

Drug Class Review on Targeted Immune Modulators

Preliminary Scan Report

December 27 2007

The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for, any particular drug, use or approach. RTI-UNC Evidence-based Practice Center does not recommend or endorse any guideline or recommendation developed by users of these reports.

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OBJECTIVE

The purpose of this preliminary updated literature scan process is to provide the Participating Organizations with a preview of the volume and nature of new research that has emerged subsequent to the previous full review process. Provision of the new research presented in this report is meant only to assist with Participating Organizations' consideration of allocating resources toward a full update of this topic. Comprehensive review, quality assessment and synthesis of evidence from the full publications of the new research presented in this report would follow only under the condition that the Participating Organizations ruled in favor of a full update. The literature search for this report focuses only on new randomized controlled trials, and actions taken by the FDA or Health Canada since the last report. Other important studies could exist.

Date of Last Update

September 2006 (searches through April 2006)

Scope and Key Questions

The Oregon Evidence-based Practice Center wrote preliminary key questions, identifying the populations, interventions, and outcomes of interest, and based on these, the eligibility criteria for studies. These key questions were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project (DERP). The participating organizations of DERP are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. The participating organizations approved the following key questions to guide this review:

1. How do included drugs compare in their effectiveness for alleviating symptoms and stabilizing the disease in patients with RA, JRA, AS, PsA, Crohn's disease, UC, and plaque psoriasis?
2. What are the comparative incidence and severity of complications of these drugs?
3. Do the included drugs differ in effectiveness or adverse events in different age, sex, or ethnic groups, or in patients taking other commonly prescribed drugs?

Inclusion criteria

Populations

- Adult patients with moderately to severe rheumatoid arthritis
- Pediatric patients with juvenile rheumatoid arthritis
- Adult patients with ankylosing spondylitis
- Adult patients with psoriatic arthritis
- Adult patients with Crohn's disease
- Adult patients with ulcerative colitis
- Adult patients with plaque psoriasis

Interventions

Eight different treatments in four different classes are being evaluated:

Anti TNF

- Infliximab (Remicade[®])
- Etanercept (Enbrel[®])
- Adalimumab (Humira[®])

Interleukin-1 Receptor antagonist

- Anakinra (Kineret[®])

Anti-CD11a

- Efalizumab (Raptiva[®])
- Alefacept (Amevive[®]) Cytotoxic T lymphocyte antigen immunoglobulin (CTLA 4-Ig)
- Abatacept (Orencia[®])

Anti – CD 20a

- Rituximab (Rituxan[®])

Effectiveness outcomes

- Quality of Life
- Functional capacity
- Employability, productivity
- Clinical improvement (e.g. ACR, DAS, BASFI, PASI)
- Pain
- Reduction in the number of swollen or tender joints
- Hospitalizations
- Mortality
- Rebound

Safety outcomes

- Overall adverse events
- Withdrawals due to adverse events
- Serious adverse events reported
- Specific adverse events (e.g. lymphoma, serious infectious diseases, congestive heart failure)

Study design

- For effectiveness, controlled clinical trials and good quality systematic reviews
- For safety, in addition to controlled clinical trials, observational studies will be included.

METHODS

Literature Search

To identify relevant citations, we searched Ovid MEDLINE, Ovid MEDLINE Daily Update, and Ovid MEDLINE In-Process & Other Non-Indexed Citations from July 2006 through December 17, 2007 using terms for included drugs and indications, and limits for humans, English language, and randomized controlled trials or controlled clinical trials. We also searched FDA (<http://www.fda.gov/medwatch/safety.htm>) and Health Canada (http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2006/index_e.html) websites for identification of new drugs, indications, and safety alerts. All citations were imported into an electronic database (EndNote 8.0) and duplicate citations were removed.

Study Selection

One reviewer assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above.

RESULTS

Overview

Searches resulted in 668 citations. Of those, there are 70 new potentially relevant studies (see Appendix A, attached). The following table shows the topics being studied.

Rheumatoid arthritis - 10	Juvenile rheumatoid arthritis - 0
Ulcerative colitis - 4	Crohn's disease - 4
Psoriatic arthritis - 9	Plaque psoriasis - 8
Ankylosing spondylitis - 4	Safety - 29
Background - 2	

New Drugs

None at this time.

New Safety Alerts

FDA:

Rituxan (Rituximab)

Audience: Oncologists, Rheumatologists, other healthcare professionals, and consumers

Indication: Treatment of CD20-positive, B-cell, non-Hodgkins lymphoma and for moderately-to-severely-active rheumatoid arthritis when there has been inadequate response to other treatments.

[Posted 12/18/2006] FDA and Genentech informed healthcare professionals of important emerging safety information about Rituxan. Two patients died after being treated with Rituxan for systemic lupus erythematosus (SLE). Rituxan is approved for the above indication and is prescribed off-label for other serious diseases and conditions such as SLE. The cause of death was a viral infection of the brain called progressive multifocal leukoencephalopathy (PML) that is caused by reactivated JC virus which is present in about 80 percent of adults. Physicians should maintain a high index of suspicion for the development of PML in patients under treatment with Rituxan.

Health Canada:

August 8, 2007 Reports of Progressive Multifocal Leukoencephalopathy (PML) following RITUXAN use in Systemic Lupus Erythematosus and Vasculitis (off-label use) based upon review of recent post marketing and clinical safety reports.

Appendix A. Abstracts of potentially relevant new studies of Targeted Immune Modulators

1. Allaart, C. F., Y. P. Goekoop-Ruiterman, et al. (2006). "Aiming at low disease activity in rheumatoid arthritis with initial combination therapy or initial monotherapy strategies: the BeSt study." *Clin Exp Rheumatol* 24(6 Suppl 43): S-77-82.

AIM: To evaluate the efficacy and safety of four different treatment strategies for patients with early rheumatoid arthritis (RA). **METHODS:** In the BeSt study, 508 patients with newly diagnosed (< 2 years) active RA were randomised to be treated according to four treatment strategies: 1. sequential monotherapy, 2. step up to combination therapy (both starting with methotrexate), 3. initial combination therapy with methotrexate, sulphasalazine, and a tapered high dose of prednisone, and 4. initial combination therapy with methotrexate and infliximab. Three-monthly therapy adjustments were dictated by calculation of the Disease Activity Score (DAS), with the goal to achieve and maintain a DAS \leq 2.4. Functional ability was measured every 3 months with the Health Assessment Questionnaire. Radiographs of hands and feet were assessed yearly, blinded for patient identity and treatment, and in random order, to measure joint damage progression (Sharp/van der Heijde score). **RESULTS:** After 2 years of treatment, 80% of all patients achieved the goal of DAS \leq 2.4, and 42% reached clinical remission (DAS < 1.6). Initial combination therapy, either with prednisone (group 3) or with infliximab (group 4), resulted in earlier improvement in functional ability, more continuous clinical remission (DAS < 1.6), and less joint damage progression than initial monotherapy (groups 1 and 2). Patients in groups 1 and 2 needed more therapy adjustments, including introduction of combination therapy with prednisone or infliximab, to achieve a DAS \leq 2.4, whereas many patients in groups 3 and 4 were able to taper their medication to sulphasalazine or methotrexate, respectively, monotherapy. The adverse events profile was comparable in all groups. The presence or absence of rheumatoid factor, HLA DR4, or anti-CCP was not associated with radiologic damage progression. **CONCLUSION:** In patients with early, active RA, remarkable clinical improvement and suppression of joint damage progression can be achieved with frequent, objectively steered treatment adjustments. The best chance for an early clinical and radiologic response lies with initial combination therapy with either methotrexate, sulphasalazine and prednisone or with methotrexate and infliximab, which can be tapered to DMARD monotherapy once low disease activity is achieved.

2. Berends, M. A., R. J. Driessen, et al. (2007). "Etanercept and efalizumab treatment for high-need psoriasis. Effects and side effects in a prospective cohort study in outpatient clinical practice." *J Dermatolog Treat* 18(2): 76-83.

BACKGROUND: Since the beginning of 2005, etanercept and efalizumab are officially registered and reimbursed for the treatment of recalcitrant psoriasis in The Netherlands. **OBJECTIVE:** The evaluation of the efficacy, safety and adverse events of etanercept and efalizumab treatment in daily practice. **METHODS:** A prospective cohort study was carried out for patients treated with etanercept or efalizumab between February 2005 and March 2006. **RESULTS:** Over the past 13 months 45 individuals were treated with etanercept and 17 subjects were treated with efalizumab. The cohort represented a high-need population. At week 12, 82% of the subjects treated with 2 x 50 mg etanercept/week and 71% of the

subjects treated with 2 x 25 mg etanercept/week reached a PASI-50. Efficacy of etanercept treatment was comparable to the results of clinical trials. For efalizumab, efficacy in responding patients was also comparable to clinical trial data, but the percentage of dropouts was substantial. During biologic treatment, safety was preserved and mainly mild adverse events were reported. **CONCLUSION:** Etanercept and efalizumab are effective and safe treatments of psoriasis, even in a high-need population. Etanercept was able to sustain the clinical improvement throughout 24 weeks, whereas efalizumab was not in 47% of subjects.

3. Bernatsky, S., M. Hudson, et al. (2007). "Anti-rheumatic drug use and risk of serious infections in rheumatoid arthritis." *Rheumatology (Oxford)* 46(7): 1157-60.

OBJECTIVES: To assess the risk of severe infections associated with the use of traditional disease-modifying anti-rheumatic drugs (DMARDs) and glucocorticoid agents in rheumatoid arthritis (RA). **METHODS:** Our study was a case-control design nested within a cohort of 23 733 RA patients studied between 1 January 1980 and 31 December 2003. Matching on age and gender, and adjusting for comorbidity and physician use, conditional logistic regression was used to estimate the effect of specific drugs on the rate ratio (RR) for infections requiring hospitalization. **RESULTS:** The risk for all infections requiring hospitalization appeared to be most elevated with current exposures to cyclophosphamide [RR: 3.26, 95% confidence interval (CI): 2.28-4.67] and systemic glucocorticoid agents (RR: 2.56, 95% CI: 2.29-2.85); azathioprine was associated with a moderate increased risk (RR: 1.52, 95% CI: 1.18-1.97). There was a suggestion of increased risk of pneumonia due to methotrexate (RR: 1.16, 95% CI: 1.02-1.33). The results were similar for the period before and after the introduction of anti-tumour necrosis factor (TNF) agents. The RR point estimate for anti-TNF agents suggested about a 2-fold increased risk for all infections, but the estimate was imprecise. **CONCLUSIONS:** In this large cohort of RA patients, the most heightened risk of serious infections was seen with the use of glucocorticoid agents and immunosuppressive DMARDs. Assessments of infection risk related to newer and emerging therapies should carefully consider concomitant medication exposures, including traditional DMARDs and glucocorticoid therapy.

4. Bhatia, J. K., B. I. Korelitz, et al. (2007). "A prospective open-label trial of Remicade in patients with severe exacerbation of Crohn's disease requiring hospitalization: a comparison with outcomes previously observed in patients receiving intravenous hydrocortisone." *J Clin Gastroenterol* 41(7): 677-81.

PURPOSE: To evaluate treatment response to intravenous (IV) infliximab (IFX) as a first-line therapy in patients hospitalized for severe Crohn's disease and compare it with our earlier data using IV hydrocortisone. **METHODS:** Seventeen cases received IFX (5 mg/kg) and were matched for the same goal of therapy to those who had received hydrocortisone (300 mg/d). The Crohn's and Colitis Foundation of America-International Organization of Inflammatory Bowel Disease (CCFA-IOIBD) score was obtained for the IFX-treated cases on admission and daily and the Crohn's disease activity index (CDAI) score weekly throughout the hospitalization and compared with those who received hydrocortisone. Discharge was guided by the same criteria in both groups. **RESULTS:** For the IFX group, the admission mean CCFA-IOIBD score was 13.5 (+/-4.4). Eight of 17 patients achieved a clinical response with a mean score of 4 (+/-1.5), representing a $\geq 50\%$ reduction from baseline to discharge. The mean admission score for the hydrocortisone group was 17.75 (+/-

7.1) with 13 of 16 achieving a mean score of 4.5 (+/-2.3). The mean discharge score for the 17 IFX patients was 6.9 (+/-3) and for the hydrocortisone group was 5.9 (+/-3.2). Median length of hospitalization for the IFX patients was 4 days (range 1 to 9) and 7.5 (5 to 15) days for the hydrocortisone group ($P < 0.001$). **CONCLUSIONS:** IFX therapy was an effective first-line agent in patients with severe Crohn's disease who require hospitalization and therefore a primary treatment option. Most patients receiving IFX can anticipate a briefer hospitalization than with IV hydrocortisone. Failure of an early response can provide an opportunity to consider an alternate form of therapy sooner with IFX than with hydrocortisone.

5. Bhosle, M. J., S. R. Feldman, et al. (2006). "Medication adherence and health care costs associated with biologics in Medicaid-enrolled patients with psoriasis." *J Dermatolog Treat* 17(5): 294-301.

BACKGROUND: Costs and patients' adherence related to biologics are important factors to consider while making informed decisions regarding therapy with biologics in psoriasis management. **OBJECTIVE:** To examine predictors of adherence related to biologics, total health care costs, and service utilization among psoriasis patients. **METHODS:** This was a longitudinal cohort study of psoriasis patients (<65 years old) enrolled in North Carolina Medicaid who were prescribed biologics (alefacept, efalizumab, and etanercept). Patients' medication adherence, health care costs, and service utilization patterns in the pre- and post-biologics period were examined. **RESULTS:** Adherence to biologics was significantly higher compared with the other psoriasis medications (0.66 vs 0.39; $p < 0.001$). Prescription costs were significantly higher in the post-biologics period (3796.77 US dollars vs 11,706.32 US dollars; $p < 0.001$). However, total health care costs in the post-biologics period did not differ significantly from the pre-biologics period (14,662.22 US dollars vs 16,156.10 US dollars; $p > 0.05$). Patients' adherence and health care costs did not differ significantly across the biologics. After controlling for other variables, patients had a significantly lower number of hospitalizations in the post-biologics period ($p < 0.001$). **CONCLUSIONS:** Although costs associated with prescriptions for biologics were higher, total health care costs did not differ significantly in the post-biologics period. Biologics had a better adherence rate compared with other psoriasis medications.

6. Bobbio-Pallavicini, F., R. Caporali, et al. (2007). "High IgA rheumatoid factor levels are associated with poor clinical response to tumour necrosis factor alpha inhibitors in rheumatoid arthritis." *Ann Rheum Dis* 66(3): 302-7.

OBJECTIVE: To investigate whether rheumatoid factor isotypes and anti-cyclic citrullinated peptide (anti-CCP) antibodies are related to clinical response in patients with rheumatoid arthritis treated with tumour necrosis factor alpha (TNFalpha) inhibitors. **METHODS:** The study was carried out on 132 patients with advanced rheumatoid arthritis refractory to disease-modifying antirheumatic drugs. Patients were treated with infliximab ($n = 63$), etanercept ($n = 35$) or adalimumab ($n = 34$). All patients completed 1 year of follow-up, and 126 were evaluable for clinical response according to the disease activity score (DAS) criteria. IgM, IgA and IgG rheumatoid factors and anti-CCP antibodies were assessed by ELISA both before anti-TNFalpha treatment and 1 year later. **RESULTS:** The DAS response was reached in 66% of evaluable patients (61% infliximab, 65% etanercept and 76% adalimumab; $p = 0.354$). A significant reduction in the rheumatoid factor level was reported

by all treatment groups after 1 year. The frequency of positive tests for the different antibodies did not differ between responders and non-responders at baseline; however, significantly higher IgA rheumatoid factor levels were reported by the non-responder group (130.4 U/ml (interquartile range 13.8-276.7) v 24.8 U/ml (10.2-90.8); $p = 0.003$). A significant decrease ($p < 0.001$) in the levels of all rheumatoid factor isotypes in the responder group was reported after 1 year of treatment, whereas anti-CCP antibody levels were not significantly affected. **CONCLUSIONS:** According to the clinical response, anti-TNFalpha agents seem to reduce IgM, IgG and IgA rheumatoid factor levels. More interestingly, high pretreatment levels of IgA rheumatoid factor are associated with a poor clinical response to TNFalpha inhibitors.

7. Brassard, P., A. Kezouh, et al. (2006). "Antirheumatic drugs and the risk of tuberculosis." *Clin Infect Dis* 43(6): 717-22.

BACKGROUND: We aimed to quantify the rate of *Mycobacterium tuberculosis* disease (TB) among a cohort of patients with rheumatoid arthritis (RA) and to assess whether the independent use of disease-modifying antirheumatic drugs (DMARDs) is associated with the risk of developing TB. **METHODS:** The study was performed using the PharMetrics Patient-Centric database (PharMetrics). The cohort consisted of all subjects with $> \text{ or } = 1$ occurrence of a diagnosis of RA during an inpatient or outpatient visit during the period of September 1998 through December 2003. Conditional logistic regression was used in a nested case-control analysis to estimate the rate ratio (RR) of TB with any use of biological or traditional DMARDs during the year before the index date. We also assessed the interaction between DMARDs and the current use of corticosteroids. **RESULTS:** The cohort consisted of 112,300 patients with RA. A total of 386 cases of TB were identified, which resulted in an overall rate of 2.19 cases per 1000 person-years. The adjusted RR of TB for biological DMARD use is 1.5 (95% CI, 1.1-1.9). Use of traditional DMARDs was also independently associated with TB (RR, 1.2; 95% CI, 1.0-1.5). RRs of developing TB disease with the use of biological or traditional DMARD were lower among current users of corticosteroids than among noncurrent users of corticosteroids. **CONCLUSION:** We found that the use of biological and traditional DMARDs is associated with an increased risk of developing TB in patients with RA, mainly among noncurrent users of corticosteroids.

8. Braun, J., N. McHugh, et al. (2007). "Improvement in patient-reported outcomes for patients with ankylosing spondylitis treated with etanercept 50 mg once-weekly and 25 mg twice-weekly." *Rheumatology (Oxford)* 46(6): 999-1004.

OBJECTIVES: The objective of this study was to assess the humanistic impact of ankylosing spondylitis (AS), and compare the effect of etanercept 50 mg once-weekly (QW), etanercept 25 mg twice-weekly (BIW) and placebo on patient-reported outcomes (PROs). **METHODS:** In a 12-week, double-blind, placebo-controlled multicenter study, 356 patients with active AS received etanercept 50 mg QW, etanercept 25 mg BIW or placebo (3:3:1 randomization, respectively). PROs were assessed using Bath Ankylosing Spondylitis Functional Index, Bath Ankylosing Spondylitis Activity Index fatigue item, EuroQOL-5D (EQ-5D) utility, EQ-5D visual analog scale and the Medical Outcomes Short Form Questionnaire (SF-36) scores at baseline and at regular intervals. Mean changes from baseline in PROs were analysed using analysis of covariance to assess differences between etanercept and placebo, or between the two etanercept groups. **RESULTS:** Consistent with earlier reports, AS was

associated with quality of life (QOL) impairment and functional limitations, similar to or worse than cancer, congestive heart failure, diabetes or depression. Treatment with etanercept 50 mg QW or 25 mg BIW significantly improved QOL and functional status compared with placebo. High proportions of patients achieved clinically meaningful improvements in all PRO measures, including physical function, fatigue, pain, psychosocial domains and general health status. Improvements were similar with the two etanercept dose regimens.

CONCLUSIONS: The more convenient etanercept 50 mg QW dose regimen significantly improves function and QOL in patients with AS, similarly to the standard dosing of 25 mg BIW, supporting its use for AS therapy.

9. Brocq, O., C. H. Roux, et al. (2007). "TNFalpha antagonist continuation rates in 442 patients with inflammatory joint disease." *Joint Bone Spine* 74(2): 148-54.

OBJECTIVE: To evaluate TNFalpha antagonist continuation rates in patients with rheumatoid arthritis (RA), ankylosing spondylitis (AS), or psoriatic arthritis (PsA).

METHODS: We retrospectively reviewed the charts of patients treated with etanercept, infliximab, or adalimumab at our teaching hospital. Drug continuation was evaluated using Kaplan-Meier survival curves. The logrank test was used to compare continuation rates.

RESULTS: We identified 442 patients who were prescribed 571 TNFalpha antagonist treatments between August 1999 and June 2005. Among them, 304 had RA, 92 AS, and 46 PsA. In the RA group, continuation rates were high with etanercept (n=157; 87% after 12 months and 68% after 24 months) and adalimumab (n=43, 83% and 66%) but significantly lower with infliximab (n=104, 68% and 46%; P=0.0001 vs. etanercept and P=0.01 vs. adalimumab). In the AS group, in contrast, infliximab (n=53) showed significantly higher continuation rates (89% and 83%) than did etanercept (n=39; 76% after 12 months: P=0.03). Overall continuation rates were higher in AS than in RA (P=0.01). **CONCLUSION:** Continuation was better with etanercept than with infliximab in patients with RA, whereas the opposite was noted in patients with AS.

10. Burmester, G. R., X. Mariette, et al. (2007). "Adalimumab alone and in combination with disease-modifying antirheumatic drugs for the treatment of rheumatoid arthritis in clinical practice: the Research in Active Rheumatoid Arthritis (ReAct) trial." *Ann Rheum Dis* 66(6): 732-9.

OBJECTIVE: To evaluate the safety and effectiveness of adalimumab alone or in combination with standard disease-modifying antirheumatic drugs (DMARDs) for the treatment of rheumatoid arthritis (RA). **METHODS:** Patients with active RA despite treatment with DMARDs or prior treatment with a tumour necrosis factor antagonist participated in a multicentre, open-label clinical study of adalimumab 40 mg every other week for 12 weeks with an optional extension phase. Patients were allowed to continue with pre-existing traditional DMARDs. Long-term safety results are reported for all patients (4210 patient-years (PYs) of adalimumab exposure). The observed effectiveness results at week 12 are reported using American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) response criteria. **RESULTS:** Among the 6610 treated patients, adalimumab was generally well tolerated. Serious infections occurred in 3.1% of patients (5.5/100 PYs, including active tuberculosis, 0.5/100 PYs). Demyelinating disease (0.06%) and systemic lupus erythematosus (0.03%) were rare serious adverse events. The standardised incidence ratio of malignancy was 0.71 (95% CI 0.49 to 1.01). The standardised

mortality ratio was 1.07 (95% CI 0.75 to 1.49). At week 12, 69% of patients achieved an ACR20 response, 83% a moderate, and 33% a good EULAR response. Adalimumab was effective in combination with a variety of DMARDs. The addition of adalimumab to antimalarials was comparably effective to the combination of adalimumab and methotrexate. CONCLUSIONS: Considering the limitations of an open-label study, adalimumab alone or in combination with standard DMARDs appeared to be well tolerated and effective in 6610 difficult-to-treat patients with active RA treated in clinical practice.

11. Cole, J., A. Busti, et al. (2007). "The incidence of new onset congestive heart failure and heart failure exacerbation in Veteran's Affairs patients receiving tumor necrosis factor alpha antagonists." *Rheumatol Int* 27(4): 369-73.

The objective of this study was to evaluate the incidence of new onset or worsening congestive heart failure in Veteran's Affairs (VA) patients who have received infliximab, etanercept, or adalimumab, and to compare mortality rates in these patients to control populations. We enrolled three groups of patients for this retrospective study: TNF-alpha group (n = 103), a rheumatoid arthritis (RA) control group (n = 100), and a control group without RA (n = 100). All patients at our VA facility who had received at least one dose of the TNF-alpha antagonists were included in the TNF-alpha group. Admissions for CHF did not differ between the three groups: TNF-alpha 7 (6.7%), RA control 8 (8%), non-RA control 7 (7%); P = 0.940. Mortality rates were not significantly different: TNF-alpha 4 (3.8%), RA control 7 (7%), non-RA control 11 (11%); P = 0.147. Our study showed no difference between the three groups in either CHF exacerbation or mortality.

12. Colombel, J. F., W. J. Sandborn, et al. (2007). "Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial." *Gastroenterology* 132(1): 52-65.

BACKGROUND & AIMS: This study evaluated the efficacy and safety of adalimumab, a fully human, anti-tumor necrosis factor monoclonal antibody administered subcutaneously, in the maintenance of response and remission in patients with moderate to severe Crohn's disease (CD). METHODS: Patients received open-label induction therapy with adalimumab 80 mg (week 0) followed by 40 mg (week 2). At week 4, patients were stratified by response (decrease in Crohn's Disease Activity Index \geq 70 points from baseline) and randomized to double-blind treatment with placebo, adalimumab 40 mg every other week (eow), or adalimumab 40 mg weekly through week 56. Co-primary end points were the percentages of randomized responders who achieved clinical remission (Crohn's Disease Activity Index score $<$ 150) at weeks 26 and 56. RESULTS: The percentage of randomized responders in remission was significantly greater in the adalimumab 40-mg eow and 40-mg weekly groups versus placebo at week 26 (40%, 47%, and 17%, respectively; P $<$.001) and week 56 (36%, 41%, and 12%, respectively; P $<$.001). No significant differences in efficacy between adalimumab eow and weekly were observed. More patients receiving placebo discontinued treatment because of an adverse event (13.4%) than those receiving adalimumab (6.9% and 4.7% in the 40-mg eow and 40-mg weekly groups, respectively). CONCLUSIONS: Among patients who responded to adalimumab, both adalimumab eow and weekly were significantly more effective than placebo in maintaining remission in moderate to severe CD through 56 weeks. Adalimumab was well-tolerated, with a safety profile consistent with previous experience with the drug.

13. Curtis, J. R., J. M. Kramer, et al. (2007). "Heart failure among younger rheumatoid arthritis and Crohn's patients exposed to TNF-alpha antagonists." *Rheumatology (Oxford)* 46(11): 1688-93.

OBJECTIVES: New onset heart failure (HF) has been associated with the use of TNF-alpha antagonists etanercept and infliximab based upon spontaneous adverse event reports. HF clinical trials of these agents were stopped early due to futility or worsening of existing HF. A potential association between etanercept and infliximab and new onset HF has been studied minimally at a population level. **METHODS:** Using administrative claims from a large U.S. health care organization, we identified rheumatoid arthritis (RA) and Crohn's disease (CD) patients receiving infliximab or etanercept (exposed), and comparator cohorts of RA and CD patients receiving non-biologic immunosuppressives (unexposed). We studied adults < 50 years to reduce potential confounding related to common age-related comorbidities. Based on abstracted medical records of suspected HF cases, a physician panel adjudicated cases as definite, possible or no HF. **RESULTS:** Among 4018 RA and CD patients with mean duration follow-up of 18 months, 9 of 33 suspected HF cases (identified using claims data) were adjudicated as definite (n = 5) or possible (n = 4) HF. The relative risk of HF among TNF-alpha antagonist-treated RA and CD patients was 4.3 and 1.2, respectively (P = NS for both). The absolute difference in cumulative incidence of HF among infliximab or etanercept-exposed compared to unexposed patients was 3.4 and 0.3 cases per 1000 persons for RA and CD (P = NS), respectively, yielding a number needed to harm of 294 for RA and 3333 for CD. **CONCLUSION:** We found only a small number of presumed HF cases (n = 9, or 0.2%) in a large population of relatively young RA and CD patients. Although there was an increased relative risk of incident, HF that was not statistically significant among those exposed to TNF-alpha antagonists compared to those unexposed, larger cohorts are needed to provide more precise risk estimates and permit adjustment for potential confounding.

14. Curtis, J. R., C. Martin, et al. (2007). "Confirmation of administrative claims-identified opportunistic infections and other serious potential adverse events associated with tumor necrosis factor alpha antagonists and disease-modifying antirheumatic drugs." *Arthritis Rheum* 57(2): 343-6.

15. Curtis, J. R., N. Patkar, et al. (2007). "Risk of serious bacterial infections among rheumatoid arthritis patients exposed to tumor necrosis factor alpha antagonists." *Arthritis Rheum* 56(4): 1125-33.

OBJECTIVE: To evaluate the risk of serious bacterial infections associated with tumor necrosis factor alpha (TNFalpha) antagonists among rheumatoid arthritis (RA) patients. **METHODS:** A retrospective cohort study of US RA patients enrolled in a large health care organization identified patients who received either TNFalpha antagonists or methotrexate (MTX). Administrative data were used to identify hospitalizations with possible bacterial infections; corresponding medical records were abstracted and reviewed by infectious disease specialists for evidence of definite infections. Proportional hazards models evaluated time-dependent infection risks associated with TNFalpha antagonists. **RESULTS:** Hospital medical records with claims-identified suspected bacterial infections were abstracted (n=187) among RA patients who received TNFalpha antagonists (n=2,393; observation time 3,894

person-years) or MTX (n=2,933; 4,846 person-years). Over a median followup time of 17 months, the rate of hospitalization with a confirmed bacterial infection was 2.7% among the patients treated with TNFalpha antagonists compared with 2.0% among the patients treated with MTX only. The multivariable-adjusted hazard ratio (HR) of infection among the patients who received TNFalpha antagonists was 1.9 (95% confidence interval [95% CI] 1.3-2.8) compared with patients who received MTX only. The incidence of infections was highest within 6 months after initiating TNFalpha antagonist therapy (2.9 versus 1.4 infections per 100 person-years; multivariable-adjusted HR 4.2, 95% CI 2.0-8.8).

CONCLUSION: The multivariable-adjusted risk of hospitalization with a physician-confirmed definite bacterial infection was approximately 2-fold higher overall and 4-fold higher in the first 6 months among patients receiving TNFalpha antagonists versus those receiving MTX alone. RA patients were at increased risk of serious infections, irrespective of the method used to define an infectious outcome. Patients and physicians should vigilantly monitor for signs of infection when using TNFalpha antagonists, particularly shortly after treatment initiation.

16. Davis, J. C., Jr., D. Revicki, et al. (2007). "Health-related quality of life outcomes in patients with active ankylosing spondylitis treated with adalimumab: results from a randomized controlled study." *Arthritis Rheum* 57(6): 1050-7.

OBJECTIVE: To evaluate the impact of adalimumab on health-related quality of life (HRQOL) in patients with active ankylosing spondylitis (AS). **METHODS:** Patients \geq 18 years enrolled in the Adalimumab Trial Evaluating Long-Term Efficacy and Safety in Ankylosing Spondylitis, a randomized controlled study, were randomly assigned to receive either adalimumab 40 mg subcutaneously or placebo every other week for 24 weeks. **AS**essment of Ankylosing Spondylitis (ASAS) International Working Group criteria were used to evaluate clinical efficacy. HRQOL outcomes were assessed using the Short Form 36 (SF-36) Health Survey and Ankylosing Spondylitis Quality of Life (ASQoL) Questionnaire. **RESULTS:** A total of 315 patients enrolled (208 in the adalimumab group and 107 in the placebo group). Patients in the adalimumab group showed significant improvements in SF-36 Physical Component Summary (PCS) and ASQoL scores versus placebo at weeks 12 and 24 ($P < 0.001$). The observed differences between adalimumab and placebo patients exceeded the a priori minimum important difference (MID) at the group level, and significantly more adalimumab-treated patients achieved improvements greater than the MID on the patient level. These data suggest the HRQOL improvements were clinically meaningful. No differences were observed in SF-36 Mental Component Summary (MCS) scores. Significant differences favoring adalimumab were observed for SF-36 domains physical function, bodily pain, role-physical, general health, vitality, social function, and role-emotional. There was significant association between HRQOL improvements (measured by SF-36 PCS and MCS, and ASQoL scores) and ASAS clinical responses ($P < 0.001$). **CONCLUSION:** Adalimumab significantly improved physical health status and overall HRQOL through 24 weeks in patients with active AS.

17. De Filippis, L., A. Caliri, et al. (2006). "Improving outcomes in tumour necrosis factor a treatment: comparison of the efficacy of the tumour necrosis factor a blocking agents etanercept and infliximab in patients with active rheumatoid arthritis." *Panminerva Med* 48(2): 129-35.

AIM: The aim of this study was to evaluate the differences between infliximab and etanercept, in terms of clinical efficacy and rapidity of action. **METHODS:** We selected 32 patients with rheumatoid arthritis (RA) with an incomplete response to disease modifying anti-rheumatic drugs (DMARDs), and randomly assigned them to etanercept or infliximab. We evaluated the efficacy after 14, 22, 54 weeks of treatment, using the American College of Rheumatology (ACR) 20, 50 and 70 criteria, and the improvement of quality of life using the Health Assessment Question-naire (HAQ). **RESULTS:** After 14 weeks, the 54.4% of patients was considered ACR-responders in the etanercept group, whereas, in the infliximab group, the percentage of responders was 74.4%: infliximab gave better results for the tender joint count and for physician's global assessment. After 22 weeks, no significant difference was present. After 54 weeks, etanercept resulted more effective than infliximab for tender joint count (TJC) value, for visual analogic scale (VAS) for pain score, for global disease assessment value, with 74.4% of patients considered ACR-responders in the group treated with etanercept and 60% in the group treated with infliximab. As regards HAQ, patients in the infliximab group presented higher scores at week 14, but in weeks 22 and 54, patients in the etanercept group showed better results. Therefore, both infliximab and etanercept are efficacious in RA, but infliximab is more efficacious than etanercept in week 14. Vice versa, in week 54 etanercept is the most efficacious drug. **CONCLUSIONS:** Physicians have 2 weapons in their armamentarium, with the same target but distinct clinical, pharmacokinetic and pharmacodynamic properties.

18. den Broeder, A. A., M. C. Creemers, et al. (2007). "Risk factors for surgical site infections and other complications in elective surgery in patients with rheumatoid arthritis with special attention for anti-tumor necrosis factor: a large retrospective study." *J Rheumatol* 34(4): 689-95.

OBJECTIVE: To identify risk factors for surgical site infection (SSI) in patients with rheumatoid arthritis (RA) with special attention for anti-tumor necrosis factor (anti-TNF) treatment. **METHODS:** All patients with RA who had undergone elective orthopedic surgery since introduction of anti-TNF were included in a retrospective parallel-cohort study with a one-year followup. Primary endpoint was a SSI according to the 1992 Centers for Disease Control and Prevention criteria and/or antibiotic use. Cohort 1 did not use anti-TNF, cohort 2 used anti-TNF but had either stopped (2A) or continued anti-TNF preoperatively (2B), the cutoff point being set at 4 times the half-life time of the drug. Infection rates were compared between cohorts, and logistic regression analysis was performed to examine risk factors. **RESULTS:** In total, 1219 (768 patients) procedures were included, and crude infection risks were 4.0% (41/1023), 5.8% (6/104), and 8.7% (8/92) in cohorts 1, 2A, and 2B, respectively. Elbow surgery (OR 4.1, 95% CI 1.6-10.1), foot/ankle surgery (OR 3.2, 95% CI 1.6-6.5), and prior skin or wound infection (OR 13.8, 95% CI 5.2-36.7) were associated with increased risk of SSI, whereas duration of surgery (OR 0.42, 95% CI 0.23-0.78) and sulfasalazine use (OR 0.21, 95% CI 0.05-0.89) were associated with decreased risk. Perioperative use of anti-TNF was not significantly associated with an increase in SSI rates (OR 1.5, 95% CI 0.43-5.2). **CONCLUSION:** The most important risk factor for SSI is history of SSI or skin infection. Although our study was not powered to detect small differences in infection rates, perioperative continuation of anti-TNF does not seem to be an important risk factor for SSI.

19. Dixon, W. G., D. P. Symmons, et al. (2007). "Serious infection following anti-tumor necrosis factor alpha therapy in patients with rheumatoid arthritis: lessons from interpreting data from observational studies." *Arthritis Rheum* 56(9): 2896-904.

OBJECTIVE: In a recent observational study, we found that the risk of serious infection following anti-tumor necrosis factor alpha (anti-TNFalpha) therapy in patients with rheumatoid arthritis (RA) was not importantly increased compared with the background risk in routinely treated RA patients with similar disease severity. Observational data sets are, however, subject to a number of important biases related to selection factors for the timing of starting and stopping therapy. Infection risk is also likely to vary with duration of therapy. This study was undertaken to examine the influences of these biases and of the method of analysis on the risk of infection. **METHODS:** We compared the risk of serious infection in 8,659 patients treated with anti-TNFalpha with that in 2,170 patients treated with traditional disease-modifying antirheumatic drugs (DMARDs) recruited to the British Society for Rheumatology Biologics Register. We applied a number of statistical models in which we varied the length of the followup period by using different definitions of the date of discontinuation of treatment and different lag periods of risk following drug cessation. **RESULTS:** When the at-risk period was defined as "receiving treatment", the adjusted incidence rate ratio comparing patients receiving anti-TNFalpha therapy with patients receiving DMARD therapy was 1.22 (95% confidence interval [95% CI] 0.88-1.69). Limiting followup to the first 90 days, however, revealed an adjusted incidence rate ratio of 4.6 (95% CI 1.8-11.9). Rates of infection were increased in the 90 days immediately following drug discontinuation and beyond, explained by selection factors for drug discontinuation. **CONCLUSION:** These findings show that overall, the way in which UK rheumatologists select patients for starting and discontinuing anti-TNFalpha therapy explains our previous finding of no increase in risk. However, there may be important increases in true risk, notably early in the course of treatment, that would become more evident depending on the definition of at-risk period.

20. Dixon, W. G., K. Watson, et al. (2006). "Rates of serious infection, including site-specific and bacterial intracellular infection, in rheumatoid arthritis patients receiving anti-tumor necrosis factor therapy: results from the British Society for Rheumatology Biologics Register." *Arthritis Rheum* 54(8): 2368-76.

OBJECTIVE: To determine whether the rate of serious infection is higher in anti-tumor necrosis factor (anti-TNF)-treated rheumatoid arthritis (RA) patients compared with RA patients treated with traditional disease-modifying antirheumatic drugs (DMARDs). **METHODS:** This was a national prospective observational study of 7,664 anti-TNF-treated and 1,354 DMARD-treated patients with severe RA from the British Society for Rheumatology Biologics Register. All serious infections, stratified by site and organism, were included in the analysis. **RESULTS:** Between December 2001 and September 2005, there were 525 serious infections in the anti-TNF-treated cohort and 56 in the comparison cohort (9,868 and 1,352 person-years of followup, respectively). The incidence rate ratio (IRR), adjusted for baseline risk, for the anti-TNF-treated cohort compared with the comparison cohort was 1.03 (95% confidence interval 0.68-1.57). However, the frequency of serious skin and soft tissue infections was increased in anti-TNF-treated patients, with an adjusted IRR of 4.28 (95% confidence interval 1.06-17.17). There was no difference in infection risk between the 3 main anti-TNF drugs. Nineteen serious bacterial intracellular

infections occurred, exclusively in patients in the anti-TNF-treated cohort. **CONCLUSION:** In patients with active RA, anti-TNF therapy was not associated with increased risk of overall serious infection compared with DMARD treatment, after adjustment for baseline risk. In contrast, the rate of serious skin and soft tissue infections was increased, suggesting an important physiologic role of TNF in host defense in the skin and soft tissues beyond that in other tissues.

21. Feagan, B. G., W. Reinisch, et al. (2007). "The effects of infliximab therapy on health-related quality of life in ulcerative colitis patients." *Am J Gastroenterol* 102(4): 794-802. **OBJECTIVES:** The impact of infliximab induction and maintenance therapy on health-related quality of life (HRQL) was evaluated in patients with ulcerative colitis (UC). **METHODS:** In two placebo-controlled, double-blind studies (the Active Ulcerative Colitis Trials 1 and 2 [ACT 1 and 2]), 728 patients were randomized to placebo or infliximab 5 mg/kg or 10 mg/kg. Infusions were administered at weeks 0, 2, 6, and every 8 wk thereafter, up to week 22 (ACT 2) or 46 (ACT 1). Changes in Inflammatory Bowel Disease Questionnaire (IBDQ) and Medical Outcomes Study 36-Item Short Form Health Survey physical and mental component summary (PCS and MCS, respectively) scores were analyzed. **RESULTS:** Baseline scores for the pooled patient population indicated substantial impairment in HRQL. Improvement at week 8 in the total IBDQ score was significantly greater in the infliximab 5-mg/kg (40, $P < 0.001$) and 10-mg/kg (36, $P < 0.001$) groups compared with the placebo group (28). Improvement at week 8 was also significantly greater in the infliximab 5- and 10-mg/kg groups for the PCS (6.8 and 5.9, respectively) and MCS (5.9 and 6.4, respectively) compared with placebo (PCS = 3.7, MCS = 3.0, $P < 0.01$ for all comparisons). Continued benefit was seen at weeks 30 and 54 with infliximab maintenance therapy ($P < 0.001$ for all comparisons). Improvement in total IBDQ score correlated significantly ($P < 0.001$) with improvement in both PCS and MCS scores, and Mayo score. **CONCLUSIONS:** Infliximab therapy substantially improved HRQL in patients with UC. This benefit was sustained through 1 yr with maintenance infliximab therapy.

22. Frankel, E. H., B. E. Strober, et al. (2007). "Etanercept improves psoriatic arthritis patient-reported outcomes: results from EDUCATE." *Cutis* 79(4): 322-6. Experience Diagnosing, Understanding Care, and Treatment With Etanercept (EDUCATE) is a multicenter, phase 4, 24-week, open-label study of the safety and efficacy of etanercept therapy in patients with psoriatic arthritis (PsA) in routine dermatologic practice. We present data on patient-reported outcomes (PROs) from EDUCATE, which demonstrate that subjects with PsA achieved clinically meaningful improvements in both skin- and joint-related PROs after 24 weeks of treatment.

23. Gavalas, E., J. Kountouras, et al. (2007). "Efficacy and safety of infliximab in steroid-dependent ulcerative colitis patients." *Hepatology* 44(6): 1074-9. **BACKGROUND/AIMS:** Limited data exist concerning infliximab administration in steroid-dependent ulcerative colitis (UC) patients. The aim of this study was to evaluate the efficacy and safety of infliximab in steroid-dependent disease. **METHODOLOGY:** Sixteen corticosteroid-dependent patients who received infusions of infliximab (5 mg/kg) at 0, 2 and 6 weeks and thereafter every 8 weeks (Group A), were compared with eight patients treated with methylprednisolone (0.8-1 mg/kg body weight) daily for three weeks followed by a

tapering regimen up to the minimal dose to maintain a symptom-free condition (Group B). Steroid dependency was defined as recurrent flare-up on steroid reduction or withdrawal, or as the clinical need for steroid treatment twice within six consecutive months or three times within a year. Disease activity was assessed at recruitment, and clinical response was evaluated according to the two non-invasive indices [SEO and Simple Clinical Colitis Activity Index (SCCAI) scores]. RESULTS: In Group A, complete long-term response occurred in 68.75% and partial response in 18.75% of patients. Moreover, in the long-term follow-up, both SCCAI (10.37 +/- 2.27 vs. 3.31 +/- 2.65, $p < 0.001$) and SEO (209.33 +/- 13.6 vs. 123.3 +/- 34.8, $p < 0.001$) scores demonstrated a significant improvement. In group B, comparable features were also obtained regarding complete long-term (62.5%) and partial (25%) responses; both SCCAI (7.37 +/- 1.4 vs. 3.5 +/- 3.58, $p = 0.039$) and SEO (181.0 +/- 27.1 vs. 135.3 +/- 44.1, $p = 0.038$) scores also improved significantly. Six of eight patients in the methylprednisolone-treated group B developed Cushing-like symptoms. CONCLUSIONS: Infliximab appears to be a good alternative therapeutic regimen in steroid-dependent UC patients associated with long-term potential toxicity.

24. Genevay, S., A. Finckh, et al. (2007). "Tolerance and effectiveness of anti-tumor necrosis factor alpha therapies in elderly patients with rheumatoid arthritis: a population-based cohort study." *Arthritis Rheum* 57(4): 679-85.

OBJECTIVE: Limited data have been published on tolerance to and efficacy of classic or biologic disease-modifying antirheumatic drugs in elderly patients with rheumatoid arthritis (RA). The goal of the present study was to evaluate the tolerance to and effectiveness of anti-tumor necrosis factor (anti-TNF) agents in elderly patients ($>$ or $=65$ years old) with RA (ERA) in comparison with younger patients (YRA). METHODS: The Swiss Clinical Quality Management program for RA is a longitudinal population-based cohort. All patients who had received at least 1 dose of anti-TNF agents between January 1997 and November 2005 were included and categorized according to their age. Tolerance was assessed by analyzing discontinuation rates of anti-TNF agents. Effectiveness of these agents was assessed by analyzing RA disease activity (Disease Activity Score in 28 joints [DAS28]) and functional disability (Health Assessment Questionnaire [HAQ]) after anti-TNF initiation. RESULTS: Among 1,571 patients with RA treated with anti-TNF agents, 344 were $>$ or $=65$ years of age at treatment initiation. Drug discontinuation rates (median time 3 years) and mean change in DAS28 scores at 2 years (-0.65 versus -0.58) were identical in ERA and YRA. However, HAQ score improved significantly less in ERA (-0.02) than in YRA (-0.1) and a subsequent analysis revealed that this finding was essentially due to patients >75 years of age. CONCLUSION: Age in itself should not interfere with the decision to treat elderly patients with RA with anti-TNF agents. In a subset of patients ages >75 years, no functional improvement according to HAQ should be expected despite improvements in disease activity.

25. Genovese, M. C., P. J. Mease, et al. (2007). "Safety and efficacy of adalimumab in treatment of patients with psoriatic arthritis who had failed disease modifying antirheumatic drug therapy." *J Rheumatol* 34(5): 1040-50.

OBJECTIVE: To demonstrate the safety and efficacy of adalimumab for the treatment of active psoriatic arthritis (PsA) in patients with an inadequate response to disease modifying antirheumatic drugs (DMARD). METHODS: In a placebo controlled, double-blind,

randomized, multicenter study, patients were treated for 12 weeks with subcutaneous injections of adalimumab 40 mg every other week (eow) or placebo, followed by a period of open-label treatment with adalimumab 40 mg eow. The primary efficacy endpoint was the percentage of patients who met the American College of Rheumatology (ACR20) core criteria at Week 12. Secondary efficacy measures included the modified Psoriatic Arthritis Response Criteria (PsARC) and assessments of disability, psoriatic lesions, and quality of life. For missing data, nonresponder imputation was used for ACR and PsARC scores and last observation carried forward for other measures. RESULTS: A total of 100 patients received study drug (51 adalimumab, 49 placebo). At Week 12, an ACR20 response was achieved by 39% of adalimumab patients versus 16% of placebo patients ($p = 0.012$), and a PsARC response was achieved by 51% with adalimumab versus 24% with placebo ($p = 0.007$). At Week 12, measures of skin lesions and disability were statistically significantly improved with adalimumab. After Week 12, open-label adalimumab provided continued improvement for adalimumab patients and initiated rapid improvement for placebo patients, with ACR20 response rates of 65% and 57%, respectively, observed at Week 24. Serious adverse events had similar frequencies during therapy with placebo (4.1%), blinded adalimumab (2.0%), and open-label adalimumab (3.1%). No serious infections occurred during adalimumab therapy. CONCLUSION: In this study of patients who had active PsA and a previous, inadequate response to DMARD therapy, adalimumab was well tolerated and significantly reduced the signs, symptoms, and disability of PsA during 12 weeks of blinded and 12 weeks of open-label therapy. Adalimumab also improved psoriasis in these patients.

26. Gisbert, J. P., Y. Gonzalez-Lama, et al. (2007). "Systematic review: Infliximab therapy in ulcerative colitis." *Aliment Pharmacol Ther* 25(1): 19-37.

AIM: To perform a systematic review and meta-analysis on the efficacy and tolerance of infliximab in ulcerative colitis. METHODS: Selection of studies: evaluating efficacy of infliximab in ulcerative colitis. For the meta-analysis, randomized clinical trials comparing infliximab vs. placebo/steroids. Search strategy: electronic and manual. Study quality: independently assessed by two reviewers. Data synthesis: meta-analysis combining the odds ratios (OR). RESULTS: Thirty-four studies (896 patients) evaluated infliximab therapy in UC, with heterogeneous results. Mean short-term (2.3 weeks) response and remission with infliximab was 68% (95% CI 65-71%) and 40% (36-44%). Mean long-term (8.9 months) response and remission was 53% (49-56%) and 39% (35-42%). Five randomized double-blind studies compared infliximab with placebo, the meta-analysis showing an advantage ($P < 0.001$) of infliximab in all endpoints (short-/long-term response/remission): ORs from 2.7 to 4.6, and number-needed-to-treat (NNT) from 3 to 5. Similar infliximab response was calculated independently of the indication (steroid-refractory/non-steroid-refractory) or the dose (5/10 mg/kg). Adverse effects were reported in 83% and 75% of the infliximab and placebo-treated patients (OR = 1.52; 95% CI 1.03-2.24; number-needed-to-harm (NNH) was 14). CONCLUSION: Infliximab is more effective than placebo, with an NNT from 3 to 5, for the treatment of moderate-to-severe UC, achieving clinical remission in 40% of the patients at approximately 9 months of follow-up. Further studies are necessary to confirm the long-term efficacy of infliximab in ulcerative colitis.

27. Gladman, D. D., P. J. Mease, et al. (2007). "Adalimumab improves joint-related and skin-related functional impairment in patients with psoriatic arthritis: patient-reported

outcomes of the Adalimumab Effectiveness in Psoriatic Arthritis Trial." *Ann Rheum Dis* 66(2): 163-8.

OBJECTIVE: To evaluate the effects of adalimumab on patient-reported outcomes of joint-related and skin-related functional impairment, health-related quality of life, fatigue and pain in patients with psoriatic arthritis (PsA). **METHODS:** Patients with moderately- to severely-active PsA were treated with adalimumab, 40 mg, every other week, or placebo, in this 24-week, randomised, controlled trial. Patient-reported outcomes included the Health Assessment Questionnaire Disability Index (HAQ DI), Short-Form 36 Health Survey (SF-36), the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) Scale and the Dermatology Life Quality Index (DLQI). **RESULTS:** Adalimumab (n = 151) and placebo (n = 162) groups were comparable with respect to baseline demographics and disease severity. Significant changes from baseline in HAQ DI were reported for adalimumab v placebo (-0.4 v -0.1, p<0.001) at both 12 and 24 weeks. At week 24, significant improvements in the SF-36 domains of physical functioning, role-physical, bodily pain, general health, vitality and social functioning, as well as the physical component summary score, were observed for adalimumab versus placebo (p<0.01). These reported changes in HAQ DI and SF-36 were also clinically important. Significantly more patients treated with adalimumab had complete resolution of functional loss (HAQ DI = 0) and dermatological-related functional limitations (DLQI = 0) compared with placebo at weeks 12 and 24 (p< or =0.001). Adalimumab led to significantly greater improvements in FACIT-Fatigue scores, pain scores, and disease activity measures versus placebo at 12 and 24 weeks (p<0.001 for all). **CONCLUSIONS:** Adalimumab improved physical-related and dermatological-related functional limitations, HRQOL, fatigue and pain in patients with PsA treated for 24 weeks.

28. Gladman, D. D., P. J. Mease, et al. (2007). "Adalimumab for long-term treatment of psoriatic arthritis: forty-eight week data from the adalimumab effectiveness in psoriatic arthritis trial." *Arthritis Rheum* 56(2): 476-88.

OBJECTIVE: To evaluate the efficacy and safety of treatment with adalimumab, a fully human anti-tumor necrosis factor (anti-TNF) monoclonal antibody, over 48 weeks in patients with moderate to severe psoriatic arthritis (PsA). **METHODS:** Patients who completed the Adalimumab Effectiveness in Psoriatic Arthritis Trial (ADEPT), a 24-week, double-blind study of adalimumab versus placebo in PsA, could elect to receive open-label adalimumab, 40 mg subcutaneously every other week after week 24. Radiographs were obtained at week 48 and were read with radiographs obtained previously. Clinical and radiographic efficacy data were analyzed overall and in patient subsets. Safety data were collected over 48 weeks. **RESULTS:** At week 48, patients from the adalimumab arm of ADEPT (n = 151) had achieved American College of Rheumatology 20% improvement (ACR20), ACR50, and ACR70 response rates of 56%, 44%, and 30%, respectively. Among those evaluated with the Psoriasis Area and Severity Index (PASI) (n = 69), PASI50, PASI75, PASI90, and PASI100 response rates (> or =50%, > or =75%, > or =90%, and 100% reduction in PASI scores, respectively) were 67%, 58%, 46%, and 33%, respectively (ACR and PASI response rates were analyzed using nonresponder imputation). Improvements in disability, as measured by the Disability Index of the Health Assessment Questionnaire (mean change in score -0.4) were sustained from week 24 to week 48. At week 24 and week 48, the mean changes from baseline in the modified total Sharp score were -0.1 and 0.1, respectively, for patients who

received adalimumab for 48 weeks (n = 133), and 0.9 and 1.0, respectively, for patients who received placebo for 24 weeks followed by adalimumab for 24 weeks (n = 141). Adalimumab demonstrated clinical and radiographic efficacy regardless of whether patients were receiving methotrexate (MTX) at baseline. Adalimumab was generally safe and well tolerated through week 48. **CONCLUSION:** Adalimumab improved joint and skin manifestations, reduced disability, and inhibited radiographic progression over 48 weeks in patients with PsA who were participants in ADEPT. MTX use at baseline was not required for clinical or radiographic efficacy. Adalimumab had a good safety profile through week 48.

29. Goekoop-Ruiterman, Y. P., J. K. de Vries-Bouwstra, et al. (2007). "Patient preferences for treatment: report from a randomised comparison of treatment strategies in early rheumatoid arthritis (BeSt trial)." *Ann Rheum Dis* 66(9): 1227-32.

OBJECTIVE: To determine treatment preferences among patients with recent onset rheumatoid arthritis participating in a randomised controlled trial comparing four therapeutic strategies. **METHODS:** A questionnaire was sent to all 508 participants of the BeSt trial, treated for an average of 2.2 years with either sequential monotherapy (group 1), step-up combination therapy (group 2), initial combination therapy with tapered high-dose prednisone (group 3), or initial combination therapy with infliximab (group 4). Treatment adjustments were made every 3 months to achieve low disease activity (DAS < or =2.4). The questionnaire explored patients' preferences or dislikes for the initial therapy. **RESULTS:** In total, 440 patients (87%) completed the questionnaire. Despite virtually equal study outcomes at 2 years, more patients in group 4 reported much or very much improvement of general health: 50%, 56%, 46% and 74% in groups 1-4, respectively (overall, P<0.001). Almost half of the patients expressed no preference or aversion for a particular treatment group, 33% had hoped for assignment to group 4 and 38% had hoped against assignment to group 3. This negative perception was much less prominent in patients actually in group 3. Nevertheless, 50% of patients in group 3 disliked having to take prednisone, while only 8% in group 4 disliked going to the hospital for intravenous treatment. **CONCLUSIONS:** Within the limitations of our retrospective study, patients clearly preferred initial combination therapy with infliximab and disliked taking prednisone. After actual exposure, this preference remained, but the perception of prednisone improved. Patient perceptions need to be addressed when administering treatment.

30. Gordon, K. B., R. G. Langley, et al. (2006). "Clinical response to adalimumab treatment in patients with moderate to severe psoriasis: double-blind, randomized controlled trial and open-label extension study." *J Am Acad Dermatol* 55(4): 598-606.

BACKGROUND: Tumor necrosis factor is pivotal in the pathogenesis of psoriasis. Adalimumab is a fully human monoclonal immunoglobulin G1 antibody that neutralizes tumor necrosis factor. **OBJECTIVES:** We sought to assess the efficacy and safety of adalimumab in patients with moderate to severe plaque psoriasis. **METHODS:** In this multicenter, randomized, double-blind, placebo-controlled study, 147 patients received adalimumab (40 mg every other week or 40 mg/wk) or placebo. After 12 weeks of blinded therapy, patients taking adalimumab could continue their assigned dosages in a 48-week extension trial; patients taking placebo were switched to adalimumab (40 mg every other week). **RESULTS:** At week 12, 53% of patients taking adalimumab every other week, 80% of patients taking adalimumab weekly, and 4% of patients taking placebo achieved 75%

improvement in Psoriasis Area and Severity Index score ($P < .001$). Responses were sustained for 60 weeks. No new safety signals were noted compared with the existing adalimumab clinical safety database. **LIMITATIONS:** The study was insufficiently powered to detect rare adverse events associated with adalimumab. **CONCLUSIONS:** Adalimumab significantly improved psoriasis and was well tolerated for 60 weeks.

31. Gottlieb, A. B., L. Kircik, et al. (2006). "Use of etanercept for psoriatic arthritis in the dermatology clinic: the Experience Diagnosing, Understanding Care, and Treatment with Etanercept (EDUCATE) study." *J Dermatolog Treat* 17(6): 343-52.

OBJECTIVE: To assess the efficacy and tolerability of etanercept to treat psoriatic arthritis. **MATERIALS AND METHODS:** A total of 1,122 patients who had active psoriatic arthritis were enrolled in a Phase 4, non-randomized, open-label, single-arm, 24-week study. These patients had clinically stable, plaque psoriasis involving $\geq 10\%$ body surface area and joint disease (either ≥ 2 swollen and ≥ 2 tender/painful joints for ≥ 3 months, or ≥ 1 joint with sacroiliitis or spondylitis). They received etanercept therapy 50 mg subcutaneously once weekly for 24 weeks. **RESULTS:** After 24 weeks of treatment, 865 patients (77.1%; 95% CI: 74.64-79.55%) achieved a 'mild or better' score on the physician global assessment of psoriasis and were improved from baseline. Mean improvement in body surface area involvement was 16.9 percentage points (15.89-17.91). Patient global assessment of psoriasis, joint pain, and joint disease scores were improved by means of 2.2 (2.15-2.34), 2.7 (2.53-2.84), and 1.5 (1.39-1.55), respectively. Thirty-five patients (3.1%) experienced at least one serious adverse event. No patient died during the study. **CONCLUSIONS:** These results support the effectiveness and tolerability of etanercept treatment in patients with psoriatic arthritis being treated at dermatology clinics.

32. Gottlieb, A. B., P. J. Mease, et al. (2006). "Clinical characteristics of psoriatic arthritis and psoriasis in dermatologists' offices." *J Dermatolog Treat* 17(5): 279-87.

OBJECTIVE: To describe the skin and joint disease of patients with psoriatic arthritis being treated in dermatology clinics. **METHODS:** A total of 1122 patients who had active psoriatic arthritis were enrolled in a Phase 4, non-randomized, open-label, single-arm, 24-week study. They were treated at 108 community and 17 academic dermatology centers. These patients experienced clinically stable, plaque psoriasis involving $\geq 10\%$ body surface area and joint disease (either ≥ 2 swollen and ≥ 2 tender/painful joints for ≥ 3 months, or ≥ 1 joint with sacroiliitis or spondylitis). **RESULTS:** In general, patient demographics and disease characteristics did not appear to differ between academic and community dermatology sites. Based on patient-reported assessments, patients rated the severity of their baseline joint symptoms lower than the severity of their skin disease. Baseline skin and joint disease measures were not correlated. Psoriatic arthritis was newly diagnosed in 23% of the patients. Most had received prior therapy for psoriasis, but only half had received systemic therapy for psoriatic arthritis. **CONCLUSION:** Assessment for joint disease in psoriasis patients being treated at dermatology clinics may facilitate earlier psoriatic arthritis diagnosis and treatment initiation, which may prevent disability and other negative impacts.

33. Grijalva, C. G., C. P. Chung, et al. (2007). "Assessment of adherence to and persistence on disease-modifying antirheumatic drugs (DMARDs) in patients with rheumatoid arthritis." *Med Care* 45(10 Supl 2): S66-76.

OBJECTIVE: Biologic disease-modifying antirheumatic drugs (DMARDs) are efficacious for treating rheumatoid arthritis (RA). However, measurements of relative effectiveness, including treatment adherence and persistence, are lacking. We evaluated adherence and persistence during new episodes of use of traditional and biologic DMARDs. **METHODS:** Using Tennessee Medicaid databases (1995-2004), we assembled a retrospective cohort of patients diagnosed with RA, and identified new episodes of use for 12 DMARD regimens. We evaluated persistence through survival analyses, and adherence within episodes through the medication possession ratio. A risk score was included in the analyses to account for measured confounders. **RESULTS:** We identified 14,932 patients with RA; 6018 patients had 10,547 episodes of new use of DMARDs. Considering methotrexate as the reference and after adjustment for measured confounders, episodes of new use of sulfasalazine [adjusted hazard ratio (aHR) = 1.59; 95% confidence interval (CI) = 1.47-1.72] and infliximab alone (aHR = 1.37, 95% CI = 1.09-1.73) were more likely to be discontinued; and new episodes of etanercept (aHR = 0.82, 95% CI = 0.73-0.92) and methotrexate + adalimumab (aHR = 0.63, 95% CI = 0.48-0.84) were less likely to be discontinued. Compared with methotrexate, adherence was higher for leflunomide, infliximab, etanercept, and adalimumab and lower for sulfasalazine and all combined therapies. **CONCLUSIONS:** We developed an approach to assess persistence on and adherence to the most common DMARD therapies. In this large cohort, persistence and adherence to leflunomide and most biologic DMARD therapies were at least comparable to methotrexate. Adherence was lower for sulfasalazine and all combined therapies.

34. Heiberg, M. S., C. Kaufmann, et al. (2007). "The comparative effectiveness of anti-TNF therapy and methotrexate in patients with psoriatic arthritis: 6 month results from a longitudinal, observational, multicentre study." *Ann Rheum Dis* 66(8): 1038-42.

OBJECTIVES: To compare the response to treatment with tumour necrosis factor (TNF) inhibitors and methotrexate (MTX) monotherapy in patients with psoriatic arthritis (PsA) within a real-life clinical setting. **METHODS:** We analysed data from an ongoing longitudinal, observational multicentre study in Norway. Our data comprised 526 cases of patients with PsA who received either anti-TNF treatment (n = 146) or MTX monotherapy (n = 380) and were followed for at least 6 months with measures of disease activity, health status and utility scores. A propensity score was computed to adjust for channelling bias. The changes in measures of disease activity and health-related quality of life from baseline to 3- and 6-month follow-up were compared between the groups with adjustments for the baseline value of the dependent variable and the propensity score (analyses of covariance (ANCOVA)). **RESULTS:** The groups were significantly different at baseline with respect to demographic and disease activity measures. The variables included in the propensity score were age, sex, number of previous disease modifying anti-rheumatic drugs (DMARDs), presence of erosive disease, treatment centre and investigator's global assessment. The adjusted changes at 6 months were significantly larger in the anti-TNF group for ESR, DAS-28, M-HAQ, patient's assessments of pain, fatigue and global disease activity on a visual analogue scale (VAS) and 4 out of 8 SF-36 dimensions. **CONCLUSIONS:** Clinical

improvement was superior with TNF inhibitors compared to MTX monotherapy in patients with PsA, when assessed in this setting of daily clinical practice.

35. Jacobsson, L. T., C. Turesson, et al. (2007). "Treatment with TNF blockers and mortality risk in patients with rheumatoid arthritis." *Ann Rheum Dis* 66(5): 670-5.

OBJECTIVE: To assess mortality in patients with rheumatoid arthritis (RA) treated with tumour necrosis factor (TNF) inhibitors, compared with a standard RA population.

METHODS: Patients were recruited from a regional register, which includes over 90% of patients with RA treated with TNF blockers in the area in 1999 or later, and a local community-based cohort of patients with RA, established in 1997. Of a total of 1430 patients in the combined cohort <80 years old, 921 received treatment with TNF inhibitors during the study period. The total cohort was linked with the national register for cause of death.

Overall mortality in those treated versus those not treated with TNF blockers was estimated using standardised mortality ratios and time-dependent Cox proportional hazards. **RESULTS:** There were 188 deaths per 7077 person-years at risk in the total cohort. Controlling for age, sex, disability and baseline comorbidity, the adjusted HR for death was 0.65 (95% CI 0.46 to 0.93) in those treated with anti-TNF versus those not treated. The effect was significant in women (HR = 0.52, 95% CI 0.33 to 0.82) but not in men (HR = 0.95, 95% CI 0.52 to 1.71).

CONCLUSION: After adjusting for disease severity, treatment with TNF inhibitors was found to be associated with a reduced mortality in women but not men with RA. These findings are compatible with a critical role for inflammation in RA-associated premature mortality.

36. Kaur, N. and T. C. Mahl (2007). "Pneumocystis jiroveci (carinii) pneumonia after infliximab therapy: a review of 84 cases." *Dig Dis Sci* 52(6): 1481-4.

Anti-tumor necrosis factor-alpha therapy, infliximab, has become an established effective therapy for Crohn's disease and rheumatoid arthritis. However, infliximab has been associated with various opportunistic pathogens such as tuberculosis, histoplasmosis, listeriosis, aspergillosis, and *Pneumocystis jiroveci (carinii)* pneumonia. We reviewed the FDA Adverse Event Reporting System for cases of *Pneumocystis* associated with infliximab use from January 1998 through December 2003. The database revealed 84 cases of PCP following infliximab therapy. Concomitant immunosuppressive medications included methotrexate, prednisone, azathioprine, 6-mercaptopurine, and cyclosporine. Mean time between infliximab infusion and onset of symptoms of pneumonia, when reported, was 21 days (+/-18 days; n=40). Twenty-three of the 84 (27%) patients died. The use of infliximab is associated with PCP infection. Further, the mortality rate for *Pneumocystis* following the use of infliximab is significant. The potential for severe disease, mortality, and often subtle presentation of these infections warrant close follow-up and careful monitoring after therapy.

37. Kavanaugh, A., C. Antoni, et al. (2006). "Effect of infliximab therapy on employment, time lost from work, and productivity in patients with psoriatic arthritis." *J Rheumatol* 33(11): 2254-9.

OBJECTIVE: To examine the effect of infliximab on employment status, time lost from work, and productivity in a double-blind, placebo-controlled study of patients with active psoriatic arthritis (PsA). **METHODS:** Two hundred adult patients with PsA were randomized to intravenous infusions of either infliximab 5 mg/kg or placebo at Weeks 0, 2, 6, 14, and 22,

with early escape at Week 16. Employment status, workdays missed, and productivity were assessed at baseline and at Week 14. The effect of PsA on daily productivity was assessed using a visual analog scale. RESULTS: At baseline, similar percentages of patients in both treatment groups were employed and similar percentages missed workdays; the mean productivity score at baseline was similar between groups (roughly 3 on a scale of 0 to 10). At Week 14, median productivity increased significantly in the infliximab group compared with the placebo group (67.5% vs 9.2%; $p < 0.0001$). Compared with the placebo group, higher proportions of patients in the infliximab group improved employment status from unemployed at baseline to employed at Week 14 (11.5% vs 0%; $p = 0.084$) and from part-time to full-time employment (30.0% vs 10.0%; $p = 0.582$). Among patients employed at baseline and Week 14, a lower proportion of patients in the infliximab group than in the placebo group had missed workdays in the 4 weeks prior to Week 14 ($p = 0.138$). CONCLUSION: After 14 weeks of treatment, infliximab improved productivity in patients with active PsA. There was also a trend toward increased employment and reduced time lost from work for patients treated with infliximab.

38. Kavanaugh, A., G. G. Krueger, et al. (2007). "Infliximab maintains a high degree of clinical response in patients with active psoriatic arthritis through 1 year of treatment: results from the IMPACT 2 trial." *Ann Rheum Dis* 66(4): 498-505.

OBJECTIVE: To evaluate the efficacy and safety of infliximab through 1 year in patients with psoriatic arthritis (PsA) enrolled in the IMPACT 2 trial. METHODS: In this double blind, placebo controlled, phase III study, 200 patients with active PsA were randomised to receive infusions of infliximab 5 mg/kg or placebo at weeks 0, 2, 6, and every 8 weeks thereafter through 1 year. Patients with persistent disease activity could enter early escape at week 16, and all remaining placebo patients crossed over to infliximab at week 24. Patients randomised to infliximab who had no response or who lost response could escalate their dose to 10 mg/kg starting at week 38. Clinical efficacy was assessed based on the proportion of patients achieving ACR 20 and PASI 75 responses. Major clinical response (that is, maintenance of ACR 70 response for 24 continuous weeks) was assessed for the first time in PsA. RESULTS: Through 1 year of treatment, 58.9% and 61.4% of patients in the randomised infliximab and placebo/infliximab groups, respectively, achieved ACR 20; corresponding figures for PASI 75 were 50.0% and 60.3%. At week 54, major clinical response was achieved by 12.1% of patients in the infliximab group. The safety profile of infliximab through week 54 was consistent with that seen through week 24. Two malignancies occurred: basal cell skin cancer (placebo) and stage I Hodgkin's lymphoma (infliximab). CONCLUSION: Infliximab maintains a high degree of clinical efficacy and continues to be well tolerated in patients with PsA through 1 year of treatment.

39. Kristensen, L. E., T. Saxne, et al. (2006). "Impact of concomitant DMARD therapy on adherence to treatment with etanercept and infliximab in rheumatoid arthritis. Results from a six-year observational study in southern Sweden." *Arthritis Res Ther* 8(6): R174.

The objective of this work is to compare the adherence to therapy of patients receiving etanercept and infliximab during first tumour necrosis factor (TNF)-blocking treatment course in rheumatoid arthritis. Special emphasis is placed on potential predictors for treatment termination and the impact of concomitant methotrexate (MTX) or other disease-modifying antirheumatic drugs (DMARDs). Patients ($n = 1,161$) with active rheumatoid

arthritis, not responding to at least two DMARDs including MTX starting etanercept or infliximab therapy for the first time, were included in a structured clinical follow-up protocol. Information on diagnosis, disease duration, previous and ongoing DMARDs, treatment start and termination, as well as cause of withdrawal was prospectively collected during the period of March 1999 through December 2004. Patients were divided into six groups according to TNF-blocking drugs and concomitant DMARDs. Five-year level (one-year) of adherence to therapy was 36% (69%) for patients receiving infliximab in combination with MTX compared with 65% (89%) for patients treated with etanercept and MTX ($p < 0.001$). Cox regression models showed that the risk for premature treatment termination of patients treated with infliximab was threefold higher than for etanercept ($p < 0.001$). Also, the regression analysis showed that patients receiving concomitant MTX had better treatment continuation than patients treated solely with TNF blockers ($p < 0.001$). Moreover, patients receiving concomitant MTX had superior drug survival than patients receiving other concomitant DMARDs ($p < 0.010$). The superior effect of MTX was associated primarily with fewer treatment terminations because of adverse events. In addition, the study identifies low C-reactive protein level, high age, elevated health assessment questionnaire score, and higher previous number of DMARDs as predictors of premature treatment termination. In summary, treatment with etanercept has higher adherence to therapy than treatment with infliximab. Concomitant MTX is associated with improved treatment continuation of biologics when compared with both TNF blockers as monotherapy and TNF blockers combined with other DMARDs.

40. Menter, A., S. R. Feldman, et al. (2007). "A randomized comparison of continuous vs. intermittent infliximab maintenance regimens over 1 year in the treatment of moderate-to-severe plaque psoriasis." *J Am Acad Dermatol* 56(1): 31 e1-15.

BACKGROUND: Previous studies of infliximab in psoriasis have demonstrated rapid improvement with induction therapy and sustained response with regularly administered maintenance therapy.

OBJECTIVE: The efficacy and safety of continuous (every-8-week) and intermittent (as-needed) maintenance regimens were compared. **METHODS:** Patients with moderate-to-severe psoriasis ($n = 835$) were randomized to induction therapy (weeks 0, 2, and 6) with infliximab 3 mg/kg or 5 mg/kg or placebo. Infliximab-treated patients were randomized again at week 14 to continuous or intermittent maintenance regimens at their induction dose. **RESULTS:** At week 10, 75.5% and 70.3% of patients in the infliximab 5 mg/kg and 3 mg/kg groups, respectively, achieved PASI 75; 45.2% and 37.1% achieved PASI 90 (vs 1.9% [PASI 75] and 0.5% [PASI 90] for placebo; $P < .001$). Through week 50, PASI responses were better maintained with continuous compared with intermittent therapy within each dose, and with 5 mg/kg compared with 3 mg/kg continuous therapy.

LIMITATIONS: Longer term (>1 year) maintenance therapy and further study of infliximab serum concentrations over this period, in both PASI 75 responders and non-responders, would be preferable. **CONCLUSIONS:** Through week 50, response was best maintained with continuous infliximab therapy. Infliximab was generally well-tolerated in most patients.

41. Mertz, L. E. and J. E. Blair (2007). "Coccidioidomycosis in rheumatology patients: incidence and potential risk factors." *Ann N Y Acad Sci* 1111: 343-57.

Coccidioidomycosis is a potentially serious fungal infection contracted in endemic areas of the desert southwestern United States. Limited information exists about its incidence and

clinical course in patients with rheumatic diseases, who may be at higher risk of symptomatic or disseminated coccidioidomycosis because of either the rheumatic disease itself or its treatment. We analyzed the incidence and risk factors for symptomatic and complicated coccidioidomycosis in our academic rheumatology practice in central Arizona. Between January 1, 2000, and June 30, 2006, coccidioidomycosis was diagnosed in 1.9% of the overall practice and in 3.1-3.6% of patients with rheumatoid arthritis (RA). The annual incidence was 1% in patients recently diagnosed with RA and 2% among patients with recently initiated infliximab treatment. Coccidioidomycosis was identified only in patients with inflammatory rheumatic diseases and extrathoracic dissemination occurred only to joints in two patients. Corticosteroids, immunosuppressive medications, and tumor necrosis factor inhibitors (TNFIs) appeared to be risk factors for symptomatic, but not disseminated coccidioidomycosis.

42. Michaud, K. and F. Wolfe (2006). "The association of rheumatoid arthritis and its treatment with sinus disease." *J Rheumatol* 33(12): 2412-5.

OBJECTIVE: To determine if rates of sinus disease are increased in patients with rheumatoid arthritis (RA) and whether RA treatment alters the risk of sinus disease. **METHODS:** As part of a longitudinal study of rheumatic disease outcomes, 7,243 patients with RA, 1,667 with osteoarthritis (OA), and 447 with fibromyalgia (FM) were evaluated for important sinus problems in 2003. We defined an important sinus problem as one that required a physician visit. **RESULTS:** The lifetime prevalence of sinus disorders among all patients was 42.9%. During the previous 6 months 22.3% of patients with RA, 23.9% with OA, and 25.1% with FM visited a physician for a sinus problem and 22.4%, 23.9%, and 25.1% , respectively, received a prescription medication for a sinus problem. After adjustment for age and sex, the rate of physician visits for a sinus problem was significantly lower for patients with RA (22.1%) compared to patients with OA (24.8%). The strongest predictor of sinus problems among all patients was a history of allergy or asthma. Sinus problems were more common among users of etanercept: odds ratio (OR) 1.2; 95% confidence interval (CI): 1.0-1.4 univariably, and OR 1.2; 95% CI: 1.0-1.4 multivariably. Sulfasalazine (OR 0.7; 95% CI: 0.5-0.9) and leflunomide (OR 0.8; 95% CI: 0.7-1.0) had a protective effect on sinus problems. **CONCLUSIONS:** Sinus problems are decreased in patients with RA compared to OA and FM. Slight protective effects on sinus problems are noted with sulfasalazine and leflunomide, and a slight increase in risk of sinus problems is noted with etanercept.

43. Militello, G., A. Xia, et al. (2006). "Etanercept for the treatment of psoriasis in the elderly." *J Am Acad Dermatol* 55(3): 517-9.

This study's objective was to analyze the effect of etanercept on Psoriasis Area and Severity Index (PASI) 50, PASI 75, and Dermatology Life Quality Index in geriatric and nongeriatric populations. We conducted a post hoc analysis of two large phase III randomized placebo trials of etanercept. There were no statistically significant differences between the elderly and young with regard to the number of patients reaching a PASI 50 or PASI 75 at any of the 3 dosing regimens. Baseline Dermatology Life Quality Index scores were not statistically significant between both groups and both the elderly and young had similar changes in Dermatology Life Quality Index with therapy. A limitation of the study was the small number of patients in the elderly group. In conclusion, psoriasis and its treatment has a similar impact on quality of life in the elderly as it does in the young.

44. Papp, K. A., I. Caro, et al. (2007). "Efalizumab for the treatment of psoriatic arthritis." *J Cutan Med Surg* 11(2): 57-66.

BACKGROUND: Psoriatic arthritis (PsA) is an inflammatory arthritis associated with psoriasis. Efalizumab, a T cell-targeted, recombinant human monoclonal antibody, is approved for the treatment of adult patients with chronic moderate to severe plaque psoriasis. The effect of efalizumab therapy on PsA has not previously been investigated. **OBJECTIVE:** This phase II randomized, double-blind, placebo-controlled multicenter study evaluated the efficacy and safety of efalizumab for the treatment of PsA. **METHODS:** Patients were required to be on at least one of the following concomitant systemic therapies for PsA: nonsteroidal anti-inflammatory drugs, corticosteroids, and/or sulfasalazine or methotrexate. One hundred fifteen patients with active PsA were enrolled and randomized in the study. Of these, 107 were treated weekly with efalizumab 1 mg/kg or placebo for 12 weeks, followed by 12 additional weeks of open-label efalizumab. **RESULTS:** At week 12, 28% of efalizumab-treated patients achieved ACR-20 response (a 20% reduction from the baseline in the American College of Rheumatology response criteria), the primary end point, compared with 19% of placebo patients ($p = .27$). The safety profile was comparable between efalizumab- and placebo-treated patient groups, regardless of methotrexate background therapy, and no worsening of joint disease occurred with efalizumab therapy. **CONCLUSIONS:** Efalizumab was not effective in treating PsA; efalizumab therapy did not worsen PsA. The efalizumab safety profile does not appear to be altered with the concomitant use of methotrexate therapy.

45. Ramos-Casals, M., P. Brito-Zeron, et al. (2007). "Autoimmune diseases induced by TNF-targeted therapies: analysis of 233 cases." *Medicine (Baltimore)* 86(4): 242-51.

Tumor necrosis factor (TNF)-targeted therapies are increasingly used for a rapidly expanding number of rheumatic and autoimmune diseases. With this use and longer follow-up periods of treatment, there are a growing number of reports of the development of autoimmune processes related to anti-TNF agents. We have analyzed the clinical characteristics, outcomes, and patterns of association with the different anti-TNF agents used in all reports of autoimmune diseases developing after TNF-targeted therapy found through a MEDLINE search of articles published between January 1990 and December 2006. We identified 233 cases of autoimmune diseases (vasculitis in 113, lupus in 92, interstitial lung diseases in 24, and other diseases in 4) secondary to TNF-targeted therapies in 226 patients. The anti-TNF agents were administered for rheumatoid arthritis (RA) in 187 (83%) patients, Crohn disease in 17, ankylosing spondylitis in 7, psoriatic arthritis in 6, juvenile RA in 5, and other diseases in 3. The anti-TNF agents administered were infliximab in 105 patients, etanercept in 96, adalimumab in 21, and other anti-TNF agents in 3. We found 92 reported cases of lupus following anti-TNF therapy (infliximab in 40 cases, etanercept in 37, and adalimumab in 15). Nearly half the cases fulfilled 4 or more classification criteria for systemic lupus erythematosus (SLE), which fell to one-third after discarding preexisting lupus-like features. One hundred thirteen patients developed vasculitis after receiving anti-TNF agents (etanercept in 59 cases, infliximab in 47, adalimumab in 5, and other agents in 2). Leukocytoclastic vasculitis was the most frequent type of vasculitis, and purpura was the most frequent cutaneous lesion. A significant finding was that one-quarter of patients with vasculitis related to anti-TNF agents had extracutaneous involvement. Twenty-four cases of

interstitial lung disease associated with the use of anti-TNF agents were reported. In these patients, 2 specific characteristics should be highlighted: the poor prognosis in spite of cessation of anti-TNF therapy, and the possible adjuvant role of concomitant methotrexate. In conclusion, the use of anti-TNF agents has been associated with an increasing number of cases of autoimmune diseases, principally cutaneous vasculitis, lupus-like syndrome, SLE, and interstitial lung disease.

46. Reinisch, W., W. J. Sandborn, et al. (2007). "Response and remission are associated with improved quality of life, employment and disability status, hours worked, and productivity of patients with ulcerative colitis." *Inflamm Bowel Dis* 13(9): 1135-40. **BACKGROUND:** Impairment of health-related quality of life, employment, and productivity has been documented in patients with moderate to severe ulcerative colitis. **METHODS:** Using prospectively collected data from the Active Ulcerative Colitis Trials 1 and 2, we examined the impact of clinical response or remission, as defined using the Mayo score, on health-related quality of life, employment, disability, productivity, and hours worked per week. These analyses were based on observed data and included all 728 patients, regardless of their randomized treatment group (i.e., placebo and infliximab patients were grouped for analysis). Changes in Inflammatory Bowel Disease Questionnaire (IBDQ) and Medical Outcomes Study 36-Item Short Form (SF-36) scores among nonresponders, responders, and patients in remission were compared. In addition, changes in employment, disability status, productivity, and hours worked per week of patients in clinical remission and patients not in clinical remission were compared. **RESULTS:** Ulcerative colitis patients in clinical response or remission had significantly improved IBDQ and SF-36 scores at week 30 compared with those of nonresponders ($P < 0.001$). Among those not employed at baseline, including those receiving disability compensation, greater percentages of patients in remission at week 30 were employed (20.6%) and not receiving disability compensation (58.8%) than were those not in remission (8.3% and 20.0%, respectively; $P < 0.05$ for both comparisons). At week 30, improvements from baseline in productivity and both actual and fully productive hours worked per week were greater for patients in remission compared with those not in remission ($P < 0.05$ for all three comparisons). **CONCLUSIONS:** These results confirm the validity of response and remission as defined using the Mayo score.

47. Russell, A. S., G. V. Wallenstein, et al. (2007). "Abatacept improves both the physical and mental health of patients with rheumatoid arthritis who have inadequate response to methotrexate treatment." *Ann Rheum Dis* 66(2): 189-94. **OBJECTIVE:** To examine the impact of added abatacept treatment on health related quality of life (HRQoL) in patients with rheumatoid arthritis (RA) who have inadequate response to methotrexate (MTX). **METHODS:** The impact of abatacept treatment on HRQoL was examined in a longitudinal, randomised double blind, placebo controlled clinical trial. Effects of treatment on HRQoL were examined using repeated measures analysis of covariance and comparing rates of change in HRQoL across treatment groups. The relationship between American College of Rheumatology (ACR) clinical markers and disease duration with changes in HRQoL indicators was also examined. Finally, a responder analysis was used to examine the percentage of patients who improved by 0.5 SD in 12 months or who reached the normative levels seen in the US general population. **RESULTS:** Statistically significant improvements in the abatacept group relative to controls were observed across a range of

HRQoL measures, including physical function, fatigue, all eight domains of the SF-36, and the physical and mental component summaries (PCS and MCS). Improvements were seen as early as day 29 for fatigue and for five out of eight SF-36 domains. By day 169, all HRQoL measures were significantly better with abatacept than with placebo. HRQoL gains were associated with greater ACR clinical improvement, and the effects were consistent for patients with different disease duration. A significantly greater percentage of patients treated with abatacept reached normative levels of PCS, MCS, physical functioning, and fatigue compared with patients treated with MTX alone. **CONCLUSION:** Combined abatacept and MTX treatment produces significant improvements across a wide range of HRQoL domains in patients with RA.

48. Ruysen-Witrand, A., L. Gossec, et al. (2007). "Complication rates of 127 surgical procedures performed in rheumatic patients receiving tumor necrosis factor alpha blockers." *Clin Exp Rheumatol* 25(3): 430-6.

OBJECTIVE: Tumor necrosis factor (TNF) blockers have been reported to increase the risk of infections, thrombosis, and delayed healing. However, there is little data on the risk of complications after surgery in rheumatic patients receiving TNF blockers. The aim of this study was to assess the complication rate after surgery in such patients, to assess the effect of interrupting TNF blocker therapy, and to identify other potential predictors of complications. **METHODS:** This was a systematic, retrospective monocenter study of all patients treated with TNF blockers and who underwent surgery. Complications were recorded and complication rates were compared based on the type of surgery and the timing of the discontinuation of TNF blockers before surgery (above 2 or 5 half-lives). The complication rates were compared with those reported in the literature (orthopaedic procedures in RA patients: 7%, abdominal surgery: 13%). **RESULTS:** Between 1997 and 2004, 770 patients were treated with TNF blockers of whom 92 underwent surgery (127 surgical procedures). The most frequent underlying disease was rheumatoid arthritis (77%). Most of the surgical procedures were orthopaedic (85%). The complication rates for orthopaedic procedures and for abdominal procedures were 13% and 43%, respectively. The infection rate after orthopaedic procedures was 6.5%. Interrupting therapy before surgery did not significantly decrease the postoperative complication risk. There were no independent factors predicting complications. **CONCLUSION:** In daily practice the complication rate after surgery is high in patients treated with TNF blockers. Discontinuing TNF therapy before surgery should be considered, although this study did not clearly demonstrate its role.

49. Sandborn, W. J., S. B. Hanauer, et al. (2007). "Adalimumab for maintenance treatment of Crohn's disease: results of the CLASSIC II trial." *Gut* 56(9): 1232-9.

BACKGROUND: Adalimumab induced clinical remission after four weeks in patients with active Crohn's disease in the CLASSIC I trial. **OBJECTIVE:** To evaluate long term efficacy and safety of adalimumab maintenance therapy in Crohn's disease in a follow-on randomised controlled trial (CLASSIC II). **METHODS:** In the preceding CLASSIC I trial, 299 patients with moderate to severe Crohn's disease naive to tumour necrosis factor antagonists received induction therapy with adalimumab 40 mg/20 mg, 80 mg/40 mg, or 160 mg/80 mg, or placebo, at weeks 0 and 2. In all, 276 patients from CLASSIC I enrolled in CLASSIC II and received open-label adalimumab 40 mg at weeks 0 (week 4 of CLASSIC I) and 2; 55 patients in remission at both weeks 0 and 4 were re-randomised to adalimumab 40 mg every other

week, 40 mg weekly, or placebo for 56 weeks. Patients not in remission at both weeks 0 and 4 were enrolled in an open-label arm and received adalimumab 40 mg every other week. With non-response or flare, these patients could have their dosages increased to 40 mg weekly. Patients in the randomised arm with continued non-response or disease flare could switch to open-label adalimumab 40 mg every other week and again to 40 mg weekly. The primary end point was maintenance of remission (CDAI <150) in randomised patients through week 56. **RESULTS:** Of 55 patients randomised at week 4, 79% who received adalimumab 40 mg every other week and 83% who received 40 mg weekly were in remission at week 56, v 44% for placebo ($p < 0.05$). In all, 204 patients entered the open-label arm. Of these, 93 (46%) were in clinical remission at week 56. Adalimumab was generally well-tolerated in all patients. **CONCLUSIONS:** Adalimumab induced and maintained clinical remission for up to 56 weeks in patients with moderate to severe Crohn's disease naive to anti-TNF treatment.

50. Sandhu, R. S., G. J. Treharne, et al. (2006). "The impact of anti-tumour necrosis factor therapy for rheumatoid arthritis on the use of other drugs and hospital resources in a pragmatic setting." *Musculoskeletal Care* 4(4): 204-22.

BACKGROUND: Anti-tumour necrosis factor (anti-TNF) therapy has been an important development for the treatment of rheumatoid arthritis (RA) but the impact of its delivery on hospital resources is still emerging. **Aims:** We audited the effect of starting anti-TNF on the use of other anti-rheumatic therapies and hospital resources in a routine secondary care setting. **METHODS:** A retrospective study of resource use before and after anti-TNF was conducted. Hospital records of 54 RA patients were studied and data taken from the time of commencing anti-TNF to 1 October 2004 and an equal time period prior to commencing anti-TNF. Identical data were collected for 54 controls not on anti-TNF. Relevant figures were extrapolated to per annum rates. Results were analysed using two-factor ANOVAs comparing the pre- versus post-anti-TNF period. Cases on intravenous (IV) versus subcutaneous (SC) anti-TNF were also compared in separate ANOVAs. **RESULTS:** Mean duration of anti-TNF therapy was 17.04 months (range 3.60-42.36). Mean pre- and 3-months post-anti-TNF Disease Activity Scores (DAS28) were 6.93 and 3.88, respectively. Cases were more likely than controls to be on oral prednisolone pre- and post-anti-TNF. Methylprednisolone requirement, number of disease-modifying anti-rheumatic drugs (DMARDs), telephone helpline contacts and duration as an inpatient reduced significantly post-anti-TNF. Day case admissions increased but outpatient appointments decreased only in cases on IV anti-TNF. **CONCLUSIONS:** In a pragmatic setting, anti-TNF therapy led to reduced need for steroid injections and other DMARDs, as well as reductions in use of several hospital resources. Wider replication of these findings will be important for planning delivery.

51. Scheinfeld, N. (2007). "Alefcept: its safety profile, off-label uses, and potential as part of combination therapies for psoriasis." *J Dermatolog Treat* 18(4): 197-208.

OBJECTIVES: To review literature regarding alefacept, a biologic therapy for psoriasis. **METHODS:** A PubMed search using the term alefacept was done through December of 2006 and articles reviewed. Abstracts concerning alefacept presented at the meeting of the Annual meeting of the American Academy of Dermatology in 2004, 2005 and 2006 were reviewed. Attention was paid to alefacept's safety profile, off-label uses, and potential as part of

combination therapy for psoriasis. **RESULTS:** Alefacept is a very safe treatment for psoriasis alone or in conjunction with other therapies. It has been used, anecdotally, with some effect in diseases besides psoriasis. **CONCLUSIONS:** The utility of checking CD4 counts while administering alefacept for 12 weeks is unclear. While no side effects have been linked to CD4 counts lower than 250/cc(3), due to the fact that in clinical trials alefacept was discontinued when the CD4 count was lower than 250/cc(3), the effect of administration of alefacept to patients with low CD4 counts is unknown. Alefacept appears to be the safest biologic therapy for the treatment of psoriasis, safety that has been borne out in patients who have received as many as nine courses of alefacept. Intramuscular alefacept's consistent ability to decrease the psoriasis area and severity index (PASI) scores in psoriatic patients is not as great as phototherapy, cyclosporine, methotrexate or tumor necrosis factor alpha blockers. Repeated courses of alefacept are best used in patients who have previously responded to the medication, so that patients who have found alefacept useful when grouped achieve higher and more consistent improvements of PASI scores with each successive course of alefacept. A test that would identify likely responders would greatly increase the utility of the medication. While reports assessing the combination of alefacept and narrow band ultraviolet B phototherapy have only studied small numbers of patients (approximately 60), the combination of phototherapy and alefacept appears synergistic and extremely effective with studied patients achieving PASI 75 in more than 75% of cases and thus merits further study. Combinations of alefacept with etanercept, acitretin, and methotrexate have been used anecdotally but effectively to treat recalcitrant psoriasis. Reported effective off-label uses of alefacept include: generalized lichen planus, alopecia areata, steroid-resistant or steroid-dependent acute graft-versus-host disease, scleroderma, nail psoriasis, and palmoplantar psoriasis.

52. Schneeweiss, S., S. Setoguchi, et al. (2007). "Anti-tumor necrosis factor alpha therapy and the risk of serious bacterial infections in elderly patients with rheumatoid arthritis." *Arthritis Rheum* 56(6): 1754-64.

OBJECTIVE: To assess the association between the initiation of anti-tumor necrosis factor alpha (anti-TNFalpha) therapy and the risk of serious bacterial infections in routine care. **METHODS:** This was a cohort study of patients with rheumatoid arthritis (RA) in whom specific disease-modifying antirheumatic drugs (DMARDs) were initiated. Patients were Medicare beneficiaries ages 65 years and older (mean age 76.5 years) who were concurrently enrolled in the Pharmaceutical Assistance Contract for the Elderly provided by the state of Pennsylvania. A total of 15,597 RA patients in whom a DMARD was initiated between January 1, 1995 and December 31, 2003 were identified using linked data on all prescription drug dispensings, physician services, and hospitalizations. Initiation of anti-TNFalpha therapy, cytotoxic agents other than methotrexate (MTX), noncytotoxic agents, and glucocorticoids was compared with initiation of MTX. The main outcome measure was serious bacterial infections that required hospitalization. **RESULTS:** The incidence of serious bacterial infections was, on average, 2.2 per 100 patient-years in this population (95% confidence interval [95% CI] 2.0-2.4). Glucocorticoid use doubled the rate of serious bacterial infections as compared with MTX use, independent of previous DMARD use (rate ratio [RR] 2.1 [95% CI 1.5-3.1]), with a clear dose-response relationship for dosages >5 mg/day (for < or = 5 mg/day, RR 1.34; for 6-9 mg/day, RR 1.53; for 10-19 mg/day, RR 2.97; and for > or = 20 mg/day, RR 5.48 [P for trend < 0.0001]). Adjusted models showed no

increase in the rate of serious infections among initiators of anti-TNFalpha therapy (RR 1.0 [95% CI 0.6-1.7]) or other DMARDs as compared with initiators of MTX. **CONCLUSION:** In a large cohort of patients with RA, we found no increase in serious bacterial infections among users of anti-TNFalpha therapy compared with users of MTX. Glucocorticoid use was associated with a dose-dependent increase in such infections.

53. Selvasekar, C. R., R. R. Cima, et al. (2007). "Effect of infliximab on short-term complications in patients undergoing operation for chronic ulcerative colitis." *J Am Coll Surg* 204(5): 956-62; discussion 962-3.

BACKGROUND: Total proctocolectomy and ileal pouch anal anastomosis (IPAA) is the preferred operation for patients with chronic ulcerative colitis (CUC) refractory to medical therapy. Infliximab (IFX), an antitumor necrosis factor-alpha antibody, has demonstrated efficacy in medical management of CUC. The aim of this study is to determine if IFX before IPAA impacts short-term outcomes. **STUDY DESIGN:** A prospective institutional database was retrospectively reviewed for short-term complications after IPAA for CUC.

Postoperative outcomes were compared between patients who received pre-IPAA IFX and those who did not. **RESULTS:** Between 2002 and 2005, 47 patients received IFX before IPAA, and 254 patients received none. There were no gender ($p = 0.16$) or body mass index ($p = 0.07$) differences between groups. IFX patients were younger than non-IFX patients (mean age 28.1 to 39.3 years) ($p < 0.001$). In IFX patients, 70% were receiving preoperative IFX, azathioprine, and corticosteroids. Mortality was nil. Overall surgical morbidity was similar: 61.7% and 48.8%, IFX and non-IFX, respectively ($p = 0.10$). Anastomotic leaks ($p = 0.02$), pouch-specific ($p = 0.01$) and infectious ($p < 0.01$) complications were more common in IFX patients. Multivariable analysis revealed IFX as the only factor independently associated with infectious complications (odds ratio [OR] = 3.5; CI, 1.6-7.5). In a separate analysis, incorporating age, high-dose corticosteroids, azathioprine, and severity of colitis, IFX remained significantly associated with infectious complications (OR = 2.7; CI, 1.1-6.7). **CONCLUSIONS:** CUC patients treated with IFX before IPAA have substantially increased the odds of postoperative pouch-related and infectious complications. Additional prospective studies are required to determine if IFX alone or other factors contribute to the observed increases in infectious complications.

54. Seong, S. S., C. B. Choi, et al. (2007). "Incidence of tuberculosis in Korean patients with rheumatoid arthritis (RA): effects of RA itself and of tumor necrosis factor blockers." *J Rheumatol* 34(4): 706-11.

OBJECTIVE: To elucidate the incidence rate and relative risk of tuberculosis (TB) in patients with rheumatoid arthritis (RA) and in patients with RA treated with tumor-necrosis-factor (TNF) blockers in Korea. **METHODS:** Using data from the Korean National Tuberculosis Association (KNTA) as a control and data from a single-center cohort of patients with RA, we conducted an evaluation of 1285 patients with RA not exposed to TNF blockers and reviewed medical records of 90 and 103 patients with RA treated with infliximab and etanercept, respectively, between 2001 and 2005. **RESULTS:** The mean incidence rate of TB, reported by the KNTA, was 67.2 per 100,000 person years (PY) from 2001 to 2004. In the TNF-blocker-naive RA cohort, 9 cases of TB developed during 3497 PY of followup (257 per 100,000). In the infliximab-treated RA group, 2 cases of TB developed during 78.17 PY of followup (2558 per 100,000 PY), and there was no case of TB during

73.67 PY of followup in the etanercept-treated RA group. The risk of TB was higher in RA patients not treated with TNF blockers (sex- and age-adjusted risk ratio 8.9; 95% confidence interval 4.6-17.2), and in those treated with infliximab (sex- and age-adjusted risk ratio, 30.1; 95% confidence interval, 7.4-122.3) compared with the general Korean population.

CONCLUSION: The risk of TB infection is 8.9-fold higher in Korean patients with RA and 30.1-fold higher in RA patients treated with infliximab, compared with the general Korean population.

55. Shikiar, R., M. Heffernan, et al. (2007). "Adalimumab treatment is associated with improvement in health-related quality of life in psoriasis: patient-reported outcomes from a phase II randomized controlled trial." *J Dermatolog Treat* 18(1): 25-31.

BACKGROUND: Psoriasis substantially impairs the health-related quality of life (HRQOL) of patients, and a comprehensive evaluation of treatment includes HRQOL measures.

OBJECTIVE: To assess the impact of adalimumab on patient-reported outcomes (PROs) of patients with moderate to severe psoriasis. **METHODS:** In a Phase II, randomized, controlled trial, the efficacy and safety of two dosages of adalimumab (40 mg weekly or every other week) versus placebo were assessed for 12 weeks in the treatment of moderate to severe plaque psoriasis. Patients completed the Dermatology Life Quality Index (DLQI), Short-Form 36 (SF-36) Health Survey, and EuroQOL-5D (EQ-5D) at baseline and 12 weeks. The primary endpoint was the percentage of patients achieving a $>$ or $=75\%$ reduction in the Psoriasis Area and Severity Index score (PASI 75). Investigators assessed PASI and Physician's Global Assessment (PGA) scores. **RESULTS:** Adalimumab patients (either dosage) displayed significantly greater improvements versus placebo patients in DLQI, EQ-5D, and SF-36 Mental Component Summary scores, as well as in Bodily Pain, Vitality, Social Functioning, Role-Emotional, and Mental Health domains. The adalimumab 40-mg weekly group also reported significantly greater improvements in SF-36 Physical Component Summary scores versus the placebo group. **CONCLUSION:** Both adalimumab dosages were efficacious in improving dermatology-specific and general PROs in patients with moderate to severe psoriasis.

56. Siegel, C. A., C. Hur, et al. (2006). "Risks and benefits of infliximab for the treatment of Crohn's disease." *Clin Gastroenterol Hepatol* 4(8): 1017-24; quiz 976.

BACKGROUND & AIMS: Infliximab is effective for the treatment of active Crohn's disease. However, rare but serious complications related to infliximab therapy including lymphoma, sepsis, and death have been reported. The purpose of this study was to analyze the risks and benefits of infliximab for the treatment of Crohn's disease with the goal of providing data to aid both physicians and patients in the process of making a decision about treatment. **METHODS:** A decision analytic model was constructed to determine the risks and benefits of infliximab when compared with standard therapy. The analysis simulated 2 cohorts of 100,000 patients each, with one arm receiving infliximab while the other remained on standard therapy. **RESULTS:** Model results showed that in 100,000 patients at 1 year, infliximab will lead to 12,216 more patients in remission, 4255 fewer surgeries, and 33 fewer deaths from flares of disease. This is at the cost of 201 more lymphomas and 249 more deaths related to complications from infliximab. Overall, the infliximab strategy resulted in more quality-adjusted life years (QALYs/patient) than the standard therapy strategy (.77 QALYs/patient vs .75 QALYs/patient). **CONCLUSIONS:** Despite an increased risk of

lymphoma and death associated with use of infliximab, the substantial clinical improvement and fewer surgeries as a result of infliximab result in an increase in QALYs. In properly selected patients, the benefits of infliximab could outweigh its risks. These data should help guide decision making and the informed consent process when considering the use of infliximab for the treatment of Crohn's disease.

57. Simsek, I., H. Erdem, et al. (2007). "Optic neuritis occurring with anti-tumour necrosis factor alpha therapy." *Ann Rheum Dis* 66(9): 1255-8.

OBJECTIVE: Various demyelinating disorders have been reported in association with anti-tumour necrosis factor alpha (TNFalpha) agents. The objective of this study was to review the occurrence, clinical features and outcome of optic neuritis (ON) during treatment with anti-TNFalpha agents. **METHODS:** A PubMed search was conducted to identify literature addressing the potential association between anti-TNFalpha agents and ON, following our experience with a patient having rheumatoid arthritis in whom ON developed while being treated with infliximab. **RESULTS:** 15 patients including the case presented here with ON in whom the symptoms developed following TNFalpha antagonist therapy were evaluated. Eight of these patients had received infliximab, five had received etanercept and two patients had received adalimumab. Among them, nine patients experienced complete resolution, and two patients had partial resolution, while four patients continued to have symptoms. **DISCUSSION:** Patients being treated with a TNFalpha antagonist should be closely monitored for the development of ophthalmological or neurological signs and symptoms. Furthermore, consideration should be given to avoiding such therapies in patients with a history of demyelinating disease. If clinical evaluation leads to the diagnosis of ON, discontinuation of the medication and institution of steroid treatment should be a priority.

58. Solomon, D. H. (2007). "The comparative safety and effectiveness of TNF-alpha antagonists [corrected]." *J Manag Care Pharm* 13(1 Suppl): S7-18.

OBJECTIVE: To describe the current knowledge on safety and effectiveness of the tumor necrosis factor (TNF)-alpha antagonists and identify current knowledge/ evidence gaps for study by the Agency for Healthcare Research and Quality (AHRQ) Effective Health Care Program. **BACKGROUND:** Evidence-based Practice Centers (EPCs) and the Developing Evidence to Inform Decisions about Effectiveness (DEcIDE) network of AHRQ's Effective Health Care Program will study the safety and effectiveness of biologic and nonbiologic disease-modifying antirheumatic drugs (e.g., TNF-alpha antagonists). The current knowledge of safety and effectiveness of TNF-alpha antagonists is reviewed. **SUMMARY:** Treatment of adult rheumatoid arthritis (RA) involves determining which agents are safe, effective, and cost effective for an individual. Each individual patient's health system may also play a role in which agents are chosen. Many agents are available for the management of RA, some with high cost and unknown safety. Section 1013 of the Medicare Modernization Act of 2003 authorizes AHRQ to study comparative effectiveness and safety of RA treatments through both EPCs and DEcIDE centers to develop scientific knowledge for RA management as well as through epidemiologic studies. Results will be compiled through a Clinical Decisions and Communications Science Center, then disseminated to all appropriate stakeholders, including patients, payers, and health care professionals. The current knowledge of safety and effectiveness of TNF-alpha antagonists in the treatment of RA is reviewed. Increased rates of serious infections, including *Mycobacterium tuberculosis* (MTB), or tuberculosis

reactivation, may occur with the use of TNF- α antagonists. It is still unclear if RA increases the risk of developing cancer, or if use of TNF- α antagonists increases cancer risk. CONCLUSIONS: TNF- α antagonists are costly, yet effective treatments for early and late RA. Use of these agents provides rapid relief of RA symptoms and provides positive outcomes, defined as improvements in American College of Rheumatology 20, 50, 70 scores; Health Assessment Questionnaire ratings; activities of daily living; joint space narrowing; erosions; and acute-phase reactants. Reactivation of latent MTB or onset of other infections or cancers may occur in RA patients with TNF- α antagonists.

59. Tying, S., K. B. Gordon, et al. (2007). "Long-term safety and efficacy of 50 mg of etanercept twice weekly in patients with psoriasis." *Arch Dermatol* 143(6): 719-26. OBJECTIVE: To evaluate the safety and efficacy of long-term treatment of psoriasis with etanercept, 50 mg twice weekly. DESIGN, SETTING, AND PATIENTS: A phase 3, randomized, double-blind trial with an open-label extension. A total of 618 adult patients with moderate to severe plaque psoriasis were studied at 39 medical centers in the United States and Canada from May 23, 2003, through June 22, 2005. INTERVENTIONS: Patients were randomized to receive placebo or etanercept for 12 weeks. Beginning with week 13, all patients (N=591) received etanercept. MAIN OUTCOME MEASURES: Exposure-adjusted adverse event rates were calculated. Efficacy measures included efficacy and patient global assessment of psoriasis. RESULTS: Exposure-adjusted rates of adverse events, serious adverse events, infections, and serious infections were similar for placebo and etanercept treatments. Nonneutralizing antibodies to etanercept, observed in 18.3% of patients, had no apparent effect on safety or efficacy. Patients responded within 2 weeks to etanercept, with statistically significant differences in the Psoriasis Area and Severity Index and Dermatology Life Quality Index between the etanercept and placebo groups at week 12. At week 24, after 12 weeks of open-label etanercept treatment, patients in the original placebo group had clinical benefits comparable to those of patients in the original etanercept group. As both groups progressed through the open-label period, the Psoriasis Area and Severity Index response peaked at week 48. At week 96, 51.6% of the original placebo-treated patients and 51.1% of the original etanercept-treated patients had improvements from baseline in the Psoriasis Area and Severity Index of at least 75%. CONCLUSIONS: Extended exposure to 50 mg of etanercept twice weekly resulted in exposure-adjusted rates of adverse events and infections similar to those in patients receiving placebo. Improvements in physician- and patient-reported measures of psoriasis severity were observed for up to 96 weeks of continuous etanercept therapy. Trial Registration clinicaltrials.gov Identifier NCT00111449.

60. van der Bijl, A. E., Y. P. Goekoop-Ruiterman, et al. (2007). "Infliximab and methotrexate as induction therapy in patients with early rheumatoid arthritis." *Arthritis Rheum* 56(7): 2129-34.

OBJECTIVE: To evaluate the efficacy of infliximab plus methotrexate (MTX) as induction therapy in patients with early rheumatoid arthritis (RA). METHODS: Disease-modifying antirheumatic drug (DMARD)-naive patients with active, early RA who were included as group 4 of the BeSt study were initially treated with infliximab (3 mg/kg) in combination with MTX (25 mg/week). The Disease Activity Score (DAS) was measured every 3 months. In patients with persistent low disease activity (DAS \leq 2.4) for at least 6 months, the infliximab dosage was tapered and finally discontinued; the MTX dosage then was tapered to

10 mg/week. In patients with a DAS of >2.4, the infliximab dosage was increased (maximum 10 mg/kg), and they were subsequently switched to another DMARD. Except for intraarticular administration, corticosteroids were not permitted. Functional ability and the modified Sharp/van der Heijde score were determined after 2 years of therapy. RESULTS: Of the 120 patients, 67 responders (56%) had persistent low disease activity and discontinued infliximab after a median of 9.9 months, with a median MTX dosage of 10 mg/week after 2 years. Ten other patients experienced a disease flare after discontinuation and resumed infliximab after a median of 3.7 months. Thirteen patients did not achieve persistent low disease activity and received infliximab at various dosages. Treatment was unsuccessful in 30 patients. In the 67 responders, the progression of joint damage was lower than in the 30 patients in whom treatment failed. CONCLUSION: Fifty-six percent of patients with active early RA, initially treated with infliximab plus MTX, could discontinue infliximab after achieving a DAS of ≤ 2.4 . Low disease activity was maintained in these patients while the MTX dosage was tapered to 10 mg/week.

61. van der Heijde, D., J. C. Da Silva, et al. (2006). "Etanercept 50 mg once weekly is as effective as 25 mg twice weekly in patients with ankylosing spondylitis." *Ann Rheum Dis* 65(12): 1572-7.

OBJECTIVE: To compare the efficacy, pharmacokinetics and safety of etanercept 50 mg once weekly with 25 mg twice weekly and placebo in patients with ankylosing spondylitis. METHODS: A 12-week, double-blind, placebo-controlled study compared the effects of etanercept 50 mg once weekly, etanercept 25 mg twice weekly and placebo in 356 patients with active ankylosing spondylitis (3:3:1 randomisation, respectively). The primary end point was the proportion of patients achieving a response at week 12 based on the Assessment in Ankylosing Spondylitis Working Group criteria (ASAS 20). The pharmacokinetics of etanercept 50 mg once weekly and 25 mg twice weekly were analysed. RESULTS: Baseline characteristics and disease activity were similar among the three groups: etanercept 50 mg once weekly, etanercept 25 mg twice weekly and placebo. The percentage of patients discontinuing therapy was 9.0%, 9.3% and 13.7% for the three respective groups. ASAS 20 response at 12 weeks was achieved by 74.2% of patients with etanercept 50 mg once weekly and 71.3% of those with etanercept 25 mg twice weekly, both significantly higher than the percentage of patients taking placebo (37.3%, $p < 0.001$). Percentages of patients with ASAS 5/6 response (70.3%, 72.0% and 27.5%, respectively; $p < 0.001$) and those with ASAS 40 response (58.1%, 53.3% and 21.6%, respectively; $p < 0.001$) followed a similar pattern. Significant improvement ($p < 0.05$) was seen in measures of disease activity, back pain, morning stiffness and C reactive protein levels as early as 2 weeks. Serum etanercept exposure was similar between the etanercept groups. Incidence of treatment-emergent adverse events, including infections, was similar among all three groups, and no unexpected safety issues were identified. CONCLUSIONS: Patients with ankylosing spondylitis can expect a comparable significant improvement in clinical outcomes with similar safety when treated with etanercept 50 mg once weekly or with 25 mg twice weekly.

62. van der Heijde, D., C. Han, et al. (2006). "Infliximab improves productivity and reduces workday loss in patients with ankylosing spondylitis: results from a randomized, placebo-controlled trial." *Arthritis Rheum* 55(4): 569-74.

OBJECTIVE: To examine whether clinical benefits observed after treatment with infliximab were accompanied by improvement in productivity and reduction in time lost from work in a randomized, double-blind, placebo-controlled, multicenter trial of patients with ankylosing spondylitis (AS). **METHODS:** Adults with active AS receiving standard antiinflammatory treatment were randomly assigned in a 3:8 ratio to receive infusions of placebo or 5 mg/kg infliximab at weeks 0, 2, 6, and every 6 weeks thereafter through week 24. Physical function was measured using the Bath Ankylosing Spondylitis Functional Index. The impact of disease on productivity was measured using a visual analog scale (range 0-10). Self-reported employment status and time lost at work before and during the trial were collected. Spearman's correlation coefficient was used to examine factors associated with productivity. **RESULTS:** Patients treated with infliximab had a more significant reduction in limitations of work and daily activity due to physical or emotional problems than patients treated with placebo. Of the subset of patients employed full time, patients in the infliximab group had a significantly greater improvement in productivity as early as week 6 compared with the placebo group. The median change from baseline in the productivity score at week 24 was 0.7 (median percent change 11%) in the placebo group compared with 2.1 (62%) in the infliximab group ($P < 0.05$). Daily productivity was significantly correlated with physical function and disease activity at baseline and week 24. **CONCLUSION:** The daily productivity of patients with active AS was significantly associated with functional impairment and disease activity. Infliximab treatment significantly improved productivity and reduced workday loss among employed patients with AS.

63. van der Heijde, D., A. Kavanaugh, et al. (2007). "Infliximab inhibits progression of radiographic damage in patients with active psoriatic arthritis through one year of treatment: Results from the induction and maintenance psoriatic arthritis clinical trial 2." *Arthritis Rheum* 56(8): 2698-707.

OBJECTIVE: To evaluate the effect of infliximab on progression of structural damage over 1 year in patients with active psoriatic arthritis (PsA) enrolled in the Induction and Maintenance Psoriatic Arthritis Clinical Trial 2. **METHODS:** In this double-blind, placebo-controlled study, 200 patients with active PsA were randomly assigned (1:1 ratio) to receive infusions of infliximab (5 mg/kg) or placebo at weeks 0, 2, and 6, and every 8 weeks thereafter through week 54. At week 24, patients initially assigned to receive placebo crossed over to receive infliximab (5 mg/kg). Based on predefined criteria, patients randomized to receive placebo could enter early escape by receiving infliximab (5 mg/kg) starting at week 16, and patients randomized to receive infliximab could have the dose increased to 10 mg/kg starting at week 38. Patients were analyzed according to the treatment they were randomized to receive. Radiographs of hands and feet were obtained at baseline and at weeks 24 and 54. Two readers blinded to treatment assignment and radiograph sequence independently evaluated erosions and joint space narrowing using the Sharp/van der Heijde scoring method modified for PsA. **RESULTS:** At week 24, patients randomized to receive infliximab 5 mg/kg had significantly less radiographic progression compared with patients randomized to receive placebo, with mean \pm SD changes from baseline in the total Sharp/van der Heijde score of -0.70 ± 2.53 and 0.82 ± 2.62 , respectively ($P < 0.001$). At week 54, mean \pm SD changes from baseline in the total Sharp/van der Heijde score were -0.94 ± 3.40 in patients randomized to receive infliximab and 0.53 ± 2.60 in those receiving placebo/infliximab ($P = 0.001$). **CONCLUSION:** Infliximab significantly inhibits radiographic progression in

patients with PsA as early as 6 months after starting treatment, and the beneficial effect continues through 1 year of infliximab therapy.

64. Weinblatt, M., B. Combe, et al. (2006). "Safety of the selective costimulation modulator abatacept in rheumatoid arthritis patients receiving background biologic and nonbiologic disease-modifying antirheumatic drugs: A one-year randomized, placebo-controlled study." *Arthritis Rheum* 54(9): 2807-16.

OBJECTIVE: To assess the safety of abatacept, a selective costimulation modulator, in patients with active rheumatoid arthritis (RA) who had been receiving > or =1 traditional nonbiologic and/or biologic disease-modifying antirheumatic drugs (DMARDs) approved for the treatment of RA for at least 3 months prior to entry into the study. **METHODS:** This was a 1-year, multicenter, randomized, double-blind, placebo-controlled trial. Patients were randomized 2:1 to receive abatacept at a fixed dose approximating 10 mg/kg by weight range, or placebo. **RESULTS:** The abatacept and placebo groups exhibited similar frequencies of adverse events (90% and 87%, respectively), serious adverse events (13% and 12%, respectively), and discontinuations due to adverse events (5% and 4%, respectively). Five patients (0.5%) in the abatacept group and 4 patients (0.8%) in the placebo group died during the study. Serious infections were more frequent in the abatacept group than in the placebo group (2.9% versus 1.9%). Fewer than 4% of patients in either group experienced a severe or very severe infection. The incidence of neoplasms was 3.5% in both groups. When evaluated according to background therapy, serious adverse events occurred more frequently in the subgroup receiving abatacept plus a biologic agent (22.3%) than in the other subgroups (11.7-12.5%). **CONCLUSION:** Abatacept in combination with synthetic DMARDs was well tolerated and improved physical function and physician- and patient-reported disease outcomes. However, abatacept in combination with biologic background therapies was associated with an increase in the rate of serious adverse events. Therefore, abatacept is not recommended for use in combination with biologic therapy.

65. Weinblatt, M., M. Schiff, et al. (2007). "Selective costimulation modulation using abatacept in patients with active rheumatoid arthritis while receiving etanercept: a randomised clinical trial." *Ann Rheum Dis* 66(2): 228-34.

OBJECTIVE: To investigate the efficacy and safety of abatacept in combination with etanercept in patients with active rheumatoid arthritis during a 1-year, randomised, placebo-controlled, double-blind phase, followed by an open-label, long-term extension (LTE). **METHODS:** Patients continued etanercept (25 mg twice weekly) and were randomised to receive abatacept 2 mg/kg (n = 85) or placebo (n = 36). As the effective dose of abatacept was established as 10 mg/kg in a separate trial, all patients received abatacept 10 mg/kg and etanercept during the LTE. **RESULTS:** A total of 121 patients were randomised; 80 completed double-blind treatment and entered the LTE. During double-blind treatment, the difference in the percentage of patients achieving the primary end point (modified American College of Rheumatology (ACR) 20 response at 6 months) was not significant between groups (48.2% v 30.6%; p = 0.072). At 1 year, no notable changes in modified ACR responses were observed. Subsequent to the dosing change, similar modified ACR responses were seen during the LTE. Significant improvements in quality of life were observed with abatacept and etanercept versus placebo and etanercept in five of the eight short-form 36 subscales at 1 year. More abatacept and etanercept-treated patients experienced serious

adverse events (SAEs) at 1 year than patients receiving placebo and etanercept (16.5% v 2.8%), with 3.5% v 0% experiencing serious infections. **CONCLUSION:** The combination of abatacept (at a dose of 2 mg/kg during the double-blind phase and 10 mg/kg during the LTE) and etanercept was associated with an increase in SAEs, including serious infections, with limited clinical effect. On the basis of the limited efficacy findings and safety concerns, abatacept in combination with etanercept should not be used for rheumatoid arthritis treatment.

66. Weisman, M. H., H. E. Paulus, et al. (2007). "A placebo-controlled, randomized, double-blinded study evaluating the safety of etanercept in patients with rheumatoid arthritis and concomitant comorbid diseases." *Rheumatology (Oxford)* 46(7): 1122-5.

OBJECTIVE: To evaluate the safety of etanercept in patients with rheumatoid arthritis (RA) and concomitant comorbidities. **METHODS:** The safety of etanercept (25 mg twice weekly) in RA patients with at least one comorbidity (i.e. diabetes mellitus, chronic pulmonary disease, recent pneumonia, recurrent infections) was evaluated in a 16-week placebo-controlled, randomized, double-blinded study. The primary endpoint was the incidence of medically important infections (MIIs; defined as those resulting in hospitalization or treatment with intravenous antibiotics). **RESULTS:** Data from 535 patients were analysed; the study was terminated early because of slow enrolment and lower than predicted incidence of infections. Serious adverse events (5.9% placebo, 8.6% etanercept) were most commonly observed in the cardiovascular system. Six patients (1 placebo; 5 etanercept) died during the study; four deaths were attributed to cardiovascular events. The numerically higher mortality in the etanercept group was not statistically significant [relative risk (95% CI) = 5.06 (0.59, 42.99)] but remains unexplained. No etanercept-related increase in the incidence of MIIs (3.7% placebo, 3.0% etanercept) or overall infections was observed in the total study population or in subgroups of patients who were > or = 65 yrs of age, had diabetes or had chronic pulmonary disease. **CONCLUSIONS:** Etanercept was generally well tolerated by RA patients with comorbidities. Serious adverse events and deaths occurred more frequently in the etanercept group but event numbers were small and CIs were broad, preventing reliable conclusions from being drawn. Although the study had limited statistical power, the incidence of MIIs in these patients was not increased by etanercept treatment.

67. Wolfe, F., L. Caplan, et al. (2007). "Rheumatoid arthritis treatment and the risk of severe interstitial lung disease." *Scand J Rheumatol* 36(3): 172-8.

OBJECTIVES: Interstitial lung disease (ILD) is an important complication of rheumatoid arthritis (RA) or its treatment, and is associated with substantially increased mortality. Reports have suggested that infliximab with or without azathioprine might lead to rapidly progressive or fatal ILD. We used an RA data bank to assess the associations of treatments for RA and severe ILD. **METHODS:** ILD was identified in hospitalisations and death records in 100 of 17,598 RA patients and studied in relation to RA therapy with Cox regression analyses. **RESULTS:** The incidence of hospitalisation for ILD (HILD) was 260 per 100,000 patient years. Among those hospitalised for ILD, 27.0% died. In multivariable models of current and past RA treatment, the only current treatment associated with HILD was prednisone: hazard ratio (HR) 2.5 [95% confidence interval (CI) 1.5-4.1]. Among past therapies, prednisone (HR 3.0, 95% CI 1.0-8.9), infliximab (HR 2.1, 95% CI 1.1-3.8), etanercept (HR 1.7, 95% CI 1.0-3.0), and cyclophosphamide (HR 3.7, 95% CI 0.9-15.5) were

associated with HILD. Pre-existing lung problems were identified in 67% of HILD. Only one case of HILD in the 100 hospitalisations suggested a possible temporal relationship between infliximab and HILD. CONCLUSIONS: Associations between RA treatment and HILD are confounded by the prescription of treatments for ILD such as prednisone, infliximab, etanercept, and cyclophosphamide. There is no clear pattern of causal association of treatment and ILD, and there is no clear evidence to support a causal relationship between infliximab, azathioprine, and HILD.

68. Wolfe, F. and K. Michaud (2007). "The effect of methotrexate and anti-tumor necrosis factor therapy on the risk of lymphoma in rheumatoid arthritis in 19,562 patients during 89,710 person-years of observation." *Arthritis Rheum* 56(5): 1433-9.

OBJECTIVE: To ascertain the relationship between anti-tumor necrosis factor (anti-TNF) therapy, methotrexate (MTX), and the risk of lymphoma in patients with rheumatoid arthritis (RA). This report updates our previous report during 29,314 person-years of followup. METHODS: Participants in the National Data Bank for Rheumatic Diseases (NDB) longitudinal study of long-term outcomes of RA completed semiannual questionnaires from 1998 through 2005, during 89,710 person-years of followup. Lymphoma reports were validated by medical records. The association between lymphoma and treatment was investigated using conditional logistic regression, adjusted for severity and demographic covariates. RESULTS: Of the 19,591 participants, 55.3% received biologic agents and 68.0% received MTX while enrolled in the NDB. The lymphoma incidence rate was 105.9 (95% confidence interval [95% CI] 86.6-129.5) per 100,000 person-years of exposure. Compared with the SEER (Surveillance, Epidemiology, and End-Results) lymphoma database, the standardized incidence ratio was 1.8 (95% CI 1.5-2.2). The odds ratio (OR) for lymphoma in patients who received anti-TNF therapy compared with patients who did not receive anti-TNF therapy was 1.0 (95% CI 0.6-1.8 [P = 0.875]). The OR for lymphoma in patients who received anti-TNF plus MTX therapy compared with patients who received MTX treatment alone was 1.1 (95% CI 0.6-2.0 [P = 0.710]). Infliximab and etanercept considered individually also were not associated with a risk of lymphoma. CONCLUSION: In a study of lymphoma in 19,591 RA patients over 89,710 person-years of followup, which included exposure to anti-TNF therapy in 10,815 patients, we did not observe evidence for an increase in the incidence of lymphoma among patients who received anti-TNF therapy.

69. Yamada, T., A. Nakajima, et al. (2006). "Increased risk of tuberculosis in patients with rheumatoid arthritis in Japan." *Ann Rheum Dis* 65(12): 1661-3.

OBJECTIVE: To determine the risk for tuberculosis infection in patients with rheumatoid arthritis before the anti-cytokine era in Japan. PATIENTS AND METHODS: A database of a single-institute-based large observational cohort study for rheumatoid arthritis at the Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan, was analysed. Information on the history of tuberculosis infection was collected by patient self-reporting during April and October 2003. The age-adjusted incidence rate and relative risk for tuberculosis infection were investigated. RESULTS: Among 5044 patients with rheumatoid arthritis, 483 (9.6%) patients claimed to have a history of tuberculosis infection before October 2002. The frequency of history of tuberculosis increased according to the age of the patient. Four cases of new-onset tuberculosis were identified among 5544 patients with rheumatoid arthritis during 1 year. The age-adjusted incidence of tuberculosis was

42.4/100,000 patients. The relative risk for tuberculosis was 3.21 (95% confidence interval (CI) 1.21 to 8.55), and that of men and women was 10.59 (95% CI 3.42 to 32.78) and 1.41 (95% CI 0.2 to 10), respectively. CONCLUSION: There was an increased risk of tuberculosis infection in Japanese patients with rheumatoid arthritis, especially in male patients before the introduction of anti-tumour necrosis factor treatment. These data should form the basis for the risk management of anti-cytokine treatment in Japan.

70. Zink, A., A. Strangfeld, et al. (2006). "Effectiveness of tumor necrosis factor inhibitors in rheumatoid arthritis in an observational cohort study: comparison of patients according to their eligibility for major randomized clinical trials." *Arthritis Rheum* 54(11): 3399-407. OBJECTIVE: Randomized clinical trials (RCTs) evaluate the efficacy of treatments in selected groups of patients defined by strict inclusion criteria. The value of these trials in predicting therapeutic effectiveness in "real world" patients is limited. This observational cohort study was designed to complement the knowledge obtained in RCTs by evaluating the effectiveness of tumor necrosis factor (TNF) inhibitors in patients with rheumatoid arthritis (RA) according to their eligibility for the major trials. METHODS: Using the data from the German biologics register Rheumatoid Arthritis Observation of Biologic Therapy (RABBIT [in German]), we investigated how many of the RA patients who were treated with a TNF inhibitor (infliximab, etanercept, or adalimumab) would have been eligible for the major clinical trials that led to approval of the drugs. In addition, therapeutic effectiveness was compared in the eligible and ineligible patients using the American College of Rheumatology 20% (ACR20) and 50% (ACR50) improvement response criteria. RESULTS: Only 21-33% of the patients in the RABBIT register would have been eligible for the major trials. In these patients, the ACR20 and ACR50 improvement responses, indicating therapeutic effectiveness, were comparable with the response rates in the published trials. ACR response rates were lower in those patients considered ineligible for the trials; however, absolute improvement was similar to that in eligible patients. Ineligible patients had lower baseline disease activity, more comorbidity, and lower functional status. CONCLUSION: RCT cohorts reflect only a minor proportion of the patients treated with biologic agents in routine care. In the clinic setting, the indications for treatment with biologic agents are not identical to the inclusion criteria for trials. Despite the smaller relative improvement achieved in these patients with longstanding, severe RA who would not fulfill the inclusion criteria of a major trial, the majority of such patients would nevertheless benefit from biologic therapy.