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SUMMARY

Abbott is likely to have a CHF warning added to the Humira label. J&J and Amgen will get a lymphoma warning, and it's possible J&J will get the worst wording on its label. J&J officials appeared a bit nervous at the meeting, and the potential competitive disadvantage of a specific lymphoma label may have been the reason. Amgen appeared to avoid having its TB/infection warning increased from a bold warning to a black box.

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FDA REVIEW OF THE SAFETY OF RHEUMATOID ARTHRITIS THERAPIES

On March 4, 2003, the FDA's Arthritis Advisory Panel reviewed the safety of Amgen's Enbrel (etanercept), Johnson & Johnson's Remicade (infliximab), and Abbott Laboratories' Humira (adalimumab), and it was mostly a non-event. The FDA appeared to consider tuberculosis, congestive heart failure, and lymphoma as class issues, even if slightly different from agent to agent. Overall, the meeting is unlikely to impact use of any or all of the agents.

When the meeting was announced, there was a general concern that the lymphoma risk with one or all of the drugs had increased to a point where the future of the drugs was in question, but the issue did not rise to that level of seriousness. While there is still a lymphoma question with all of these drugs, the panel found that there just is not enough data to draw any conclusions yet, and the rate may not be worse than in the rheumatoid arthritis population in general.

Possible explanations for why the adverse events would be different among the three anti-TNFs:

- Differing mechanisms of action
- Differing affinity, avidity of binding
- Differing ability to lyse TNF-bearing monocytes
- Differing immunogenicity

Each of the companies reviewed the safety data for its drug. All have agreed to study 1,000-2,000 patients for five years for malignancies and serious infections.

- Abbott is following ~1700 Phase I, II and III patients who chose to stay on long-term continuation therapy. They will be followed for five years. In addition, the company is running a European registry with approximately 3,000-5,000 patients.
- J&J officials said they are following every patient in their clinical trials for five years, whether they stay on Remicade or not. In addition, the company said registries will take it close to 20,000-30,000 patients.

FDA CONCERNS

All three anti-TNF agents are efficacious, an FDA official said, but he warned that "each is associated with uncommon but serious adverse events."

Current FDA TNF Inhibitor Labeling

Warnings	Enbrel	Remicade	Humira
TB	Bold warning	Black box	Black box
CHF	Warning	Contraindicated	None – but warning likely to be added
Lymphoma/ malignancies	None – but warning being considered	None – but warning being considered	Label warning

LYMPHOMA

This is a concern with all the TNF agents; the question is just whether it is worse with one than another. An FDA official said, "It is biologically plausible that the TNF blockers may cause lymphomas. There is a rich body of medical literature associating immuno-disregulation and lymphomas." Another FDA official said, "Because of their immunomodulatory properties, there is concern. Assessment is difficult because it is hard to maintain a comparator control arm in long-term studies. So, an approach is to compare observed rates to expected rates in the population. But the lymphoma incidence is reported to be several fold higher among RA patients, especially those with higher levels of disease activity."

Malignancies and Lymphomas in TNF Inhibitor Patients

Measurement	Enbrel	Remicade	Humira
Number of patients	3389	2421	2400
Malignancies observed in clinical trial patients	12	23	46
Lymphomas observed in clinical trial patients	9	6	10 (half diffuse large B-cell)
Expected incidence	2.6	0.15	1.85
SIR as reported by the FDA	2.31	6.98	5.42
MedWatch reports of lymphomas	390 of which 63 were biopsy-proven	473 of which 95 were biopsy proven	N/A

* All RA studies.

Industry speakers all disputed any increased lymphoma risk from the TNF inhibitors. An Abbott official said, "The lymphoma rate (with Humira) is higher than placebo but similar to a matched RA population…Adalimumab does not contribute to an increased risk of cancer or lymphoma in the RA population." A U.K. rheumatologist speaking for Amgen said, "I don't think there is any increased risk from the anti-TNF agents above what they have from RA." An Amgen official said, "Lymphoma reports with Enbrel are rare, and the rate in our trials is consistent with the expected (SIR) rate in RA of 2.31." A J&J official agreed, "Lymphomas are more common in the overall RA population than in the general population…In 743 methotrexate-naïve patients with early RA, the SIR with Remicade was 0, but in 555 DMARD-resistant RA patients on Remicade, the SIR was 8.9%…of the six Remicade patients who got lymphomas, four were RA patients with increased risk factors, and two were Crohn's patients…both of whom only got one dose of Remicade."

Remicade came out the worst on the SIR lymphoma score. A J&J official warned, "Be careful comparing products because the patient populations were not necessarily the same. Some studied patients with late RA, and others studied patients with early RA, and I think that makes a difference." However, an FDA official responded, "Most companies started in DMARD failures and then moved to early RA." Another FDA official said, "It will be important to see more trials in early disease to characterize (the lymphoma) patterns."

J&J introduced an epidemiologist who has started a registry of 18,555 RA patients being treated by 908 doctors, and he disputed the finding that Remicade is worse than the other TNF inhibitors in terms of lymphoma. He said, "Preliminary findings showed that 71 cases of lymphoma have been reported since the first of these drugs was launched – 45 in RA, 20 in Crohn's, and six in other diseases…Lymphomas are more common in overall RA…An SIR of 2.6 for lymphoma was observed in Remicade-treated patients compared with the general population. The current evidence is insufficient to reach conclusions on whether Remicade increases the risk of lymphomas."

Dr. Wolfe's Lymphoma Findings

RA patients with:	SIR
No MTX	1.3
MTX alone	1.5
Remicade	2.6
Enbrel	3.8

A J&J official said there is no relationship between higher doses of Remicade and lymphomas or opportunistic infections. Another J&J official suggested that an elevated risk of lymphoma is associated with:

- High inflammatory activity
- Functional class III/IV
- Small and large joint involvement
- Use of conventional immunosupressants
- Possibly Crohn's Disease

There was a long debate over whether SIRs are an appropriate way to characterize the incidence of lymphoma. An epidemiologist said, "SIRS are useful, provided you use the appropriate database."

LIVER ENZYME ELEVATIONS WITH REMICADE AND ENBREL

An FDA official said, "(Liver enzyme elevations are) a signal for Aventis's Arava (leflunomide) and thus of interest for TNF blockers…Liver failure appears to be a rare event. While there are a large number of people on TNF inhibitors, a chance occurrence is unlikely, but causality cannot be ruled out, and some concern remains warranted."

CONGESTIVE HEART FAILURE (CHF)

Enbrel has a warning label in CHF, and Remicade a contraindication, and it appears the FDA also is considering a warning for Humira. An FDA official said, "We will be discussing it with Abbott…and we have tentatively approached Abbott about that...and this discussion will facilitate that."

Both Remicade and Enbrel (but not Humira) have been tested in CHF– Enbrel in the RENAISSANCE and RECOVER trials and Remicade in the ATTACH trial – and both companies dropped further development in CHF. Abbott has never tested Humira in CHF. An FDA official said, "The data suggest deleterious effects of Remicade in CHF…and the data in Enbrel shows concerning trends. We don't know the effects of Humira because studies are unavailable…We cannot provide reassurance to doctors that patients with milder heart failure are at lower risk of Enbrel-induced deleterious effects…There was no evidence Enbrel is beneficial in CHF. The data suggest it is harmful, but the results are not conclusive. The key finding of concern was a trend towards a higher mortality in RENAISSANCE…With Remicade all one might conclude is that the 5 mg/kg dose is not clean; there seem to be deleterious effects at this dose, and there is no evidence of benefit. The numbers are small, but there is a strong trend suggesting an increased mortality in CHF patients, though the mechanism is unclear…Data from the trials raise concerns about the safety of Remicade and Enbrel, and post marketing data raise concerns about new-onset CHF. A comprehensive analysis of the databases of all three is warranted, and specific language for labeling is currently under discussion."

Incidence of CHF and the TNF-inhibitors

	Enbrel	Remicade	Humira
Post-marketing reports of CHF	30	21	N/A

The companies responded:

- An Amgen official said his company would submit five-year CHF data on Enbrel to the FDA in summer 2003. He denied that the RECOVER and RENAISSANCE trials were stopped for safety, "There were several predefined analyses that the DSMB evaluated, and there were discussions and rules for stopping the trial for efficacy and for safety. Efficacy was to be stopped if it was not likely there would be an ability to show at least a 10% benefit with Enbrel, and, on that basis, the study was stopped. The DSMB said it did not meet their criteria for stopping based on safety."
- An Abbott official said, "We have not done specific trials in CHF nor do we intend to. We looked into our RA patient database to look for signals."
- A J&J official said, "There have been 158 cases of CHF with Remicade, and 28 of these patients had no known history of heart failure, no acute precipitating event or risk factor. We are presently discussing these cases with the FDA."

OTHER NEW/ UNEXPECTED SERIOUS ADVERSE EVENTS

These are demyelinating events, autoantibodies and new autoimmune diseases, including very uncommon, new, lupus-like cases. An Abbott official said his company has seen four cases of CNS demyelination with Humira, and two of these resolved spontaneously.

FDA QUESTIONS TO THE ADVISORY PANEL AND PANEL MEMBER RESPONSES

QUESTION 1: *Please comment on the characteristics of the cases of lymphomas observed in patients treated with TNF inhibitors relative to the experience in the general population and relative to the experience in people with underlying RA or Crohn's Disease.*

ANSWER: It is probably a class effect, with similar rates for all the TNF inhibitors, but the risk appears small.

Comments:

- "Based on the data, this resembles the RA pattern."
- "Some of the lymphomas in RA are related to other therapies...so we have two confounding factors."
- "I was struck by what we are not seeing. We don't see Kaposi's Sarcoma or excess melanoma. And we don't see lymphoma in the heart failure trials, and I find that reassuring on the safety of these compounds as a class. There may be some difference among them, but I'm reassured by what we don't see."
- "I don't expect more lymphoma with Enbrel than with RA. There may be some increase with monoclonal antibodies, but even then patients are exposed to other agents and causality can't be determined. The statement in the Humira labeling was very fair on notifying people on what the potential is – that there is a need for more data before we can say it is caused by these drugs."
- Another suggested it is a class effect, noting, "We didn't see information about concomitant medications, duration

of treatment or dose, so it is very difficult to separate out the underlying association between lymphoma in RA and those due to these drugs….I heard the risk is constant over time...but I think the risk might not be constant, that it might increase."

QUESTION 2: *Please discuss the strength of the available evidence and any conclusions you are able to draw regarding an association between TNF-blocking treatments and lymphoma.*
ANSWER: There is not enough data yet to decide; it may take longer to know if there is a relationship.

Comments:

- "The number are small, and any sensitivity analysis could lead to different conclusions…so the evidence is not overly strong. Concomitant medications, duration of treatment, prognostic factors -- without knowing all that, you can't reasonably understand the nature of the association. And I would have more comfort with data six to 12 months from now after longer follow-up."
- An FDA official wondered: "I'm not sure we can do better than we have now. I'm impressed by the national database that indicates most of the adverse events are coming from patients and not doctors, and that adds to the problem…I see five of 10 lymphoma events occurring between 21 and 28 months after exposure. My provocative question is -- if one does something to cause cancer, what is the lag time?" A panel member responded: "It peaked five to six years after treatment after Chernobyl. In HIV, you see lymphomas at the tail of the disease course when immunosuppresion is very profound. Here, where do you start the clock, at the beginning of RA or when the patient receives the anti-TNF? My hypothesis is when the RA diagnosis is made, so maybe a year of follow-up is not helpful."
- "I agree that there is a clumping between 600 and 800 days, and that indicates to me that there might be an increasing risk for some period of time, and that argues for one to two year follow-up as necessary to assess the full risk."
- "The risk is not equal for all three drugs."

QUESTION 3: *All three manufacturers have committed to following 1,000-2,000 patients with RA for a minimum of five years. Should the companies be asked to obtain additional specific types of information not normally assessed in patient management that could help elucidate the relationship between anti-TNF therapy and lymphoma?*
ANSWER: That may not be enough patients or long enough, so try to mine other large databases.

Comments:

- An FDA official wondered, "Is the juice worth the squeeze on the companies for more data?"
- "We still won't know underlying rate in RA in the future…because I don't think anyone will go untreated."
- "While studies of 1,000-2,000 sound large, with respect to the kinds of rates we think might be a concern, those look rather small. And five year follow-up may be too short."
- "I have trouble with how trial patients are selected, and I'm more comfortable with registries."
- A panel member said, "MedWatch...is not a good way to dig for data. How is the FDA using the Tennessee Medicaid database and other large databases to capture information?" An FDA official responded, "We are contracting with United Healthcare to use their claims database. Very roughly, there are four million covered lives, but when you look at patients on TNF inhibitors, the numbers become very small…It is very challenging and very expensive for us...but we are trying to get independent, real-world data."

QUESTION 4: *Please discuss how best to communicate information about lymphomas to health care providers and patients.*
ANSWER: Leave it up to the doctors.

Comments:

- "It's important not to scare patients. Nothing we heard today will keep them from these agents, but they need to be vigilant."
- "When subspecialists sit down with patients, those are the people it should be up to."
- "The label is what the sales force uses, and any difference (in labels) is going to be brought to my attention."

QUESTION 5: *Should the SIR of the general population or the SIR of RA patients be presented (in the label warning about lymphoma)?*
ANSWER: The panel and industry said different SIRs would be too confusing. Some FDA officials appeared to prefer specific (different) SIRs for each product, but other FDA officials thought all the labels should be similar.

Comments:

- "Using SIR will be confusing…I had to learn about SIR for this panel. If you have to explain three different SIRS, it is too complicated."
- A J&J official said, "I may be going out on a limb. This panel is familiar with NSAIDs and COX2s. The incidence of GI bleeds has been registered as a range for the different products, and that is done partly to prevent one competitor from differentiating based on non-comparative data, and I think it has been pretty much agreed that for a Cox-2 to differentiate itself, it has to do a large trial. Since we don't have comparator data here, and our data is so varied, maybe the same approach would work."

QUESTION 6: *Should the labels be similar for all three TNF inhibitors?*
ANSWER: The panel thought so, but not all FDA officials agreed.

Comments:

- "I like the Humira label."
- "It should be the same language across all three…I would argue against a boxed warning based on this data. We know enough to state a concern, but not enough for a boxed warning."
- "Less (in the label) is better from a physician standpoint."
- An Amgen official said, "We proposed a label in the fall of last year…and I'm sure that is awaiting this discussion. We believe the products should be individually assessed on their own data, and we personally think our SIR doesn't justify a warning label."
- A J&J lymphoma expert said, "I am in favor of putting the SIR in the label, but…I'm against putting it in a warning box." A J&J official added, "These products can't be compared because of a number of confounding factors."
- An FDA official said, "A label isn't necessarily the best way, but it is a way we can control."

QUESTION 7: *Please comment on the data observed in the randomized clinical trials in patients with NYHA Class III/IV HF as well as the spontaneous reports of adverse cardiac events in RA patients. Is it reasonable to discuss CHF-related safety concerns in labels for all TNF-blocking agents? Other than product label changes that will caution against use in patients with pre-existing CHF or who develop CHF while on treatment, should the companies be asked to develop additional procedures for CHF risk management? An FDA official wanted to know if this appears to be a class effect and all the agents should have the same wording as the precaution in the Enbrel label.*
ANSWER: The panel appeared to think the labels should be very similar if not identical, but they did not agree with a heart failure expert that these drugs should not be given to patients with heart failure.

Comments:

- "I do think the data suggest that for Enbrel and Remicade, there is a concern – and the other (Humira) lucked out by not studying CHF…so I think we should have consistent labeling on all three, based on the data in hand."
- "The Enbrel label as it exists now…is perfectly adequate."
- "I think the Humira label should be more like Enbrel than Remicade…There may be people with mild heart failure who would benefit from these medications where we can treat the heart failure. As long as we can manage the heart failure, they may benefit from the medication, but we need to recognize that we may make the heart failure worse."
- An epidemiologist said, "We don't see (in our registry) any increased rate of heart failure, and even a suggestion in the other direction, but many people don't know they have heart failure until they end up in the hospital, so I think the warning may be overstated."
- Dr. Milton Packer, a renowned heart failure expert said, "There is no relationship between ejection fraction and severity of heart failure. The only way we judge severity is symptoms. Ejection fraction and symptom relationship is poor….My personal view and that of many of us in the heart failure community – and it is a view that is not popular with everyone – is that I wouldn't give any of these drugs to anyone with heart failure. People with heart failure are fragile. When they get worse, sometimes you can't make them better. I don't want to discuss labeling, but there is a concern such that heart failure patients shouldn't get these drugs." But a panel member responded, "I respect Dr. Packer, but it is not right to go beyond the data we have. These are substantially different molecules, and it is not reasonable to lump the results together and say the worst tells us what we do with all of them."

OTHER INTERESTING COMMENTS

➢ A panel member compared this panel to the Oncologic Drugs Advisory Committee (ODAC), saying this panel is very different because it is more focused on rare side effects.

➢ An FDA official said, "The sequence is entirely human-derived but studies demonstrate there is some immunogenicity."

➢ A J&J official said over 90% of Remicade is prescribed by subspecialists.

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