

Abatacept (Orencia®, Bristol-Myers Squibb Company)

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Rheumatoid arthritis (RA) is a chronic, systemic, inflammatory disease which leads to bilateral joint pain and may result in significant disability. Antigen-dependent activation of T-cells is thought to be the initiating event in RA, with T-cells promoting proliferation of synovial lining and endothelial cells, cytokine secretion, stimulation of the production of proinflammatory cells, and autoantibody production.¹

Abatacept is a selective modulator of the CD80 or CD86-CD28 costimulatory signal which is required for full T-cell activation.² It is FDA-approved for reducing the signs and symptoms of RA, inducing major clinical response, slowing the progression of structural damage, and improving physical function in RA patients with moderate-to-severe disease who have had an inadequate response to other disease-modifying, anti-rheumatic drugs (DMARDs) or tumor necrosis factor (TNF) antagonists.

PHARMACOLOGY

Abatacept is a selective costimulator modulator.² The molecule is a soluble fusion protein which contains the extracellular domain of human cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) which is linked to the modified Fc portion of human immunoglobulin G1. In unaltered disease, antigen-presenting cell proteins CD80 or CD86 bind to the CD28 protein on T-cells, thus facilitating T-cell activation and RA disease progression. Abatacept competes with CD28 for binding of CD80 and CD86. Abatacept's greater affinity for CD80 and CD86 allows it to selectively modulate T-cell activation. The binding inhibits sustained T-cell proliferation and the production of select pro-inflammatory cytokines.² Abatacept inhibits T-cell function, but does not deplete T cells.

PHARMACOKINETICS

Steady-state for abatacept appears to be achieved after 60 days of therapy, resulting in a trough concentration of about 24 mcg/mL.² No accumulation has been observed after multiple infusions at 10 mg/kg dosing. Dose ranges from 2 to 10 mg/kg produced proportional increases in C_{max} and AUC. In an analysis of population pharmacokinetics, a trend towards an increasing rate of clearance with increasing body weight was observed. Factors studied which did not affect clearance of abatacept include age, sex, and concomitant treatment with the drugs methotrexate, nonsteroidal anti-inflammatory drugs, corticosteroids, and TNF blocking agents.

Summary

Indication: Abatacept (Orencia®, Bristol-Myers Squibb) is a selective costimulation modulator approved by the Food and Drug Administration (FDA) for the treatment of moderate-to-severe rheumatoid arthritis (RA).

Monitoring Parameters: Patients receiving abatacept should be monitored for signs and symptoms of infection, malignancy, and hypersensitivity reactions.

Dose: Patients weighing less than 60 kg should receive a dose of 500 mg of abatacept. Patients weighing 60 to 100 kg should receive a dose of 750 mg of abatacept. Patients weighing greater than 100 kg should receive a dose of 1 gram of abatacept. Abatacept should be administered as a 30-minute intravenous infusion. After the first dose, abatacept should be administered two to four weeks later and then once every four weeks thereafter. Abatacept may be given as monotherapy or in combination with disease-modifying, anti-rheumatic drugs (DMARDs) other than tumor necrosis factor (TNF) antagonists.

Cost: The average wholesale price (AWP) for abatacept is \$562.50 for a 250 mg vial. For a 75 kg patient, the cost for one treatment is \$1687.50, and the cost of the first year of therapy for this patient is estimated at \$21,937.50.

 ARCHIVES OF PHARMACOTHERAPY PERSPECTIVES
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PUBLISHED CLINICAL STUDIES

Clinical response in RA trials is measured using the American College of Rheumatology (ACR) criteria, which were developed in an effort to standardize the measurement of clinical improvement for RA drugs. The FDA uses ACR scores to determine the eligibility of a new RA drug for approval. An ACR 20 score indicates a 20 percent reduction in ACR-defined signs and symptoms of RA, and ACR 50 or ACR 70 scores indicate 50 and 70 percent reductions, respectively.

Active rheumatoid arthritis despite methotrexate therapy (six-month study)

A multi-center, randomized, double-blind, placebo-controlled study was conducted by Kremer et al to evaluate the efficacy, safety, and immunogenicity of CTLA4Ig (abatacept) added to existing methotrexate therapy in 339 patients with active rheumatoid arthritis.³ Patients were randomized to receive either 2 mg/kg abatacept, 10 mg/kg abatacept, or placebo over a six-month period. The study drug was administered intravenously

over 30 minutes on days one, 15, and 30 and monthly thereafter. The study sponsor (Bristol-Myers Squibb) was involved in the design, data collection, and analysis of the study.

Patients were required to have active rheumatoid arthritis characterized by ten or more swollen joints, twelve or more tender joints, and C-reactive protein levels of at least 1 mg/dL. Inclusion criteria also included methotrexate therapy at a dose of 10 to 30 mg weekly for at least six months, with a stable dose for at least twenty-eight days prior to study enrollment. Pregnant or nursing women were excluded. All disease-modifying antirheumatic drugs, including leflunomide and infliximab, were discontinued prior to enrollment.

The primary efficacy endpoint in this study was the percentage of patients who achieved an ACR 20 score six months after the beginning of therapy. ACR 50 and ACR 70 scores were secondary outcomes. ACR response was measured at day 1, 15, 30, and then monthly throughout the study. Patients were asked about any adverse events at each visit. A study investigator assessed the event, and its relationship to the study medication. The safety assessment of the study was overseen by a data and safety monitoring board. Immunogenicity was assessed with drug-specific antibody levels to abatacept from serum samples drawn at days one, 30, 90, and 180. Antibodies to both the whole drug molecule and the CTLA4 portion alone were measured. Health-related quality of life was assessed at baseline, 90 days, and 180 days with use of the Medical Outcomes Study 36-Item Short-Form General Survey (SF-36).

A significantly higher percentage of patients who received abatacept at a dose of 10 mg/kg achieved an ACR 20, ACR 50,

or ACR 70 response at six months than those who received placebo (see Table 1). Significantly more patients in the 2 mg/kg abatacept group achieved an ACR 50 or ACR 70 response than placebo.

Abatacept was well tolerated, with no deaths or opportunistic infections reported after six months of therapy. Adverse effects were reported at a similar rate between treatment and placebo groups. Only one of the serious adverse events was thought to be possibly related to abatacept therapy; a patient in the 2 mg/kg group was hospitalized due to cellulitis of the foot. The discontinuation rate because of adverse events was lowest in the 10 mg/kg abatacept group.

The majority of patients had preexisting antibodies to abatacept, with one patient in both the 2 mg/kg and 10 mg/kg abatacept treatment groups seroconverting for CTLA4-specific antibodies. No patients showed evidence of seroconversion for abatacept-specific antibodies. Patients in the 10 mg/kg abatacept treatment group had significant improvements from baseline scores on the SF-36 survey. All improvements were significantly greater than those in the placebo group ($p < 0.05$).

Active rheumatoid arthritis despite methotrexate therapy (twelve-month study)

In an extension of the Kremer study above, clinical efficacy, safety, and immunogenicity of abatacept was evaluated after twelve months of therapy, with a double-blind, randomized, placebo-controlled trial.⁴ The same population of 339 patients with active RA despite methotrexate therapy was included in the evaluation.

Again, the primary efficacy endpoint was an American College of Rheumatism (ACR) response of 20 (ACR20) at six months.

TABLE 1. CLINICAL EFFICACY OF ABATACEPT AT SIX MONTHS

	Placebo + Methotrexate (n = 119) (% of patients)	Abatacept 2 mg/kg + Methotrexate (n = 105) (% of patients)	Abatacept 10 mg/kg + Methotrexate (n = 115) (% of patients)	Abatacept 2 mg/kg vs. Placebo group (p value)	Abatacept 10 mg/kg vs. Placebo group (p value)
ACR 20	35.3	41.9	60	0.31	<0.001
ACR 50	11.8	22.9	36.5	<0.05	<0.001
ACR 70	1.7	10.5	16.5	<0.05	<0.001

TABLE 2. EFFICACY OF ABATACEPT AFTER 12 MONTHS

	Placebo + Methotrexate (% of patients)	2 mg/kg Abatacept + Methotrexate (% of patients)	10 mg/kg Abatacept + Methotrexate (% of patients)	10 mg/kg Abatacept vs. Placebo (p value)
ACR 20 at day 60	34.5%	NA	56.5%	<0.001
ACR 20 at day 360	36.1%	NA	62.6%	<0.001
ACR 50 at day 30	5.9%	NA	13.9%	0.039
ACR 50 at day 90	12.6%	NA	24.3%	0.02
ACR 50 at day 360	20.2%	NA	41.7%	<0.001

NA = not available

TABLE 3. ADVERSE EFFECTS OF ABATACEPT AFTER 12 MONTHS

	2 mg/kg Abatacept	10 mg/kg Abatacept	Placebo
Nasopharyngitis (% of patients)	18.1%	14.8%	9.2%
Headache (% of patients)	16.2%	14.8%	15.1%
Nausea (% of patients)	11.4%	13.9%	14.3%
Arthralgia (% of patients)	16.2%	NA	NA
Cough (% of patients)	NA	NA	12.6%

NA = not available

The secondary endpoints were ACR50 and ACR 70 responses, as well as components of the ACR data set. Physical function was also determined, using the Modified Health Assessment Questionnaire (MHAQ). Patients were monitored for adverse events and immunogenicity.

Forty-eight patients in the placebo group discontinued therapy, as compared to 31 and 25 patients in the 2 mg/kg and 10 mg/kg treatment groups. There was no significant difference in discontinuation rate due to adverse effects between the 10 mg/kg group and the placebo group; however there was a significant difference in discontinuation rate due to lack of efficacy. A significant difference in the percent of patients in the placebo and 10 mg/kg treatment groups achieving an ACR 20 score was observed by day 60 of the study. There was no significant difference between the placebo and the 2 mg/kg treatment groups. ACR 50 and ACR 70 response rates were significantly higher in the 10 mg/kg treatment group starting on day 30.

Patients achieved higher scores in physical function as assessed by M-HAQ from baseline in those receiving 10 mg/kg abatacept than those receiving placebo, from 30 days through 1 year of the study; the difference was statistically significant. The most common adverse events are reported in Table 3.

Immunogenicity testing was performed on all patients. None of the patients seroconverted to anti-abatacept antibodies. Two patients developed antibodies to the CTLA4-T portion of the molecule. One of these patients developed these antibodies only transiently, and the other patient withdrew from the study.

Active rheumatoid arthritis with an inadequate response to at least three months of anti-TNF-alpha therapy

Efficacy and safety of abatacept was studied in patients with active rheumatoid arthritis who had received at least three months of anti-TNF-alpha therapy in a randomized, double-blind, phase 3 trial.⁵ Patients enrolled in the study had shown an inadequate response to either etanercept, infliximab, or both, and were required to have a washout of at least 28 or 60 days, respectively, before study entry. Adalimumab was not in widespread use at the time of this study. Patients had to have at least 10 swollen joints, at least 12 tender joints, and C-reactive protein levels of at least 1 mg/dL. Patients were required to have been taking an oral DMARD or anakinra for at least 3 months, with the dose remaining stable for at least 28 days. Oral corticosteroid use was also allowed as long as the dose had remained stable for at least 28 days.

Patients were randomized to receive either placebo or abatacept at a dose approximating 10 mg/kg. Patients weighing less than 60 kg who were randomized to receive abatacept received 500 mg of abatacept, those weighing 60-100 kg received 750 mg, and those weighing greater than 100 kg received 1000 mg. Study medication was administered as a 30-minute infusion on days one, 15, and 29, and every 28 days thereafter, up to and including day 141.

The two primary endpoints evaluated the proportion of patients achieving an American College of Rheumatism (ACR) response of 20 (ACR 20) at six months, and the proportion of patients with an improvement in the Health Assessment Questionnaire (HAQ) disability index score at six months of at least 0.3 from baseline. Secondary endpoints included ACR 50 and ACR 70 responses at six months. Changes in disease activity were assessed with the use of the Disease Activity Score 28 (DAS28). Changes in health-related quality of life from baseline were assessed using the SF-35 at six months.

Patients were randomized in a 2:1 ratio to receive abatacept or placebo, respectively, with 258 patients receiving abatacept, and 133 receiving placebo. A total of 322 patients completed 24 weeks of therapy; 223 in the abatacept group and 99 in the placebo group. Lack of efficacy was the main reason for discontinuation in both groups; 5.4% of patients in the abatacept group and 20.3% of patients in the placebo group did not complete the study due to lack of efficacy. The majority of patients were receiving methotrexate therapy (75.6% of the abatacept group and 82% of the placebo group).

Significantly more patients in the abatacept group achieved an ACR 20 response at six months, with 50.4% of abatacept-treated patients and 19.5% of placebo-treated patients achieving this endpoint. Rates of ACR 50 and ACR 70 responses were also significantly higher in the abatacept group at six months. Table 4 details the different response rates.

Clinically meaningful rates of improvement in physical function, defined as an improvement in the HAQ disability index of at least 0.3 from baseline, were also significantly higher in the abatacept group, with 47.3% of abatacept-treated patients achieving improvement versus 23.3% of placebo-treated patients.

Rates of remission, as measured by the DAS28, at six months were significantly higher in the abatacept group (10%) than in the placebo group (0.8%). Furthermore, more patients in the abatacept group had a lower level of disease activity at six months than did patients in the placebo group. The abatacept group also

TABLE 4. EFFICACY OF ABATACEPT IN A SIX-MONTH TRIAL IN PATIENTS REFRACTORY TO TNF-ALPHA INHIBITOR THERAPY

	Abatacept (% of patients)	Placebo (% of patients)	P value
ACR 20 at 6 months	50.4	19.5	<0.001
ACR 50 at 6 months	20.3	3.8	<0.001
ACR 70 at 6 months	10.2	1.5	0.003

had significantly greater improvements from baseline in SF-36 scores.

Rates of adverse events, serious adverse events, and serious infections were similar between groups (see Table 5). The rates of discontinuation because of adverse events were low and similar between the two groups, with 3.5% of abatacept and 3.8% of placebo patients withdrawing from the study for this reason.

Immunogenicity to abatacept was low, with one patient developing antibodies to the immunoglobulin portion of the molecule and two patients developing antibodies to the CTLA4-binding portion of the molecule.

Unpublished Studies

The AIM (Abatacept in Inadequate responders to Methotrexate) trial, available only in a series of abstracts, is a randomized, double-blind, placebo-controlled, multicenter Phase III trial involving the use of abatacept versus placebo in patients with active RA despite methotrexate treatment. Multiple abstracts have been published reporting preliminary data from this trial. They are reported in Table 7 [page 51]. The trial demonstrated that the addition of abatacept produced improvements in ACR20 and radiologic assessment of disease progression in patients who were not responding to methotrexate alone. One-year results from the ASSURE (Abatacept Study of Safety in Use with other Rheuma-

toid arthritis therapies) trial have also been published in abstract form and are also reported in Table 7. ASSURE is a randomized, placebo-controlled trial comparing abatacept with placebo during one-year add-on treatment with one or more of either the biological DMARDs or non-biological DMARDs. This trial has identified safety concerns when abatacept is used in combination with the biological DMARDs.

DRUG INTERACTIONS

Patients receiving abatacept should not receive concurrent treatment with TNF-alpha antagonists. These include infliximab (Remicade®), etanercept (Enbrel®), and adalimumab (Humira®). Live vaccinations should not be given during treatment with abatacept or within three months of its discontinuation because of the effect that abatacept has on the immune system. Though not proven, the response to some vaccines may be altered by abatacept therapy.⁶

ADVERSE EFFECTS AND PRECAUTIONS

The most common adverse effects reported with abatacept include nasopharyngitis, headache, nausea, and arthralgia, all of which have occurred with an incidence of less than 20% in clinical trials.¹ Adverse effects most frequently requiring intervention were due to

TABLE 5. ADVERSE EFFECTS OF ABATACEPT IN A SIX-MONTH TRIAL OF PATIENTS REFRACTORY TO ANTI-TNF-ALPHA INHIBITOR THERAPY

Adverse Effect	Abatacept number (% of patients)	Placebo number (% of patients)	P value
Any adverse event	205 (79.5)	95 (71.4)	0.08
Serious adverse events	27 (10.5)	15 (11.3)	1
Serious infections	6 (2.3)	3 (2.3)	0.97
Headache	32 (12.4)	7 (5.3)	0.03
Nasopharyngitis	20 (7.8)	8 (6.0)	0.53
Nausea	17 (6.6)	9 (6.8)	0.95
Sinusitis	16 (6.2)	5 (3.8)	0.31
Upper respiratory tract infection	15 (5.8)	10 (7.5)	0.51
Diarrhea	15 (5.8)	7 (5.3)	0.82
Bronchitis	15 (5.8)	6 (4.5)	0.59
Back pain	35 (13.6)	7 (5.3)	0.92
Infusion reactions	13 (5)	4 (3)	0.3

TABLE 6. COST COMPARISON OF OTHER BIOLOGICAL RESPONSE MODIFIERS USED IN THE TREATMENT OF RA

Medication	Dose	Annual Cost (AWP)
Abatacept	500 mg for patients weighing less than 60 kg, 750 mg for patients weighing 60 to 100 kg, and 1 gram for patients weighing greater than 100 kg (clinic administered)	\$21,937.50*
Adalimumab	40 mg every other week (self-administered)	\$20,451.60
Anakinra	100 mg/day (self-administered)	\$74,561.76
Etanercept	50 mg every week (self-administered)	\$20,451.60
Infliximab	3 mg/kg every eight weeks (clinic administered)	\$7365.06**

*Abatacept cost is for a 75 kg patient, with a dose of 750 mg, and is for the first year of therapy

** Infiximab cost is for a 75 kg patient, with a dose of 225 mg every eight weeks

infection, including upper respiratory tract infections, bronchitis, herpes zoster, pneumonia, and localized infection.

In clinical trials, the frequency of malignancy was similar between patients receiving abatacept and placebo; however rates of lung cancer and lymphoma were higher in the abatacept group than the placebo group. The significance of the higher incidence of lymphoma is not known because patients with RA are two to four times more likely than the general population to develop lymphoma, particularly if they have active RA.²

Infusion-related reactions were also more common in the abatacept group (9%) than the placebo group (6%). Patients with chronic obstructive pulmonary disease (COPD) receiving abatacept experienced more adverse events than those treated with placebo (97% vs. 88%, respectively). COPD patients should be monitored closely for worsening of respiratory status. The respiratory problems which developed more frequently in COPD patients than placebo patients included COPD exacerbations, cough, rhonchi, dyspnea, and pneumonia.⁵ Patients should be screened for latent tuberculosis before therapy is initiated.

Data demonstrating safety and efficacy of abatacept therapy beyond two years is not available. As a condition of approval, the FDA has required an ongoing open-label extension study to assess safety and risk after 5 years of therapy.⁷ The FDA has also required an ongoing postmarketing pharmacoepidemiology study to assess the short- and long-term risk of hospitalizations due to infections and an assessment of the short- and long-term risk of malignancy and infection compared with other DMARDs.

COST, DOSE, AND HOW SUPPLIED

Abatacept is supplied in single-use vials containing 250 mg of drug. The manufacturer recommended dose is 500 mg for patients weighing less than 60 kg, 750 mg for patients weighing 60 to 100 kg, and 1 gram for patients weighing greater than 100 kg. The AWP for abatacept is \$562.50 for a 250 mg vial. For a 75 kg patient, the cost for one treatment is \$1687.50, and the cost of the first year of therapy for this patient is estimated at \$21,937.50. Table 6 lists cost comparisons of abatacept with other RA drugs on the market. Abatacept is only available through specialty pharmacy distribution systems, and each patient must be enrolled with the company and receive a patient identification number.

CONCLUSION

The treatment of rheumatoid arthritis has made significant advances in the past decade, and the addition of abatacept to the arsenal of therapies represents the next chapter in the understanding of the science behind this immunologic disease. Abatacept is a novel drug in the treatment of rheumatoid arthritis, although its cost and the lack of experience with long term use should limit its use to patients who are refractory to or have had serious reactions to other treatments. The development of other costimulatory modulators is expected, and should help expand options for this disease even further. ●

Rachel B. Sykes is a pediatric specialty resident at the University of North Carolina Hospitals. At the time this monograph was written, she was a pharmacy practice resident at the University of Wisconsin Hospital and Clinics.

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New Members

Welcome to the newest members of PSW (4-01-06 through 7-31-06)

Aisha G. Ashraf, PharmD
Keith Bibelhausen
Andrea G. Clausen, CPhT
Joli R. Dace, RPh, PharmD
Dena M. Jacobs, RPh

Rick A. Michalski, RPh, JD
Michelle M. Perantoni, PharmD
Christopher P. Sanders, RPh
Betsy S. Turk, RPh
Allan Zimmerman, RPh, MBA

TABLE 7. UNPUBLISHED ABATACEPT ABSTRACTS

REFERENCES

Westhovens et al¹
Emery et al²
Steinfeld et al³
Genant et al⁴
Westhovens et al⁵
Kremer et al⁶
AIM trial

STUDY POPULATION

Adult patients with active RA with inadequate response to methotrexate treatment

STUDY DESIGN

Phase III, randomized double blind, placebo-controlled multi-center study

STUDY DRUG

Abatacept ~10 mg/kg (n=433) versus placebo (n=219)

Infusions on days 1, 15, 29, and then monthly for 12 months.

All patients also received methotrexate. One additional nonbiological DMARD could be added after 6 months if needed.

KEY FINDINGS

Primary outcomes were ACR20 at month 6 and structural damage progression at 1 year

Secondary outcomes were ACR50 and ACR70 at month 6 and all ACR scores at 1 year

ACR20 at 6 months
Abatacept 67.9% (P<0.001)
Placebo 39.7%

ACR20 at 12 months
Abatacept 73.1% (P<0.001)
Placebo 39.7%

ACR 50 at 6 months
Abatacept 39.9% (P<0.001)
Placebo 16.8%

ACR 50 at 12 months
Abatacept 48.3% (P<0.001)
Placebo 18.2%

ACR 70 at 6 months
Abatacept 19.8% (P<0.001)
Placebo 6.5%

ACR 70 at 12 months
Abatacept 28.8% (P<0.001)
Placebo 6.1%

DAS28 ≤3.2
6 months
Abatacept 30.1% (P<0.001)
Placebo 10%

12 months
Abatacept 42.5% (P<0.001)
Placebo 9.9%

DAS28 <2.6
6 months
Abatacept 14.8% (P<0.001)
Placebo 2.8%

12 months
Abatacept 23.8% (P<0.001)
Placebo 1.9%

Patients treated with abatacept demonstrated significant improvements in physical function and reductions in pain.

Patients treated with abatacept demonstrated significantly less structural damage progression, as measured by erosion score and joint space narrowing.

DAS28 = Disease Activity Score 28 – scores <2.6=remission; scores ≤3.2=low disease activity

REFERENCES

Weinblatt et al⁷
ASSURE trial

STUDY POPULATION

Adult patients with RA who were also receiving biological or non-biological DMARDs

STUDY DESIGN

Phase III, randomized double blind, placebo-controlled trial

STUDY DRUG

Abatacept 10 mg/kg
+ biological (n=103)
+nonbiological (n=856)

vs.
Placebo
+ biological (n=64)
+nonbiological (n=418)

Treated monthly for 12 months

KEY FINDINGS

Primary outcome was safety.

While the overall incidence of adverse events was similar in patients receiving abatacept vs. placebo (90.3% vs 86.5%), the patients treated with abatacept + a biological DMARD had a two-fold greater risk of developing an infection or serious adverse event.

Patients treated with abatacept + biological DMARDs had more safety concerns than patients receiving placebo or patients receiving abatacept + nonbiological DMARDs (no P values reported)

Total adverse events
Abatacept + biological DMARDs: 95.1%
Other 3 treatment groups: 86-89%

Discontinued therapy due to adverse events:
Abatacept + biological DMARDs: 8.7%
Other 3 treatment groups: 3-5%

Neoplasms
Abatacept + biological DMARDs: 6.8%
Other 3 treatment groups: 1.5-4%

Infections
Abatacept + biological DMARDs: 19.4%
Other 3 treatment groups: 6-9%

1. Westhovens R, Schiff M, Dougados M, et al. Abatacept increases activity levels in rheumatoid arthritis patients with inadequate responses to methotrexate or anti-TNF therapy [abstract]. *Ann Rheum Dis* 2005; 64(Suppl III):398.
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7. Safety of abatacept in patients with active rheumatoid arthritis receiving background non-biologic and biologic DMARDs: 1-year results of the ASSURE trial. *Ann Rheum Dis* 2005; 64(Suppl III):60.