PRIORITY BRIEFING
The purpose of this briefing paper is to aid Stakeholders in prioritising topics to be taken further by PenCLAHRC as the basis for a specific evaluation or implementation research project. They were complied in 2-3 days.

Is it ever possible to reduce (or withdraw) tumour necrosis factor alpha (TNFa) inhibitors from people with rheumatoid arthritis (RA) without the disease recurring?

Question ID: 8
Question type: Intervention
Question: Is it ever possible to reduce (or withdraw) tumour necrosis factor alpha (TNFa) inhibitors from people with rheumatoid arthritis (RA) without the disease recurring?

Population: People with RA whose disease is in continuous remission after two years of treatment with a TNFa inhibitor (adalimumab, etanercept, and infliximab).

Intervention: Undertake a multi centre randomised controlled trial in people with RA which is in continuous remission (two years) during treatment with a TNFa inhibitor. The randomisation would be between withdrawal of the treatment (either phased or immediate) and continued treatment at current licensed doses.

Control: Continued treatment at current licensed doses.

Outcome: Some people with RA treated with TNFa inhibitors may be able to stop treatment completely, whilst others may reduce the frequency of dosing. These reductions would decrease the exposure to a toxic drug and the cost to the health community.

Rheumatoid Arthritis:
Rheumatoid arthritis (RA) is a chronic disease that primarily affects the joints causing pain, swelling and inflammation. It most commonly begins between the ages of 20 and 40 years but can affect people of any age, and has unpredictable periods of inflammatory activity. RA is an autoimmune disease and frequently leads to bone erosion, reduced range of movement, fluctuating pain and psychological distress, and culminates in disability. Most people with RA require lifelong hospital follow up. There is no cure but early diagnosis and treatment can ease symptoms and progression. The ultimate aim of management is to achieve disease remission for the patient. Remission has been defined in a number of ways. Each definition includes elements of a lack of signs and symptoms of disease activity and some require evidence that disease progression has been stopped. Where remission cannot be achieved, the aim is to minimise disease activity in order to optimise the chances of preventing progressive damage to joints and consequent disability. The longer the remission period, or the least

amount of disease activity that can be achieved, the better will be the long-term outcome.

TNFa inhibitors:

Tumour necrosis factor alpha (TNFa) is a chemical produced by the body's immune system that promotes inflammation in and around the rheumatoid joint. Three TNF antagonists (inhibitors) are approved for the treatment of RA: etanercept (Enbrel®), infliximab (Remicade®), and adalimumab (Humira®). These drugs reduce the activity of TNF, they are similar in their efficacy at decreasing signs and symptoms of RA, slowing or halting radiographic damage, and improving function and quality of life and work in broadly the same way. Dosage varies according to the drug from weekly to eight-weekly and improvements can normally be seen within weeks. Early concerns regarding the toxicity of these agents are now being investigated with data accumulating on substantial numbers of patients treated worldwide and for longer periods of time. Negative side effects include: increased risk of infection, development of a clinical syndrome (fever, chills, body aches and headaches), injection site reactions, and increased risk of lymphomas. The cost of these drugs is high and insurance reimbursement issues have limited the use of these agents for some patients.

The Health Problem

There are over 400,000 people with rheumatoid arthritis (RA) in the UK. Approximately 12,000 people are newly diagnosed with RA each year in the UK. Overall occurrence of RA is 2–4 times greater in women than men. A minimum of six months of remission or minimal disease activity indicates sustained management.

The economic impact of this disease includes: direct cost to the NHS and associated healthcare support services; indirect costs to the economy, including the effects of early mortality and lost
productivity; personal impact of RA and subsequent complications on patients and their families.

Although the course of RA is variable, within two years of diagnosis patients usually experience moderate disability, and after 10 years 30% are severely disabled. Life expectancy in patients with RA is also reduced. Approximately one third of patients cease work because of the disease within two years of onset, and this prevalence increases thereafter. The total costs of RA in the UK, including indirect costs and work related disability, have been estimated at between £3.8 billion and £4.75 billion per year.

Approximately 22% (£280k out of £1.3million) of the Plymouth PCT monthly budget for Payment by Results (PbR) excluded drugs is spent on treating RA with the TNFa inhibitors adalimumab, etanercept, and infliximab – though these costs vary month to month. These three TNFa inhibitors are the three most expensive items on the Plymouth PCT budget for PbR excluded drugs and are more costly than all other treatments including those for cancer, age related

macular degeneration and HIV. It is likely that these figures are reflected in other Peninsula PCTs.

At Plymouth Healthcare NHS Trust there are currently approximately 320 people with RA being treated with TNFa inhibitors, with the number increasing each year. Although the absolute number of people with RA treated with TNFa inhibitors may be relatively low, the nature of its chronic course with an often near normal life expectancy, means that the total lifetime cost per person is likely to be higher than, say, a malignancy where expensive drugs often extend life by months to 1-2 years. Local information for the wider Devon and Cornwall area is not known.

Guidelines:
NICE guidance (2009) *Rheumatoid Arthritis: a national clinical guideline for management and treatment in adults* suggest that TNFa inhibitors should be discontinued if there is inadequate improvement in symptoms.

In Plymouth for the proportion of people who have *any* positive response with TNFa (about 60/100 of those in whom it is tried), they are then generally kept on TNFa unless there is an adverse event. In people who do not respond (30-40/100) it is stopped after a maximum of 6 months (although there are reports that patients continue to take TNFa after showing no response to the drug in other places).

NHS Priority
Regional
SW SHA Priorities framework 2008-11
- Improve the productivity of clinical activity, with 50% of the potential achieved by 31 March 2011.

Local
Local perspective
- Plymouth hospitals aim to maintain good symptom control in long-term conditions

Existing Research

Published research
No reviews were found in the searches that were conducted. A small number of studies were retrieved looking at the discontinuation of TNFa therapy in RA. Most of these report positive potential for the reduction or withdrawal of TNFa drugs in RA remission.[1-8, 10-12] No studies were found that looked at reducing the dosage of TNFa. There are number of important issues to consider. Firstly, there seems to be some dispute over the definition of remission.[8,9] Current definitions, whilst dealing with 'clinical' indications of remission, do not discuss structural and physical characteristics of remission. In particular, one study[4] reports that interruption of TNFa remission therapy will result in continual progress in joint damage (physical changes as measured by Magnetic Resonance Imaging - MRI)

despite sustained clinical remission (as measured by the Disease Activity Score - DAS). This definition is likely to impact on the perceived success of any treatment drugs. Secondly, many of the studies do not conduct follow-up for longer periods of time, most are conducted for 6-24 months with only two studies conducting 4 and 5 year follow-up. Third, the patients involved in these studies also vary greatly, ranging from 18 – 61 years with varying lengths of time living with the active disease or in remission. Some studies report that optimal treatment strategies have still yet to be established,[8] this follows as studies report varying rates of successful TNFa free remission before relapse. Some studies show an increasing rate of relapse as the period of TNFa discontinuation increases[1,3] however there seems to be at least one year of TNFa drug-free remission (without relapse) possible in most studies and longer periods also occur.[7] There is some suggestion that TNFa drugs with methotrexate can improve outcomes of function and quality of life better than sole treatment with methotrexate[7] but this needs to be studied further. Between the studies it may also be possible that there are differences in the performance of the three TNFa drugs in terms of the TNFa and relapse-free remission period.[4,6,12]

Ongoing Research:

There is a lot of ongoing research in this area at present:

1) A prospective study looking at maintenance of remission after discontinuation of Adalimumab (12 month follow-up). Due to complete Dec 2010 in Italy.
2) A trial also looking at maintenance of remission after discontinuation of Adalimumab (12month follow) also looking at incidence of flare and physical function. Due to complete July 2011 in Sweden.
3) Randomized controlled trial assessing the impact of progressive spacing of TNF treatment versus DMARD maintenance on the maintenance of remission and risk of relapse. Due to complete September 2011 in France.
4) Randomised trial assessing the impact of reducing or withdrawing Etanercept (follow-up over 63 weeks). Due to complete March 2011 in Denmark, Norway, Finland and Sweden.
5) Randomized controlled trial assessing the impact of Etanercept withdrawal on maintenance of remission (28 day follow-up). Due to complete December 2011 in the Netherlands.

Feasibility:

Anecdotally some rheumatologists in the Peninsula support patients in reducing the frequency of dosing of TNFa inhibitors.

References

1) Brocq, O., E. Millasseau, et al. (2009). "Effect of discontinuing TNFalpha antagonist therapy in patients with remission of rheumatoid arthritis." Joint Bone Spine **76**(4): 350-5.
OBJECTIVE: The objective of this study was to determine the time to relapse after tumor necrosis factor alpha (TNFalpha) antagonist discontinuation in patients with remission of rheumatoid arthritis (RA). METHODS: Among 304 patients taking TNFalpha antagonist therapy for RA, 21 achieved a remission and were taken off the TNFalpha antagonist. Remission was defined as DAS28<2.6 for at least 6 months without nonsteroidal inflammatory drugs or more than 5 mg of prednisone per day but with disease-modifying antirheumatic drug (DMARD) therapy if needed. The same TNFalpha antagonist was restarted in the event of a relapse (DAS28>3.2). RESULTS: The 21 patients had a mean age of 61 years, a mean disease duration of 11.3 years, and a mean remission duration at TNFalpha antagonist discontinuation of 19.2 months. The TNFalpha antagonist was infliximab in 2 patients, adalimumab in 5, and etanercept in 14; and 14 patients were taking a concomitant DMARD. The number of patients still in remission after TNFalpha antagonist discontinuation was 9/20 after 6 months and 5/20 after 12 months. Mean time to relapse was 14.7 weeks. While off TNFalpha antagonist therapy, 3 of the 5 relapse-free patients after 12 months were on DMARD therapy, compared to 11 of the 15 patients who relapsed. Compared to the 15 patients who relapsed, the 5 relapse-free patients had a longer time on TNFalpha antagonist therapy (56 months vs. 35 months, P=0.012) and a longer time in remission on TNFalpha antagonist therapy (35 months vs.14.5 months, P=0.04). The 15 patients who relapsed consistently achieved a remission after resuming TNFalpha antagonist therapy; the remission occurred within 2 months in 13 patients. CONCLUSION: TNFalpha antagonist discontinuation in patients in remission of RA was followed by a relapse within 12 months in 75% of cases. Relapsing patients responded well to resumption of the same TNFalpha antagonist.

2) Caramaschi, P., S. Pieropan, et al. (2008). "[Sustained response to infliximab treatment in two cases of early rheumatoid arthritis that has been maintained after drug withdrawal]." Reumatismo **60**(3): 221-3.
The authors report two cases of active seropositive rheumatoid arthritis who were treated in an early phase of the disease with infliximab plus methotrexate obtaining a clinical remission. The benefit was maintained after the discontinuation of the anti-TNF alpha inhibitor for adverse events, indicating that the early administration of the drug may be followed by a sustained remission.

3) Goekoop-Ruiterman, Y. P., J. K. de Vries-Bouwstra, et al. (2007). "Comparison of treatment strategies in early rheumatoid arthritis: a randomized trial." Annals of Internal Medicine **146**(6): 406-15.
BACKGROUND: In patients with early rheumatoid arthritis, initial combination therapies provide earlier clinical improvement and less progression of joint damage after 1 year compared with initial monotherapies (as demonstrated in the BeSt study). OBJECTIVE: To evaluate whether the initial clinical and

radiographic efficacy of combination therapies could be maintained during the second year of follow-up in patients with early rheumatoid arthritis. DESIGN: Randomized, controlled clinical trial with blinded assessors. SETTING: 18 peripheral and 2 university medical centers in the Netherlands. PATIENTS: 508 patients with early active rheumatoid arthritis. INTERVENTION: 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). Trimonthly treatment adjustments were made to achieve low disease activity. MEASUREMENTS: Primary end points were functional ability (Health Assessment Questionnaire) and Sharp-van der Heijde score for radiographic joint damage. RESULTS: Groups 3 and 4 had more rapid clinical improvement during the first year; all groups improved further to a mean functional ability score of 0.6 (overall, P = 0.257) and 42% were in remission (overall, P = 0.690) during the second year. Progression of joint damage remained better suppressed in groups 3 and 4 (median scores of 2.0, 2.0, 1.0, and 1.0 in groups 1, 2, 3, and 4, respectively [P = 0.004]). After 2 years, 33%, 31%, 36%, and 53% of patients in groups 1 through 4, respectively, were receiving single-drug therapy for initial treatment. There were no significant differences in toxicity. LIMITATIONS: Patients and physicians were aware of the allocated group, and the assessors were blinded. CONCLUSIONS: Currently available antirheumatic drugs can be highly effective in patients with early rheumatoid arthritis in a setting of tight disease control. Initial combination therapies seem to provide earlier clinical improvement and less progression of joint damage, but all treatment strategies eventually showed similar clinical improvements. In addition, combination therapy can be withdrawn successfully and less treatment adjustments are needed than with initial monotherapies.

4) Lagana, B., A. Picchianti Diamanti, et al. (2009). "Imaging progression despite clinical remission in early rheumatoid arthritis patients after etanercept interruption." International Journal of Immunopathology & Pharmacology **22**(2): 447-54.
The aim of this preliminary study is to evaluate clinical and imaging response in twenty patients with early Rheumatoid Arthritits (eRA) treated with Etanercept (Etn) + Methotrexate (Mtx) and to investigate whether clinical and MRI remission may be maintained after biological therapy interruption. Assessment included: radiography, Visser score and anti-CCP antibodies at baseline; disease activity score in 44 joints (DAS44), rheumatoid factor (RF), Magnetic Resonance Imaging (MRI) of hands and wrists at baseline (T0), 12 (T1), and 24 months (T2). MRI was scored for synovitis, bone oedema and erosions (OMERACT study); patients who reached clinical and imaging remission at T1 were considered eligible for interrupting Etn. At T1 8/20 (40 percent) patients showed a total remission, DAS44 from 5 (T0) to 1.4 (T1); $p<0.02$, whereas the other 12/20 (60 percent) showed an improvement, without complete remission, DAS44 from 4.8 (T0) to 2.8 (T1); $p<0.05$. Etn was therefore interrupted in the first group of patients (group A), whereas it was continued in the other group (group B). At T2, group A maintained clinical remission and group B showed further not significant DAS44 reduction from T1. At T1, a significant reduction in synovitis, bone oedema and total score ($p<0.01$) was observed both in group A and in group B.

At T2, group A showed an increase in all the MRI scores that was significant for the synovitis and total score, whereas group B exhibited a further not significant reduction. This preliminary study reports an excellent clinical and imaging response in eRA patients treated with Etn with total remission in 40 percent of them after a 1-year therapy period. However, it indicates that joint damage may progress, despite a sustained clinical remission, after Etn suspension.

5) Miyamura, T., K. Sonomoto, et al. "Discontinuation of etanercept in patients with rheumatoid arthritis who were in clinical remission." Clin Rheumatol **29**(1): 87-90.
The appearance of tumor necrosis factor blockers changes the treatment goal of rheumatoid arthritis (RA) to include not only the inhibition of bone destruction, but also the induction of remission. We, herein, report two cases with RA that showed a prolonged remission after the discontinuation of etanercept. The two cases were 27 and 38 years of age, and their disease durations were 6 and 14 months, respectively. Their disease activity score 28 (DAS28) before treatment were 4.43 and 5.07, respectively. Case two was resistant to infliximab as determined by previous treatment with this therapy. Both cases showed a dramatic clinical response and discontinued etanercept in the 15th month and the 14th month after the start of treatment, respectively. No exacerbation of arthritis was evident after the discontinuation of etanercept as supported by the maintenance of DAS28 at less than 2.6. Moreover, after the discontinuation of etanercept, radiographic progression was not evident and decreased modified Sharp scores were observed for at least 1 year in both cases. These findings indicate that clinical and radiographic remission is possible in some patients with RA after the discontinuation of etanercept.

6) Nawata, M., K. Saito, et al. (2008). "Discontinuation of infliximab in rheumatoid arthritis patients in clinical remission." Mod Rheumatol **18**(5): 460-4.
Biologic drugs are effective but are also expensive, and it is difficult to evaluate the duration of treatment. Infliximab, an anti-TNFalpha antibody, suppresses arthritic activity and inhibits bone destruction in patients with rheumatoid arthritis (RA). Here, we document that infliximab could be discontinued after clinical remission in RA patients. Among 172 patients with RA who reached clinical remission following infliximab (3 mg/kg) and methotrexate (MTX, >6 mg/w), nine patients with sustained remission discontinued it. Clinical assessment was based on a disease activity score (DAS) that included a 28-joint count/erythrocyte sedimentation rate (DAS28-ESR). The disease was assessed before and after the start of infliximab treatment, and concomitant drug treatment-in the order of corticosteroid, nonsteroidal anti-inflammatory drugs (NSAIDs), and disease-modifying anti-rheumatic drugs (DMARDs) other than MTX-was gradually discontinued. We considered patients for discontinuation of infliximab treatment after remission (DAS28-ESR<2.6) had been sustained for more than 24 weeks. The nine patients able to discontinue treatment were all females, with a mean age of 53.8 years; eight patients were at stage I or II. The mean duration of disease was 28.7 months, and these patients were on corticosteroid treatment equivalent to a mean of 2.28 mg prednisolone (PSL). These nine patients all met the remission standard-that DAS28-ESR<2.6 for >or=24 weeks) -and so their

treatment with concomitant drugs was discontinued. After the discontinuation of infliximab, the mean period of sustained remission was 14.2 months and the longest period was 29 months. The duration of disease was significantly shorter and the points from Steinbrocker's stage-classification were significantly lower in the infliximab-discontinued group than in the infliximab-continued group. Strategic reductions and/or discontinuations of concomitant treatment were performed in RA patients who attained clinical remission (DAS28<2.6) through treatment with infliximab and MTX. Nine patients successfully discontinued infliximab after maintaining clinical remission for more than 24 weeks. After infliximab was discontinued, clinical remission and suppression of joint destruction were maintained with MTX alone, especially in early RA patients.

7) Quinn, M. A., P. G. Conaghan, et al. (2005). "Very early treatment with infliximab in addition to methotrexate in early, poor-prognosis rheumatoid arthritis reduces magnetic resonance imaging evidence of synovitis and damage, with sustained benefit after infliximab withdrawal: results from a twelve-month randomized, double-blind, placebo-controlled trial." Arthritis Rheum **52**(1): 27-35. OBJECTIVE: Anti-tumor necrosis factor alpha agents are among the most effective therapies for rheumatoid arthritis (RA). However, their optimal use is yet to be determined. This 12-month double-blind study attempted remission induction using standard therapy with or without infliximab in patients with early, poor-prognosis RA. The primary end point was synovitis (measured by magnetic resonance imaging [MRI]). Clinical observations continued to 24 months. METHODS: All patients had fewer than 12 months of symptoms. Assessments included full metrologic evaluation, laboratory tests, radiographs, functional evaluation using the Health Assessment Questionnaire (HAQ), and quality of life measurement using the RA Quality of Life (RAQoL) questionnaire. MRI was performed at 0, 4, 14, and 54 weeks; MR images were scored blindly. Patients received methotrexate (MTX) and were randomized to receive either infliximab or placebo for 12 months. RESULTS: Twenty patients were recruited (mean age 52 years, mean symptom duration 6 months, mean C-reactive protein level 42 mg/liter, and 65% rheumatoid factor positive). At 1 year, all MRI scores were significantly better, with no new erosions in the infliximab plus MTX group; a greater percentage of infliximab plus MTX-treated patients fulfilled the American College of Rheumatology (ACR) 50% and 70% improvement criteria (78% versus 40% in the placebo plus MTX group and 67% versus 30%, respectively) and had a greater functional benefit ($P < 0.05$ for all comparisons). Importantly, at 1 year after stopping induction therapy, response was sustained in 70% of the patients in the infliximab plus MTX group, with a median Disease Activity Score in 28 joints (DAS28) of 2.05 (remission range). At 2 years, there were no significant between-group differences in the DAS28, ACR response, or radiographic scores, but differences in the HAQ and RAQoL scores were maintained ($P < 0.05$). CONCLUSION: Remission induction with infliximab plus MTX provided a significant reduction in MRI evidence of synovitis and erosions at 1 year. At 2 years, functional and quality of life benefits were sustained, despite withdrawal of infliximab therapy. These data may have significant implications for the optimal use of expensive biologic therapies.

8) Saleem, B., S. Nizam, et al. (2006). "Can remission be maintained with or without further drug therapy in rheumatoid arthritis?" Clin Exp Rheumatol **24**(6 Suppl 43): S-33-6.
Remission is now the accepted goal of management in rheumatoid arthritis (RA). This article highlights the controversies surrounding the definition of remission and reviews the potential of current treatment options to achieve remission. Defining "true" remission can be difficult based on current criteria, which do not consider structural and physical function. Nonetheless, considerable advances in recent years have made the concept of remission a realistic goal. In early RA, substantial and largely irreversible radiographic damage is seen in 60% of patients within the first 2 years of diagnosis. Early therapeutic intervention would ideally lead to reduction in long-term disability in RA and likelihood of inducing and maintaining remission. Long-term maintenance therapy with disease-modifying antirheumatic drugs (DMARDs) has been shown to be effective in preventing flares of disease. Stopping therapy for short periods does not necessarily lead to flares, but the effect on long-term radiographic damage and potential to achieve similar levels of disease control following reinstatement of therapy is not established. Early use of tumour necrosis factor (TNF)-antagonist therapy (e.g. infliximab) has been shown to lead to significant improvement in disease activity measures (clinical and radiologic outcomes) when compared to monotherapy or combination DMARD and corticosteroid therapies. Response was shown to be sustained in 70% of patients receiving TNF-blocking therapy 1 year after stopping treatment. This suggests the significant role of TNF-blocking therapy in enabling sustainable remission without need for long-term administrations, which has important implications for favourable health economics. At present, little published evidence exists on the effects of withdrawal of TNF-blocking therapy in patients with established RA in remission. In conclusion, evidence indicates that remission is a realistic goal, but more evidence is required to establish optimal treatment strategies and define criteria for remission that include imaging and immunological as well as clinical assessment of the disease state.

9) Sesin, C. A. and C. O. Bingham, 3rd (2005). "Remission in rheumatoid arthritis: wishful thinking or clinical reality?" Semin Arthritis Rheum **35**(3): 185-96.
OBJECTIVES: To review the concept of remission in rheumatoid arthritis (RA), as defined by the Food and Drug Administration (FDA), the American College of Rheumatology (ACR), and the European League Against Rheumatism (EULAR). To delineate differences between significant clinical improvements, very low disease activity, and the achievement of true remission. To evaluate the prevalence of these outcomes with biologic therapy and traditional disease-modifying antirheumatic drugs (DMARD) regimens. METHODS: The MEDLINE database was searched for the key words "remission" and "rheumatoid arthritis." Efficacy data of RA clinical trials from 1985 to 2004 are based on a literature review of medical journals and abstracts from rheumatology meetings. We review 3 well-defined sets of criteria established by the ACR, EULAR, and the FDA for measuring remission. RESULTS: Defining remissions in clinical trials and clinical practice requires appropriate standardized and objective outcome measures,

such as the ACR and EULAR remission criteria. Traditional DMARDs often provide symptom relief, improvements in physical function, and the slowing of radiographic progression in patients with RA, but rarely lead to the complete cessation of RA activity. Remission, as defined by the ACR criteria, has been observed in 7 to 22% of patients treated with traditional DMARD monotherapy (ie, gold, penicillamine, methotrexate [MTX], cyclosporine A, or sulfasalazine), but these remissions have often been short-lived. Treatments with DMARD combinations, biologic monotherapy, and biologic combination therapy with MTX offer greater hope and may facilitate the higher rates of remission. Clinical trial results have shown that newer DMARDs such as leflunomide or the combination of multiple DMARDs can generally elicit greater EULAR remission rates (ranging from 13 to 42%) than monotherapies. Biologic combinations with MTX have also been shown to induce significant remission (as defined by the EULAR criteria) in RA patients, with a 31% rate observed with infliximab plus MTX at 54 weeks, a 50% rate observed for adalimumab plus MTX after 2 years of therapy, and a 41% rate observed for etanercept plus MTX after 2 years of therapy. CONCLUSIONS: In the era of biologics and combination therapy, identifying remission or at least very low disease activity as the ultimate goal in RA therapy should become the new standard for the outcome of all RA trials. The criteria established by the FDA, the ACR, and the EULAR represent an important step toward achieving this goal.

10) Tanaka, Y., T. Takeuchi, et al. "Discontinuation of infliximab after attaining low disease activity in patients with rheumatoid arthritis: RRR (remission induction by Remicade in RA) study." Ann Rheum Dis.
BACKGROUND: Tumour necrosis factor (TNF) inhibitors enable tight control of disease activity in patients with rheumatoid arthritis (RA). Discontinuation of TNF inhibitors after acquisition of low disease activity (LDA) is important for safety and economic reasons. OBJECTIVE: To determine whether infliximab might be discontinued after achievement of LDA in patients with RA and to evaluate progression of articular destruction during the discontinuation. METHODS: 114 patients with RA who had received infliximab treatment, and whose Disease Activity Score, including a 28-joint count (DAS28) was <3.2 (LDA) for 24 weeks, were studied. RESULTS: The mean disease duration of the 114 patients was 5.9 years, mean DAS28 5.5 and mean modified total Sharp score (mTSS) 63.3. After maintaining LDA for >24 weeks by infliximab treatment, the drug was discontinued and DAS28 in 102 patients was evaluated at year 1. Fifty-six patients (55%) continued to have DAS28<3.2 and 43% reached DAS<2.6 at 1 year after discontinuing infliximab. For 46 patients remission induction by Remicade in RA (RRR) failed: disease in 29 patients flared within 1 year and DAS28 was >3.2 at year 1 in 17 patients. Yearly progression of mTSS (DeltaTSS) remained <0.5 in 67% and 44% of the RRR-achieved and RRR-failed groups, respectively. The estimated DeltamTSS was 0.3 and 1.6 and Health Assessment Questionnaire-Disability Index was 0.174 and 0.614 in the RRR-achieved and RRR-failed groups, respectively, 1 year after the discontinuation. CONCLUSION: After attaining LDA by infliximab, 56 (55%) of the 102 patients with RA were able to discontinue infliximab for >1 year without progression of radiological articular destruction.

11) van der Kooij, S. M., Y. P. Goekoop-Ruiterman, et al. (2009). "Drug-free remission, functioning and radiographic damage after 4 years of response-driven treatment in patients with recent-onset rheumatoid arthritis." Annals of the Rheumatic Diseases **68**(6): 914-21.
OBJECTIVES: To compare the occurrence of drug-free remission, functional ability and radiological damage after 4 years of response-driven treatment according to four different treatment strategies for rheumatoid arthritis (RA). METHODS: Patients with recent-onset, active RA (n = 508) were randomly assigned to four different treatment strategies: (1) sequential monotherapy; (2) step-up combination therapy; (3) initial combination therapy with prednisone and (4) initial combination therapy with infliximab. Treatment was adjusted based on 3-monthly disease activity score (DAS) assessments, aiming at a DAS < or =2.4. From the third year, patients with a sustained DAS <1.6 discontinued treatment. RESULTS: In total, 43% of patients were in remission (DAS <1.6) at 4 years and 13% were in drug-free remission: 14%, 12%, 8% and 18% of patients in groups 1-4, respectively. The absence of anti-cyclic citrullinated peptide antibodies, male gender and short symptom duration were independently associated with drug-free remission. Functional ability and remission were maintained in all four groups with the continuation of DAS-driven treatment, without significant differences between the groups. Significant progression of joint damage was observed in 38% and 31% of patients in groups 3 and 4 versus 51% and 54% of patients in groups 1 and 2 ($p<0.05$, group 4 versus groups 1 and 2, group 3 versus group 2). CONCLUSIONS: In patients with recent-onset active RA, drug-free remission was achieved in up to 18% of patients. DAS-driven treatment maintained clinical and functional improvement, independent of the treatment strategy. Joint damage progression remained significantly lower after initial combination therapy compared with initial monotherapy.

12) Weinblatt, M. E., E. C. Keystone, et al. (2006). "Long term efficacy and safety of adalimumab plus methotrexate in patients with rheumatoid arthritis: ARMADA 4 year extended study." Annals of the Rheumatic Diseases **65**(6): 753-9.
OBJECTIVE: To evaluate the efficacy and safety of adalimumab plus methotrexate (MTX) given for up to 4 years in patients with active, longstanding rheumatoid arthritis. METHODS: Patients responding inadequately to MTX were entered into a 24 week, controlled study (ARMADA) with adalimumab plus MTX or placebo plus MTX, and some were enrolled in a subsequent open label extension. The efficacy and safety of treatment were evaluated. Additional analyses were made for those patients whose corticosteroid and/or MTX dosages were adjusted during the extension. RESULTS: Of 271 patients in the original ARMADA trial, 262 received at least one dose of adalimumab and were evaluated. At the time of analysis, 162/262 (62%) patients had remained in the study and received treatment for a mean of 3.4 years. Withdrawals were for lack of efficacy (8%), adverse events (12%), and other reasons (18%). In 147 patients who completed 4 years' treatment, efficacy achieved at 6 months was maintained. At 4 years, 78%, 57%, and 31% had achieved ACR20/50/70; 43% achieved clinical remission (DAS28 <2.6); and 22% had no physical function abnormalities (HAQ = 0). Results were similar for 196 patients who received

treatment for 2-4 years. Efficacy was maintained in many patients when dosages were decreased (corticosteroids (51/81 (63%) patients), MTX (92/217 (42%)), or both (25/217 (12%))). Serious adverse events were comparable during open label treatment and the controlled phase. Serious infections occurring during open label treatment and the blinded period were similar (2.03 v 2.30 events per 100 patient-years, respectively). CONCLUSIONS: Adalimumab plus MTX sustained clinical response and remission in patients with RA during 4 years. The safety profile during the first 6 months was similar to that after 4 years' follow up. Reduction of corticosteroid and/or MTX dosages did not adversely affect long term efficacy.