

Table 1: Characteristics of Infliximab and Etanercept

Characteristic	Infliximab (Remicade)	Etanercept (Enbrel)
molecular description	chimeric monoclonal antibody, human constant and murine variable regions	recombinant human protein, ligand binding portion of 75 kilodalton TNFR fused to Fc portion of IgG1
molecular weight	149 kilodaltons	150 kilodaltons
mechanism of TNF- α inhibition	binds to TNF- α and prevents infliximab-bound TNF- α from binding with TNFR	decoy receptor for TNF- α
association constant	10^{10} M^{-1}	(not described in product labeling)
affinity for TNF- β (lymphotoxin α , which also binds to TNFR)	NO	YES
lysis of cells expressing transmembrane TNF- α	YES, in vitro	NO
elimination half-life	210 hours	115 hours
clinical indication	moderate to severe or fistulizing Crohn's disease; adjunctive use with methotrexate in rheumatoid arthritis refractory to methotrexate alone	moderate to severe rheumatoid arthritis, second line therapy in moderate to severe polyarticular juvenile rheumatoid arthritis
dosage and administration in RA	3 mg/kg (intravenous) initially and at 2 and 6 weeks, then every 8 weeks thereafter	0.4 mg/kg (25 mg in adults) twice weekly (3 to 4 days apart) as a subcutaneous injection
dosage and administration in CD	5 mg/kg as a single intravenous infusion; in fistulizing disease, repeat doses at 2 and 6 weeks	(not a labeled indication in CD)
patients treated, worldwide*	147,000 (10/1998 - 3/2001, 29 months)	102,000 (11/1998 - 4/2001, 29 months)
patients treated, US	121,000 (82% of worldwide)	96,000 (94% of worldwide)
patients treated, non-US	26,000 (18% of worldwide)	6,000 (6% of worldwide)
phone number to facilitate adverse event reporting	NO	YES

*manufacturers' estimates

Table 2: Major Categories of Reports for Etanercept and Infliximab

Advere Event Category		Etanercept	Infliximab	Etan / Influx
Approximate Total Cases Reported		18500	2300	8.0
Category	Organ System	% of Total	% of Total	Number Ratio
1	Neurologic	13	20	5.4
2	Psychiatric	2.3	5.0	3.7
3	Cardiac	5.6	15	3.1
4	Vascular	4.6	19	1.9
5	Pulmonary	10	30	2.7
6	Gastrointestinal	13	24	4.5
7	Hepatobiliary	0.7	4.0	1.4
8	Renal	1.5	4.6	2.6
9	Reproductive	1.4	1.2	9.3
10	Musculoskeletal	11	17	5.3
11	Dermatologic	18	22	6.3
12	Hematologic	2.5	7.0	2.8
13	Endocrine	0.3	0.6	3.9
14	Metabolic	2.2	4.0	4.6
15	Immunologic	0.6	8.0	0.6
16	Infection	22	26	7.1
17	Neoplastic	1.9	5.6	2.8
18	General and Administration Site	45	34	11
Categories per Reported Case		1.6	2.5	0.6

**Table 3: Post-Licensure Safety Surveillance of Infliximab and Etanercept *
(Licensure through June 30, 2001, US and Foreign) ***

Adverse Event Reports	Infliximab				Etanercept			
	Deaths	% Deaths of Total	Total	% Total of All	Deaths	% Deaths of Total	Total	% Total of All
All Reports	201	9	2,300	100	290	2	18,400	100
Demyelination	1	100	1	0.04	0	0	15	0.08
Aplastic Anemia	0	na	0	0	5	71	7	0.04
Intestinal Perforation	3	75	4	0.2	0	0	3	0.02
Systemic Lupus	1	100	1	0.04	1	4	25	0.14
Infections	228	25	901	39	291	6	5,143	28
Sepsis	67	52	130	6	72	50	145	0.8
Pneumonia	51	35	145	6	124	22	553	3
Bacterial Infections	181	29	616	27	228	12	1,941	11
Mycobacteria	16	17	93	4	5	28	18	0.1
Listeriosis	4	25	16	0.7	1	100	1	0.01
Fungal Infections	24	28	86	4	13	7	186	1
Histoplasmosis	1	7	15	0.7	0	0	1	0.01
Aspergillosis	3	75	4	0.2	3	60	5	0.03
Candidiasis	8	29	28	1	5	7	73	0.4
Coccidioidomycosis	0	0	2	0.1	0	na	0	0
Cryptococcosis	0	na	0	0	1	25	4	0.02
P. Carinii Pneumonia	6	38	16	0.7	3	60	5	0.03
Viral Infections	7	7	94	4	19	3	553	3
Organism Undefined	11	12	92	4	28	1	2,443	13
Lymphoma	2	20	10	0.4	4	15	26	0.1
Congestive Heart Failure	10	53	19	0.8	11	17	66	0.4

* The figures reflect number of reports in AERS with the adverse event identifier. These figures, therefore, are larger than the actual numbers of cases due to: (1) duplicate and follow up reports for the same case being counted as separate reports, and (2) a particular report may include multiple adverse event terms.

**Table 4: Opportunistic Infections in Etanercept or Infliximab Therapy
(Post-Licensure Reports, US and Foreign, as of September 2000)**

Infection	Etanercept (N=2782)	Infliximab (N=226)
Herpes Zoster	82 (2.9%)	2 (0.9%)
Fungal Infections NOS	52 (1.9%)	5 (2.2%)
Herpes Simplex	42 (1.5%)	10 (4.4%)
Candida (all types)	35 (1.3%)	5 (2.2%)
Meningitis	9 (0.3%)	0
Tuberculosis	3 (0.1%)	17 (7.5%)
PCP	3 (0.1%)	6 (2.6%)
Aspergillosis	3 (0.1%)	4 (1.8%)
Cryptococcosis	3 (0.1%)	0
Histoplasmosis	0	3 (1.3%)
Listeriosis	0	3 (1.3%)

Table 5: Ten Cases of Life-Threatening Histoplasmosis after Immunotherapy Using Infliximab or Etanercept

Case	Age Sex	Indication Agent	State	Dose	* Number of Doses	* Time (days)	Clinical Presentation and Course	Diagnostic Biopsy, Culture, or Test
1	52 F	RA infliximab	Ohio	3 mg/kg	3	50 - 60	fever, dyspnea, weight loss, diffuse interstitial pneumonitis; recovered	transbronchial biopsy
2	61 M	RA infliximab	Alabama	3 mg/kg	3	50 - 60	fever, malaise, cough, dyspnea, abnormal CXR, BOOP; outpatient management, recovered	transbronchial biopsy
3	45 F	RA infliximab	Iowa	3 mg/kg	1	30 - 40	malaise, pneumonia, hilar lymphadenopathy, hypotension, acute renal failure; recovered	transbronchial biopsy
4	78 F	RA infliximab	Wisconsin	3 mg/kg	6	10 - 20	fever, malaise, weight loss, interstitial pneumonitis, CHF, shock; patient expired	open lung biopsy
5	67 F	RA infliximab	Tennessee	3 mg/kg	1	10 - 20	dyspnea, neutropenia, thrombocytopenia, abnormal LFT; recovered	transbronchial & liver biopsies
6	11 M	CD infliximab	Tennessee	5 mg/kg	2	5 - 10	fever, sinusitis, interstitial pneumonitis, acute HC exposure; recovered	open lung biopsy
7	19 M	CD infliximab	Louisiana	5 mg/kg	2	130 - 150	fever, cough, night sweats, HSM, anemia, thrombocytopenia; recovered	liver & marrow biopsies
8	38 M	CD infliximab	Kentucky	5 mg/kg	5	150 - 180	fever, malaise, cough, myalgia, neutropenia, pulmonary nodules, DIC; recovered	transbronchial biopsy & blood culture
9	42 M	CD infliximab	Ohio	5 mg/kg	2	50 - 60	fever, cough, pulmonary nodules, right flank pain, abnormal LFT, cytopenias, DIC; recovered	transbronchial biopsy & blood culture
10	38 M	RA etanercept	Indiana	25 mg	95	320 - 350	fever, malaise, weight loss, abnormal LFT, pancytopenia; recovered	blood anti-HC IgM urine HC antigen

Footnotes for Table 5

* When more than one dose of infliximab were given, the approximate time interval in days to clinical presentation was measured from the first dose. Indic = indication for infliximab; CD = Crohn's disease; RA = rheumatoid arthritis; CHF = congestive heart failure; CXR = chest X-ray; BOOP = bronchiolitis obliterans and organizing pneumonia; HC = *Histoplasma capsulatum*; HSM = hepatosplenomegaly; DIC = disseminated intravascular coagulopathy; LFT = liver function tests; NR = not reported.

Case 2: The histoplasmosis in this patient was more indolent than in the other 9 patients. The patient required hospitalization only for bronchoscopy and biopsy, after which he was managed successfully as an outpatient with itraconazole. Tissue histopathology was interpreted initially as idiopathic BOOP before a definitive diagnosis of histoplasmosis was made.

tubular carcinoma of the breast, resected 1984; large cell lymphoma of the kidney, resected 1988; cardiomyopathy secondary to adriamycin

avoid renal toxicity anticipated with amphotericin B therapy.

Case 6: The patient's fistulizing CD improved remarkably with a single dose of infliximab. The patient reported cleaning an old barn which housed many pigeons; within 24 hours of cleaning the barn, he began to have fevers unresponsive to antibiotics. His rapidly deteriorating condition required management in the intensive care unit within 10 days of receiving infliximab. Upon recovery with amphotericin therapy,

patient is doing well on infliximab therapy as of June 2001 (31 months after recovering from infliximab-related histoplasmosis).

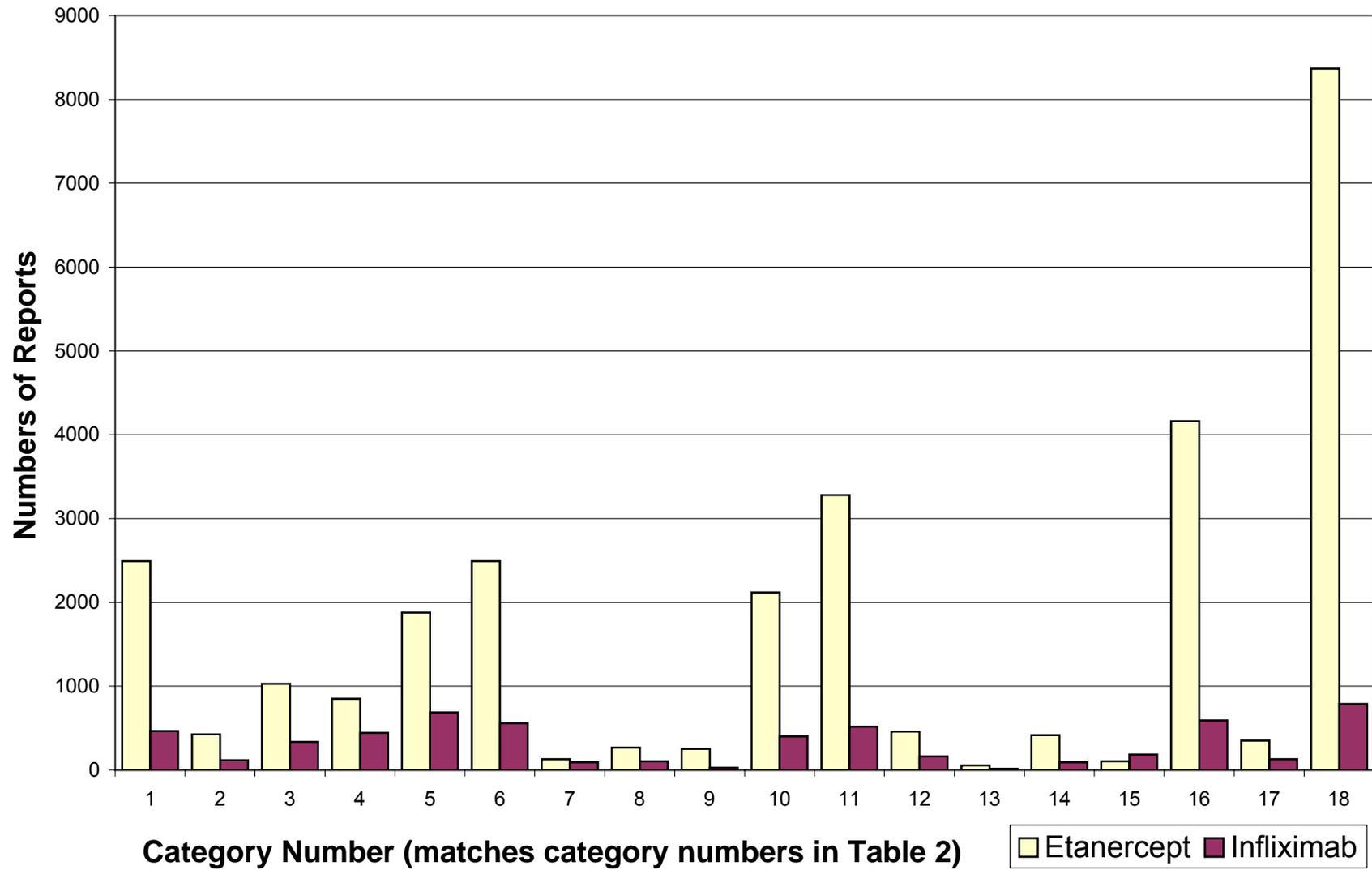
Case 10: The only case of etanercept-related histoplasmosis case reported to FDA as of June 2001. As with the 9 infliximab-related cases, the patient resided in an HC endemic region (Indiana) and received concomitant immunosuppressive medications other than the TNF- α antagonist, including methotrexate and prednisone. The initial workup for pancytopenia included fungal serologies for overwhelming infection,

and is doing well as of June 2001 on etanercept, methotrexate, and prednisone. Etanercept has been effective in controlling previously refractory RA.

Table 6: Twelve Cases of Listeriosis in Patients Treated with Infliximab or Etanercept

Age Sex	TNF α & Indication	Dose	Number of Doses	Days to Event	Clinical History and Outcome	Listeria Culture
34 F	infliximab, RA	3 mg/kg	2	290	fever, headache, and abdominal pain; underwent cholecystectomy with post operative hemiparesis and dysarthria; cranial abscess on head CT; expired	blood
60 M	infliximab, RA	3 mg/kg	2	35	successful treatment of anal abscess yet remained ill; outpatient blood culture positive for Listeria, outpatient treatment intravenous ampicillin	blood
73 M	infliximab, RA	3 mg/kg	1	41	nausea, vomiting, headache, lethargy, and diarrhea for 3 days; Listeria monocytogenes meningitis treated with ampicillin/cephalosporine; recovered	cerebrospinal fluid
74 F	infliximab, RA	3 mg/kg	6	240	Listeria meningitis; expired 5 days after hospitalization	blood
78 M	infliximab, RA	3 mg/kg	3	70	fever, headache, confusion, atrial fibrillation, and pulmonary edema; on antibiotic therapy for Listeria meningitis	cerebrospinal fluid
80 M	infliximab, RA	3 mg/kg	2	not reported	fever, weakness, confusion; Listeria sepsis & meningitis; expired	blood and cerebrospinal fluid
F	infliximab, RA	3 mg/kg	multiple	100	improvement of all joints after initiating infliximab therapy, except one; Listeria found in that joint	not reported
17 F	infliximab, CD	5 mg/kg	1	4	fever, lethargy, headache, hypotension 13 days after admission for leukopenia; antibiotic therapy for Listeria and Candida sepsis	blood
39 F	infliximab, CD	5 mg/kg	3	80	fever, headache, joint pain, confusion; Listeria meningitis treated with ampicillin; recovered but remains paralyzed in one eye	cerebrospinal fluid
64 F	infliximab, CD	5 mg/kg	1	12	initial presentation with fractured vertebra and Listeria sepsis; second hospitalization for pseudomembranous colitis; expired	blood
67 M	infliximab, CD	5 mg/kg	3	not reported	fever, weakness, lethargy, rigors, diarrhea, and Listeria sepsis; recovered	blood
72 M	etanercept, RA	50 mg	not reported	30	etanercept and methotrexate for one month; fever, chills, headache, dizziness; Listeria sepsis unresponsive to antibiotic therapy; pt expired	blood

Figure 1: Relative Numbers of Etanercept and Infliximab Reports



Category	Organ System	Etanercept	Infliximab
1	Neurologic	2492	464
2	Psychiatric	425	116
3	Cardiac	1030	335
4	Vascular	851	444
5	Pulmonary	1879	688
6	Gastrointestinal	2492	556
7	Hepatobiliary	130	91
8	Renal	269	105
9	Reproductive	252	27
10	Musculoskeletal	2119	401
11	Dermatologic	3281	517
12	Hematologic	458	162
13	Endocrine	55	14
14	Metabolic	416	91
15	Immunologic	105	184
16	Infection	4160	590
17	Neoplastic	352	128
18	General and Administration Site	8370	790