++++
Safety	+++	+++	++ Infusion reactions Flu-like symptoms Mild infections Antibody formation TB activation	+++ Mild infections Flu-like symptoms Injection site reactions	+++ Burning on injection Black box for TB
Pediatric use	No	No	No	Yes	No
Monitoring	Weekly CD-4	Platelets monthly	Initial PPD	Initial PPD	Initial PPD
Status	Approved	Approved	Phase III	Psoriatic arthritis approved; psoriasis BLA filed	Phase II completed
Speed of onset	+	+++	++++	++/+++	++++
Administration	IM	SQ	IV	SQ	SQ
Issues	Efficacy Cost of failure	Rebound	Infection Dose creep	Rare CF, MS, Lymphoma, TB	N/A
Features	Durable response	Fast and convenient	Best response	Fast and convenient	N/A

How do doctors choose among the biologics? Many said they leave the choice to patients, or they tailor the therapy to patient lifestyles and preferences. A speaker said, "I make the decision by talking to the patients and finding what they are looking for…If it is a 70-year-old who is comfortable coming to the office, was recently widowed and likes seeing the staff, she may get Amevive. Busy travelers who want to do something at home are candidates for Raptiva…I give patients the data…I say Amevive works slowly, but we can add UVB. And if they think that is a pain, we look at something else." Another said, "My approach is first to use UVB plus acitretin. Then, I try methotrexate or biologics – I'm not sure which of these first, but cost is an issue. I list them and see which the patients want. Then, if all else fails, I use cyclosporine, combination therapy or lastly hydroxyurea… Patients may ask for inappropriate treatment…There are real risks to systemic treatments, so use good judgment and remember that sometimes you have to say no."

Comparison of Efficacy of Biologic Agents in Psoriasis
(FDA-approved dose in gray)

Measurement	Number of Patients	PASI-75	PASI-90
Enbrel 25 mg weekly	160	14%	3%
Enbrel 25 mg twice-a-week	162	34%	12%
Enbrel 50 mg twice-a-week	164	49%	22%
Remicade 3 mg/kg/month	N/A	72%	45.5%
Remicade 5 mg/kg/month	N/A	88%	57.6%
Humira 40 mg EOW	46	53%	24%
Humira 40 mg weekly	50	80%	48%
Raptiva	N/A	27.9%	N/A
Amevive 10 mg IM	N/A	21%	≤20%
Amevive 15 mg IM	N/A	33%	N/A

Most community dermatologists said they currently are using Enbrel either exclusively or for the majority of their psoriasis patients. A few are prescribing a little Amevive or putting an occasional patient on Raptiva, but it is Enbrel that they prefer. The reason for Enbrel's popularity is best described as a "comfort" issue. It is not one factor, but a constellation that makes them comfortable with Enbrel. A New Jersey dermatologist said, "Enbrel will be No. 1. Not because it has been out the longest, but because it is safer and works better. We are more familiar with Enbrel. I would need a reason to change from Enbrel beyond a PASI score – like cost."

Among the factors making doctors feel comfortable with Enbrel are:

- **History.** It has been around long enough that hundreds of thousands of patients have taken it.
- **Experience in rheumatology.** They are not the first doctors to be using it. They like the idea that the rheumatologists have used it successfully for several years.
- **Safety.** The side effects are reasonable. They are not particularly concerned about the Remicade side effects, but they are not too worried about serious adverse events with Enbrel.
- **Administration.** Patients inject Enbrel themselves, so use involves less work for the dermatologist.
- **Reimbursement.** Reimbursement is easiest for this of all the biologics, for psoriasis as well as psoriatic arthritis, though it is not problem-free. Reimbursement is a struggle with all biologics, but much less with Enbrel than Amevive and Raptiva. A Maine dermatologist said, "Cost and reimbursement are still a big issue for all biologics."

Following are some of the other interesting comments that speakers made about specific products:

12-Week Results of Phase II Trial of Humira for Psoriasis

Measurement	Placebo n=52	Humira: 80 mg loading dose then 40 mg EOW n=46	Humira: two 80 mg loading doses then 40 mg weekly n=50
PASI-50	17%	76%	88%
Primary endpoint: PASI-75	4%	53%	80%
PASI-90	0	24%	48%
Secondary endpoint: Physicians Global Assessment (PGA) of clear or almost clear	2%	49%	76%
Reasons for Discontinuations			
Adverse events	1 patient	2 patients	2 patients
Lack of efficacy	1 patient	None	None
Abnormal lab value	None	None	1 patient
Adverse Events			
Any adverse event	65.4%	62.2%	78.0%
Headache	15.4%	8.9%	14.0%
Injection site pain	5.8%	6.7%	12.0%
Nausea	5.8%	6.7%	2.0%
Elevated triglycerides	0	6.7%	2.0%
Cough	3.8%	0	6.0%
Sinus congestion	0	2.2%	6.0%
Fatigue	5.8%	2.2%	4.0%

ABBOTT'S Humira (adalimumab)

Preliminary data from a 12-week, double-blind, placebo-controlled Phase II dose-finding study of Humira in psoriasis was presented (by poster). It appears that Humira is **less** effective than Remicade but safer – and **more** effective than Enbrel but perhaps not as safe. An expert said, "Humira is not as safe as Enbrel, but it is more Remicade-like, and it will replace Remicade…But Enbrel is like a Volvo, and a lot of people like Volvos for their safety."

Critics suggested the safety of Humira wasn't as "clean" as Enbrel. They claimed the injection site pain also was greater with Humira. A doctor explained, "Enbrel injections don't hurt, and Humira injections do. I think that is because of the vehicle used or the pH of Humira." However, other sources said the Humira stinging usually lasts less than 30 minutes.

Using one or two loading doses of 80 mg makes Humira act quickly, similar to Remicade. The principal investigator said, "With every-other-week dosing it takes three or four doses to get to steady state. With a 12-week trial we did a loading dose…In my opinion the 40 mg every week dose is better." Asked about the use of PASI-75 as the primary endpoint, he said, "I think PASI-75 is not an unreasonable benchmark. It is what the FDA wants, but it is not appropriate for clinical management."

Following are some of the comments by speakers and other doctors about Humira:

- "Even though it is supposed to be fully humanized, it does have tachyphylaxis, and it seems you do get dosage creep – having to use it more frequently – which affects the cost…They (Abbott/Humira) are further behind in our specialty...and the data is mostly from rheumatology… My preliminary impression is the drug is more Remicade-like than Enbrel-like." *Asked on what his tachyphylaxis charge is based,* he responded, "I'm generalizing from the rheumatology practice with Humira…There has been dosage creep to once-a-week or more frequently (with Humira)…There is evidence of auto-antibody formation, though (Humira) is supposed to be fully human. And there is some evidence of patient tachyphylaxis with continued treatment in RA. The preliminary experience is really anecdotal, and that may be true for psoriasis as well."
- "It is extremely fast acting and has very high rates of efficacy…It is almost comparable to Remicade…It is clearly a drug to keep an eye on."
- "There's burning on injection with Humira, which lasts 30-60 minutes, that doesn't occur with Enbrel. It's mentionable, but it won't stop people from using Humira."
- "Humira will replace Remicade, but it won't replace Enbrel because of the black box warning."

AMGEN/IMMUNEX'S Enbrel (etanercept)

Amgen submitted the Enbrel psoriasis indication data to the FDA in July 2003 and is awaiting a decision. An official said, "We hope the FDA will approve the drug in 2004, and we'll be off to the races." However, dermatologists are not waiting for FDA approval to use Enbrel to treat psoriasis. As of June

2003, an Amgen official estimated that 215,000 patients world-wide had been treated with Enbrel, for a total of 398,000 patient-years, and he said 3,000 dermatologists were prescribing Enbrel at the end of 2003.

There were three key pieces of Enbrel news at this meeting:

1. Enbrel can be safely stopped without rebound. Symptoms resume at a median of three months, but there is no rebound. An expert said, "It shows you can retreat, and the patient will do equally well. I'm not recommending intermittent therapy, but there are situations – when patients lose insurance, get pregnant, have an operation, etc. – where you need to stop the drug. It is comforting to know you can stop it and restart it without giving up the benefit." Another speaker said, "A study of giving Enbrel for six months and then abruptly stopping it, then re-treating patients, found that at Week 24, the same response was obtained. So, Enbrel doesn't get its efficacy reduced even if there is a gap in between use, and that is encouraging. It is also encouraging that no rebound is seen."

2. A high dose (50 mg twice-a-week) for the first 12 weeks is more effective than the approved dose. A speaker said, "Doubling the dose seems to have better efficacy all around."

3. The dose can be stepped down over time. A speaker explained, "You can start high and cut back for 75% of patients. You can start with 50 mg twice-a-week and after 12 weeks cut back to 25 mg twice-a-week."

The 652-patient U.S. Phase III double-blind trial design was:

- Patients were randomized to active treatment received 24 weeks of Enbrel.
- Patients in the placebo group received 12 weeks of placebo followed by 12 weeks of Enbrel 25 mg BIW.
- After 24 weeks of double-blind treatment, responders (PASI ≥50) had Enbrel withdrawn and were followed monthly until disease relapsed.

Step-down conclusions:

- 50 mg Enbrel BIW for two weeks provided rapid, significant clearance of psoriasis in almost half of patients.
- Despite decreasing the dose from 50 mg BIW to 25 mg BIW after Week 12, treatment success was maintained in a large majority of patients, and almost a third of those who had not responded at Week 12 did so by Week 24, even on the reduced dose.

Phase III Enbrel Re-Treatment Study

Drug	PASI-75 at 12 weeks	PASI-75 at 24 weeks	Median days to relapse after withdrawal	PASI-75 at re-treatment Week 12	PASI-75 at re-treatment Week 24
Placebo/25 mg BIW	4%	33%	85	36%	38%
Enbrel 25 mg QW	14%	25%	70	19%	19%
Enbrel 25 mg BIW	34%	44%	85	40%	49%
Enbrel 50 mg BIW	49%	59%	91	45%	58%

- An Amgen official commented, "We think Enbrel hits the sweet spot…Step-down is the best value and gets on top of the disease with the speed the dermatologist wants to see."

Amgen's marketing points for Enbrel vs. its competitors appear to be:

- No rebound. It is safe to withdraw Enbrel.
- Intermittent therapy is possible, though not advocated. Once relapse occurs, treatment can be resumed and psoriasis clearance can be re-established.
- No neutralizing antibodies form during initial treatment or re-treatment.
- After rapid, high-level clearance is established, patients can be maintained on a lower dose.

Following are some of the comments by speakers and other doctors about Enbrel:

➢ **Relapse**. "Patients gradually relapse when Enbrel is withdrawn...The mean relapse time is 85 days. Relapse time gradually increases in a dose-responsive manner, so higher doses take longer to relapse. There is no rebound – only one case in 462 patients."

➢ **Side effects.** "There have been reports of TB, MS and optic neuritis issues post-marketing. There hasn't been a lot of noise, but you need to keep that in mind…Sepsis is a big concern...and there are rare cases of TB…I would urge all of us to screen patients for TB."

- ***Question to speaker:*** "We just had a rheumatology patient who died from an opportunistic infection on Enbrel…Do you anticipate a problem with this?"
- ***Speaker's answer:*** "This hasn't happened in psoriasis yet…Might it happen sometime? Yes. In thousands of patient years with Enbrel, it is a very, very rare occurrence. But I can't say it never happens."

➢ **Efficacy.** A speaker said, "This is a 'Fire and Forget' drug." Another expert said, "If you get out to 24 months and don't have results, it is time to go to something else…If my patients aren't happy by 24 months, we have to make a decision about what to do."

➢ **First-line therapy**. "Could we start with Enbrel without prior systemic therapy? I believe we could in certain patients."

➢ **Non-responders**. "When non-responders are continued beyond 24 weeks, a significant proportion (about one-third) improve."

➢ **Durability**. "Enbrel has more durability than Raptiva, with similar efficacy…If you can get a high enough dose of Enbrel out of the insurance company, then there is even more activity."

➢ **Pediatrics.** Enbrel is approved for pediatric use.

➢ **Pulmonary sarcoidosis.** "An open label study for pulmonary sarcoidosis was stopped due to early and late treatment failures. Remicade may be strong enough to work, but Enbrel does not appear potent enough for this disease."

BIOGEN'S Amevive (alefacept)

An investigator reported on the first three patients in an ongoing 12-patient study of tapering cyclosporine in patients on the combination of Amevive and cyclosporine. All three patients successfully reduced their cyclosporine use without their disease worsening significantly.

Following are some of the comments by speakers and other doctors about Amevive:

➢ **Malignancy**. "The concern is malignancies, but that doesn't appear to be an issue." Another speaker said, "The FDA is worried about malignancies. That doesn't appear to be a problem…but I don't know if, further down the road, it will be a problem."

➢ **Pregnancy**. "I really do believe – though I'm not advocating pregnancies in patients on biologics – that Amevive's Category B rating and the treatment-free periods make this a safe biologic."

➢ **Adverse events**. "The frequency of adverse events does not increase as you give more and more Amevive courses…You might expect to see opportunistic infections, but we don't…In fact, patients are getting fewer side effects (over time)…There have been fewer infections in Amevive patients with CD-4≤250 than CD-4≥250."

➢ **Efficacy**. "Among patients who reached PASI-75, the response was six to seven months…so this is a goldmine if they can figure out which patients will respond to this drug." Another expert said, "You can't call it quits early on this drug. You have to wait for the 12 weeks." A third expert said, "The company is advertising that Amevive gives a seven-month remission…but it needs to clarify what that means…Only patients eligible for that are patients who get a PASI-75, and that is 21% of patients…The average Amevive patient is not necessarily getting clear and staying clear for seven months…If there were a pharmacogenomic analysis telling you in whom it will work, this would be a good drug… Amevive needs to be given for 12 weeks, and there is some data at this meeting that you get better results if it is given for 16 weeks." Another speaker said, "Psoriasis is a life-long disease, and you need to take 12-month data with a grain of salt. Amevive doesn't give 'sock-o' results in the short-term, but with continued treatment, patients show more response." A fourth speaker said, "Amevive works slowly…There is excellent response, but it takes time…Combining it with six to nine weeks of NB-UVB gives much, much faster response… You get the same results with broad band UVB. So, I've started using narrow band UVB to give a quicker response… There is clearly a synergy."

➢ **CD-4.** A speaker suggested that CD-4 monitoring may be able to be cut back in the future, "Studies are underway that may show it is not necessary to do weekly counts." Whether drops in CD-4 correlate with response is still an open question. One expert insisted that patients whose CD-4 count drops quickly and significantly are most likely to respond to Amevive, but another expert argued that a CD-4 count drop does not correlate with improvement.

➢ **Cost**. "Because Amevive works in so few patients, I worry about the cost of failure…It is not fair to call it quits until 18 weeks…You may need five patients to find one that responds well." Another speaker said, "The efficacy of Amevive is the lowest, and it is slow…You really have to hang on for 18-21 weeks to see if it works…And the cost of failure is high – $10,000-$12,000 – and you might not know if a patient responds until you spend that much. With all the other biologics, you get some signal of response early."

➢ **Monitoring**. A speaker said, "I find one of the biggest nuisances is the T-cell monitoring for the Amevive patient, who calls and wants the results…It is a lot of aggravation... Slow-infusion IV is the kiss of death in our specialty – which is why Amevive dropped the IV option. Dermatologists don't need to act like rheumatologists." Another expert said, "Studies are underway that may show it isn't necessary to do weekly CD-4 counts."

➢ **Reimbursement**. A new J code has been issued for Amevive – J0215. Not all insurance companies have converted to the new J code, but Medicare did. Doctors use a 99214 code for billing, the IM is 90782, lab 36415, and a nurse visit 99211. A nurse said, "There has been a debate on the 99214 follow-up code…but with the face-to-face time and evaluation of vital signs and labs, I assure you the insurance companies I discussed it with feel comfortable with this code." Another speaker said, "Amevive insurance was a problem at first...but it is getting easier."

GENENTECH'S Raptiva (efalizumab)

The outlook for Raptiva does not appear very good. Doctors are offering it to patients, but most seem to think that Enbrel is a better option. The big problem – and the one that speakers kept emphasizing – is rebound. One expert said, "Third party payors decide. When Enbrel is approved, Raptiva will have a hard time. Raptiva is new, and Enbrel has good efficacy, good safety and no rebound…I would use Raptiva for a patient with multiple sclerosis or who has a family member with MS."

A pooled analysis of the efficacy and safety from Phase III Raptiva trials was presented. The investigator said there was nothing particularly new in the findings. The study confirmed efficacy and found no new safety issues. Rebound was experienced by 13.8% of patients by the National Psoriasis Foundation's definition of return to 125% of baseline within three months of discontinuation. The investigator said, "The number goes down with combination therapy, but there is no

data on that…This is not a significant issue for me, but others disagree."

Genentech earned praise for its reimbursement program. A source said, "Genentech has done a great job with reimbursement. They have a HIPAA form patients sign that lets the Genentech sales rep see the chart. And they have a great needle collection program."

Following are some of the comments by speakers and other doctors about Raptiva:

➢ **Thrombocytopenia**. "Thrombocytopenia is a very, very small risk…Thrombocytopenia may or may not be a real phenomenon, but you are being asked to monitor for that monthly, at least in the beginning."

➢ **Rebound**. Several speakers emphasized that Raptiva "should never be discontinued abruptly." One said, "You need an exit strategy…The rebound issue may be minimized by using combination and sequential therapy with a lot of tapering rather than abrupt discontinuation." Another commented, "When patients are coming off Raptiva, you need to be careful…Flare is more likely to occur in patients with poor response to Raptiva. I suggest Raptiva be tapered by overlapping with topicals, UVB or Soriatane." A third said, "Rebound is a concern. A significant number of patients – 13.8% – flare upon discontinuation." A fourth speaker said, "Median time to relapse is 64-70 days, which I would call a soft landing…but 13.8% get a little worse after stopping therapy, which is most likely to occur in patients who did not achieve PASI-50…This drug should not be discontinued without a second drug being available." Another expert said, "Patients who discontinue have had severe, profound flares… That is not acceptable in an environment where patients – for managed care or other reasons – might need to interrupt therapy abruptly…Patients on systemic corticosteroids who stop can convert to pustular psoriasis, which can be potentially life-threatening, and we need to be sure that this doesn't happen with (Raptiva)."

➢ **Malignancy**. "Malignancies do not appear to be increased, but non-melanoma skin cancers were seen (20 observed cases vs. seven expected)."

➢ **Antibodies**. "Antibodies form (6.3% incidence), but that doesn't affect the PASI score."

➢ **Pregnancy**. This agent has the worst pregnancy label (Class C), but speakers emphasized that only Genentech did animal pregnancy studies, so no one really knows the teratogenicity of the other biologics. One speaker said, "For all intents and purposes Raptiva can be considered a Category B for pregnancy…I met yesterday with someone who ran a pregnancy registry in oncology for liver transplants…and we included some of our cyclosporine pregnancies to show no increased risk of teratogenicity with these drugs…So, I hope in the years ahead, as the companies keep building data, they will open a huge new market for women of childbearing age." Another speaker said, "Raptiva has an issue with the mouse immune system, so it got a worse category…I wouldn't want to plan having a woman become pregnant on any of these…None of these have the retinoid-type toxicity...There have been a few pregnancies in all of these biologics that went to completion, and there were no abnormalities, but time will tell."

➢ **Efficacy.** "You have to hold the patient's hand for the first six months, but after that patients seem to do well."

➢ **Safety.** "There is no increase in adverse events during 24 months of treatment…But there are two concerns.

- *One is minor*. For the first one, two or maybe three injections people get flu-like symptoms, but that goes away. So, I initiate with a lower dose – 0.7 mg/kg instead of usual dose of 1 mg/kg.
- *The other is rare*. In some patients, the psoriasis flares when the medication is stopped. There are two ways to look at this:
  - **a.** 13.8% of study patients had rebound defined as 125% or more of pre-Raptiva baseline PASI vs. 11.1% of placebo patients.
  - **b.** 0.7% had 'serious worsening of psoriasis' vs. 0 in the placebo group."

JOHNSON & JOHNSON'S Remicade (infliximab)

Speakers all agreed that this is the most effective biologic for psoriasis, but there is little enthusiasm for an infusion therapy among dermatologists.

Following are some of the comments by speakers and other doctors about Remicade:

➢ **Infusions**. A speaker said, "Some doctors wonder how we can do infusions…but I'm frequently surprised by younger doctors who say doing an IV infusion doesn't bother them. In the real world, there is absolutely no reason a competent physician like a dermatologist can't be doing infusions…The big concern in the dermatology community is about infusing a drug that has been used in RA and Crohn's for many, many years (5+) and used globally in >400K pts. This has really revolutionized the practice of rheumatology…About 70% of rheumatologists have adopted this treatment. My personal bias is that if rheumatologists can do this, dermatologists can, too."

➢ **Efficacy**. A speaker said, "Remicade gives absolutely spectacular results…There is no doubt this gives better results than any other drug hitherto, including cyclosporine." Another speaker said, "No drug works better than infliximab in psoriasis…Nothing out there works this fast or this well." A third speaker said, "In psoriasis, there is no drug that works better than infliximab; 88% of patients get PASI-75 in 10 weeks…There is nothing out there that works this fast or this well…Almost everyone gets PASI-50, and a very significant percentage get PASI-90…And the duration is very long; 52% of patients maintain PASI-50 for more than eight months." Another expert commented, "Remicade works best, especially for a quick fix, but it is more complicated to give. The good news is that it works very well. The bad news is, there are

possibly more risks." Another doctor added, "Remicade seems to lose efficacy if you continue it, probably because we don't give it with methotrexate."

➢ **Dosing**. An expert commented, "The 5 mg dose is the one likely to be used after the Phase II studies are done." Another speaker said, "In Phase III, we will study dose creep and see if we can determine dosing for the long haul."

➢ **Duration**. A speaker said, "The big issue about this drug – until the Phase III is completed, which hopefully will be within a year – is that you get dramatic results in 12 weeks, but with monotherapy, will those dramatic results last over the year when it is not used with methotrexate…And will there be dose creep?" Another speaker said, "The duration is very long – with 53% maintaining PASI-50 more than eight months. In Phase III, we will study dose creep and see if we can determine dosing for the long haul."

➢ **Reimbursement**. An expert said, "Getting approved for Remicade has proven very difficult…because it is an off-label use…Medicare and some Aetna plans have endorsed this for psoriatic arthritis, so it is important to document psoriatic arthritis complaints early on."

➢ **Pyoderma gangrenosum.** A source said, "It is a good agent for patients. It is not the end-all be-all in pyoderma gangrenosum associated with Crohn's, but it has efficacy in some patients."

SYSTEMIC AGENTS FOR PSORIASIS

ALLERGAN'S oral Tazorac (tazarotene)

Data was presented from the long-term, open-label trial, in which 263 patients were treated with 4.5 mg oral tazarotene (in a gel capsule) once-daily for up to 52 weeks and then followed for an additional 12 weeks post-treatment. Most patients showed clinical improvement within four weeks, and the majority achieved moderate to complete clearing of symptoms by Week 12. The improvement generally lasted through 24 weeks. An investigator said, "All oral tazarotene studies have shown that a majority of patients achieved moderate to complete clearing by Week 12 of treatment. And of particular significance, a majority of patients maintained their improvements for at least 12 weeks after treatment was discontinued." Another speaker said, "One-third of patients achieved PASI-75 at three months…The half-life is shorter than Accutane…People seem to keep getting better to Week 56…It could be used as a first-line therapy and could be combined with anything – methotrexate, cyclosporine, biologics, etc."

Among the key findings from this Phase III trial were:

➢ **Side Effects.** Most side effects were mild, including 4% arthalgia (joint pain), 3% myalgia, 2% infection, 2% back pain, 2% alopecia (hair loss), 1% dermatitis, 1% abnormal liver tests, <1% cheilitis (dry lips), dry skin, headache, and pruritis (itch). The side effect still hanging over oral tazarotene is osteopenia (bone density loss), particularly in men. The DXA studies in the Phase III trial looked good, but experts said the company will need to continue to monitor this to see if a problem develops with longer treatment. A speaker said, "Oral retinoids tend to leave some erythema behind…Old people don't care, but young people get annoyed…so this may be good for combination therapy…It is a good partner for almost every biologic that comes along…All the biologics sometimes need help…So, it is good to have something relatively safe that can help."

➢ **Dropouts.** 41% of patients dropped out of the trial: 14% due to side effects, 8% for lack of efficacy, and 19% for other reasons. A speaker said, "The safety is pretty good – 8% alopecia, which is higher than we saw at six months – but bone mineral density went down in some patients." Sources did not appear concerned with the dropouts in this trial, and even competitors did not criticize the study on this basis. The overall dropout rate was 41%, with 14% due to adverse events, 8% due to lack of efficacy, and 19% for other reasons.

➢ **Efficacy.** Sixty-eight percent of patients had moderate to complete clearing by Week 24 (≥50% global improvement), 44% had at least a marked improvement (≥75% global improvement) by Week 36, and 28% achieved clinical success (i.e., ≥2-grade improvement in OLA score) by Week 16. There were significant reductions from baseline in mean scores for plaque elevation, scaling and erythema from Week 2 through at least Week 64 for all lesions overall, elbow and knee lesions and trunk and limb lesions. Significant reductions also were seen from baseline in the mean scores for pruritis and scalp psoriasis from Week 2 through at least Week 64. More than one in five (22%) had no-to-minimal psoriasis by Week 24 and maintained this level over the remaining 28 weeks of treatment. Oral tazarotene was effective in reducing both fingernail and toenail psoriasis with significant reductions from baseline from Week 16 on.

➢ **Duration of effect.** The majority of patients maintained improvements in their disease state throughout the treatment period and for at least 12 weeks post-treatment (Week 64). A speaker said, "The improvement is maintained over time. It doesn't drop off precipitously when the drug is stopped. There is just slow regression."

➢ **Combination therapy.** An expert said, "Oral Tazorac can be used for: first-line therapy; combination with methotrexate, cyclosporine, phototherapy or biologics; and sequential therapy."

➢ **Potential chemoprotectivity.** A speaker said, "Tazorac may be chemopreventive for skin cancer."

Another study – the Tazorac Expansion Study – of 312 patients who previously completed 12 weeks of treatment (on both placebo and oral tazarotene) but did not exhibit any improvement were enrolled in a 12-week extension trial. The majority of patients experienced moderate to complete clearing by Week 12 of the extension trial; 3% of patients discontinued therapy due to side effects.

Oral Tazarotene Long-Term Data

Measurement	Week 16	Week 24	Week 36	Week 52	Week 64
≥50% global improvement	~68%	68%	~68%	~62%	~53%
≥75% global improvement	30%	~40%	44%	~40%	~30%
≥2-grade improvement in OLA score	28%	~35%	~35%	30%	~22%

There appear to be three potential advantages of oral tazarotene over Soriatane:

1. **Shorter half-life.** This appears to be the key advantage over Soriatane because it may mean less teratogenicity.
2. **Less alopecia** (hair loss). This is next in importance. Alopecia is not entirely eliminated, but it is reduced to what is considered an acceptable level (8%).
3. **Better cardiac profile**. The lack of negative effect on triglycerides is considered good, and all sources expect that finding to continue to bear out over time, but it is not a critical issue.

Sources agreed that it is the pregnancy label that is important. A Minnesota doctor said, "I like retinoids, and I use Soriatane. I would feel compelled to use oral tazarotene if the pregnancy restriction were less than three years, but I wouldn't use it if it had a one year or longer pregnancy warning." A New Jersey dermatologist said, "Soriatane is a very good drug. If the pregnancy issue isn't there, I will switch all women to oral tazarotene, but it won't be a quick switch. I will definitely try oral tazarotene."

But questions about the pregnancy label are making the outlook for oral tazarotene murky. There has been an assumption that oral tazarotene will get a pregnancy label similar to Roche's Accutane, which warns women not to get pregnant for at least a month after stopping Accutane. Oral tazarotene researchers said Allergan's basis for a less-restrictive label is PK studies showing a shorter half-life than Soriatane and no interaction with alcohol, but detailed information on these tests was not presented. Furthermore, an investigator said the company told him that the label will look more like the Soriatane label, which bans pregnancy for three years after taking it.

Oral tazarotene is expected to be approved by the end of 2004, and sources believe Allergan is poised to give it a big push. One doctor said, "Allergan has shrewd marketers. They are putting a lot of time and effort into Tazorac. I expect they will start marketing even before it is approved." Another expert said, "Allergan is well-placed in the dermatology office, and it will expand Tazorac beyond a replacement for Soriatane." A speaker said, "Retinoids are like primer. If you ask what color paint is used most, the answer is primer because it makes every paint work better...If Allergan doesn't make the same mistakes as Roche, which marketed Soriatane saying it worked fast, fine and alone…If Allergan does that, it will be a minor player, but if Allergan markets smarter and says Tazorac doesn't work fast, so feel free to combine it, then I think it can be very much appreciated."

The use of PGA and OLA scores instead of PASI scores may complicate marketing. It may be a little confusing when it comes to comparing the therapies, but sources do not believe it will be a problem with the FDA. One expert commented, "People like to compare PASI scores, but you can't really do that because there are no head-to-head trials. But marketing will be a little difficult, and there will be some confusion. But the measurements used are the way dermatologists practice." A New York doctor said, "OLA is not an issue. We've been dealing with retinoids for a long time. I need to see on my own how it works…I would rather use an oral if I can." Another doctor said, "The number of patients studied with oral tazarotene is an issue, but, on the other hand, PASI is suspect. The proof will be in the pudding. Not having to get prior authorization for oral tazarotene will help. Most of the time Enbrel is approved, but so far, I haven't gotten any approvals for Amevive or Raptiva." A Texas doctor added, "If oral tazarotene is priced right and if no prior authorization is needed, it will win."

Doctors said they generally try not to keep patients on oral retinoids for too long, and most said they rotate treatment after a year. Sources could not estimate yet how long they will leave patients on oral tazarotene. A Minnesota doctor said, "This is not a life-time drug. It is very drying, so I taper use after three months to a couple of years." A Texas dermatologist said, "Oral tazarotene could be a long-term therapy like Accutane, which is supposed to be used for five months, but is really used much longer." A speaker commented, "Oral tazarotene tends to peak in efficacy at 16-20 weeks…It does seem to have milder cutaneous effects and less impact on triglycerides, but there was a minor impact on bone. I don't think we would keep a patient on this continuously for a year." Another expert said patients who achieve results may remain on oral tazarotene drug long-term, "You don't need to stop it when the patient clears. You keep it going to avoid flares."

There was no information available at the AAD meeting on how Allergan intends to price oral tazarotene, but cost definitely will affect adoption, dermatologists agreed.

Academic experts predicted that dermatologists would switch rapidly – almost "instantaneously" and completely – from Soriatane to oral tazarotene when it is approved. They predicted that oral tazarotene would have larger sales than Soriatane because it would be used widely in combination with other agents, including biologics and UVB. One expert said, "Dermatologists know retinoids. They are very confident with them, and I think we will switch. It looks like Roche is exiting the market. It's withdrawn its sales force. Some patients may not want to switch, but Tazorac will have the lion's share…I see the possibility of adding Tazorac or it having a cost-sparing effect (on biologics)…Dermatologists

also like combination therapy, and I think this is a great combination drug…Tazorac will compete with biologics for new patients." Another doctor said, "I'll switch instantaneously. Roche left the market, and Allergan is committed to the dermatology field…Tazorac will compete with biologics and become the preferred combination drug…I would urge the company to do a study in combination with UVB."

However, community dermatologists may not abandon Soriatane as quickly as the academics predicted. Rather, they expect oral tazarotene to become a step between topicals and biologics because of cost. They emphasized that they are familiar with oral retinoids and comfortable with them, and they stressed their concern with the cost of the biologics. They speculated that oral tazarotene could have some negative impact on biologic usage, particularly if managed care dictates oral tazarotene as part of a step-up treatment approach to psoriasis. A California doctor said, "I'm used to Soriatane. I have several patients on that. I try Soriatane before a biologic unless it is contraindicated. If oral tazarotene is reasonably priced, I'll try that before a biologic – providing it has a better pregnancy label. But the osteopenia is a concern." A Texas doctor said, "In our region, I think it will be a three-step program: topical, systemic, and then a biologic for patients who fail those."

Doctors offered these comments on how they would choose between Soriatane and oral tazarotene:

- *Florida:* "They are about equal in efficacy, but Soriatane has been around for years. Soriatane has been proven effective. I want more data than oral tazarotene has so far…Connetics made a good move in buying Soriatane; it needs more promotion."
- *Tennessee:* "I won't switch that quickly. I don't believe all the hype. I'll try it, and see for myself how it works. But the pregnancy label is not a big deal. I don't have that many female patients who would be candidates, and I wouldn't give it to women who could get pregnant unless it had a 30-day label like Accutane. If it had a one-year label, I wouldn't use it in women of child-bearing age…I will do more oral retinoids with a light box than with biologics."
- *Rhode Island:* "I won't rock the boat with Enbrel responders, but I'll switch non-responders, and I'll try oral tazarotene first in new patients."
- *Texas:* "Oral tazarotene is really exciting. We love Accutane, and I think oral tazarotene will delay use of biologics – if the cost is reasonable."

CONNETICS/ROCHE'S Soriatane (acitretin)

During the AAD meeting, Connetics and Roche announced that Connetics is buying the U.S. rights to Roche's Soriatane (acitretin) for psoriasis. Approximately 17,000 U.S. patients were on Soriatane in 2003, accounting for $41 million in revenue for Roche. Doctors had expected Soriatane to fade from the landscape when Allergan's oral tazarotene is approved, and they had already noticed that Roche had stopped promoting Soriatane. In fact, Roche did not even have a booth at the AAD meeting.

Obviously, Connetics' purchase of Soriatane changes the picture. Connetics officials said the company intends to have its 85-person sales and marketing team aggressively market Soriatane. One commented, "Roche under-promoted Soriatane. It's not a priority for them. Accutane was the priority. Dermatologists are not the core, and Roche's (Soriatane) sales force was gone in December 2003." Dr. Lincoln Krochmal, Executive Vice President for Research and Product Development at Connetics, emphasized:

- **Familiarity**. Soriatane has a six-year history, and doctors are familiar with it. He said, "Soriatane has a long history of safety and efficacy, and it can be used in combination with other therapies, where you can use less of it."
- **Dosing**. Soriatane will come in two different doses.
- **Experience**. Soriatane has been used by more than a million patients world-wide.
- **First-line.** He explained, "Biologics aren't first-line therapy. Other therapies are needed first, and Soriatane is first-line."
- **Broad approval.** Soriatane is approved for five types of psoriasis, and oral tazarotene will, initially at least, be approved only for plaque psoriasis.

Asked how Connetics expects to position Soriatane against oral tazarotene and why doctors should use Soriatane instead, Dr. Krochmal pointed out that oral tazarotene is still teratogenic, and he warned against assuming oral tazarotene

Comparison of Soriatane and Oral Tazarotene

Characteristic	Soriatane	Oral Tazarotene
Dosage	10 mg and 25 mg capsules	One dosage
Indications	5 types of psoriasis (plaque, erythrodermic, pustular, guttate, and palmar-plantar)	Plaque psoriasis
Data	Long-term	52 weeks
Efficacy	76% of patients show statistically significant improvement by 8 weeks	~68% show ≥50% global improvement at 16 weeks
Pregnancy	48-hour half-life; Not indicated for women of child-bearing age	18-hour half-life which could lead to less restrictive label in women of child-bearing age
Adverse events	Liver toxicity, Pancreatitis, Increased cranial pressure, Cheilitis	Less cheilitis; No liver toxicity; Small bone loss warranting monitoring, especially in men
Lipid levels	Can be altered	Not affected
Cardiovascular affects	Possible	None reported

would have a more favorable pregnancy label (perhaps similar to Accutane) than Soriatane. He also claimed that the literature for Soriatane shows a higher PASI-50 and PASI-75 at 12 weeks and at one year than for oral tazarotene. He said, "The efficacy of Soriatane looks superior, and we believe the safety of tazarotene remains to be seen…Safety may be related to dosing. We think the side effects will be comparable to Soriatane…Both products will be good in building the oral retinoid market."

Dr. Krochmal expects Connetics to be able to expand the market for Soriatane. He said, "We will grow the market beyond 17,000 patients through education to the public and doctors. Our sales force will explain the benefits and do what Roche didn't do – assist in dosing and how to minimize side effects…Soriatane is not a drug focused on women of child-bearing potential…Less than 2% of patients on Soriatane are in that category. We will promote it for adult males and females of non-child-bearing age…And we will suggest that doctors try this before biologics." A speaker at a psoriasis session added, "Since Soriatane is neither immunosuppressive nor cytotoxic, it can be used without the risk of reducing a patient's resistance to common infections."

NOVARTIS'S oral pimecrolimus

This oral agent for psoriasis continues to chug along, slowly but steadily. The FDA requested additional drug-drug interaction studies before it would approve the design of the pivotal Phase III safety trial. The company reportedly has completed those studies, and they were described as looking "fine."

Novartis also reformulated the tablet, using a different dose to get the same bioavailability. Thus, the dose for Phase III is likely to be about 35 mg BID.

The Phase III trial is due to start in late September 2004, which means the drug probably could not be on the U.S. market before late 2006. The FDA wants two-year data, but the company could submit on one-year data, and a one-year interim look at the trial is planned. This data could be presented at AAD in 2006.

As soon as this Phase III trial gets underway, Novartis is planning to do two short-term (12-week) pivotal Phase III efficacy trials. Novartis reportedly is planning a big global push for this drug and was described as taking the time to coordinate the trials and filings.

The only new data on this agent at the AAD meeting was some PK data, looking at what exposures led to an increase in disease. Researchers found that there was a linear relationship in drug effect based on dosage, but there was no difference in drug effect based on race. Women showed a stronger effect from each dose tested compared to men, but a researcher said this is most likely due to their smaller size. This suggests the company may need to market two dosage levels.

A speaker discussing oral pimecrolimus offered these comments:

- "Oral pimecrolimus is twice as effective as oral tacrolimus."
- "A 50-patient study found no clinically significant change in blood pressure, ECG, safety, lab tests, or renal function, no effect on glucose toleration, and no serious adverse events…There was only a transient feeling of warmth after drug intake which occurred irregularly but was not considered unpleasant by patients."
- "There is no rebound."
- "Steady state is achieved after five to 10 days."
- "PK is linear."
- "A pharmacogenetics study examined >7,500 genes, finding pimecrolimus…down-regulates genes related to the pathophysiology of psoriasis action."

TOPICAL AGENTS

NOVARTIS'S Elidel (topical pimecrolimus) and FUJISAWA'S Protopic (topical tacrolimus ointment)

The marketing war between these two treatments for atopic dermatitis (AD) heated up at the AAD meeting. Each company presented head-to-head trials showings its product is superior.

Novartis responded with its own head-to-head comparisons. These trials found that Elidel has comparable efficacy and safety to Protopic but that Elidel is better tolerated than Protopic. The irritation and stinging are less and last much shorter with Elidel in this study

Doctors who were questioned about their use of these two treatments for atopic dermatitis generally rated them fairly comparable in terms of efficacy. However, most sources said they are using more Elidel for three reasons:

1. They see the Novartis sales reps more often.
2. Novartis provides more samples. A North Carolina doctor said, "They work the same, but sampling is definitely a factor. I get more Elidel samples. Fujisawa doesn't give me any. I asked Fujisawa about that, but I still don't have any samples…Novartis is just a better marketer."
3. Elidel is a cream, and Protopic is an ointment.

Use of both products (but probably Elidel more than Protopic) is likely to increase somewhat over the next year because off-label use is growing for: oral lichen planus, vitiligo, pyoderma gangrenosum, lupus erythramatosis, and dermatomyositis. A California doctor said, "My Elidel use is expanding because I'm using it more off-label for peri-oral dermatitis and occasionally for contact dermatitis." Another doctor said, "I'm using more Elidel off-label for seborrheic dermatitis and inverse psoriasis." A Pennsylvania

dermatologist said, "I use both Elidel and Protopic. Their efficacy is similar, but they are irritating in different patients. These are only okay medications. There are a good percentage who don't improve or don't like them." Another doctor said, "I'm using more Elidel in non-atopic patients."

Fujisawa-Sponsored Head-to-Head Trials of Protopic vs. Elidel

Measurement	Study 20-02-004 in adults with mild to severe AD		Study 20-02-005 in pediatric patients with moderate to very severe AD		Study 20-02-006 in pediatric patients with mild AD	
	Protopic n=177	Elidel n=173	Protopic n=96	Elidel n=92	Protopic n=142	Elidel n=147
Withdrawals						
Due to lack of efficacy	2%	5%	4%	8%	1%	8%
Due to adverse events	3%	4%	4%	7%	1%	6%
Other	12%	8%	14%	17%	16%	12%
Results						
Change in EASI at Week 6	74% (p<.001)	54%	83% (p=.0002)	70%	75% (p=.03)	66%
Clear or almost clear by IGADA (Investigator's Global Atopic Dermatitis Assessment)	51% (p=.0002)	31%	38% (p=.006)	20%	54% (p=.04)	42%
Change in BSA at Week 6	68% (p=.0002)	48%	68% (p=.0002)	41%	71% (p=.07)	61%
Change in itch score	69% (p=.04)	52%	67% (p=.005)	43%	71% (p=.76)	72%
Adverse Events						
Burning/stinging	19%	12%	6%	9%	6%	9%
Increased itch	10%	5%	6%	11%	7%	9%
Skin infection	1%	2%	2%	2%	1%	1%

Novartis-Sponsored Head-to-Head Trials of Elidel vs. Protopic

Measurement at Day 4	Elidel 1% n=71	Protopic .03% n=70	p-value
Toleration			
Erythema or irritation	8%	18.5%	P=.039
Erythema or irritation that lasted >30 minutes but <12 hours	0	85%	---
Itching	9%	20%	P=.022
Warmth/stinging/burning	20%	17%	Nss
Warmth/stinging/burning that lasted >30 minutes	0	67%	---
PK Study			
>lower limit of quantification in the blood	12%	36%	P<.05

CONNETICS

Connetics has established itself in the dermatology field with its proprietary foam drug delivery system, dubbed VersaFoam. Two of its foam products for atopic dermatitis and seborrheic dermatitis already are FDA-approved: Olux (clobetasol propionate 0.05%) and Luxiq (betamethasone valerate 0.12%).

Among the products the company has in development are:

- **Extina**, a foam ketoconazole for seborrheic dermatitis that may see off-label use for other conditions.
- **Actiza**, a foam clindamycin for acne.
- **Velac**, a gel combination of clindamycin and tretinoin for treating acne.

Doctors are enthusiastic about foams, and they predicted Extina and Actiza will do well. A California doctor said, "Extina sounds good – provided the cost is reasonable. Actiza is a good idea, too." A Minnesota doctor said, "Foams are nice for some patients. Patients complain about the texture of ketoconazole, so they will like Extina. But foams are very expensive, and insurance companies give me a log of grief over that, or the patient has to pay a higher co-pay." An Iowa dermatologist said, "Foam is more cosmetically elegant. It is appealing. It is a new concept, and younger folks are looking for something new." A New York doctor said, "Foam is just repackaging to sell a product, but people want new things." A Texas doctor said, "Foam looks very good. It penetrates better that other things, so Actiza and Extina should do well. I'm excited about them. They are very impressive. But I'm not interested in Velac." Another doctor said, "Foam products are good. They are better tolerated, and patients like them. A lot of dermatologists like them, too. They think they are sexy, and their patients like them. Extina and Actiza will do well."

Sources were less enthusiastic about Velac, but they still had some positive comments about the product. A North Carolina doctor said, "The problem will be cost. I don't see a lot of demand for this because of the cost." Another doctor said, "I may consider Velac because I have a lot of acne patients on both medications separately." A Minnesota doctor said, "I am receptive to Velac. It might help patients with compliance."

DERMAL FILLERS

Many of the dermatologists who attended the AAD meeting do cosmetic procedures, including fillers and botulinum toxin, but most said they do not concentrate on this area in the same way as the high-volume cosmetic surgeons who attended the American Academy of Cosmetic Surgery in January 2004. The same trends were apparent at both meetings, though the AAD dermatologists generally were more reserved in their approach to new products.

MEDICIS' Restylane

Dermatologists expect to use Restylane, and there is a fair amount of excitement over this product. However, they also

expect to continue using collagen. In fact, many dermatologists plan to combine collagen and Restylane, using Inamed's CosmoDerm or CosmoPlast first and then Restylane. The lidocaine in the CosmoDerm will numb the area and make the Restylane injection less painful, sources explained. A New Jersey dermatologist said, "Restylane and Botox complement each other. They work wonderfully together. Patients who are cosmetically-minded will have the opportunity, with both of these, to achieve results much quicker and safer." A speaker said, "I'm a big fan of CosmoPlast and CosmoDerm …I like collagen…It provides a scaffolding, a structure to the skin…and it contains lidocaine, so it is less painful...If you want to use CosmoDerm with Restylane or Hylaform, use CosmoDerm first, so the patients don't feel the pain of the Restylane or Hylaform…CosmoDerm and CosmoPlast have the least down time. If someone needs to be on TV tomorrow, CosmoDerm and CosmoPlast are my choice…But the big trend is combination use, with collagen first."

No doctor was found who is continuing to import Restylane from Canada now that it is approved in the U.S., even though the U.S. price ($210) is higher than the Canadian price (US$160). However, sources pointed out that there is a group of dermatologists who buy other products, including botulinum toxin-A from outside the country and may do the same with Restylane. A doctor said, "The price increase was not enough to dissuade patients who are cosmetically-inclined." Another doctor said, "I tried to buy Restylane from Canada (post-approval), but the pharmacy charged me more than I pay in the U.S."

INAMED

➢ **Hylaform.** There was little excitement about Hylaform, but it was included in every discussion of hyaluronic fillers, and most sources expect it to find a role. An expert said, "It will find some use because it is not as viscous as Restylane, so it goes in easier. And if it is priced less, that will help usage. Even if it is priced the same, but doctors get more in the syringe, that will help." Another doctor commented, "Hylaform will be easier to get than Restylane. And Inamed has been good to me in the past and very supportive. But I will buy Hylaform – but patients are asking for Restylane." A third said, "I prefer Hylaform for the lips because it is softer…It feels natural and doesn't give you a lumpy lip feeling."

Comparison of Medicis' Restylane and Inamed's Hylaform

Characteristic	Restylane	Hylaform
Feel	Firm	Softer
Longevity	4-6 months	4-6 months
Source	Rooster combs	Streptococcal bacteria
Cross linking	Less	More

➢ **Juvederm.** There was little or no awareness of this product among general dermatologists, but it was discussed at one lecture. The speaker said, "The next trend is homogenous gels of hyaluronic acid…and that's Juvederm, which is very popular in Europe and is causing a lot of excitement right now. It has a slower degradation by hyaluronidase."

AVENTIS'S New-Fill (formerly Sculptra)

This filler is comprised of poly-L-lactic acid microparticles (40-63 microns in size). The substance has been used for years in other products, such as sutures. Like Botox, it comes as a sterile lyophilized cake in a bottle and is reconstituted with 5 cc of sterile water. A speaker said, "This is not really a filler…It gets the fibroblasts to start producing collagen…When the patients leave the office, they don't look that different…So it is a different mindset…The immediate mechanism of action is saline. Then there is a delayed reaction, which the histology suggests is the formation of new collagen. Six months post-injection, we see new collagen formation. What is exciting about this product is that usually we see patients once a month for three or four times...and slowly there is more and more response…Once the effect gets there, it lasts about two years…This is exciting to me because we can trick the body into filling itself…I believe what I will do is use this and put Hylaform or collagen on top of it, so I get an immediate gratification while waiting for longer-term results."

Experts were divided on how this product is likely to be used. Lips are the only area on which experts all agree – New-Fill *cannot* be used for lips.

- **Niche?** Two prominent filler experts insisted New-Fill will be a niche product. They described it as "wonderful for deep volumetric filling, below the dermis," but they said it cannot – and should not – be used for more surface filling (e.g., nasolabial folds) because it can cause granuloma formation. A Florida doctor explained, "New-Fill is a volumizer. It is not for fine lines. It is for contouring, for deep filling. You inject it beneath the dermis. There is more chance of granulomas if it is injected in the dermis. It is great for deep filling because collagen depositions don't last. It will be a fabulous niche product. It won't compete with other fillers." Another expert said, "This is a good product for devolumization, for HIV lipoatrophy and before a face lift, but it is a niche product that won't compete with fillers. It is more a volumizer than a filler. It is injected deeply. These are the deepest injections we will be doing."

- **Wide off-label use?** Two other experts insisted New-Fill will initially be used as a deep filler but will increasingly be used off-label for everything except lips. A Florida doctor said, "New-Fill is a really effective filling for long-term soft tissue. It is phenomenal. It can be used everywhere except the lips. Initially, it will be marketed as a deep filler, but it will be used for nasolabial folds, and probably everywhere…The effect lasts several years…It won't replace Restylane and Hylaform. The skill set will be different, and it flows differently...Restylane and Hylaform are perfect in lips,

and this never will be…New-Fill has the potential to be a very significant product."

- **Too early to predict?** Another two speakers said the jury is still out on this product. A Texas doctor commented, "New-Fill was originally designed for HIV lipoatrophy, but fillers are fillers, and we are great experimenters…On the other hand, patients may be reluctant to use New-Fill. There may be some stigma to its use because of its use for lipoatrophy. Patients won't want to say 'I'm getting New-Fill' the way they say 'I'm getting Botox,' because they could be construed as AIDS patients. It's a status thing."

BOTULINUM TOXIN

A speaker who is a very large Botox user commented, "Botox rules, but there will be competitors. Males need to be treated differently and with higher doses…Indications for botulinum toxin use are expanding in the lower face and adjunctive use...The more we learn, the safer botulinum toxin is."

ALLERGAN'S Botox (botulinum toxin-A)

With repeated use, there is a prolonged effect to Botox, which means that patients can go longer between injections. That was the conclusion of a panel of botulinum experts. One said, "Patients tend to have longer intervals between treatments due to skin remodeling effects." Another said, "You need to back off the total number of units over time. There definitely is a step-wise alteration (in usage)…Most patients show subtle differences (in usage) over time – over two or three years."

Hyperhidrosis

Allergan is seeking FDA approval to use Botox to treat hyperhidrosis, and dermatologists are very excited about this. An expert estimated that 2.8% of the American population has hyperhidrosis, which translates into about 7.8 million people. The vast majority of these have axillary hyperhidrosis, with palm and foot hyperhidrosis much less common.

This expert estimated that – even if Botox does not get an indication for axillary hyperhidrosis – about 10% of these patients will seek treatment with Botox because awareness is increasing. If the FDA grants the indication, she believes about 20% of eligible patients will seek treatment. This expert currently has about 80 hyperhidrosis patients out of approximately 500 Botox patients, so she doesn't expect her usage to double, but she expects many more doctors to start treating it and to increase their use. How many of the patients who seek treatment actually get it will depend on insurance coverage, which is likely to improve dramatically with FDA approval.

Other dermatologists questioned at the meeting about the outlook for Botox for this indication estimated that from 1%-5% of their current Botox patients are getting it for hyperhidrosis. They predicted that this would increase to 5%-15% of Botox patients if hyperhidrosis were approved by the FDA. That is, they predicted a hyperhidrosis approval would increase the Botox market by 10%, from about $400 million to $440 million. A Florida doctor said, "I'm already treating hyperhidrosis, without reimbursement. It's a big market, but a lot of people don't want to admit they have it. The arms are what bother people the most because of clothes and the odor." A California doctor said, "A lot of people have this problem, but they can't afford the treatment. If it were approved and reimbursed, my use would go up 10-fold from 3-4 patients a year to 30-40."

Only a few carriers currently pay for Botox treatment of hyperhidrosis. Doctors generally charge $900-$1,500 for both axilla. A speaker said he uses ICD-9 Code 780.9 for hyperhidrosis, CPT Code 64614, which reimburses him $294.96 for the procedure, and HPCPS Code J0585 for the Botox, which is reimbursed at $4.39/unit. The treatment lasted six months in clinical trials, but experts said it actually lasts more like nine to 12 months in clinical practice.

Use of Botox to treat hyperhidrosis of the palms and the soles of the feet is unlikely to be impeded by approval of axillary hyperhidrosis. In fact, axillary approval could help encourage patients with palm or foot problems to seek treatment, and it may improve the reimbursement climate for palms and soles. A Florida doctor said, "Feet and hands are more difficult to treat because they are more painful." A California doctor said,

12-Month Botox Axillary Hyperhidrosis Trial

Measurement	50 units Botox per axilla n=104	75 units Botox per axilla n=110	Placebo n=108
Treatment satisfaction	85%	84%	20%
Primary endpoint #1: ≥2 grade improvement in Hyperhidrosis Disease Severity Scale (HDSS) from baseline 4 weeks after first treatment	75% (p<.0001)	75% (p<.0001)	25%
Patients who require a second treatment within 52 weeks			
≥2 grade improvement in Hyperhidrosis Disease Severity Scale (HDSS) from baseline in next 4 weeks	85% (p<.0001)	74% (p<.0001)	26%
Duration of effect			
% of patients requiring only 1 treatment in 52 weeks	43%	42%	12%
Median duration of effect in patients with ≥2 grade improvement in HDSS	205 days	197 days	96 days
Median duration of effect in patients requiring a second treatment	159 days	182 days	62 days
Adverse events			
Injection site pain	12%	9%	8%
Injection site bleeding	5%	6%	3%
Non-axillary sweating	10%	6%	4%

"We could probably get feet and palms covered if axillary is approved (for reimbursement)."

Typically, doctors use 50 units of Botox per axilla. Higher doses may be more effective, but a speaker warned doctors that (1) insurance is likely to really balk at that, and (2) there is a concern with neutralizing antibodies at the higher dose.

INAMED'S Dysport (botulinum toxin-A)

There did not appear to be the same undercurrent of dissatisfaction with Allergan among dermatologists at this meeting as surfaced at the recent American Academy of Cosmetic Surgery meeting. AAD doctors have taken a rather fatalistic view of the Botox price increases, and most said they passed the cost along to their patients. However, several sources explained that they are not high-volume Botox users, and they said they would not be surprised to hear that high-volume users are upset with Allergan, opening the door to a competitor. Furthermore, most dermatologists questioned at the AAD meeting felt that Dysport would be able to compete with Botox, especially if it is priced lower. However, they indicated doctors generally will choose one product or the other – not use both.

The principal investigator said the responders all had a zero rating on the maximum frown scale to be called a responder. This is a new scale, which he said the company "worked with the FDA" to develop.

The first indication for which Inamed will submit Dysport is reported to be glabellar lines, and that is the currently approved usage for Allergan's Botox. However, a speaker noted that Dysport works as well as Botox for hyperhidrosis. He cited a study published in 2001 in which 145 hyperhidrosis patients were treated with Dysport, and 81.4% reported excellent results, and 63.4% were completely satisfied.

Phase II Dysport Dose-Finding Study

Measurement	Placebo	25 units	50 units	75 units
Investigator analysis at maximum frown (ITT analysis)				
30 days	6.5%	68%*	77%*	86%*
60 days	2.2%	44%*	63%*	73%*
90 days	3.2%	16%*	40%*	47%*
Primary endpoint #1: 120 days	1.1%	5.7% (p=.071)	26% (p<.001)	27% (p<.001)
Patient analysis at maximum frown (ITT analysis)				
30 days	10.8%	74.7%*	84.9%*	84.0%*
60 days	10.8%	66.7%*	77.2%*	78.7%*
90 days	7.5%	4.9%*	61.5%*	72.3%*
Primary endpoint #2: 120 days	6.5%	19.5% (p=.005)	41.8% (p<.001)	50.5% (p<.001)
Adverse events				
Any adverse event	55.3%	58.9%	67.4%	55.3%
Severe adverse events	2.1%	0	1.1%	2.1%
Ptosis	0	0	0	3 (1 confirmed 2 not clinical)

* p<.05

The Phase III Dysport trial design has been submitted to the FDA, and Inamed is awaiting a decision by the FDA. An investigator said he thinks it will be another three or four months before that trial gets underway. There is no evidence that manufacturing issues are contributing to – or responsible for – the delay in the start of the Phase III trial of Dysport. Ipsen currently manufactures Dysport in Europe, and an expert said there are no plans to move the manufacturing to the U.S.

MELANOMA

In 2022 melanoma is expected to be the most prevalent cancer in the U.S., with a projected 2,901,333 cases. A speaker told dermatologists:

- Learn to use a dermatoscope. He said, "No matter how good you are at diagnosis, you will be better when you learn to use these." His favorite is 3Gen's DermLite because it is small and light-weight.
- Realize that not all patients want to know the stage of their disease. He said, "If patients don't want to know their stage, then don't do a sentinel node biopsy."
- High dose interferon is currently the best adjuvant therapy available. He said, "It prolongs the disease-free interval…and some studies suggest it may prolong survival, but there is no data on that yet."
- Melanoma vaccines have been disappointing. He said, "In the future, maybe vaccines will get better, but I'm not holding my breath any more."
- Immune response modifiers (IRMs), like 3M's Aldara (imiquimod) are an exciting area. He said 3M has a new IRM in Phase I trials – an IV study in Minnesota and a topical study at Dartmouth and Oklahoma.

MISCELLANEOUS

ADVANCED IMMUNITY

This company is starting a 12-week Phase II trial in the U.S. and Canada of its peptide-T, an 8 amino acid peptide for psoriasis. It currently is administered IV, but the company is working on intranasal, subcutaneous, oral and inhaled dosing. The advantage to this agent would most likely be cost. So far, about 400 patients have been treated, and the side effect profile looks good.

CELGENE'S Thalmid (thalidomide)

A speaker commented, "I think the response is very mediocre (in sarcoidosis)."

ALEXION'S eculizumab

A speaker said, "Interest has waned in dermatomyositis (DM), and it is not being pursued."

JOHNSON & JOHNSON'S Anti-IL-12

Several speakers mentioned this monoclonal antibody during lectures on new psoriasis agents on the horizon, and they sounded very enthusiastic about its outlook. One expert described IV administration in an open label trial in 18 patients with moderate/severe psoriasis. Dosing was 0.1 mg/kg, 0.3 mg/kg, 1 mg/kg and 5 mg/kg. The speaker said, "All patients met PASI-75 by Weeks 8-10." He concluded: "IL-12 seems an appropriate target. Early treatment suggests a clinical effect. Safety is yet to be determined. The Phase II trial is ongoing. This is a very hopeful story." Another expert said, "This is very potent. It is possible it will be able to be dosed once a month. But it has only been tested in a small number of patients." Another said, "From early testing, this appears to be an important molecule...Physiologically, it appears to be doing what it is supposed to do"

Phase I Results of Johnson & Johnson's Anti-IL-12

Measurement	0.1 mg/kg n=4	0.3 mg/kg n=4	1 mg/kg n=5	5 mg/kg n=5
Baseline PASI	11	18.2	14.7	13.6
PASI-75 at Week 2	1 patient	2 patients	4 patients	5 patients
Safety	+++	+++	++	N/A

WYETH'S Anti-IL-12

Wyeth also reportedly has an anti-IL-12, but an expert said he had not seen any evidence that Wyeth was testing it in psoriasis. ♦