Trends-in-Medicine

March 2003
By Lynne Peterson

SUMMARY

Despite pressure from HMOs to use OTC Claritin, most allergy specialists are still prescribing brand antihistamines, and Aventis' Allegra is the winner. ♦ Merck's Singulair is starting to catch on in allergic rhinitis, with use expected to increase. ♦ A study of Idec Pharmaceuticals IDEC-152 for allergic rhinitis was disappointing, showing safety but no efficacy. ♦ A study of Inspire Pharmaceuticals' P2Y2 for allergic rhinitis, INS37217 showed safety and "a hint" of efficacy. ♦ Genentech/Novartis/Tanox's anti-IgE, Xolair, generated a lot of attention. Doctors consider it safe, effective, and likely to be approved this year. They plan to use Xolair for an average of 7% of their patients, which includes high off-label use, particularly for food allergies but not for allergic rhinitis. Doctors expect managed care to cover Xolair, but cost will be a limiting factor. ♦ Tanox's TNX-901 looks promising to treat peanut allergies, but Xolair may be developed instead by Genentech-Tanox-Novartis.

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THE AMERICAN ACADEMY OF ASTHMA, ALLERGY AND IMMUNOLOGY (AAAAI)
Denver, CO
March 8-11, 2003

There was not a great deal of new and exciting news out of this meeting, though the interest in anti-IgE (Xolair) was high.

ALLERGIC RHINITIS AND ASTHMA

Allergic rhinitis afflicts 10-15% of the population (28-42 million Americans), and about 50% or more of asthmatics have allergic rhinitis. Half of allergic rhinitis patients experience symptoms for more than four months a year, and 20% have symptoms for at least 9 months a year. In a study of patients from 1996, 58% of all patients with allergic rhinitis received at least one prescription drug that year for its treatment.

The current management of allergic rhinitis is, in this order:

1. Environmental control to prevent it.
2. Antihistamines for relief of symptoms.
3. Nasal steroids as controllers.
4. Immunotherapy.

A Late-Breaking Abstract found that intranasal corticosteroids reduce the risk of hospitalization for asthma in patients with concomitant asthma and allergic rhinitis. The study examined an insurance database of 215,000 patients, which found 234 patients with concomitant asthma and allergic rhinitis. Researchers concluded that use of inhaled steroids was associated with a significant reduction

Risk for Asthma-Related ER Visits and Hospitalizations in Relation to Inhaled Steroid and/or Antihistamine use

Drug	Crude Odds Ratio	Adjusted Odds Ratio	Statistical Significance	% Reduction
Risk for Asthma-Related ER Visits				
Inhaled steroid (ICS)	.90	.75	Yes	N/A
Antihistamine (AH)	1.18	.88	No	N/A
ICS+AH	.88	.37	Yes	63%
Risk for Asthma-Related Hospitalizations				
ICS	.78	.56	Yes	N/A
AH	.94	.68	No	N/A
ICS+AH	.59	.22	Yes	78%

in the risk of ER visits and hospitalizations. Antihistamines alone were **not** associated with a significant reduction of risk, but the combination of inhaled steroid and antihistamine appeared to have an additive effect though the additive effect was not greater than with inhaled steroids

ANTIHISTAMINES

The FDA still has not made a decision on the Wellpoint (Blue Cross/Blue Shield) petition to make other brand antihistamines – Aventis' Allegra (fexofenadine) and Pfizer's Zyrtec (cetirizine) – over-the-counter. An FDA official said, "This decision (on OTC status) has both scientific and political overtones." All three currently are approved for urticaria, which is not an OTC indication, and additional studies will be required for OTC labeling for urticaria.

Ten doctors were questioned about how the market is changing for second generation antihistamines – Allegra, Zyrtec and Schering Plough's Clarinex (desloratadine). Most said they are still able to prescribe brand antihistamines without restrictions. A Georgia doctor said, "I'm still writing prescriptions for brands, but I haven't been asking patients if they fill them or if they buy OTC Claritin." A West Virginia doctor said, "Most insurance still covers the brands." A Pennsylvania doctor said, "I haven't seen any restrictions yet." A Texas doctor said, "The insurance companies are trying to say they are all equally efficacious. They are pushing Claritin OTC, and they recommend Claritin OTC, but so far we are winning the battle by saying the drugs are not equivalent and by recommending a different product. However, Clarinex is harder to get approved."

Four doctors said it has gotten more difficult to prescribe brands. A California doctor said, "Many HMOs are requiring OTC Claritin, though some may allow a brand with a higher co-pay or pre-authorization. PPOs are making brands second tier with a high co-pay." A Kentucky doctor said, "One carrier will not cover any brand antihistamines at any tier." Another doctor said, "One insurance company stopped covering all brand antihistamines, but I think the others will follow suit." A Georgia family practice doctor said, "Brand antihistamines require a prescription from an allergist. I can't write prescriptions for them any longer."

Doctors so far have said HMOs want OTC Claritin used, but if they write a letter saying the patient failed OTC Claritin, then they can get coverage for one or more of the brand drugs, depending on the formulary.

Advertising and samples used to affect market share, but doctors interviewed at this meeting said that formularies are the new drivers of brand market share. A West Virginia doctor said, "Sales reps are now out of the loop. They are kind of helpless. Decisions are driven by formularies." A California doctor said, "The most helpful sales reps are providing pre-authorization forms to help us get their drug reimbursed." A Kentucky doctor said, "HMO formularies are in charge, and they are changing week by week."

In this environment, it appears that Allegra has taken the lead. A West Virginia doctor said, "My choices are narrowing, but Allegra is winning." Another doctor said, "The biggest HMOs don't cover Clarinex, so I mostly use Allegra and Zyrtec." A New Hampshire doctor said, "Claritin is less effective than Allegra, so we use Allegra, which is on the formulary."

How do Allegra and Claritin compare? Several doctors described Allegra as the most potent, but most sources agreed that Clarinex is more comparable to Allegra. A Georgia doctor said, "Allegra is equivalent to Clarinex. Claritin is the weak sister." A West Virginia doctor said, "Allegra is more potent than Claritin and probably comparable to Clarinex, but there is not enough data on Clarinex to be sure. Allegra has done a lot of head-to-head studies. It will do better for a while." A Pennsylvania doctor said, "Zyrtec is best but it puts me to sleep. Allegra is the least sedating. Claritin is like placebo." A Kentucky doctor said, "I'm using 40% Allegra, 40% Clarinex and 20% Zyrtec."

There was a suggestion that doctors might be writing prescriptions for inhaled steroids or Merck's Singulair (montelukast) for allergic rhinitis patients who are unable to get formulary coverage for antihistamines, but doctors said that is not happening. A Georgia doctor said, "The sales reps say that is just a (Merck) marketing ploy." Another doctor said, "I'm definitely not doing that. Singular is not more effective. Blue Cross stopped covering Singulair without prior authorization."

INHALED STEROIDS

SCHERING-PLOUGH'S Asmanex

Schering had quite a few posters at the meeting in an effort to keep this agent in front of doctors, but the sales reps weren't talking about it at the booth. The sales reps don't know when it is going to be available, and company officials were refusing to discuss it. A speaker said Schering is hoping for approval by fall 2003, but he did not appear to have any real knowledge about timing.

Several speakers emphasized that all inhaled steroids are equally efficacious. However, they do have differences in terms of:

- Potency.
- Formulation.
- PK (how long they stay in the lung).
- Duration of effect.

Doctors questioned about the outlook for Asmanex warned that Schering will face several hurdles launching Asmanex, including:

- It is monotherapy.
- It will have to compete with GlaxoSmithKline's popular combination therapy, Advair. A speaker said, "What I really like about Advair is it improves compliance. Patients get reinforcement from the beta agonists (Serevent) that they don't get from the inhaled steroid (Flovent)…I think the combination doubles compliance."
- It also will have to compete with Altana's Alvesco (ciclesonide), and this may be a more serious competitor in some ways than Advair.

ALTANA/AVENTIS'S Alvesco

Alvesco (ciclesonide) is a dry powder inhaled steroid for asthma. The formulation is not a suspension but a solution with very small droplet size.

Ciclesonide appears to have several advantages over other inhaled steroids, including:

- Equal or better efficacy than budesonide (AstraZeneca's Pulmicort) and fluticasone (GlaxoSmithKline's Flovent).
- QD dosing.
- Local side effects comparable to placebo and fewer than with other inhaled steroids.
- Less suppression of cortisol than other inhaled steroids, even at a high (1600 µg) dose.
- Lung activation.
- Greater lung deposition than other inhaled steroids.

The Ideal Inhaled Corticosteroid*

Positive Characteristics of the ideal Inhaled Corticosteroid	Alvesco	Other Inhaled Corticosteroids with this feature
High pulmonary Bioavailability	Yes	Montelukast and fluticasone but not budesonide
Small particle size	Yes	beclamethasone dipropionate
High receptor binding strength	Yes	GlaxoSmithKline's Flovent (fluticasone) is most potent
Protein binding	Yes	None
Rapid clearance	Yes	All except AstraZeneca's Pulmicort (budesonide)
Long pulmonary half-life	Yes	Pulmicort
Prodrug structure	Yes	Pulmicort
Lipid conjugation	Yes	Pulmicort
Lipophilicity	Yes	All

*Based on Aventis poster

LONG-ACTING BETA AGONISTS

In January 2003, GlaxoSmithKline stopped the SMART trial, a safety study of its long-acting beta agonist, Serevent (salmeterol), and preliminary data indicates there is a small but real increased risk of serious asthma-related events, including death, with salmeterol. However, **none of the doctors questioned about the SMART trial were concerned about the findings, and all agreed that the trial would *not* change their prescribing practices.**

The SMART trial was supposed to enroll 60,000 patients to examine the occurrence of serious and life-threatening occurrences with salmeterol vs. placebo, and had enrolled less than half that at the time of termination. Data adjudication and analysis is still ongoing. Initial analyses indicate an elevated risk (though small absolute risk) of serious asthma-related events, including death, with salmeterol. The signal was particularly strong among African-Americans.

An FDA official said, "Labeling changes are anticipated presently and further changes may be warranted when fully analyzed data are available…The trial was terminated mainly for futility. The company was having trouble recruiting patients, and it projected that even out to 60,000 patients, it would not have ruled in or out a problem with serious adverse events. It wasn't stopped for a clear safety signal. It is unclear at this point how this trial applies to GlaxoSmithKline's Advair [a combination of 50 mcg Serevent and Flovent (fluticasone propionate 100 mcg)]. Inhaled corticosteroids do not appear to be the entire answer…We need to see the data, meet with the sponsor, and see how the findings apply both to salmeterol as a single agent and to Advair. We have no reason to think this is unique to salmeterol, that it is only a problem with salmeterol, so we have to look at what this means for all long-acting beta agonists."

PDE4s

A session on PDE4s was well-attended – particularly by researchers from a variety of pharmaceutical companies. PDE4s have been very difficult to develop, and many have fallen by the wayside over the past 10 years. All either didn't work or had excessive nausea or liver abnormalities. Nausea is difficult to study preclinically because there are no good animal models that predict human nausea, and the mechanism of action of emetic side effects is unclear. A Pfizer official said, "My take on the nausea is that the PDE4s are more emetic when given orally – and emetic in multiple ways." Researchers believe that one of the four PDE4 subtypes (a-b-c-d) may be associated with the nausea, and the current thinking is that the problem is the D subtype.

Speakers were hopeful that one of the current agents in development will get approved, but they predicted that PDE4s will have a tough time at the FDA. One said, "PDE4s will need to set new policy at the FDA to get approved, with less emphasis on FEV_1 and more emphasis on symptoms and exacerbations for COPD." Sources believe a PDE4 is likely to be approved in the U.S. before Europe because of stricter European rules on tissue reversibility.

These experts also expressed strong interest in looking at PDE4s to treat rheumatoid arthritis, irritable bowel syndrome and other disorders.

Merck

Two years ago, it appeared that Merck had the lead in PDE4s with an agent in Phase II development, but Merck is still in Phase IIb development. A researcher said the study has been enrolling slowly because the inclusion criteria are very stringent, with only about 1 in 50 patients qualifying.

GlaxoSmithKline

GlaxoSmithKline now has the lead with its Ariflo (cilomilast, SB-207499), which was filed for COPD in Europe in January 2003, and sources here thought it had been submitted to the FDA already. Ariflo has not shown any real benefit in asthma, and, accordingly, its development for asthma has been stalled in Phase II. A speaker said, "A study in moderate asthma did not find this to be a steroid-replacement."

There is some emetic potential with Ariflo at high doses. The DLT is 20 mg; in Phase I at this dose, 12 of 18 patients had so much nausea that a second dose could not be administered. Thus, the company is seeking approval at 15 mg BID in COPD.

Speakers agreed that doctors and COPD patients are anxious for a new agent. They said that Ariflo will be used off-label in asthma if it is approved for COPD, but they were not confident the FDA would approve Ariflo.

Reportedly, Glaxo is working on an inhaled version of Ariflo.

Altana

In mid-2002, Altana announced that the regulatory filing for its PDE4, roflumilast, was being delayed, but the company would not explain this other than to say that it wanted additional data, and that this was not a unilateral recommendation by its co-marketing partner, Pharmacia. Officials did not explain whether it was additional safety or efficacy data that they would be collecting.

At AAAAI, a Pfizer official said it is not clear yet whether roflumilast will become a Pfizer product as result of the Pharmacia/Pfizer merger. He said the European Union is not asking Pfizer to divest any respiratory drugs as a condition of merger approval, but he said U.S. regulators have not issued their ruling on this yet. In addition, Pfizer is moving carefully right now on roflumilast because it has its own PDE4 in development.

Reportedly, there is no excess of GI toxicity (nausea or vomiting) with roflumilast at expected doses, but there is some emetic potential at high doses. A speaker said, "There is less GI toxicity with drugs that cone on slowly rather than are given by bolus, and roflumilast is naturally slow release." However, several sources warned that, though roflumilast appears to look promising at this point, it has not been published.

Roflumilast does appear efficacious. A speaker said, "In moderate asthma, roflumilast was as effective as inhaled steroids, and it acts very much like an inhaled steroid…In a Phase III study in COPD, there was not much difference in efficacy between 250 µg/day and 500 µg/day." Another speaker said, "Roflumilast is 2 log more potent than Ariflo in inhibiting eosinophils."

Efficacy	Ariflo	Roflumilast
Reduction in asthma exacerbations	-25% - 30%	-48%

Other PDE4s in development include:

- **Pfizer's PD-168787.** A year and a half ago this was in Phase I, and a Pfizer official would not comment on its current status except to say that Pfizer would not discuss the drug until it was ready to enter Phase III. However, he did admit that Pfizer has seen some nausea and vomiting with its agent.
- **Schering Plough's D4418**, in Phase I.
- **Icos' IC-485** in Phase II.
- **Glenmark Pharmaceuticals' GRC-3015**.

FDA: The Regulatory Perspective

FDA officials offered some interesting information on a variety of topics not discussed above.

Albuterol

The American Lung Association (on behalf of AAAAI and others) has petitioned the FDA to remove the essential use status of CFC-albuterol, and this remains under review. An FDA official said, "The one tough issue to grapple with in this is the issue of price. Name brand HFA albuterols are priced like name-brand CFC albuterols, but they are somewhat more expensive than the generics, and the government and consumer groups have an interest in this decision."

INTERMUNE'S Actimmune

An FDA official insisted that a placebo-controlled trial in idiopathic pulmonary fibrosis (IPF) is possible and reasonable (for Actimmune).

Miscellaneous

- The FDA will soon issue final guidance requiring that all future MDIs for oral inhalation have dose-counters/indicators, but the rule does not pertain to DPIs/nasal inhalers.
- Allergy and asthma are not considered appropriate areas for accelerated approvals.
- The agency plans to develop guidance documents in COPD over the next months to a year.
- Two FDA officials emphasized that it is not the vote at an Advisory Committee that is important to the FDA – it is the discussion and debate.

Following is information on specific companies and their products:

ALCON

Alcon is continuing to work on a nasal spray version of its ophthalmic eyedrop, Patanol (olopatadine hydrochloride), for non-allergic rhinitis. However, this agent is proceeding ***very*** slowly. A year and a half ago, it was in Phase II trials, and a source said that it is still at least two years from market.

Patanol nasal spray (and it is expected to have a different name for this formulation) would compete with Wallace Laboratories' Astelin, which is the only nasal spray antihistamine on the market at this time. Non-allergic rhinitis (nasal antihistamines) is a much smaller market (less than half the size) than allergic rhinitis, but it still is a substantial market, with room for a good agent to expand sales.

IDEC PHARMACEUTICALS

Idec's IDEC-152 appears safe but efficacy was not shown in allergic rhinitis; none of the doses showed greater efficacy than placebo. There were 131 patients in the Phase II trial of IDEC-152 (Study 152-04), with 105 on drug and 26 on placebo. All patients got an IV injection once a month for four months. The patients did not appear to be well matched, but an investigator and company officials insisted the variations are not important.

There was no decrease in C D23+ B cells. The half life was about nine days but could not be determined for the 0.25 dose. There were no Grade 3 or Grade 4 adverse events, no infusion reactions and no T-cell depletion. However, one patient developed anti-IDEC-152 antibodies by day 142 (with no associated adverse events).

Study 152-04 Adverse Events

Side Effects	Drug	Placebo
Upper respiratory infection	14.3%	7.7%
Nasopharyngitis	9.5%	7.7%
Pharyngitis	8.6%	11.5%
Sinusitis	7.6%	11.5%
Headache	6.7%	15.4%
Sinus headache	6.7%	3.8%

The preliminary efficacy was comparable to placebo. Overall percentage use of rescue antihistamines was 86% for all treatment groups. There were notable declines in total ragweed-specific IgE with IDEC-52.

Study 152-04 Efficacy

Measurement	IDEC-152				Placebo
	0.25 mg	1.0 mg	2.0 mg	4.0 mg	
Rhinitis Symptom Score on days 57-59 (sneezing, rhinorrhea, nasal congestion, eye symptoms, and nasal-ear-palate pruritis)	10.1	12.3	10.7	11.9	9.4

Researchers concluded:

1. The drug was safe and well-tolerated. Adverse events were comparable to placebo.
2. The Rhinitis Symptom Score (RSS) was comparable to placebo:
   a. The results were confounded potentially by the high incidence of antihistamine use in all groups.
   b. Exploration of alternative dosing and dosing regimens are warranted in future studies.

Study 152-04 Demographics

	IDEC-152				Total drug	Placebo
	0.25 mg	1.0 mg	2.0 mg	4.0 mg		
Number of patients	27	27	24	27	105	26
Age	40	43	37	39	41	38
Mean total IgE (IU/mL)	300.3	140.5	178.3	216.6	210.2	133.4
Mean ragweed-specific IgE (kU/L)	10.8	12.9	7.2	8.2	9.9	8.3

3. IDEC-152 produced notable declines in both total and ragweed-specific IgE that were sustained post-ragweed season.
4. Ongoing studies in allergic asthma will provide greater understanding of the role of CD23 and the potential utility of IDEC-152 in all rhinitis. However, a researcher said the ongoing asthma trial is "not huge," is a dose-ranging study, and is still enrolling patients. He expected results to be available in about six months.

A researcher indicated IDEC-152 drug is not yet ready for Phase III in allergic rhinitis, and needs more Phase II studies for that indication. He also commented that, as a very expensive therapy, it needs to show a substantial effect or it won't be used. Other sources at the meeting suggested this agent will never become commercially available.

GENENTECH/NOVARTIS/TANOX'S Xolair

FDA officials said no advisory committee has been scheduled yet for Xolair (omalizumab). The Pulmonary-Allergy Drugs Advisory Committee is meeting May 15-16, but Xolair is not yet scheduled for either day.

A speaker discussed the outlook for Xolair, assuming its approval. He highlighted data on its utility in seasonal allergic rhinitis (SAR) and in combination with rush immunotherapy for (SAR). He said, "This will be expensive therapy. You won't put a patient on anti-IgE and then do four, five or six months of immunotherapy. You will probably want to rush the immunotherapy fairly quickly."

Eighteen allergy specialists were interviewed about their plans for Xolair use. Based on these doctors, it would appear that use of Xolair will be limited only by managed care coverage – but doctors expect managed care to approve its use. Most (but not all) academic centers plan to use it, but so do most (but not all) private practice doctors, so it does not appear Xolair will be restricted to tertiary centers.

Good safety. Only three doctors still have questions about the long-term safety of Xolair. The others have become comfortable with the safety of Xolair and believe that the company has laid FDA concerns to rest.

Good efficacy. Doctors generally agreed that the efficacy is sufficient to encourage use of Xolair. The most conservative comment came from an Ohio doctor who said, "There is a positive effect, but it's not dramatic." A New York doctor said, "It works very well, but the limiting factor is price, so it is not cost effective." A Kentucky doctor said, "Patient acceptance is high, which is counter intuitive, but the data that matters to patients – symptom relief -- is strong."

High excitement. 13 are excited about Xolair. Many but not all of these have been involved in Xolair trials. A Missouri doctor said, "That's why we decided to get into the trials – because we are excited about this." A California doctor said, "It's one of the most exciting things at this meeting. I went to a morning seminar on anti-IgE, and it was overflowing."

FDA approval likely. All but one doctor predicted the FDA would approve Xolair this year. (NOTE: The Tanox president said Genentech believes it will be on the May 15-16 Pulmonary-Allergy Drugs Advisory Committee agenda but has not been official notified yet.) The dissenter said, "It won't launch this year. Genentech has been very tight-lipped at this meeting about Xolair, and I think the FDA will have more questions." However, this was not the attitude of the other doctors, who all expect to have Xolair available this year.

Narrow label. Most doctors expect the drug to get a narrow label – severe asthma. A California doctor said, "I expect a narrow label, but that won't affect use."

A specialists' drug. Most sources hope and expect that Xolair will be restricted to use by allergists and pulmonologists, and will not be used by primary care doctors. A Tennessee doctor said, "It should be restricted to specialist use, not primary care doctors."

Niche product. The question is how large this niche is. A New York doctor said, "Xolair will be used for steroid-dependent asthmatics, but I only have one or two of these on oral steroids, and those are mostly compliance-issue patients." A California doctor said, "With the new asthma medications, we can control asthma in 99% of patients. Xolair will be very useful for the other 1%. I have patients ready for it now." When doctors were asked how many patients in their practice are likely to get Xolair (given insurance constraints), the estimates varied widely – from none to 1%, 5% and up to 15%. On average, doctors estimated that 7% of their patients are likely to get Xolair.

High off-label use. Off-label use is likely to be high. Ten doctors said they will use it off-label, mostly for food allergy (especially peanuts), but a few also plan to use it for latex allergy, eczema, atopic dermatitis, and/or systemic anaphylaxis to drugs. Most expect managed care to pay for off-label use in severe conditions. A Colorado doctor said, "I'll use it for food allergy. It's very promising to protect against anaphylactic shock." A Kentucky doctor said, "I won't be able to use it off-label because of insurance coverage and cost." A New York doctor said, "It would be wonderful for seasonal hay fever, but the cost will make that use hard."

Not for allergic rhinitis. DNA is pushing use of Xolair in severe allergic rhinitis, but most sources were resistant to that idea, preferring to restrict it – at least initially – to asthma and anaphylactic allergies. A California doctor said, "It is not better than inhaled steroids for allergic rhinitis."

Use only limited by cost and insurance coverage. A knowledgeable source estimated that Xolair will cost about $10,000-$12,000 per year. A New Jersey doctor said, "Cost will be overwhelming." A Midwest doctor said, "I don't think it will be hard to convince carriers to pay for it." A Tennessee doctor said, "Use will be dictated by cost and insurance coverage." A California doctor said, "It will be over-used. Use will only be limited by insurance companies."

INSPIRE PHARMACEUTICALS

Inspire's INS37217, a P2Y2 inhibitor, looks interesting, particularly for post-nasal drip associated with allergic rhinitis. The Phase II data had very small numbers, but the data was positive – for the 10 mg dose. Experts said they are encouraged by the findings, but one source emphasized that this is "a pilot study" only with "a hint of efficacy." The question company researchers couldn't answer about the Phase II data are:

a. ***Why was there no dose response curve for either efficacy or side effects?*** The 5 mg and 40 mg showed little efficacy, but 10 mg seemed to work.

b. ***Why was there such a high placebo effect with the PM dose?***

c. ***Why hasn't the company done any QT studies yet?*** (And they haven't.)

Inspire has taken INS37217 into Phase III with the 10 mg dose, and enrollment in that trial is complete, with data due in late 2Q03 (via press release, according to a company official). An expert said the things to watch in the Phase III trial will be:

a. Safety (infection, bleeding, systemic effects, cough).

b. Symptom relief . Does it provide total relief? What is the rhinorrhea effect?

JOHNSON & JOHNSON'S Remicade

Physicians are testing Johnson & Johnson's Remicade (infliximab) in severe asthma, but J&J doesn't appear interested in pursuing this indication. A doctor presented a single case study of Remicade used to treat a patient with severe steroid-resistant asthma and COPD. After three infusions of 5 mg/kg, he concluded: "Anti-TNFs may serve as a beneficial immune modulator in treatment of severe steroid-resistant asthma. Unfortunately, due to the short duration of treatment, the modest increases in lung function were transient." However, this doctor has now convinced the patient's insurance company to try another course of Remicade in the same patient.

In COPD, a speaker said the Remicade data has not been overwhelming. He commented, "I haven't heard of RA patients throwing away their inhalers."

MERCK'S Singulair

Singular (montelukast) has found a place in asthma, and it is finding a place in allergic rhinitis. A speaker said, "Leukotriene modifiers are safe and effective for SAR. The relief is comparable to antihistamines (10%-15% beyond placebo, though patients perceive antihistamines as having greater benefit than that). What bothers people the most is systemic symptoms – flu-like symptoms, sluggishness – and that is what will ultimately decide Singular placement, and that is what we will have to find out over the next year. There is no convincing evidence showing a synergy between leukotriene modifiers (e.g., Singulair) and antihistamines. Use one or the other or alternate them, but there is no strong indication to use both. There is a theoretical ability for leukotriene modifiers to synergize with intranasal corticosteroids. I think they will synergize in patients still having symptoms despite use of nasal steroids…Leukotriene modifiers are a first line therapy as an alternative to antihistamines, including patients for whom antihistamines are no longer available on formulary."

Eight allergy specialists were asked about the outlook for Singulair in allergic rhinitis. Most have already been detailed and have started using it in a few patients. A Kentucky doctor said, "I tried it, but I wasn't impressed." A West Virginia doctor said, "I'm a strong proponent of Singulair for asthma, but there is not enough data to use it in allergic rhinitis." A Georgia doctor said, "It is too early to tell how Singulair will do in allergic rhinitis." An Ohio doctor said, "I've used it in a few patients as an add-on in place of an antihistamine. It may have a role in non-allergic rhinitis. Merck is putting a lot of muscle behind it." A Texas doctor said, "Now that it's approved in seasonal allergic rhinitis, use will grow."

SCHERING PLOUGH

Morale among the sales reps was remarkably high. They are putting quite a bit of effort into Foradil (formoterol) which Schering bought from Novartis in 2002. Reps were questioning doctors, trying to find what they like and don't like about Foradil. Some, but not all, reps who see primary care doctors are selling both Zetia and respiratory products, which gives them a boost, but the other reps don't seem to wish they were in cardiology instead of respiratory. Rather, they have we-can-get-through-this and things-will-get-better-eventually attitude.

SEPRACOR

In March 2002, Sepracor received a non-approvable letter from the FDA for Soltara (tecastemizole, formerly norastemizole). A Sepracor official said the company is reviving Soltara, answering the FDA's concerns in the non-approvable letter one at a time. He indicated the company expects to re-file in 2004.

A senior FDA official, asked how difficult it is to overcome a non-approvable letter, said the FDA used to issue fewer non-approvable letters, but he indicated the majority of non-approvables can eventually be overcome. He did not address Soltara directly, but he was surprisingly positive about the ability of companies to overcome non-approvable letters.

TANOX

About 1.5 million Americans have peanut allergy, and 50-100 die every year from unintended ingestion. Tanox has developed a new anti-IgE therapy to treat peanut allergy, TNX-901, and the Phase II data looks very promising. The drug has FDA fast-track status, but the company has no plans for a Phase III trial, and TNX-901 may never be developed.

The decision of what to do with TNX-901 now rests with the same consortium – Novartis-Genentech-Tanox – which is developing Xolair, and decisions about its future will be made mostly by Genentech. Genentech, reportedly will not even consider what to do with TNX-901 until the FDA rules on Xolair (Note: The PDUFA date for Xolair is in June 2003). A Tanox official said Xolair and TNX-901 are equally effective in treating peanut allergy. Thus, if Xolair is approved to treat asthma, Genentech will have to choose between conducting Phase III trials of TNX-901 or seeking expanded labeling for Xolair for peanut allergy.

In a Phase II, double-blind, randomized, dose-ranging trial of TNX-901 in 82 patients with a history of immediate hypersensitivity to peanuts, patients were given one of three doses once every four weeks for four months. The primary endpoint was change from baseline in the threshold dose of peanut flour that induced hypersensitivity. Adverse events were similar to placebo, though most patients experienced some mild injection site reaction. A researcher reported that the 450 mg dose significantly and substantially increased the threshold of sensitivity to peanuts, on average, from half peanut to nine peanuts – an effect that should translate into protection against most unintended ingestion of peanuts. He said, "Anti-IgE therapy is not a cure for peanut allergy. We believe that patients would have to continue the injections for the benefits to persist, and they would still need to be careful about what they eat."

Phase II TNX-901 Results

	Placebo	150 mg TNX-901	300 mg TNX-901	450 mg TNX-901
Number	23	19	19	21
Means baseline threshold sensitivity	300.0	435.5	533.2	177.6
% of patients with at least a 0.9 log increase in the threshold of sensitivity	22%	53%	47%	76% (p=0.002)
% of patients reaching highest level of testing	4%	0	21%	24%
Increase in serum-free IgE levels (IU/mL)	199.5	262.0	158.9	242.0
Change from baseline in free-IgE levels at the end of Week 4	Up 4%	Down 88.4%	Down 89.3%	Down 93.2%
Change from baseline in free-IgE levels at the end of Week 4	N/A	Down 71.6%	Down 79.1%	Down 88.7%