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LONG-TERM EFFICACY AND SAFETY DEMONSTRATED FOR RHEUMATOID ARTHRITIS TREATMENTS

SAN ANTONIO, TEXAS – Two studies demonstrating the long term safety and effectiveness of two anti-TNF agents – etanercept (Enbrel®) and adalimumab (HUMIRA®) – in the treatment of rheumatoid arthritis will be presented this week at the American College of Rheumatology Annual Scientific Meeting in San Antonio, Texas.

Etanercept and adalimumab are self-injectable medications known as biologic response modifiers that work to suppress the tumor necrosis factor (TNF) proteins that are associated with joint inflammation. Suppressing tumor necrosis factor has been a beneficial therapy in the day-to-day lives of many patients with rheumatoid arthritis. Both agents are known to be very effective in the treatment of rheumatoid arthritis but since they are fairly new drugs there is limited information about their long term effectiveness and safety. A seven year study of treatment of patients with early and long-standing rheumatoid arthritis with etanercept found continued effectiveness and no increase in toxicity over time. Similarly, a four year study of adalimumab plus methotrexate in the treatment of long-standing moderate to severe rheumatoid arthritis reported sustained improvement in arthritis with no new safety concerns. Both treatments allowed patients to take lower doses of corticosteroid medications and methotrexate.

Etanercept was approved in 1998 and is indicated for reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active rheumatoid arthritis; it can be used alone or in combination with methotrexate. Adalimumab was approved in 2002 and is indicated for reducing signs and symptoms and inhibiting the progression of structural damage in adult patients with moderately to severely active RA who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDs); it can be used alone or in combination with methotrexate or other DMARDs.

“The efficacy and safety of adalimumab seen in six month clinical trials continues in long-term follow-up for up to four years,” said Michael Schiff, MD, Director, Clinical Research, Denver Arthritis Clinic, and lead investigator in the study.

“We report the longest experience with etanercept and show that it continues to be effective with long term therapy in patients with active rheumatoid arthritis and not only allows for a reduction in background corticosteroid doses but is well tolerated and serious side effects are rare,” said Michael Weinblatt, MD, Professor of Medicine Brigham and Women’s Hospital and Harvard Medical School, and lead investigator in the study.

The American College of Rheumatology is the professional organization for rheumatologists and health professionals who share a dedication to healing, preventing disability and curing arthritis and related rheumatic and musculoskeletal diseases. For more information on the ACR's annual meeting, see www.rheumatology.org/annual.

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Editor's Notes: Dr. Schiff and Dr. Weinblatt will present their research during a scientific session at the ACR Annual Scientific Meeting from 12:15 – 2:00 pm CT (1:15 – 3:00 pm ET) on Monday, October 18 in Exhibit Hall C-D of the Henry B. Gonzalez Convention Center.

Presentation Number: 356

Efficacy and Safety of Over 7 Years of Etanercept (Enbrel®) Therapy in North American Patients With Early and Long-Standing Rheumatoid Arthritis

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PURPOSE: To assess the long-term efficacy and safety of etanercept (ETN) therapy in patients with early RA (disease duration ≤ 3 years; ERA) and in patients with long-standing RA (LRA) whose disease has failed to respond to at least 1 disease-modifying antirheumatic drug (DMARD).

METHODS: Efficacy endpoints were analyzed for patients who received ETN 25 mg twice weekly in ERA studies (n = 207) and LRA studies (n = 644) and in those who continued to receive this dosage for over 6 years in ERA extension studies and over 7 years in LRA extension studies. Other DMARDs, including methotrexate, were permitted during the extension studies. Safety and persistence data were analyzed for all patients who received ETN (all dosages) in ERA studies (n = 558) and LRA studies (n = 884, including 69 pediatric patients).

RESULTS: Significant improvements in multiple measures of disease activity have been achieved with ETN therapy and sustained for 7 years of treatment (Table). ERA patients were exposed to ETN for a median of 5.5 years, and LRA patients were exposed for a median of 5.6 years. Currently, 323 of the 558 ERA patients (58%) and 391 of the 884 LRA patients (44%) continue to receive ETN. The most common reasons for discontinuing ETN were adverse events (10% ERA, 12% LRA), refusal of subject (7% ERA, 8% LRA), and lack of efficacy (6% ERA, 10% LRA). Most patients have been able to withdraw concomitant corticosteroids and methotrexate while receiving ETN. Over time, rates of adverse events and serious adverse events in patients receiving ETN have remained low and are consistent with rates observed in the placebo groups from the controlled phase of the studies. A total of 28 patients have died (ERA, n = 7; LRA, n = 21), including 4 from malignancy and 4 from cardiac disease, whereas 53 deaths were expected. A total of 11 cases of sepsis have been reported (ERA, n = 3; LRA n = 8), resulting in 2 deaths. In up to 7 years of etanercept treatment, 9 cases of lymphoma (ERA, n = 2; LRA, n = 7) have been diagnosed, and 2 cases were expected. To date, no cases of tuberculosis or opportunistic infections have been observed.

Long-term Efficacy of Etanercept ^a	Year 2	Year 4	Year 6	Year 7	Last Visit
	ERA / LRA	ERA / LRA	ERA / LRA	ERA / LRA	ERA / LRA
N ^b	161 / 412	136 / 429	87 / 341	- / 104	207 / 644
Proportion Achieving ACR 20 (%)	82 / 72	79 / 78	82 / 73	- / 62	65 / 57
Proportion Achieving ACR 50 (%)	56 / 44	57 / 51	61 / 52	- / 44	48 / 38
Proportion Achieving ACR 70 (%)	34 / 21	31 / 25	41 / 26	- / 20	30 / 18

CRP (median % improvement)	81 / 67	80 / 76	89 / 75	- / 67	80 / 63
HAQ (mean % improvement)	58 / 32	53 / 36	52 / 28	- / 12	47 / 21
^a Yearly analysis used a completers dataset and Last Visit analysis used a last on-study observation carried forward (LOCF) dataset					
^b Includes adult patients receiving etanercept 25 mg twice weekly with sufficient data for efficacy evaluation					
ERA = Early RA, LRA = long-standing RA, CRP = C-reactive protein, HAQ = health assessment questionnaire					

CONCLUSIONS: These results demonstrate the durability of response of etanercept in relieving the signs and symptoms of RA. Improvements in multiple measures of efficacy were sustained for up to 7 years of therapy, and the safety profile of etanercept appears to be unchanged with long-term treatment.

Disclosure: **M. Weinblatt**, Amgen Inc. 2, 5, 8; Wyeth 5; **M. Genovese**, Amgen Inc. 2, 5, 8; Wyeth 2, 5; **L. Moreland**, Amgen Inc. 2, 5, 8; **J. Bathon**, Amgen Inc. 2; Bristol-Myers-Squibb 2, 5; Abbott 2; Centocor 2; IDEC/Genentech 2; **J. Kremer**, Amgen Inc. 2, 5, 8; Centocor 2, 5, 8; Abbott 2, 5, 8; Aventis 2, 5, 8; Prometheus 2, 5; **R. Fleischmann**, Amgen Inc. 2, 5, 8; Wyeth 1, 2, 5, 8; **M. Schiff**, Amgen Inc. 2, 5, 8; Wyeth-Ayerst 2, 5, 8; Abbott 2, 5, 8; Centocor 2, 5, 8; Genentech 5; **J. Whitmore**, Amgen Inc. 1, 3; **B. White**, Amgen Inc. 1, 3.

Presentation Number: 353

Significant Clinical Improvements at 6 Months Are Sustained Over 4 Years in Patients with Rheumatoid Arthritis Treated with Adalimumab (HUMIRA®) plus Methotrexate

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PURPOSE: To assess the efficacy and safety of adalimumab plus methotrexate (MTX) treatment and the impact on the use of concomitant medications in patients with long-standing moderate to severe rheumatoid arthritis (RA) over 4 years of treatment.

METHODS: Patients who completed 4 randomized clinical trials (ARMADA, STAR, DE005 and DE037) were invited to enroll in an open-label extension in which all received adalimumab 40 mg sc eow and most received MTX. Patients were seen every 6 months and assessed for therapeutic efficacy and safety. A subset analysis of dose changes in concomitant MTX and corticosteroids was conducted.

RESULTS: Of 846 patients enrolled in this open-label period, comprising 2381 patient years, 81% were treated with adalimumab for ≥ 2 years, 49% ≥ 3 years, and 12% ≥ 4 years. The rate of withdrawals was 6 to 9% per year. Of 211 (25%) patients who withdrew, 53 (6%) withdrew for lack of efficacy, 75 (9%) for adverse events, and 83 (10%) for other reasons. Significant clinical improvements observed after 6 months were sustained over 4 years (Table 1). At last visit, 20% of all patients achieved DAS28 <2.6 , 24% had 0 tender joints, 21% had 0 swollen joints, and 44% achieved HAQ ≤ 0.5 --all parameters of remission. Analysis of MTX doses for 565 patients indicated MTX decreases in 176 (31%) patients, increases in 40 (7%), 330 (58%) had no change, and information was incomplete for 19 (3%). Of 42 patients identified as receiving corticosteroid therapy, steroid use decreased in 23 (55%) patients and 19 (45%) had no change. The rate of serious adverse events was 0.01 events per patient year (E/PY), serious infections 0.03 E/PY, malignancies 0.03 E/PY.

Percent change of mean clinical improvement from baseline*					
Criteria	Months of Exposure				
	6	12	24	36	48
N	742	539	661	398	101
DAS28	39	44	45	47	50
TJC (0-68)	64	69	72	75	78
SJC (0-66)	58	67	69	68	61
CRP	14	33	29	28	37
HAQ	45	43	47	47	50

*All values significant at $p \leq 0.001$ vs. baseline except CRP at 6 months

CONCLUSIONS: Patients with long-standing RA who achieved clinical response at 6 months while treated with adalimumab plus MTX maintained clinical improvements and experienced low or no disease activity for

up to 4 years. Overall, patients treated with adalimumab plus MTX reduced their use of steroids and MTX while maintaining control of their disease. Adalimumab was safe and well tolerated over 4 years of therapy.

Disclosure: **M.H. Schiff**, Abbott Laboratories 2, 5, 8; Amgen 2, 5, 8; Centocor 2, 5, 8; Aventis 2, 5, 8; Wyeth-Ayerst 2, 5, 8; **M.H. Weisman**, Abbott Laboratories 2, 5; Amgen 2; Centocor 2, 5; BioRad 2; Prometheus 2, 5; **S.B. Cohen**, Abbott Laboratories 2, 5, 8; Amgen 2, 5, 8; Centocor 2, 5, 8; Merck 2, 5, 8; Aventis 2, 5, 8; **A.F. Kavanaugh**, Abbott Laboratories 2, 5; Centocor 2, 5; Amgen 2, 5; **G.T. Spencer-Green**, Abbott Laboratories 1, 3; **J.L. Perez**, Abbott Laboratories 3; **T.T. Mydler**, Abbott Laboratories 1, 3; **O.G. Segurado**, Abbott Laboratories 1, 3.