

The Use of Biological Agents in the Treatment of Rheumatoid Arthritis

Peng-Thim Fan,¹MD, FACP, Keng-Hong Leong,²MD, FRCP (Edin), FAMS

Abstract

Rheumatoid arthritis is a common and potentially devastating condition which did not have good treatment options until recently. Pharmacological treatment should not just comprise anti-inflammatory agents and corticosteroids. The current therapeutic approach is to start a disease modifying agent early in the illness to prevent eventual joint damage. Older disease modifying anti-rheumatic drugs (DMARDs) include methotrexate, sulphasalazine and hydroxychloroquine. Newer ones such as leflunomide and cyclosporine are also used. A recent advance in the management of rheumatoid arthritis is the use of biological agents which block certain key molecules involved in the pathogenesis of the illness. They include tumour necrosis factor (TNF)-blocking agents such as infliximab, etanercept and adalimumab, the anti-CD 20 agent rituximab and CTLA-4 Ig abatacept. Other agents which are in development include anti-IL6 tocilizumab, anti-CD22 and anti-lymphostat B. In this review, the efficacy and side effects of these agents, their impact on current clinical practice and future trends are discussed.

Ann Acad Med Singapore 2007;36:128-34

Key words: Abatacept, Anti-TNF, Rituximab

Introduction

The treatment of rheumatoid arthritis (RA) has gone through many major changes in the past 100 years. Historically, it was essentially untreatable and many patients like the French impressionist painter Renoir had to live with the ravages of the disease through sheer courage and determination. In 1948, the use of corticosteroids was introduced which seemed at first to be an extremely effective treatment but the severe side effects of long-term therapy soon limited their use.

The concept that drugs should be used to slow down damage caused by the disease rather than simply to control symptoms resulted in various agents being introduced, which were initially called SAARDS or “slow acting anti-rheumatic drugs.” These included drugs such as intramuscular or oral gold salts, D-penicillamine, anti-malarial agents, sulphasalazine and methotrexate (MTX).¹ The term SAARD was replaced with disease modifying anti-rheumatic drug (DMARD) and currently MTX is the most commonly used DMARD in several rheumatic

diseases, particularly in rheumatoid arthritis and possibly psoriatic arthritis. Other commonly used DMARDs include sulphasalazine, hydroxychloroquine and leflunomide.

As we begin to understand the pathogenesis of auto-immune disease and the contribution of the different pathways of activation of inflammation and tissue damage, we are able to identify new targets for therapy. Many of these new medications modify the immune response by blocking the effect of pro-inflammatory cytokines or by acting on various immune cells such as the B lymphocyte or the interaction between the T cell and the antigen-presenting cell (APC). Recent studies have shown that 50% of patients with rheumatoid arthritis are disabled within 10 years of the onset of disease and survival is reduced.² With the advent of more potent drugs, the strategy of treating rheumatoid arthritis has changed. In the past, there was a tendency to start a DMARD late in the illness when erosions or deformities were established. Current practice is to start a DMARD early on in the illness in order to prevent joint damage.³

¹ affiliation not provided

² Private Practice, Gleneagles Medical Centre, Singapore

Address for Correspondence: Dr Leong Keng Hong, Leong Keng Hong Arthritis & Medical Clinic, 6 Napier Road, #04-18 Gleneagles Medical Centre, Singapore 258499.

Email: kenghong@singnet.com.sg

Targetted Therapy – Chance of a Cure?

The advances made in the understanding of autoimmunity have led to the idea that a cure may be possible if the initiating event in the pathogenesis of rheumatoid arthritis can be modified or stopped. However, research with vaccines and agents blocking the interaction of the T cell and APC has not resulted in any outcome that even looks like a cure. This is because the immune system is complex and there does not seem to be a single key cytokine or process which drives the whole series of events (Fig. 1).

Maini et al⁴ were instrumental in elucidating the major role of tumour necrosis factor alpha (TNF- α) and paving the way for TNF blocking agents to become one of the major advances in the treatment of inflammatory arthritis. It appears, though, that TNF is not the central cytokine it was once thought to be in the pathogenesis of rheumatoid arthritis. Other cytokines such as interleukin-1 (IL-1) and IL-6 also do not play a central dominant role. Inhibiting any one of these cytokines may produce very effective control of the disease but it does not constitute a cure, since the disease returns after a variable interval when treatment is stopped. In a substantial proportion of patients, the disease progresses even if treatment is sustained. Other approaches have been shown to be effective. These include eliminating

circulating CD20 positive B lymphocytes and blocking the co-stimulatory signal (CD28-CD80/86) for T cell-APC interaction.

There are several ways of inhibiting the action of an inflammatory cytokine which usually exerts its effect after binding to its cell surface receptor. Soluble receptors or monoclonal antibodies bind to the cytokine and compete for binding with the cell surface receptor. Alternatively, receptor antagonists or monoclonal antibodies bind to the cell surface receptor and prevent the cytokine from binding.

Although none of these newer agents achieve a permanent drug-free remission, they are much more effective than the older DMARDs in reducing symptoms, reducing or stopping joint damage and preventing functional disability. They have been shown to be effective in patients who are refractory to conventional DMARDs. These drugs work very well in patients with long-established disease of 12 years or more as well as in those with early disease of less than 3 years duration. Patients with early disease respond much better than those with long-standing disease. In these patients, complete remission can be accomplished with the TNF-inhibitors. Several trials show that combining a TNF-inhibitor with MTX is particularly effective and far superior to using either drug alone. Radiographic damage can be

The Integrated Immune Response and Pathogenesis of Rheumatoid Arthritis

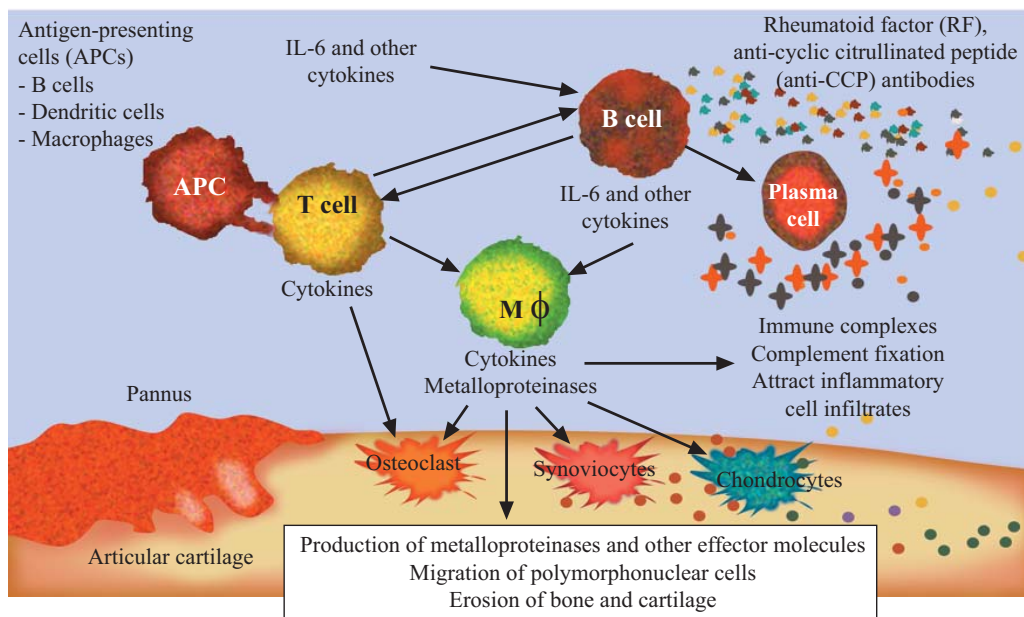


Fig. 1. The integrated immune response and pathogenesis of rheumatoid arthritis.

stopped entirely with such treatment.

These observations have led to the idea that there is a window of opportunity within which aggressive treatment of RA can produce permanent remission.⁵ Several professional organisations, including the American College of Rheumatology (ACR), have adopted new aggressive strategies. It is likely that the same approach may also be effective in managing ankylosing spondylitis and psoriatic arthritis.

Efficacy of Biological Response Modifiers

In clinical trials with rheumatoid arthritis and psoriatic arthritis, outcome measures for disease activity are the ACR 20, 50 and 70, which indicate 20%, 50% or 70% improvement in various parameters such as number of tender and swollen joints, C reactive protein, pain on visual analogue scale and physician or patient global assessment.^{6,7} Some trials use the Disease Activity Score 28 (DAS 28), which is similar. Another outcome measure determines the extent of joint damage as assessed by X-rays and the most common scoring system is the van der Heijde-modified Sharp score which quantifies erosions and joint space narrowing. Finally, trials also assess the impact on functional disability quality of life. The common tools used are the Health Assessment Questionnaire (HAQ) and the Short Form 36 (SF-36). The latter has the added dimension of measuring general mental health (psychological distress and well-being). There are also various scores and indices relevant to psoriasis and ankylosing spondylitis.⁸

The earliest approved biologic response modifier is anakinra, an IL-1 receptor antagonist.^{9,10} It is administered as a daily subcutaneous injection and has efficacy in treating RA when used alone or in combination with MTX. It is not commonly used since the TNF-inhibitors show much greater efficacy in comparison and have a more convenient dosing regimen. However, it is a valuable drug in the treatment of some diseases such as adult Still's disease and systemic-onset juvenile idiopathic arthritis, where it works much better than the TNF-inhibitors.^{11,12}

Among the TNF-blocking agents, the first to be introduced was infliximab (Remicade), followed by etanercept (Enbrel) and adalimumab (Humira). Infliximab and adalimumab are monoclonal antibodies directed against TNF while etanercept is a construct of 2 TNF receptors (p75 receptors) linked to the Fc portion of IgG1, giving rise to an immunoglobulin-like molecule. Clinical trials with the 3 agents show high efficacy in RA patients who failed traditional non-biologic DMARDs. The anti-TNF agents can be used alone or in combination with MTX,^{13,14} but the combination has superior efficacy.¹⁵⁻¹⁸ After 12 months of anti-TNF with MTX compared to placebo with MTX, all 3 agents show ACR 20, 50 and 70 responses in the order of

60% versus 25% , 40% versus 10% and 20% versus 5% respectively. Modified Sharp scores are even more impressive, indicating that these agents prevent joint damage as assessed by serial X-rays out of proportion to their ability to reduce clinical signs and symptoms of disease.⁵ There is also improvement in function as assessed by HAQ.

Other studies show that the use of a combination of these agents with MTX early on in the course of RA has the highest efficacy and far superior disease and radiographic progression compared to using MTX alone.¹⁸⁻²² This further supports the concept of treating RA aggressively early in the disease in order to achieve better long-term outcomes.

The 3 TNF blocking agents have also been approved in several countries for the treatment of ankylosing spondylitis and psoriatic arthritis.²³⁻³⁰ Etanercept is approved for skin psoriasis and for juvenile idiopathic arthritis.³¹⁻³³ Infliximab is approved for Crohn's disease.³⁴ At the time of writing, adalimumab is under review for skin psoriasis and Crohn's disease.

Although the therapeutic effects of anti-TNF agents are superior to conventional DMARDs, there are still non-responders. Patients who fail 1 TNF-inhibitor may still respond well to either of the other 2 agents.³⁵⁻³⁷ Even those who fail 2 TNF-inhibitors may still respond to the third one. However, 2 newer agents have been developed with distinctly different mechanisms of action that have been shown to be effective in patients who fail 1 or more TNF-inhibitors. Rituximab is a monoclonal antibody directed against an antigen, CD20, on the surface of all B cells other than stem cells and pre-B lymphocytes. It does not affect plasma cells since they do not possess CD20 on their cell surface. Rituximab is approved for the treatment of non-Hodgkin's lymphoma and diffuse large B cell lymphoma. It exerts its effect by binding to CD20 on B cells and causing cell lysis by both complement-dependent and antibody-dependent cell mediated cytotoxicity. It has efficacy in RA patients who have failed conventional DMARDs and also in RA patients who have failed anti-TNF agents.³⁸⁻⁴⁰ For this latter group of patients, it shows efficacy in the REFLEX Trial at 24 weeks in controlling disease activity and slowing radiographic deterioration at 56 weeks.⁴¹ Abatacept is a fusion protein linking the extracellular domain of human cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) to the Fc portion of human IgG1. It works by competing for the binding between CD 28 on the T cell and CD80/86 on the antigen-presenting cell. This is an important co-stimulatory signal that is essential for T cell activation. Blocking T cell activation results in a reduction of the autoimmune process and clinical improvement is demonstrated. It is effective in patients who have an inadequate response to either MTX or 1 or more TNF-inhibitors.⁴²⁻⁴⁵

Side Effects

Infections are serious potential side effects of any drug that modifies the immune response.^{46,47} For the anti-TNF agents, one particular infection that has to be looked for is tuberculosis (TB).^{48,49} Screening for TB before starting treatment is prudent since there is a high risk for re-activation of latent TB early in the course of anti-TNF therapy. Any latent TB should be treated preferably for a month before initiating anti-TNF therapy. Recent data have documented exacerbations of hepatitis in chronic hepatitis B patients and carriers.^{50,51} Prolonged suppression of the immune response may allow for the re-activation of slow viruses such as the JC polyoma virus. Two cases of a fatal brain disease caused by JC virus, called progressive multifocal leukoencephalopathy (PML), have been reported in patients with systemic lupus erythematosus who were administered rituximab.⁵² However, anti-TNF agents are safe in patients infected with hepatitis C.⁵³⁻⁵⁵ Many of the usual signs of sepsis may be suppressed in patients treated with TNF-inhibitors, since their ability to mount an inflammatory response may be seriously compromised. Physicians looking after such patients have to be constantly on the lookout for unusual signs of infection.

It is uncertain as to whether anti-TNF agents increase the risk of lymphoma, but the current available evidence suggests that this is the case, although the magnitude of increased risk is very small.^{56,57} In the case of rituximab this is unlikely to be an issue, since it is used to treat B cell lymphoma and has a record of over 950,000 patient treatments without *de novo* lymphomas or other malignancies appearing as a result of treatment. The issue of whether treatment with anti-TNF agents poses a higher risk for solid malignancies remains unresolved.^{58,59} RA patients as a group appear to be at higher risk of developing lung cancer and lymphoma and at lower risk for developing breast and colon cancer.⁶⁰ Treatment with biologic agents has not consistently affected these risks.

There are early indications that sustained treatment with biologic agents may reduce the risk of premature mortality in RA and the higher risk of cardiovascular disease and strokes may be ameliorated.⁶¹ Infliximab and etanercept have been shown to reduce insulin resistance, with early evidence that this helps the metabolic syndrome.^{62,63}

What is the Impact of These Agents in Current Clinical Practice?

Biological response modifiers represent advancement in the treatment of autoimmune disease. In the past, there were patients in whom all existing therapies were unable to control the inflammation and subsequent destruction of their joints. For such patients, these new drugs have given them a new lease on life. For the first time, disease activity

can be well-controlled to the extent that function improves almost to normal, X-ray changes of destruction stop progressing and ACR 70 responses which were very rare in the past are now possible in about 20% of patients.

However, there are still non-responders and newer agents such as rituximab and abatacept address some of these needs, but as yet, there is no consistent way of inducing a permanent drug-free remission. Perhaps the answer may lie in combining these agents. Using 2 biological agents with different mechanisms of action may provide more profound suppression of the autoimmune disease. Unfortunately, trials combining agents with different loci of action have, to date, resulted in an increased risk of infection without any increased efficacy. This is true of combining anakinra with etanercept and abatacept with etanercept.^{64,65} In fact, the current evidence indicates that such agents should not be combined. Alternatively, there is a rationale for combining an anti-inflammatory biological agent such as a TNF blocker with a drug more effective at inhibiting bone loss and erosions like denosumab. This drug is a monoclonal antibody that binds RANK ligand, the major signal for osteoclast activation.⁶⁶ It has the unique ability to prevent bone loss and erosions without any effect on the inflammatory response.⁶⁷ Such approaches have yet to be tested in well-designed clinical trials.

A major problem in the use of these agents is cost. Insurance companies and state-funded healthcare systems set various criteria for reimbursement for these agents in an attempt to control spiraling healthcare expenditure. Nevertheless, the efficacy of these agents prompt their widespread acceptance by physicians and currently 40% of patients with RA in the United States are receiving a biologic agent.⁶⁸ In countries where there is no reimbursement, using these drugs on a long-term basis is a real challenge. In such situations, the alternative is to optimise the use of existing DMARDs. This involves the use of combination DMARDs and frequent review and escalation of therapy if the response does not meet strict preset criteria at each review.⁶⁹ Recently 2 major trials (BeST⁷⁰ and TICORA⁷¹) have demonstrated the value of such an approach. Using conventional DMARDs and a tight monitoring approach, these researchers have achieved remission rates comparable to the biologic agents. Furthermore, the BeST⁷² study shows that it is possible to use a biologic agent, infliximab, as induction treatment at the onset of early RA and the drug can then be withdrawn when remission is achieved while low disease activity is maintained using only MTX.⁷³ These approaches may prove feasible in reducing the need for prolonged use of biologic therapy. Early attempts to identify which patients are most likely to respond to a particular biologic agent have not been successful. It was thought that such patients might

have a unique profile of genes controlling TNF production or Fc receptor function. However, the technique of gene profiling using microarrays is becoming more feasible as the cost to perform these assays continue to fall and we may yet find distinct gene profiles that will allow us to match an individual patient with a specific therapy.

Future Trends

In the future, improved versions of existing drugs will become available. Anti-TNF preparations that are given as monthly subcutaneous injections are currently being developed. Other targets for therapy that are under study include IL6, CD22, CD40-CD40L, lymphostatin B and many others. It would be ideal if pathogenesis is found to be driven solely by one of these key molecules. However, this seems increasingly unlikely and there may be better ways in the future of choosing the best therapy for an individual patient based on predictive factors. Current best practice is to optimise the use of DMARDs including the newer agents. This would involve frequent titration of therapy and the use of combination DMARDs if necessary, to ensure good control of inflammation. The issue of cost needs to be addressed and in the future, every patient with inflammatory arthritis will have therapeutic options which will bring their illness into a prolonged, if not, permanent remission.

REFERENCES

- Fries JF, Williams CA, Morfeld D, Singh G, Sibley J. Reduction in long-term disability in patients with rheumatoid arthritis by disease-modifying anti-rheumatic drug-based treatment strategies. *Arthritis Rheum* 1996;39:616-22.
- Young A, Koduri G, Batley M, Kulinskaya E, Gough A, Norton S, et al. Mortality in rheumatoid arthritis. Increased in the early course of disease, in ischemic heart disease and in pulmonary fibrosis. *Rheumatology (Oxford)* 2007;46:350-7
- Odegard S, Landewe R, van der Heijde D, Kvien TK, Mowinckel P, Uhlig T. Association of early radiographic damage with impaired physical function in rheumatoid arthritis: a ten-year longitudinal observational study in 238 patients. *Arthritis Rheum* 2006;54:68-75.
- Maini RN, Breedveld FC, Kalden JR, Smolen JS, Davis D, MacFarlane JD, et al. Therapeutic efficacy of multiple intravenous infusions of anti-tumour necrosis factor alpha monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. *Arthritis Rheum* 1998;41:1552-63.
- Weisman MH. Progress toward the cure of rheumatoid arthritis? The BeSt study. *Arthritis Rheum* 2005;52:3326-32.
- Wolfe F, Pincus T, O'dell J. Evaluation and documentation of rheumatoid arthritis disease status in the clinic: which variables best predict change in therapy. *J Rheumatol* 2001;28:1712-7.
- Smolen JS, Breedveld FC, Schiff MH, Kalden JR, Emery P, Eberl G, et al. A simplified disease activity index for rheumatoid arthritis for use in clinical practice. *Rheumatology (Oxford)* 2003;42:244-57.
- Gladman DD, Helliwell P, Mease PJ, Nash P, Ritchlin C, Taylor W. Assessment of patients with psoriatic arthritis: a review of currently available measures. *Arthritis Rheum* 2004;50:24-35.
- Fleischmann RM, Schectman J, Bennett R, Handel ML, Burmester GR, Tesser J, et al. Anakinra, a recombinant human interleukin-1 receptor antagonist (r-metHuIL-1ra) in patients with rheumatoid arthritis: a large international, multicenter placebo-controlled trial. *Arthritis Rheum* 2003;48:927-34.
- Bresnahan B, Newmark R, Robbins S, Genant HK. Effects of anakinra monotherapy on joint damage in patients with rheumatoid arthritis. Extension of a 24-week randomized placebo-controlled trial. *J Rheumatol* 2004;31:1103-11.
- Fitzgerald AA, Leclercq SA, Yan A, Homik JE, Dinarello CA. Rapid responses to anakinra in patients with refractory adult-onset Still's disease. *Arthritis Rheum* 2005;52:1794-803.
- Verbsky JW, White AJ. Effective use of the recombinant interleukin 1 receptor antagonist anakinra in therapy resistant systemic onset juvenile rheumatoid arthritis. *J Rheumatol* 2004;31:2071-5.
- Moreland LW, Schiff MH, Baumgartner SW, Tindall EA, Fleischmann RM, Bulpitt KJ, et al. Etanercept therapy in rheumatoid arthritis: A randomized, controlled trial. *Ann Intern Med* 1999;130:478-86.
- van de Putte LB, Atkins C, Malaise M, Sany J, Russell AS, van Riel PL, et al. Efficacy and safety of adalimumab as monotherapy in patients with rheumatoid arthritis for whom previous disease modifying antirheumatic drug treatment has failed. *Ann Rheum Dis* 2004;63:508-16.
- Klareskog L, van der Heijde D, de Jager JP, Gough A, Kalden J, Malaise M, et al. Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. *Lancet* 2004;363:675-81.
- Lipsky PE, van der Heijde DM, St Clair EW, Furst DE, Breedveld FC, Kalden JR, et al. Infliximab and methotrexate in the treatment of rheumatoid arthritis. Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. *N Engl J Med* 2000;343:1594-602.
- Smolen JS, Han C, Bala M, Maini RN, Kalden JR, van der Heijde DM, et al. Evidence of radiographic benefit of treatment with infliximab plus methotrexate in rheumatoid arthritis patients who had no clinical improvement: a detailed sub analysis of data from the anti-tumor necrosis factor trial in rheumatoid arthritis with concomitant therapy study. *Arthritis Rheum* 2005;52:1020-30.
- Keystone EC, Kavanaugh AF, Sharp JT, Tannenbaum H, Hua Y, Teoh LS, et al. Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumour necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: a randomized, placebo-controlled, 52-week trial. *Arthritis Rheum* 2004;50:1400-11.
- Bathon JM, Martin RW, Fleischmann RM, Tesser JR, Schiff MH, Keystone EC, et al. A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. *N Engl J Med* 2000;343:1586-93. Erratum in: *N Engl J Med* 2001;344:240 and 2001;344:76.
- Breedveld FC, Emery P, Keystone E, Patel K, Furst DE, Kalden JR, et al. Infliximab in active early rheumatoid arthritis. *Ann Rheum Dis* 2004;63:149-55.
- Breedveld FC, Weisman MH, Kavanaugh AF, Cohen SB, Pavelka K, van Vollenhoven R, et al. The PREMIER study: A multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. *Arthritis Rheum* 2006;54:26-37.
- St Clair EW, van der Heijde DM, Smolen JS, Maini RN, Bathon JM, Emery P, et al. Combination of infliximab and methotrexate therapy for early rheumatoid arthritis: a randomized, controlled trial. *Arthritis Rheum* 2004;50:3432-43.
- Davis JC Jr, Van Der Heijde D, Braun J, Dougados M, Cush J, Clegg DO,

- et al. Recombinant human tumor necrosis factor receptor (etanercept) for treating ankylosing spondylitis: a randomized, controlled trial. *Arthritis Rheum* 2003;48:3230-6.
24. Gorman JD, Sack KE, Davis JC Jr. Treatment of ankylosing spondylitis by inhibition of tumor necrosis factor alpha. *N Engl J Med* 2002;346:1349-56.
 25. Cauza E, Spak M, Cauza K, Hanusch-Enserer U, Dunky A, Wagner E. Treatment of psoriatic arthritis and psoriasis vulgaris with the tumor necrosis factor inhibitor infliximab. *Rheumatol Int* 2002;22:227-32.
 26. Mease PJ, Goffe BS, Metz J, VanderStoep A, Finck B, Burge DJ. Etanercept in the treatment of psoriatic arthritis and psoriasis: a randomized trial. *Lancet* 2000;356:385-90.
 27. Mease PJ, Kivitz AJ, Burch FX, Siegel EL, Cohen SB, Ory P, et al. Etanercept in treatment of psoriatic arthritis: safety, efficacy, and effect on disease progression. *Arthritis Rheum* 2004;50:2264-72.
 28. Ogilvie AL, Antoni C, Dechant C, Manger B, Kalden JR, Schuler G, et al. Treatment of psoriatic arthritis with anti tumour necrosis factor-alpha antibody clears skin lesions of psoriasis resistant to treatment with methotrexate. *Br J Dermatol* 2001;144:587-9.
 29. Salvarani C, Cantini F, Olivieri I, Macchioni P, Padula A, Niccolo L, et al. Efficacy of infliximab in resistant psoriatic arthritis. *Arthritis Rheum* 2003;49:541-5.
 30. Mease PJ, Gladman DD, Ritchlin CT, Ruderman EM, Steinfeld SD, Choy EH, et al. Adalimumab for the treatment of patients with moderately to severely active psoriatic arthritis: results of a double-blind, randomized, placebo-controlled trial. *Arthritis Rheum* 2005;52:3279-89.
 31. Leonardi CL, Powers JL, Matheson RT, Goffe BS, Zitnik R, Wang A, et al. Etanercept as monotherapy in patients with psoriasis. *N Engl J Med* 2003;349:2014-22.
 32. Lovell DJ, Giannini EH, Reiff A, Cawkwell GD, Silverman ED, Nocton JJ, et al. Etanercept in children with polyarticular juvenile rheumatoid arthritis. *Pediatric Rheumatology Collaborative Study Group. N Engl J Med* 2000;342:763-9.
 33. Lovell DJ, Giannini EH, Reiff A, Jones OY, Schneider R, Olson JC, et al. Long-term efficacy and safety of etanercept in children with polyarticular juvenile rheumatoid arthritis: interim results from an ongoing multicenter, open-label, extended-treatment trial. *Arthritis Rheum* 2003;48:218-26.
 34. Richter JA, Bickston SJ. Infliximab use in luminal Crohn's disease. *Gastroenterol Clin North Am* 2006;35:775-93.
 35. Cohen G, Courvoisier N, Cohen JD, Zaltini S, Sany J, Combe B. The efficacy of switching from infliximab to etanercept and vice-versa in patients with rheumatoid arthritis. *Clin Exp Rheumatol* 2005;23:795-800.
 36. van Vollenhoven RF. Switching between biological agents. *Clin Exp Rheumatol* 2004;22:819-36.
 37. Gomez-Reino JJ, Carmona L: BIOBADASER Group. Switching TNF antagonists in patients with chronic arthritis: an observational study of 488 patients over a four-year period. *Arthritis Res Ther* 2006;8:R29.
 38. Cohen SB, Greenwald M, Dougados MR, Emery P, Furie R, Shaw TM, et al. Efficacy and safety of rituximab in active RA patients who experienced an inadequate response to one or more anti-TNF alpha therapies. *Arthritis Rheum* 2005;52:1830.
 39. Edwards JC, Szczepanski L, Szechinski J, Filipowicz-Sosnowska A, Emery P, Close DR, et al. Efficacy of B-cell-targeted therapy with rituximab in patients with rheumatoid arthritis. *N Engl J Med* 2004;350:2572-81.
 40. Keystone EC, Burmester GR, Furie R, Loveless JE, Emery P, Cravets MW, et al. Improved quality of life with rituximab plus methotrexate in patients with active rheumatoid arthritis who experienced inadequate response to one or more anti-TNF alpha therapies. *Arthritis Rheum* 2005;52:287.
 41. Keystone E, Furie R, Burmester GR, Loveless J, Emery P, Cravets M, et al. [AB0183] Rituximab plus methotrexate improves quality of life in patients with active rheumatoid arthritis despite previous treatment with one or more TNF inhibitors. Amsterdam: EULAR, 2006.
 42. Genovese MC, Becker JC, Schiff M, Luggen M, Sherrer Y, Kremer J, et al. Abatacept for rheumatoid arthritis refractory to tumour necrosis factor alpha inhibition. *N Engl J Med* 2005;353:1114-23.
 43. Kremer JM, Westhovens R, Leon M, Di Giorgio E, Alten R, Steinfeld S, et al. Treatment of rheumatoid arthritis by selective inhibition of T-cell activation with fusion protein CTLA4Ig. *N Engl J Med* 2003;349:1907-15.
 44. Kremer JM, Dougados M, Emery P, Durez P, Sibilia J, Shergy, W et al. Treatment of rheumatoid arthritis with the selective costimulation modulator abatacept: twelve-month results of a phase iib, double-blind, randomized, placebo-controlled trial. *Arthritis Rheum* 2005;52:2263-71. Erratum in: *Arthritis Rheum* 2005;52:3321.
 45. Kremer JM, Genant HK, Moreland LW, Russell AS, Emery P, Abud-Mendoza C, et al. Effects of abatacept in patients with methotrexate-resistant active rheumatoid arthritis: a randomized trial. *Ann Intern Med* 2006;144:865-76.
 46. Furst DE, Schiff MH, Fleishmann RM, Strand V, Birbara CA, Compagnone D, et al. Adalimumab, a fully human anti-tumour necrosis factor alpha monoclonal antibody, and concomitant standard antirheumatic therapy for the treatment of rheumatoid arthritis: results of STAR (Safety Trial of Adalimumab in Rheumatoid arthritis). *J Rheumatol* 2003;30:2563-71.
 47. Doran MF, Crowson CS, Pond GR, O'Fallon WM, Gabriel SE. Frequency of infection in patients with rheumatoid arthritis compared with controls: a population-based study. *Arthritis Rheum* 2002;46:2287-93.
 48. Mohan AK, Cote TR, Block JA, Manadan AM, Siegel JN, Braun MM. Tuberculosis following the use of etanercept, a tumour necrosis factor inhibitor. *Clin Infect Dis* 2004;39:295-9.
 49. Keane J, Gershon S, Wise RP, Mirabile-Levens E, Kasznica J, Schwietzman WD, et al. Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. *N Engl J Med* 2001;345:1098-104.
 50. Esteve M, Saro C, Gonzalez-Huix F, Suarez F, Forne M, Viver JM. Chronic hepatitis B reactivation following infliximab therapy in Crohn's disease patients: need for primary prophylaxis. *Gut* 2004;53:1363-5.
 51. Wendling D, Auge B, Bettinger D, Lohse A, Le Huede G, Bresson-Hadni S, et al. Reactivation of a latent precore mutant hepatitis B virus related chronic hepatitis during infliximab treatment for severe spondyloarthropathy. *Ann Rheum Dis* 2005;64:788-9.
 52. Available at: <http://www.fda.gov/medwatch/safety/2006/safety06.htm#Rituxan>.
 53. Zein NN; Etanercept Study Group. Etanercept as an adjuvant to interferon and ribavirin in treatment-naïve patients with chronic hepatitis C virus infection: a phase 2 randomized, double-blind, placebo-controlled study. *J Hepatol* 2005;42:315-22.
 54. Peterson JR, Hsu FC, Simkin PA, Wener MH. Effect of tumour necrosis factor alpha antagonists on serum transaminases and viraemia in patients with rheumatoid arthritis and chronic hepatitis C infection. *Ann Rheum Dis* 2003;62:1078-82.
 55. Oniankitan O, Duvoux C, Challine D, Mallat A, Chevalier X, Pawlotsky JM, et al. Infliximab therapy for rheumatic diseases in patients with chronic hepatitis B or C. *J Rheumatol* 2004;31:107-9.
 56. Geborek P, Baldstrom A, Turesson C, Gulfe A, Petersson IF, Saxne T, et al. Tumour necrosis factor blockers do not increase overall tumour risk in patients with rheumatoid arthritis, but may be associated with an increased risk of lymphoma. *Ann Rheum Dis* 2005;64:699-703.
 57. Baecklund E, Ekblom A, Sparen P, Feltelius N, Klareskog L. Disease activity and risk of lymphoma in patients with rheumatoid arthritis: nested case-control study. *BMJ* 1998;317:180-1.
 58. Setoguchi S, Solomon DH, Weinblatt ME, Katz JN, Avorn J, Glynn RJ, et al. Tumor necrosis factor alpha antagonist use and cancer in patients with rheumatoid arthritis. *Arthritis Rheum* 2006;54:2757-64. Erratum

- in: *Arthritis Rheum* 2006;54:3134.
59. Bongartz T, Sutton AJ, Sweeting MJ, Buchan I, Matteson EL, Montori V. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. *JAMA* 2006;295:2482.
 60. Wolfe F, Michaud K. The use of biologic therapy in patients with RA and existing cancer. *Arthritis Rheum* 2006;54:S425.
 61. Jacobsson LT, Turresson C, Gulfe A, Kapetanovic MC, Petersson IF, Saxne T, et al. Treatment with tumour necrosis factor blockers is associated with a lower incidence of first cardiovascular events in patients with rheumatoid arthritis. *J Rheumatol* 2005;32:1213-8.
 62. Gonzalez-Gay MA, De Matias JM, Gonzalez-Juanatey C, Garcia-Porrua C, Sanchez-Andrade A, Martin J, et al. Anti-tumour necrosis factor-alpha blockade improves insulin resistance in patients with rheumatoid arthritis. *Clin Exp Rheumatol* 2006;24:83-6.
 63. Bernstein LE, Berry J, Kim S, Canavan B, Grinspoon SK. Effects of etanercept in patients with the metabolic syndrome. *Arch Intern Med* 2006;166:902-8.
 64. Genovese MC, Cohen S, Moreland L, Lium D, Robbins S, Newmark R, et al. Combination therapy with etanercept and anakinra in the treatment of patients with rheumatoid arthritis who have been treated unsuccessfully with methotrexate. *Arthritis Rheum* 2004;50:1412-9.
 65. Weinblatt ME, Schiff MH, Goldman A, Kremer JM, Luggen M, Li T, et al. Selective co-stimulation modulation using abatacept in patients with active rheumatoid arthritis while receiving etanercept: a randomized clinical trial. *Ann Rheum Dis* 2007;66:228-34.
 66. McClung MR, Lewiecki EM, Cohen SB, Bolognese MA, Woodson GC, Moffett AH, et al. Denosumab in postmenopausal women with low bone mineral density. *N Engl J Med* 2006;354:821-31.
 67. Cohen SB. RANKL inhibition with denosumab reduces progression of bone erosions in patients with rheumatoid arthritis: month 6 MRI results [abstract]. *Arthritis Rheum* 2006;54:S831.
 68. Michaud K, Wolfe F. [FRI0090] Trends in medication use by 10,982 community rheumatoid arthritis patients in the United States from 1998 to 2005: biologic use now at 40%. Amsterdam: EULAR, 2006.
 69. Boers M, Verhoeven AC, Markuse HM, van de Laar MA, Westhovens R, van Denderen JC, et al. Randomised comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine alone in early rheumatoid arthritis. *Lancet* 1997;350:309-18. Erratum in: *Lancet* 1998;351:220.
 70. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, van Zeben D, Kerstens PJ, Hazes JM, et al. Clinical and radiological outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeST study): a randomized, controlled trial. *Arthritis Rheum* 2005;52:3381-90.
 71. Grigor C, Capell H, Stirling A, MacMahon AD, Lock P, Vallance R, et al. Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. *Lancet* 2004;364:263-9.
 72. Allaart CF, Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Breedveld FC, Dijkmans BA, Group FS. Aiming at low disease activity in rheumatoid arthritis with initial combination therapy or initial monotherapy strategies: the BeST study. *Clin Exp Rheumatol* 2006;24:S77-S82.
 73. Van Der Kooij SM. Remission induction in early rheumatoid arthritis (RA) with initial infliximab (IFX) and methotrexate (MTX) therapy: the disease course after IFX discontinuation in the BeSt trial [abstract]. *Arthritis Rheum* 2006;54:S302.