

## FDA Meeting March 2003: Update on the Safety of New Drugs for Rheumatoid Arthritis

The Arthritis Advisory Committee of the United States Food & Drug Administration (FDA) met on March 4 - 5, 2003 to examine the latest safety data on the three currently marketed TNF inhibitors – etanercept (ETAN; Enbrel®), infliximab (INFLX; Remicade®) and adalimumab (ADAL; Humira®), and on leflunomide (LEF; Arava®). Presentations by FDA officials and industry representatives reviewed the unmet need, efficacy, safety data and long term plans for safety monitoring. Because this issue is of critical importance to rheumatologists, patients, and others, detailed information of the data from these meetings will be presented in three ACR Hotlines. Part I covers the risk of lymphoma with TNF inhibitors, Part II reviews other safety data with TNF inhibitors, and Part III reviews safety issues concerning LEF. Information from the FDA meeting is available at <http://www.fda.gov/ohrms/dockets/ac/acmenu.htm>

### Part I: The Risk of Lymphoma with Rheumatoid Arthritis (RA) and TNF Inhibitors

Previous ACR Hotlines (September 2001, November 2000) addressed the safety of TNF inhibitors. The March 2003 FDA meeting was convened to update these safety concerns and to specifically focus on the issue of neoplasia and lymphoma in patients with RA receiving these agents. Safety data from controlled clinical trials (blinded and open label studies) were presented for all three drugs; post-marketing safety data are available for ETAN and INFLX. Additional safety “signals” were gleaned from the FDA Medwatch Adverse Event Reporting System (AERS) database.

**RA and Risk of Lymphoma.** In the past 20 years several population studies have shown that compared to the general population, patients with RA: 1) do not have an overall increased risk of cancer; 2) may have a lesser risk of colon cancer (possibly related to chronic NSAID use); and, 3) do have an increased risk of lymphoma, especially non-Hodgkin’s lymphoma (NHL). The relative risk of events such as cancers is usually expressed as the Standard Incidence Ratio (SIR). The SIR is the ratio of the number of observed events (e.g., cancers in TNF treated RA patients) divided by the number of expected events (e.g. cancers in an age, sex, and race matched normal population). Data on the expected number of cancers comes from the National Cancer Institutes SEER database, which is derived from 11 cancer registries around the United States and represents nearly 14% of the U.S. population. An SIR of 1 implies equal risk. SIRs >1 imply an increased risk, with higher numbers defining greater risk. Table 1 shows the SIR for malignancies and lymphoma among RA patients. These studies reveal an increased risk of lymphoma in the RA population. Large population-based studies have shown the SIR for lymphoma in RA to range from 2.4→8. Baecklund *et al* have shown that the risk of lymphoma in patients with RA increases with greater disease activity. This is noteworthy, as the patients with RA most commonly treated with TNF inhibitors to date have been those with severe active disease.

**Table 1. Risk of Neoplasia and Lymphoma in Rheumatoid Arthritis populations**

Author	Country	N (Pt-Yrs)	Yrs F/U	Cancer SIR	Lymphoma SIR
Gridley 1993	Sweden	11,683 (101,000)	20	1.0	2.4
Mellenkjaer 1996	Denmark	20,699 (144,421)	14	1.1	2.4
Isomaki 1978	Finland	46,101 (213,911)	7	1.1	5.5
Matteson 1991	Canada	530	7	1.5	8.9
Baecklund 1998*	Sweden	11,683	18	-	Low activity 1.0 Mod activity 5.4 High activity 25.8

(\*data are odds ratios rather than SIR)

**TNF inhibitor Associated Cancer and Lymphoma events.** Table 2 shows cancer and lymphoma safety data for patients with RA taking TNF inhibitors. No increased risk of malignancy overall was seen (SIR 0.98-1.1). Observed lymphoma SIRs ranged from 2.31-6.35, with wide and overlapping 95% confidence intervals (CI). These data do not permit inter-drug comparison for lymphoma rates, owing to different trial designs and patient characteristics. The data

suggest lymphoma rates in RA patients on TNF inhibitors are elevated, but it is not known if this exceeds the risk that would be expected from RA alone. In post-marketing surveillance of over 515,000 patient-years of use (ETAN, INFLX) about 160 patients with RA have been reported to develop lymphoma. The crude reporting rate in the post-marketing era is roughly 2-3 cases per 10,000 patient-years of drug exposure, which approximates that of the general population. However, there is often substantial under-reporting in post-marketing surveillance.

<b>Table 2. Neoplasia and Lymphoma Incidence Rates in RA patients on TNF Inhibitors</b>			
<b>Randomized Controlled RA Trials and Open-Label Extension RA Trials Combined</b>			
	Etanercept	Infliximab	Adalimumab
Patients / (patient-years)	3,389 / (8,336)	1,298 / (2,458)	2,468 / (4,870)
# Lymphoma observed	6 → 9	4	10
Hodgkins/Non-Hodgkins lymphoma	33% / 66%	23% / 75%	10% / 99%
# Lymphoma expected	2.59	0.63	1.8
SIR Lymphoma	2.31 → 3.47	6.35	5.42
Time to lymphoma onset: (range)	90 weeks (1-200)	(30 – 82 weeks)	77 weeks (8-181)
# Malignancies observed (including lymphomas)	55	21	46
# Malignancies expected	56.2	19.25	45.82
SIR Malignancy	0.98	1.1	1.0
<b>Postmarketing Studies (Adverse Event Reporting System; AERS)</b>			
N (patient-years)	>150,000 (>230,000)	365,000 <sup>+</sup> (554,000) <sup>+</sup>	No data available (drug approved 12/31/02)
AERS Lymphoma Reports	70	95	
RA Lymphoma Rate: N/100 pt-yrs	0.03*	0.017*	
Time to lymphoma	14±12 mos. (1.4-39.5)	312 days (27-731 d)	

\* Normal population rate is estimated to be 0.03/100 pt-yrs. + includes RA and Crohn's patients

**Etanercept.** As of 12/31/02, ETAN was used in 3,389 patients in clinical trials (8,336 pt.-yrs exposure); over 150,000 patients (>230,000 pt-yrs) have received this drug in the post-marketing era. Currently there are 1,084 patients who are in their 5<sup>th</sup> year of treatment with ETAN. During clinical trials there were six reports of lymphoma (SIR = 2.31; 95% CI 0.85-5.03); three additional trial patients developed lymphoma post-study (Total=9, SIR =3.47; 95% CI 1.59-6.59). Subset analyses of patients from the early RA cohort (mean disease duration 0.99 yrs) showed two lymphomas [SIR=3.44 (CI, 0.42 – 12.41)]; there were four lymphomas among advanced RA patients [SIR=1.99 (CI, 0.54-5.09)]. In post-marketing experience through 11/02, 70 additional cases of lymphoma have been identified. 86% were non-Hodgkin's lymphomas (NHL) vs. 14% with Hodgkin's disease; 43% were diffuse B cell lymphomas. Plans for long term follow up include several company established registries, including the 10,000 patient RADIUS study, and a recently contracted program to examine the Ingenix/ United Healthcare database that includes approximately 50,000 RA patients.

**Infliximab.** As of March 2003, INFLX was used in 1,678 patients in clinical trials mostly of RA and Crohn's disease (3,445 yrs exposure); by 8/02, 365,000 pts were treated (554,000 pt-yrs) worldwide with INFLX. Six INFLX treated patients developed lymphoma in clinical trials (including four out of 1,298 RA patients) [SIR=6.35 (CI, 1.7-16.3)]. In an early RA cohort (mean disease duration = 0.78 yrs) on MTX, no lymphomas were observed in the either the INFLX or placebo groups. Among patients with advanced refractory RA, the SIR was 8.9 (CI, 2.42-22.76). Two lymphomas occurred in Crohn's disease study patients after a single dose of infliximab. In post-marketing experience, 95 additional cases of lymphoma have been identified (73% RA, 21% Crohn's disease). Although other cancers were not more common with INFLX in RA patients (SIR=0.91), an increase in cancer (SIR = 2.01) was observed in the Crohn's population (N=1,106 patients) – presumably due to an increased risk of colon cancer that can be seen in inflammatory bowel disease. The sponsor detailed its worldwide pharmacovigilance program that will include over 13,000 RA and Crohn's patients, and 15,000 non-infliximab treated patients in long-term clinical studies or patient registries.

**Adalimumab.** Up to its U.S. approval (12/31/02), over 17 clinical trials [2,468 patients (4,870 pt-yrs)] of ADAL in RA have been conducted. These trials were done in the U.S. (50%), Europe (34%), Canada (13%) and Australia (3%). Over 2,073 patients have received ADAL for >6 mos., and 1,497 patients for >12 mos. Overall 46 malignancies were identified in this cohort (SIR= 1.0; 95% CI 0.7-1.3). There were 10 lymphomas (1 Hodgkin's / 9 Non-Hodgkin's); SIR=5.52 (95%

CI 2.6-10.0). Five of these were large B cell lymphomas. The interval from drug therapy to lymphoma ranged from 57 – 1,265 days (median 540 days). The sponsor had committed to follow >1,700 RA patients (from clinical trials) for at least five years and will also develop a 3,000-5,000 European registry to monitor these safety concerns.

**Other data.** Data from Dr Fred Wolfe’s National Databank for Rheumatic Diseases was presented. This database includes 18,557 patients from 908 U.S. rheumatologists surveyed twice yearly from 1998-June 2002. A modest increase in lymphoma was seen with TNF inhibitors (Table 3). At the FDA meeting, the point was made that in clinical trials of all three agents, six lymphomas were noted among patients treated with TNF inhibitors, compared to none among the placebo patients. However, despite comparable disease activity, the amount of time patients remained on placebo was substantially less than for patients receiving TNF inhibitors.

The patterns of lymphoma seen with TNF inhibitors (approximately 90% B cell; 85% diffuse / 15% follicular) is similar to that seen in RA, but differs from that of idiopathic lymphoma (approximately 40% follicular). The mechanisms potentially involved, including associations with EBV infection or secondary Sjögren’s syndrome, are unknown. As shown, the time interval or latency is variable. Of note, in radiation or alkylating agent-induced lymphoma, there is a peak in detection 5-6 years after exposure. In contrast, lymphoproliferative disorders related to allograft transplantation and immunosuppression vary, but may occur within a year or two of transplantation.

**Table 3. Lymphomas from the National Databank for Rheumatic Diseases**

DMARD	N	# Lymphomas	SIR (CI)
MTX & anti-TNF naïve	3,504	5	1.3 (0.4-3.1)
MTX	6,396	10	1.5 (0.7-2.7)
INFLX	6,465	9	2.6 (1.2-4.9)
ETAN	3,381	8	3.8 (1.6-7.5)

**The Bottom Line.**

- RA patients have a 2-3 fold increase in relative risk (SIR) for lymphoma; increased disease severity and activity may compound this risk.
- Analysis of patients receiving TNF inhibitors reveals an elevated SIR ranging from 2.3-6.3 in clinical trials; this suggests a lymphoma risk with TNF inhibitors higher than the general population; however this increased risk may approximate that of the populations of RA patients typically treated with this agents.
- Longer-term follow-up of patients treated with TNF inhibitors should provide important additional information
- Rheumatologists should: 1) engage in an appropriate dialogue with RA patients who are already on or are beginning therapy with these agents; 2) be aware of the signs and symptoms of lymphoma during treatment; and, 3) report these serious adverse events to the FDA.

References

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