Trends-in-Medicine

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By Lynne Peterson

SUMMARY

Dermatologists have started using Johnson & Johnson's Remicade and Immunex's Enbrel off-label to treat psoriasis, and the data on these agents looks very good. The outlook for other biologic agents in psoriasis is more questionable. Genentech/Xoma's Xanelim has a problem with rebound on and off drug, and Biogen's Amevive depresses CD4 counts. Both Amevive and Xanelim are likely to face intense regulatory scrutiny.

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American Academy of Dermatology Psoriasis Update

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An estimated seven million Americans have psoriasis, with 350,000-500,000 having severe disease. An expert estimated that one-third of psoriasis patients also have arthritis. Another expert said that 10% of psoriasis patients can't tolerate methotrexate.

Psoriasis Market

Data Point	1997	1998
All doctor visits for psoriasis	1,270,000	1,440,000
Patients ≥age 65	193,000	267,000
All psoriasis prescriptions	1,020,000	1,120,000
Steroid prescriptions for psoriasis	377,000	241,000

**Source: MedImmune analysis.*

Insurance Coverage for Psoriasis

Visits paid by:	% insured
Private insurance	69%
Medicare	15.3%
Patients	8%

Dermatologists are excited about biologics to treat psoriasis, and they already are using two of them. The hot news at this meeting was the TNF-α inhibitors – Immunex's Enbrel (etanercept) and Johnson & Johnson's Remicade (infliximab). Enbrel is approved for psoriatic arthritis (PsA), but doctors are using both Remicade and Enbrel in psoriasis as well as PsA, and use of both agents is expected to increase following this meeting. Numerous sources reported that insurance companies and managed care firms have started reimbursing for both agents in both conditions – though it often takes some arguing and paperwork first.

Use of TNF-inhibitors was encouraged by several speakers. One told doctors, "Those of you who want to start, the companies will help you. Go to the (exhibit) booths, and the sales reps will help you get (insurance) pre-authorizations, teach you the (insurance) codes to use and help you get your office started." Another speaker said, "Methotrexate is very good at improving PsA symptoms, but it doesn't prevent joint damage. Enbrel does prevent radiographic progression of disease. Perhaps we should take our methotrexate patients and switch them to Enbrel…Cyclosporine patients will be the first to move to the biologics, some of the methotrexate patients, and patients unhappy with phototherapy."

The degree to which dermatologists use Enbrel and Remicade and how they choose between them is likely to be determined by:

- *Enbrel shortages.* Even if doctors want to prescribe Enbrel – and several doctors said that was their preference because it was easier for them – there isn't enough supply for new psoriasis patients yet. The question is whether dermatologists therefore will turn to Remicade as rheumatologists have done. A Xanelim researcher said, "Together with a rheumatologist, I've set up a Psoriatic Arthritis Clinic, and we've written a lot of prescriptions for Enbrel in the past month. I've also written about 25 prescriptions for Remicade. Only Enbrel is indicated for psoriatic arthritis, so carriers have to cover that, but supply is limited"

- *Cost/Reimbursement.* There are three issues here: patient cost, doctor profits, and drug cost.
  1. *Patients.* Patients with injectible drug coverage may get Enbrel, and patients with coverage only for infused drugs may get Remicade. Patients without some form of insurance are unlikely to get either. The amount of the co-pay also may influence the choice of agent. A doctor said, "It is the out-of-pocket cost to the patient that is important, not the price of the drug."
  2. *Doctor economics.* Another doctor said, "Economics will drive the decision. Like rheumatologists, dermatologists will start doing infusions because of the economics."
  3. *Cost.* Remicade could have an advantage over other biologics if it proves to be the least expensive. (Remicade currently costs slightly less than Enbrel, and there is a suggestion that the dose of Remicade could be lower than for rheumatoid arthritis, perhaps 3 mg/kg. Along with the "drug holiday" that patients may get with this agent, it gain a distinct pricing advantage.

- *Patient choice.* Most dermatologists indicated that once multiple therapies are available, they will do what the neurologists do in multiple sclerosis: present the various options to patients and let them decide. An Immunex official worried that this approach could give Biogen a boost, since it has proven its marketing ability in the MS market. A Florida doctor said, "Patients will prefer subcutaneous administration, but insurance will dictate which is used." Another doctor said, "I won't use just one agent. I'll present Enbrel, Remicade and Amevive to my patients and let them choose. Different people want different things."

Surprisingly, several dermatologists not-so-subtly suggested that Enbrel is safer than Remicade, pointing to TB and other side effects with Remicade, but that message didn't seem to worry many sources. One expert said, "Enbrel is not the same as Remicade. Remicade has a higher likelihood of TB and other macrophage-dependent things, but you may get more remittive therapy with it. **But safety concerns won't be the factor affecting the choice of TNF."**

There are over 40 agents in development to treat psoriasis. No common measurements or trial designs are being used, so it is difficult to compare the various agents, but the key drugs appear to be:

Selected Psoriasis Drugs in Development

Company	PASI ≥75	Duration of Response
Abgenix's **anti-IL-8**	18% on ITT basis 24% of completors 33% of patients with base-line PASI ≥75 (week 15)	??
Biogen's **Amevive**	33% IM any time 21% IM at week 14 43% IM with two courses 28% IV any time 14% IV at week 14 40% IV with two courses	7 months
Genentech/ Xoma's **Xanelim**	30% at week 13 25.6% at day 84 ~60% at 6 months	6-8 weeks
IDEC's **IDEC-114**	11% in a Phase I trial	N/A
Immunex's **Enbrel**	30% at 12 weeks 35% at 14 weeks 56% at 24 weeks	Continuous therapy
Johnson & Johnson's **Remicade**	84% at 10 weeks on drug 48% 16 weeks after drug stopped	48% PASI 75 at 16 weeks post-drug
MedImmune's **MEDI-507**	N/A	N/A

NOVARTIS' pimecrolimus
(ascomycin, SDZ-ASM981).

The sleeper in psoriasis may be this oral agent. Pimecrolimus will be launched soon in the U.S. in topical ointment formulation under the brand name Elidel. The oral version will have a different name.

Last year, a researcher presented Phase I data on the oral formulation in moderate to severe psoriasis. As a reminder that randomized, double-blind, placebo-controlled, four-week trial tested pimecrolimus at 10 mg qd, 20 mg b.i.d. and 30 mg b.i.d. in 30 patients (10 in each arm) vs. 10 placebo patients. Patients were hospitalized for study weeks one and two. There were three drop-outs in the combined drug arms and none in the placebo group. A researcher said, "After 28 days, it wipes out psoriasis." There were no serious adverse events, just a transient feeling of warmth in about one-fourth of the patients.

There was no new data on the oral formulation this year, but

Novartis researchers said the drug is in a world-wide, dose-finding, Phase IIb trial that should be finished soon. It is believed the doses in that trial are 20 mg and 30 mg. This data could be presented at the World Congress of Dermatology in Paris from July 1-5, 2002, but it is more likely to be presented at the European Academy of Dermatology and Venereology in Prague from October 2-6, 2002. Novartis officials were "very excited" about the prospects for this agent.

IMMUNEX'S Enbrel
(etanercept)

Sources predicted that the number of patients diagnosed with PsA may increase sharply over the next year as a result of Enbrel's approval to treat PsA. However, when individual doctors were asked about their own practices, all insisted that (1) they already were documenting joint pain in all psoriasis patients, and (2) there was unlikely to be an increase in the number of PsA patients in their practices. It was always "other doctors" who were likely to diagnose more PsA. Rheumatologists interviewed at the meeting said they are not seeing an increase in PsA patients being referred for therapy by dermatologists. All this could be taken to mean that the number of PsA patients will go up but perhaps not as dramatically as Immunex has predicted.

Sources insisted that Enbrel works in plaque psoriasis as well as psoriatic arthritis. The response to Enbrel in psoriasis appears dramatic, and it may work even better if given longer. An expert said, "I suspect if we treat patients longer, we'll see continued improvement. My impression is that, if the drug is discontinued, the disease comes back slowly, with no rebound effect, but I haven't formally followed that." Enbrel is in a Phase II/III trial in psoriasis, which is looking at different doses and schedules.

JOHNSON & JOHNSON'S Remicade
(infliximab)

Psoriasis patients appear to respond quickly (within two weeks) and dramatically to Remicade. Remicade is in a multicenter Phase II trial in psoriasis, and it is possible J&J will submit based on that data. Interestingly, dermatologists are using Remicade -- in and out of trials – without methotrexate. Asked whether this could lead to high HACA antibody rates, experts insisted this is not a concern.

Data was presented from an investigator-sponsored Remicade study of 33 patients, and this generated a fair amount of controversy at the meeting. Researchers for other products criticized it as too small, but clinicians said they were impressed. The principal investigator said there were four mild infusion reactions, which were preventable with benadryl.

Remicade Monotherapy Study

Week	PASI ≥75	PASI ≥50
2	6%	26%
4	29%	61%
6	45%	84%
8	77%	90%
10 (end of drug therapy)	84%	90%
14	81%	98%
18	58%	81%
22	48%	65%
26 (at 16 weeks post-drug)	48%	55%

Among the comments by doctors who already are using Remicade for psoriasis were:

- California. "I've been using Remicade off-label in 12 psoriasis patients as well as some psoriatic arthritis patients, and getting coverage, especially in pediatric psoriasis. Even Blue Cross covers it for pediatric psoriasis, and that is one of the tougher payors. I'm doing at 3 mg/kg on an every-8-week schedule, doing the infusions at the hospital, but a couple of patients are on an 'as needed' basis. There is some tachyphylaxis because I've had to increase the dose to 6 mg/kg at 4-6 weeks in some patients."
- Texas. "Anecdotally, I've seen 'significant improvement' in my psoriasis patients on Remicade. I'm keeping patients on maintenance therapy every eight weeks. Managed care is paying for PsA but it is difficult in Texas."
- Maryland. "It looks like Remicade is better than Enbrel, based on some work we've done at NIH, so I'm referring patients for Remicade not Enbrel."
- Pennsylvania #1. "I won't use Enbrel or Remicade until they are FDA-approved. Then, I will ask a rheumatologist to review what I am proposing and give it his blessing. Insurance will dictate my choice between Enbrel and Remicade."
- Pennsylvania #2. "When I get home, I'm going to call up a couple of my psoriasis patients and suggest Enbrel – if I can get it. If not, I may consider Remicade. I can send the patients across the street to the infusion center, but I'd rather use Enbrel because it is easier for me."
- South Carolina. "I have patients on Remicade for psoriasis as well as psoriatic arthritis. I chose Remicade because that is what the rheumatologists like, and they are treating the psoriasis patients along with the psoriatic arthritis patients."
- New York. "There is reimbursement for Remicade now in psoriasis, but it takes a very severe patients and a lot of paperwork."

- Florida. "I'm thinking about using a TNF, but malpractice is a big issue in my state right now, so I won't use it off-label, but I'll use Enbrel for psoriatic arthritis. Either way, I'll send the patient to the rheumatologist first. Otherwise, the lawyers will wonder why psoriatic arthritis patients aren't referred to a rheumatologist."

GENENTECH/XOMA'S Xanelim
(efalizumab, anti-CD11a)

This biologic agent has been plagued with concerns about rebound, and the companies are conducting additional trials to determine the best way to get patients off the drug – tapering or switching to another agent. Now, however, there are credible reports of numerous cases of rebound in patients still on the drug. These rebounds (on and off drug) are occurring at new sites; they are not exacerbations of existing psoriasis plaques. Most, if not all, of the rebounds reportedly clear with continued therapy, but the implication is that the regulatory bar has been raised by these reports. A source said, "Small red spots (in new spots) are reasonably common. I've seen the spots. On biopsy they look like psoriasis, but I don't think it is a big issues. They go away with continued treatment. A few have been rumored to get worse, but the question is whether the washout before therapy caused it, and I haven't seen people get really worse on treatment…this does not look like the traditional Koebner effect."

Xanelim researchers insisted that patients will be willing to undergo chronic therapy with Xanelim. One said, "My patients are cyclosporine addicts because it works. If we stop it for safety concerns, some of them will go to Mexico and buy it. They don't want to stop something that works. But if patients have to come off Xanelim, it might be an issue in 5% of patients. With them you can switch to other therapy or taper them. I haven't had issues with this."

At this meeting, there was little enthusiasm for Xanelim among clinical dermatologists who were not investigators. A Florida doctor said, "All the biologics work well except Xanelim. The early word is that it doesn't work well….(but) 14% efficacy with Amevive is good in severe patients."

BIOGEN'S Amevive
(alefecept, LFA3-TIP, anti-CD2)

Investigators confirmed rumors that Amevive is expected to go before an FDA Advisory Panel in May 2002. The good news for the company is that a doctor who is a known critic of biologics apparently has said he will recuse himself because of a conflict of interest. The bad news is that several new members will be added to the panel from both the psoriasis and biologics communities, and that adds a degree of uncertainty.

More IM data was expected on Amevive re-treatment than was presented at this meeting. That data now is expected at the Society of Investigative Dermatology meeting.

Dermatologists appear convinced that this drug is approvable and will be approved by the FDA. A researcher said, "Amevive is approvable. If not, I can't see what the defect would be." Another expert commented, "Alefecept will be the first monotherapy, and I'm quite sure it will be approved." However, questions were raised about:

- *CD4 counts* (memory T-cells), which drop as low as about 250 before starting to recover and do not return to the 400-600 normal level during the time period followed. However, investigators and other experts insisted they are not concerned about this and do not expect it to be a regulatory issue. They said that they are not concerned as long as the count remains above 200. A researcher said, "There were two patients whose CD4 counts did not return enough for a second course. None of the patients who got a second course didn't recover enough for a third or fourth course. When we screen patients for entry into an Amevive trial, about 2%-5% are not candidates because their T-cell counts are too low (<250) or their lymphocytes are too low (<700)." This researcher said that in clinical practice he would monitor only lymphocytes and would do that monthly or every other month, holding the drug if and when the count fell below 500…There has been no increased incidence of infection with Amevive, even in patients with low CD4 counts…Continuous treatment with Amevive could result in a CD4 problem, but re-treatment is okay. Out to one year, patients return to within 20% of baseline." Another expert said, "T cell counts with Amevive are subnormal but still in the comfy level. I'm comfortable >100."

- *FDA approval of both IM and IV formulations* at the same time. Some sources worried that the FDA cannot or will not approve both formulations at the same time.
- *One case of rebound.* This was reported by two separate researchers who said the patient had been off Amevive for about eight weeks when the rebound occurred.

- *PASI 75 responses* after re-treatment. The way in which the data was presented was a little confusing.

Phase III Amevive Results

Course	PASI <50	PASI >50 but ≤75	PASI >75 but <90	PASI ≥90
Course 1 (n=166)	36 patients	70 patients	35 patients	28 patients
Course 2 (n-129)	14 patients	65 patients	26 patients	20 patients

Three immunologists were asked about the importance of lowered CD4 counts, and all agreed that it is very serious if the count does not quickly rebound. They predicted this issue would be of serious concern to the FDA. A North Carolina

immunologist said, "The typical CD4 count in a normal patient is 800-1200. I would be concerned if a count of 250 persisted. I would pay attention to it. Acute losses of anything are bad. You can give high dose steroids for a short time, as in autoimmune disease, and people recover, but when people have a persistently lowered CD4 level, I would be more concerned." A Texas immunologist said, "(A drug that lowers CD4 to ~250 and left it there) would not be a safe drug as far as I'm concerned. There would be serious safety concerns. If the CD4 level gets below 200 that is AIDS by definition. True AIDS is HIV positive, but CD4 lymphocytopenia is HIV-negative AIDS." Another expert said, "CD4 levels of 250-300 certainly would catch the attention of immunologists. I would be somewhat concerned about that, even with the revised criteria for treatment. The level at which you became nervous and started treatment used to be 500, and now it is 300. I don't know any immunologist who would blow this off as unimportant. Is it an artifact? If it is, dismiss it, but if it is real, then careful immunological monitoring for a long time is necessary. If I were on the FDA panel, I would put these guys through a meat grinder."

These immunologists were concerned that dermatologists do not appear to be taking the CD4 issue seriously enough. An immunologist said, "If Amevive drops the count to even 300, I would be very concerned, and I would follow those patients mighty closely." Another expert said, "If all they are going by is that no one got sick (in the trials), that is inadequate. The burden of proof is on the company. If Amevive truly drops the CD4 cell count that low, then people should be very careful of the long term consequences of this drug." A Texas doctor said, "To trivialize the importance of CD4 depletion is unfortunate. Researchers could say they haven't seen a problem so far, but to say there is no risk is crazy."

Among the immunologists' concerns are infection, vaccine inactivation and potential carcinogenesis. One said, "If you get rid of memory T-cells, you get rid of vaccine memory. I suspect the FDA will have concerns about an increased risk of infection, especially since it held up (Genentech's) Xolair because of safety concerns related to infection. If the FDA has that much concern with Xolair, then I think Amevive could be in trouble." Another said, "Some of my concerns would be pneumocystis carinii, PCP, and fungal and yeast infections." A North Carolina doctor added, "Resistance to the measles virus is predominantly mediated by CD4. Are patients going to be susceptible to measles now?"

Among the questions immunologists have about Amevive are:

- Does Amevive eliminate only psoriasis T-cells or does it wipe out all types of CD4 memory cells?
- Is this a non-specific effect or is it specific to T-cells involved in psoriasis?
- Are patients getting delayed lymphocyte proliferation or delayed hypersensitivity skin tests?
- Are patients getting functional monitoring?
- How and where is the CD4 level being measured? Is the CD-8 count changed? Is the ratio of CD4 to CD8 changed?
- How closely are patients being followed and who is doing the monitoring?
- Are there long-term animal studies for cancer development?

OTHER AGENTS IN DEVELOPMENT

ABGENIX'S anti-IL-8. A Phase IIa trial in psoriasis tested 1, 3 and 6 mg/kg, and the 3 mg/kg was the most effective; the 1 mg/kg and 6 mg/kg were both less effective. Patients got a double loading dose, then one dose every three weeks for a total of five doses. There was no rebound and no injection site reactions.

Abgenix has chosen to use fixed dosing rather than weight-based dosing, and a Phase IIb trial is underway at two fixed doses – 200 mg and 300 mg. Patients will receive treatment for 12 weeks, followed out to 36 weeks. The drug may be more effective at higher doses, but sources said it is not economically effective to produce at higher doses. Administration currently is IV (30 minute infusion), but the company is looking at a subcutaneous formulation.

Although anti-IL-8 failed in rheumatoid arthritis, Abgenix officials are upbeat about the outlook for this agent in psoriasis, and there is likely to be data from the Phase IIb trial at the Society of Investigative Dermatology meeting in May 2002 (or, if not there, then by press release). There are no plans for trials in psoriatic arthritis.

IDEC'S IDEC-114 and IDEC-131. No new data on this.

ISIS'S antisense, ISIS-2302. The company said it is not proceeding with this as a monotherapy, but may go forward as combination therapy.

PROTEIN DESIGN LABS Zenapax (daclizumab), an anti-CD25, and HuM291, anti-CD3. HuM291 may have a lower incidence of flu-like symptoms than Zenapax. PDLI plans to release the Zenapax trial data in the latter half of March 2002.

MEDIMMUNE'S MEDI-507, an anti-CD2. In two Phase II studies 9 of 79 patients dropped out. This agent also appears to have a CD4 depression issue; CD4 levels stayed subnormal from day 21 when the drug was stopped out through day 77. Subcutaneous administration lowers CD4 counts less than IV administration, but levels did not return to normal with either approach, and the effect was more delayed with subcutaneous administration

LUMENIS

Lumenis recently introduced BClear, a very slick, hand-held UVB light treatment system for mild to moderate psoriasis. The device, which costs $44,900, and can be leased over five years, was launched at the meeting, and company officials claimed there is sufficient supply to meet expected orders, though they declined to give guidance on the sales outlook. A company official said four or five patients a month would be enough to make it cost-effective for a doctor. Medicare reimbursement is under the existing UVB code, which is $50-$53 per treatment (not per lesion).

BClear will be sold by the regular Lumenis sales force, which initially will focus on selling to academic medical centers and secondarily to cosmetic dermatologists. Company officials said the typical patient will need six to eight total treatments (2-3 per week), and this light therapy can be used in combination with other treatments. They estimated that there are 3,200 dermatologists in the U.S. who write two-third of the psoriasis prescriptions, with an average of 300 patients each per year. Ten percent of these 3,200 dermatologists are the high volume doctors, treating more than 1,000 psoriasis patients a year.

Dermatologists interviewed were not very optimistic about the outlook for BClear. A doctor who said he treats 50 psoriasis patients a month said, "I'm not interested in BClear. I prefer PhotoMedex' excimer laser. I think BClear is too expensive for medical dermatologists, too." A Pennsylvania doctor said, ""It could be a niche in medical centers, but I don't think we are interested yet. If it were $10,000, it would sell like hotcakes – and I would get one for my private office." A Florida doctor said, "BClear is off the wall and reimbursement is limited. I'm not interested."

CONNETICS

Connetics has introduced two new foam formulations of the topical steroid clobetasol, Olux and Luxiq. Based on interviews with 11 dermatologists familiar with the products, the foam formulation does have the advantage of being less greasy than clobetasol gel or ointment. However, these are not considered major advances. A Virginia doctor said, "They are cosmetically eloquent." A Florida doctor said, "It is just another option." Another doctor commented, "They are nice for some patients, an option but not a huge advance."

Most doctors reserve these products for use on the scalp or other hairy areas. A New York doctor said, "They are good for men with a lot of hair." A Tennessee doctor said, "I use them on more hair bearing areas like the scalp – not the hands, though the sales reps push me to use them for that. I've had good results in the scalp but mixed results in other areas."

Doctors cited two concerns with these products:

1. *Cost*. Doctors said the products are expensive, so they are reserved them for a small segment (10%-20%) of their patients who are on topical steroids.

2. *Side effects*. Half the sources said some patients experience a short-term burning sensation, perhaps due to the preservative. A doctor said, "There's some burning, but there are easy tricks to get around that."

Currently, there are no samples available to dermatologists. A company official said this is because it proved difficult to design a foam container small enough for samples, but that hurdle has been overcome, and doctors are expected to get samples by mid-year 2002. Once samples are available, a company source reportedly predicted that sales would increase dramatically (perhaps as much as 30% within a month), but dermatologists were dubious about this prediction. Ten of 11 doctors questioned said they would not write more prescriptions if samples were available, but five said it might encourage patients to fill the prescriptions they are given. A New York doctor said, "Supplies will not affect my prescriptions. I'm not influenced by samples. But it will be easier for patients, and it will encourage patients to fill the prescription I give them." A Tennessee doctor said, "Samples can be a reminder for patients. I won't increase my prescriptions, but patients may fill more prescriptions." A Kansas doctor said, "Samples will help but not dramatically because of cost." Another doctor said, "Patients like it when I give them samples, so use may go up 10%-20% with samples.

If a doctor does not write "dispense as written," "no substitutions," or similar language, pharmacists can and do substitute cheaper forms of clobetasol. Most dermatologists said they already write the prescription to minimize this substitution. A Virginia doctor said, "I check the box for *dispense as written*, cross off *may substitute*, and write *foam* on the prescription. That should stop any substitution because there is no other foam." Another doctor said, "I should write *dispense as written*, but I don't." A Florida doctor said, "I try to write *dispense as written*, but the pharmacist in my state can ask the patient to substitute a cheaper product." ♦