

ASSURE Trial Explores the Safety of Abatacept Therapy in RA

Summarized by Jon Giles, MD

Safety data obtained from randomized clinical trials designed to evaluate the efficacy of rheumatoid arthritis (RA) drugs can be misleading for several reasons. Often, the studies are short term (6 months or less), and are highly selective of the subjects included (usually subjects with very active disease and with few medical comorbidities). In addition, background DMARDs are usually restricted to methotrexate. Real-world situations often include patients with medical comorbidities and a variety of background DMARDs. The FDA has recommended a 12-month safety study approximating “real-world” conditions for each new biologic agent prior to approval. Abatacept (Orencia) has been shown to be effective at reducing the signs and symptoms of active RA and in slowing radiographic progression of disease in patients with inadequate responses to methotrexate and TNF-inhibitors. No major safety signals were identified as a result of these efficacy trials. Here, Weinblatt et al (*Arthritis Rheum* 2006; 54(9):2807) explore the safety of abatacept therapy in “real-world” patients receiving background therapy with biologic and non-biologic DMARDs enrolled in the Abatacept Study of Safety in Use with other RA Therapies (ASSURE) trial.

Methods: Men and women with active RA despite background biologic or non-biologic DMARD therapy were randomized to receive abatacept (10 mg/kg) vs placebo in a 2:1 fashion for one year. Subjects with stable chronic conditions (e.g. CHF, COPD) were enrolled. Subjects continued background DMARDs, including biologics, with the exception of mycophenolate, cyclosporine and other calcineurin inhibitors, penicillamine, cyclophosphamide, and immunoadsorption column therapy. Safety outcomes were monitored as the primary outcome measure and included adverse events, infusion events, and incident autoimmunity. Clinical outcomes (change in HAQ, self-reported pain, and physician and patient global assessments) were assessed as secondary outcome measurements.

Results: 1,441 subjects received at least one infusion of study drug (959 abatacept, 482 placebo). Of these, 1,231 completed one year of double-blind treatment (836 abatacept, 395 placebo). Subjects were typical of RA clinical trials, with most subjects being female (82%), and White (85%), with an average age of 52 years. The average disease duration was almost 10 years. Of the 1274 subjects (88% of the total 1441 subjects) receiving non-biologic background DMARDs, 856 received abatacept and 418 received placebo. Of the 167 subjects (12% of the total 1441 subjects) receiving biologic background DMARDs, 103 received abatacept and 64 received placebo. 80% of subjects receiving background therapy with biologic DMARDs also received concomitant therapy with a non-biologic DMARD. Background therapy with methotrexate was the most common non-biologic DMARD. Corticosteroids were used in 73% of subjects, and just as frequently in those receiving biologic DMARD background therapy as those receiving non-biologic background DMARD therapy.

Summary of Safety Events in ASSURE According to Treatment Allocation and Background DMARD Treatment

	Abatacept vs. Placebo	Abatacept vs. Placebo Non-Biologic Background Therapy Only	Abatacept vs. Placebo Biologic Background Therapy Only
Overall			
Adverse Events	90% vs 87%	89.7% vs 86.1%	95.1% vs 89.1%
Serious Adverse Events	13% vs 12%	11.7% vs 12.2%	22.3% vs 12.5%
Deaths	0.5% vs 0.8% ¹	0.6% vs 1.0%	0% vs 0%
Infections			
Non-serious	56% vs 54.1% ²	54.9% vs 53.6%	65.0% vs 57.8%
Serious/Severe	2.9% vs 1.9% ³	2.6% vs 1.7%	5.8% vs 1.6% ⁴
Neoplasms			
Overall (benign & malign.)	3.5% vs 3.5% ⁵	3.2% vs 3.8%	6.8% vs 1.6% ⁶
Breast	0.1% vs 0.4%	0.1% vs 0.4%	0% vs 0%
Lung	0.3% vs 0%	0.3% vs 0%	0% vs 0%
Autoimmunity			
Overall incidence	3.3% vs 3.1%	Not specified	Not specified
Acute Infusion Reactions (severe and non-severe)			
Overall incidence	10.0% vs. 7.1%	Not specified	Not specified

1. 9 deaths were reported, 5 in the abatacept group and 4 in the placebo group: Cardiac causes in 7, unknown cause in 1, and Pneumocystis pneumonia in a placebo treated patient.
2. most commonly upper respiratory tract infections and nasopharyngitis
3. All serious infections were bacterial in origin, no opportunistic infections reported in abatacept treated subjects
4. Cellulitis, intestinal abscess, infective bursitis, pyelonephritis
5. Non-malignant skin cancers most frequent
6. 2 basal cell carcinomas and 1 squamous cell carcinoma in abatacept treated subjects

Subjects with COPD: Adverse events involving the respiratory system were more common in COPD treated subjects receiving abatacept than those receiving placebo (43.2% vs. 23.5%). Serious adverse events were also more common in subjects with COPD treated with abatacept (27% vs. 5.9%) , and included worsening of COPD symptoms and other respiratory complaints.

Conclusions: Adverse events and serious adverse events were similar between abatacept and placebo treated patients receiving background non-biologic DMARD therapy. However, in combination with background biologic DMARD therapy, abatacept therapy was associated with an increase in serious adverse events, including infections and non-malignant neoplasms. Adverse respiratory events occurred more frequently in abatacept treated patients with COPD.

Editorial Comment: These results are an important addition for all rheumatologists in clinical practice who are beginning to initiate patients on therapy with abatacept. It was hoped that abatacept may be an option for combination with TNF inhibitors for patients with particularly refractive RA. However, these results definitively argue against the combination. The awareness on the part of treating rheumatologists to the risk of COPD exacerbation and other respiratory events when treating patients with COPD with abatacept is an important message that requires broad dissemination. The lack of opportunistic infection is encouraging, but will require further post-marketing surveillance in order to be confirmed. The increase in lung cancer among abatacept treated patients will also require further vigilance. Lung cancers are thought to take many months to years to develop, so it is unlikely that abatacept therapy for less than one year could initiate a lung cancer to the stage that it would be clinically detected. However, if a continued disproportionate number of cases are reported, then further investigation will be warranted in order to define if there is a tangible risk regarding this and other forms of neoplasia.