Treatment of rheumatoid arthritis with anti-TNF-alpha agents: A reappraisal

Roberto Caporali [a,*], Francesca Bobbio Pallavicini [a], Matteo Filippini [b], Roberto Gorla [b],
Antonio Marchesoni [c], Ennio Giulio Favalli [c], Piercarlo Sarzi-Puttini [d],
Fabiola Atzeni [d], Carlomaurizio Montecucco [a]

[a] Rheumatology Unit, University of Pavia, IRCCS Policlinico S. Matteo Foundation, 27100 Pavia, Italy
[b] Rheumatology and Immunology Unit, Spedali Civili di Brescia, Brescia, Italy
[c] Day Hospital of Rheumatology, G. Pini Orthopaedic Institute, Milan, Italy
[d] Rheumatology Unit, L. Sacco University Hospital, Milan, Italy

ARTICLE INFO

ABSTRACT

It has been found that tumour necrosis factor(TNF)-alpha plays a pivotal role in the pathogenesis of rheumatoid arthritis (RA), and the development of drugs targeting this molecule has extended the therapeutical approaches to RA patients. A number of observational studies of large patient series have also been published over the last few years, many of which have been based on national registries designed to monitor the efficacy and safety of anti-TNF agents, and allow healthcare institutions to control expenditure. Registry data can also help in identifying clinical and laboratory findings capable of predicting response. It has been suggested that the percentage of responding patients is lower in everyday clinical practice than that observed in RCTs, possibly because of patient selection, the use of a washout period before inclusion (which may artificially increase disease activity), and differences in doses, co-morbidities and adherence to therapy.

A number of safety concerns have been raised since the introduction of anti-TNF agents, and they are now contraindicated in patients with advanced heart failure; however, the most widely debated current issues regard infections and neoplastic diseases.

Moreover, the marketing of new and expensive biological agents has made strictly necessary to create systems capable of monitoring their safety and effectiveness in everyday practice, including the use of longitudinal observational studies. As the first published registry of anti-TNFα-treated patients in Italy, Lombardy Rheumatology Network (LORHEN) is already making its contribution in this direction.

© 2008 Elsevier B.V. All rights reserved.

Contents

* Corresponding author.
E-mail address: caporali@smatteo.pv.it (R. Caporali).

1. Introduction

Rheumatoid arthritis (RA) is one of the most frequent chronic inflammatory joint diseases as it affects about 0.5–1% of the world's population. It is characterized by joint pain, swelling and stiffness due to joint inflammation and damage, causes disability and lost working capacity, and may cause premature death.

The treatment of RA has undergone many major changes over the last 100 years. The concept that drugs should be used to slow down the damage caused by the disease rather than simply to control symptoms led to the introduction of various agents known as disease-modifying anti-rheumatic drugs (DMARDs), of which methotrexate (MTX) is currently the most widely used, alone or in combination with other DMARDs [1]. Other frequently used DMARDs include sulphasalazine, hydroxychloroquine and leflunomide.

The cause of RA remains unknown, but the last 20 years have seen an accumulation of insights into its pathogenetic pathways [2] that have led to the identification of new therapeutic targets. Many of the new medications modify the immune response by blocking the effect of pro-inflammatory cytokines, or by acting on immune cells such as B lymphocytes or on the interaction between T cells and antigen-presenting cells (APCs).

The advent of these new drugs has also changed the strategy of treating RA, and the current practice is to start a DMARD early in the illness in order to prevent joint damage, and try to induce disease remission by means of more aggressive treatment.

2. Targeted therapy in RA

Much has been done to develop drugs specifically directed against the key molecules involved in the pathogenesis of RA. One of the first attempts was made by Maini et al., who targeted TNF-alpha as one of the main cytokines in the inflamed synovium [3], thus leading to one of the major advances in the treatment of inflammatory arthritis. Since then, more than one million patients have been treated with TNF-blocking agents, and different mechanisms of action of these agents have been identified [4]. However, it seems that

Table 1
Characteristics of the three available TNF inhibitors

TNF inhibitor	Infliximab	Etanercept	Adalimumab
Brand name	Remicade	Enbrel	Humira
Molecular structure	Human-murine monoclonal Ab IgG1K (149 kDa)	Recombinant human fusion protein (TNFR:Fc IgG1-150 kDa)	Recombinant human monoclonal Ab IgG1(148 kDa)
Administration route	iv	sc	sc
Half-life	9.5 days	3–5.5 days	10–20 days
Dosage in RA	3–7.5 mg/kg every 8 weeks	50 mg/week	40 mg every other week
Other indications [a]	AS, PsA, psoriasis, Crohn's, UC, JIA	AS, PsA, psoriasis, JIA	AS, PsA, psoriasis, Crohn's

AS: ankylosing spondylitis; PsA: psoriatic arthopathy; UC: ulcerative colitis; JIA: juvenile idiopathic arthropathy.
[a] http://www.emea.europa.eu/humandocs/Humans/EPAR 15/1/2008.

Table 2
Evaluation of clinical activity and clinical response by EULAR disease activity score (DAS)

Present DAS	>1.2	DAS improvement 0.6–1.2	0.6
≤2.4 inactive	Good response	Moderate response	No response
>2.4 and ≤3.7 moderate	Moderate response	Moderate response	No response
>3.7 very active	Moderate response	No response	No response

TNF is not the only cytokine involved in the pathogenesis of RA. Interleukin-1 (IL-1) and IL-6 also play an important role as inhibiting either can allow effective control of the disease, and other effective approaches these include depleting circulating CD20+ B lymphocytes using a monoclonal anti-CD20 antibody [1,2] and blocking the co-stimulatory signal (CD28-CD80/86) for T cell/APC interactions [1,2].

The action of inflammatory cytokines can be inhibited by soluble receptors or monoclonal antibodies that 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. All of the studies conducted so far have demonstrated that targeted therapies are more effective than classic DMARDs in reducing symptoms, reducing or stopping joint damage, and preventing functional disability: they have also been shown to be effective in patients with long-standing disease refractory to conventional DMARDs and in those with early disease. Moreover, the majority of trials show that combining a TNF inhibitor with MTX is particularly effective, and better than using either drug alone.

3. Efficacy

The disease activity outcome measures used in randomised clinical trials (RCTs) involving RA patients are the ACR 20, 50, 70 and 90 criteria, which indicate a 20%, 50%, 70% or 90% improvement in various parameters such as the number of tender and swollen joints, C-reactive protein levels, pain measured by means of a visual analogue scale (VAS), and physician or patient global assessment.

The European League Against Rheumatism (EULAR) criteria are based on disease activity scores using 44 (DAS) or 28 joints (DAS28), which provide a continuous measure of disease activity (Table 1), and other easier-to-calculate scores have recently been proposed [5]. Another important outcome measure is the extent of joint damage assessed by means of plain X-rays, for which the most widely used scoring system is the van der Heijde-modified Sharp score quantifying erosions and joint space narrowing [6]. Finally, trials also assess the impact of the disease on functional disability and the quality of life, which are most frequently evaluated by means of the Health Assessment Questionnaire (HAQ) and the Short Form 36 (SF-36), which also has the added dimension of measuring general mental health (psychological distress and well-being).

The first TNF-blocking agent on the market was infliximab (Remicade), followed by etanercept (Enbrel) and adalimumab (Humira). Infliximab and adalimumab are monoclonal

Table 3
Recommendations for the use of biological agents in the treatment of rheumatoid arthritis in Italy [27]

Specific points approved by the Italian Society for Rheumatology Executive Committee
1. Patients with active RA (DAS >3.7 or DAS28 >5.1) are eligible for the treatment with TNF blockers after the failure of an adequate trial of another effective DMARD, including MTX (at least 15 mg/week for at least 12 weeks).
2. On the basis of the major controlled clinical trials, the right time to evaluate clinical response and stop treatment in the case of a lack of response is usually 12 weeks; the maintenance of clinical response should be further evaluated every three months.
3. Failure to respond to one TNF-blocking agent does not preclude response to another.
4. Increased susceptibility to tuberculosis (TB) or the re-activation of latent TB should be considered a class characteristic of TNF-blocking agents; interestingly, although etanercept blocks the same cytokine, there have been very few reports of TB after its use.
5. Anti-TNF therapy appears to be safe in patients with chronic HCV infection who are candidates for such treatment for other co-existing medical conditions such as RA.
6. The incidence of NHL in RA patients treated with TNFα inhibitors is higher than that expected in the general population. However, as severe and active RA is a predisposing factor for NHL, it is essential to avoid a channelling bias due to the fact that only patients with active and severe disease are selected for anti-TNF therapy.
7. High-dose infliximab (10 mg/kg) seems to be associated with an increased relative risk of worsening congestive heart failure (CHF) and mortality, particularly in RA patients with NYHA class III–IV CHF.
8. The incidence of ANAs and anti-dsDNA autoantibodies is increased after TNF-blocking treatment, but there is no evidence that the patients developing such autoantibodies are at any increased risk of developing drug-induced lupus.

antibodies directed against TNF; etanercept is a construct of two TNF receptors (p75 receptors) linked to the Fc portion of IgG1 that gives rise to an immunoglobulin-like molecule (Table 2). The first clinical trials of the three agents showed that they were highly efficacious in RA patients failing on traditional non-biological DMARDs, and even more so when used in combination with MTX [7–9]. In comparison with MTX and placebo, 12 months' treatment with MTX plus any of the anti-TNF agents leads to ACR 20, 50 and 70 responses of respectively about 60% vs 25%, 40% vs 10%, and 20% vs 5%. Modified Sharp scores are even more impressive and indicate that all three prevent joint damage as assessed by serial X-rays [10], and there is also an improvement in function as evaluated by the HAQ.

The therapeutic effects of anti-TNF agents are clearly better than those obtained with conventional DMARDs, but some patients do not respond. However, a number of studies have shown that patients who fail on one TNF inhibitor may still respond well to either of the other two [11], and even those failing on two may still respond to the third. Furthermore, more recently developed agents with distinctly different mechanisms of action have been shown to be effective in patients failing one or more TNF inhibitors [12].

A number of observational studies of large patient series have also been published over the last few year, many of which have been based on national registries designed to monitor the efficacy and safety anti-TNF agents, and allow healthcare institutions to control expenditure. Registry data can also help in identifying clinical and laboratory findings capable of predicting response. It has been suggested that the percentage of responding patients is lower in everyday clinical practice than that observed in RCTs, possibly because of patient selection, the use of a washout period before inclusion (which may artificially increase disease activity), and differences in doses, co-morbidities and adherence to therapy. Kievit et al. [13] have recently compared the efficacy of anti-TNF agents in RCTs with the results recorded in the Dutch Rheumatoid Arthritis Monitoring (DREAM) registry and found lower ACR20 responses in everyday clinical practice than in the active drug groups of the RCTs, in ten out of eleven comparisons, five of which were significant. Only 34–79% of the DREAM patients fulfilled the disease activity criteria required for inclusion in a number of the RCTs, and the DREAM patients who would have been eligible showed a higher response rate than those who would have not, and their ACR20 responses were similar to those reported in the active drug groups of the RCTs. This seems to suggest that the lower response rates may be due to the less active disease observed in patients in everyday clinical practice. Similar findings have also been reported by Sokka and Pinkus [14], and Zink et al. [15]. Wolfe and Michaud concluded that RCTs exaggerate the effect of anti-TNF treatment because of their use of washout periods and selected patients [16], which seems to be supported by the data from the DREAM study [13].

These data underline the importance of registries in identifying patients in whom anti-TNF treatment may be useful, and designing appropriate guidelines for the clinical setting [17]. There are in fact a number of largely overlapping national guidelines: e.g. patients in Italy may be treated with anti-TNF agents if they show active RA (documented by DAS or DAS28) after an adequate trial of another effective DMARD, including MTX at a dose of at least 15 mg/week for at least 12 weeks [18] (Table 3).

4. Safety

A number of safety concerns have been raised since the introduction of anti-TNF agents, and they are now contra-indicated in patients with advanced heart failure [19]; however, the most widely debated current issues regard infections and neoplastic diseases [20].

Infections are potentially serious side effects of any drug that modifies immune responses [19], and bacterial and viral infections both continue to be a source of concern in TNF-treated RA patients. Once again, data from everyday clinical practice have revealed some issues that were probably underestimated by the results of RCTs, most of which did not show any statistically significant increase in the occurrence of serious infections (not surprisingly, as the selected nature of the small numbers of patients and their short follow-ups may have limited their statistical power). However, caution is also necessary when interpreting post-marketing study data as there is no control for possible

selection or indication biases, and the patients are often not followed up as closely as those participating in RCTs. Finally, significant infections and serious infections are often poorly defined, and their definitions may vary from study to study.

In the case of tuberculosis (TB), the possible reactivation of latent TB described since the marketing of anti-TNF drugs was not revealed by their RCTs [20]: more than 50% of the described cases have involved extra-pulmonary infections, and most of them have occurred in Europe in patients with a known history of TB. As TNF-alpha plays a role in the host defences against *M. tuberculosis* (particularly granuloma formation and the containment of latent disease) [19], such clinical observations have led to the introduction of TB screening before starting treatment and the use of prophylactic antibiotic treatment in patients with signs of latent TB [20]. Some serious bacterial infections have also been described in patients treated with TNF blockers, as well as opportunistic infections such as histoplasmosis, listeriosis, pulmonary aspergillosis and pneumocystis carinii pneumonia [21]. In France, it has been estimated that the risk of *Legionella* in anti-TNF treated patients is 20 times higher than in the general population [22].

On the other hand, anti-TNF agents may be safe and even beneficial in patients with chronic hepatitis C infections [23], which are believed to affect nearly 200 million people throughout the world, although it is recommended to monitor serum amino-transferase and HCV load during therapy. The data are less clear in patients with chronic hepatitis B, in whom anti-TNF therapy should only be considered together with antiviral agents such as lamivudine.

It should finally be noted that many of the usual signs of sepsis may be suppressed in patients treated with TNF inhibitors, who may not be capable of mounting an adequate inflammatory response. Physicians looking after such patients need to be alert for unusual signs of infection.

As regards malignancies, it is still not clear whether anti-TNF agents increase the risk of lymphoma; the currently available evidence suggests they do, but the magnitude of the increased risk is not clear and may be small [24]. It is worth noting that RA patients in any case are at increased risk of developing lymphoma, and that only a few studies have analysed differences in lymphoma rates between the patients treated or not with anti-TNF agents. Whether treatment with anti-TNF agents leads to a higher risk of solid malignancies is still unclear and, although the findings of most studies seem to be reassuring, more data are needed.

The majority of studies addressing safety issues in TNF-treated patients have dealt with morbidity, but two observational studies have also considered mortality, and neither noted any increased risk of death following treatment [25,26]. Moreover, there are early indications that sustained treatment with biological agents may reduce the risk of premature mortality in RA, as well as the higher risk of cardiovascular disease and strokes [27]. It has also been shown that infliximab and etanercept reduce insulin resistance, and there is early evidence that this helps the metabolic syndrome.

5. Impact of TNF-alpha blockers on clinical practice

Biological drugs represent advances in the treatment of autoimmune disease, particularly in the case of RA patients.

There used to be patients in whom none of the existing therapies could control inflammation, joint destruction and the progression of disability, whereas these new drugs now offer them an opportunity for disease control and a good quality of life [28]. They may also dramatically slow disease activity, induce a clinically disease-free status (clinical remission), and halt the progression of X-ray changes. As previously pointed, the majority of RCTs and registry reports indicate that anti-TNFα agents are much more efficacious when administered together with another DMARD, particularly MTX.

Various strategies have been proposed in order to optimise the use of biological therapies in RA. The most widely discussed aspects so far include the appropriateness of treating patients with early disease, the best approach to non-responders, and the use of the possible remission-induction and maintenance therapeutic strategy.

It has been shown that using TNF inhibitors in early RA relieves symptoms and slows the rate of joint destruction in comparison with their later use. The Early RA trial compared etanercept with MTX monotherapy in patients affected by RA for less than three years and, although the two groups showed similar ACR responses after one and two years, etanercept led to significantly less radiographic progression as measured by means of total Sharp and erosion scores at six and 24 months [29]. Similarly, the PREMIER study showed that adalimumab monotherapy in early RA (duration less than three years) was significantly more effective than MTX in slowing the rate of radiographic progression, despite comparable clinical responses [30].

However, the most impressive results in early RA have been obtained using combinations of TNF-blockers and MTX. The ASPIRE trial of infliximab was the first to investigate the use of combined treatment as first-line therapy in early RA [31]. The MTX-naive patients affected by RA for less than three years) who received infliximab plus MTX showed significantly less radiographic progression and a greater improvement in physical function after 54 weeks than those who received MTX alone. The TEMPO trial [32] showed that the response of patients with early RA to etanercept plus MTX was significantly greater than their response to MTX alone in terms of ACR, DAS and HAQ scores: The PREMIER study found that the combination of MTX and adalimumab was more effective than either drug alone in terms of all outcome measures after two years, and radiographic progression was also significantly less in the patients treated with the combination after both one and two years. A 2-year controlled trial of the immediate or delayed addition of infliximab to MTX after one year also supported the early addition of TNF inhibition to MTX therapy in patients with erosive early RA of less than three years' duration, who were taking MTX at the time of enrolment [33]. At the end of the study, the patients who had received one year of MTX alone followed by one year of combined therapy showed significantly greater structural damage than those who had received infliximab plus MTX for the full two years.

The BeSt study is probably one of the most important recently published studies in the field of early RA [34], and made head-to-head comparisons of the efficacy in a clinical setting of four of the most frequently used RA treatment strategies: sequential monotherapy, step-up combination

therapy, initial combination therapy with tapered high-dose prednisone (COBRA-like strategy), and initial combination therapy with infliximab. Tri-monthly therapy adjustments were dictated by DAS evaluations, with the goal of achieving a DAS of <2.4. After one year, 74% of the patients treated with infliximab plus MTX had achieved the goal, but so had a similar proportion of patients in the other groups, however, the difference in radiographic progression was significantly lower in the infliximab and COBRA-like groups than in the groups treated more conventionally way. The results were confirmed after two years of therapy [35].

All of the above studies confirmed that rapid and aggressive treatment of early RA, possibly DAS-driven and aiming at a low level of disease activity (the so-called tight control strategy) [36], is crucial for obtaining good clinical results in a high proportion of patients. They also clearly showed that combined first-line therapy with a TNF inhibitor and MTX is more effective than either agent alone, particularly in terms of halting radiographic progression.

Unfortunately, most institutional players are reluctant to support such an approach for economic reasons, although a number of studies have demonstrated its cost-effectiveness. For example, the ASPIRE trial evaluated the effect of infliximab therapy on the employment status of patients with early RA and, although the actual week 54 employment rates were similar among the patients receiving infliximab plus MTX and those receiving MTX alone, the former had a higher probability of maintaining their employability [37].

However, treatment failure due to lack of efficacy or adverse events is observed in up to one-third of patients, and there are even newer drugs on the market (e.g. rituximab and abatacept) and other molecules in clinical development [12]. Switching to a second- or even third-line TNF inhibitor has also now become common practice because, although similar, infliximab, etanercept and adalimumab have different molecular structures, mechanisms of action, pharmacokinetics, and efficacy in diseases other than RA, all of which provide a solid scientific rationale for switching treatments in the case of failure [11].

There have been a number of reports concerning switching TNF inhibitors in RA and, although the lack of RCTs makes it difficult to interpret the results, the aggregate data and growing clinical experience suggest that it may be beneficial. However, some still open questions require further investigation, including the differences in response rates between the patients who never responded to the previous agent and those who have lost an initial response, and the magnitude of the responses to a second or third TNF inhibitor. One Danish national registry study [38] suggests that patients switching due to lack of efficacy showed a better clinical response to the second agent, and that patients switching because of adverse effects responded equally well to both and were at low risk of discontinuing the second treatment because of adverse effects.

The efficacy of TNF inhibitors in controlling disease activity has given rise to new approaches to RA management, including considering remission a realistic goal and the possibility of maintaining the remission induced by anti-TNF treatment using conventional DMARDs. A number of studies have reported a high rate of remission in early RA using a combination of MTX and TNFα blockers, with DAS remission being achieved by respectively 19%, 34% and 43% of patients treated with MTX alone, etanercept alone or their combination; after two years of treatment, 49% of the patients receiving combination therapy showed disease remission (DAS28 <2.6), compared with 25% in each of the monotherapy arms. In the PREMIERE study, the rate of clinical remission (DAS28) among the patients treated with adalimumab plus MTX was as much as 49% after two years of treatment.

The induction-maintenance approach has been mainly supported by studies of infliximab in early RA. One pilot study has attempted inducing remission using MTX with or without infliximab in patients with poor-prognosis, early RA (symptoms <12 months) [39]; the primary endpoint was synovitis as measured by means of magnetic resonance imaging (MRI). After one year, all of the MRI scores were significantly better in the infliximab plus MTX group, and there were no new MRI erosions; the one-year ACR50 and ACR70 response rates were also significantly higher in the combination group than in the group treated with MTX alone, and the combination group received greater functional benefit. After stopping infliximab after two years, there were no significant between-group differences in terms of DAS28, ACR responses or radiographic scores, but the differences in the HAQ and RA Quality of Life scores were maintained. The authors concluded that if these findings were confirmed by larger studies, this approach could solve the economic problems associated with the early use of biological agents.

In the BeSt study, 74% of the patients treated with infliximab plus MTX achieved a low level of disease activity after a median of 12.6 months, and 50% of the "responders" (the patients who had not needed any escalation of therapy) were able to discontinue infliximab because of persistent low disease activity; 8% required the resumption of infliximab within one year. After two years, 54% of the patients initially treated with infliximab plus MTX had switched to MTX monotherapy. Radiographic progression was halted in 93% of the patients treated with infliximab plus MTX after one year, and this was maintained in the responders up to two years.

The available data suggest that the rapid control of inflammation by means of induction therapy leads to benefits in terms of function, the quality of life and structural damage. Furthermore, remission induction protocols may allow these drugs to be used for a limited period at the time when they have the best chance of making a difference.

6. Conclusions

Improved versions of existing drugs and other targeted therapies will be developed in the future, but we have so far learnt how to stratify patients prognostically as a means of deciding to start anti-TNF treatment in patients with a high probability of responding, and identifying those with rapidly progressing disease. Many studies have addressed these topics and provided important information, but we are still awaiting a complete set of clinical and biological criteria capable of classifying RA patients and predicting their responses to different treatments. At the moment, an early diagnosis, early DMARD treatment and frequent dose titrations are necessary to reduce disease activity to the point that it and the progression of disability can be halted.

Moreover, the marketing of new and expensive biological agents has made it strictly necessary to create systems

capable of monitoring their safety and effectiveness in everyday practice, including the use of longitudinal observational studies. It is likely that such systems will become increasingly important in defining the cost-effective use of drugs. As the first published registry of anti-TNFα-treated patients in Italy, LORHEN is already making its contribution in this direction [40].

Take-home messages

- TNF-α plays a pivotal role in the pathogenesis of rheumatoid arthritis.
- Many studies evaluated the efficacy and safety of anti-TNF agents.
- Registry data can help in identifying clinical and laboratory findings capable of predicting and monitoring the clinical response.
- Early diagnosis, early DMARDs and/or biological treatment and frequent dose titrations are necessary in order to reduce the disease activity and to delay or to stop the progression of disability.
- The marketing of new and expensive biological agents has made strictly necessary to create systems capable of monitoring their safety and effectiveness in everyday practice.

Conflict of interest

All of the authors have received consultancy fees or Congress invitations from Schering-Plough, Wyeth, and Abbott.

References

[1] O'Dell J. Therapeutic strategies for rheumatoid arthritis. N Engl J Med 2004;350:2591–602.
[2] Choi EH, Panayi GS. Cytokine pathways and joint inflammation in rheumatoid arthritis. N Engl J Med 2001;344:907–16.
[3] Maini RN, Breedveld FC, Kalden JR, Smolen JS, Davis D, MacFarlane JD, et al. Therapeutic efficacy of multiple intravenous infusions of antitumour necrosis factor alpha monoclonal antibody combined with low dose weekly methotrexate in rheumatoid arthritis. Arthritis Rheum 1998;41:1552–63.
[4] Gupta S, Gollapudi S. Molecular mechanisms of TNF-alpha-induced apoptosis in naive and memory T cell subsets. Autoimmun Rev 2006;5:264–8.
[5] van Gestel AM, Anderson JJ, van Riel PL, Boers M, Haagsma CJ, Rich B, et al. ACR and EULAR improvement criteria have comparable validity in rheumatoid arthritis trials. American College of Rheumatology European League of Associations for Rheumatology. J Rheumatol 1999;26:705–11.
[6] van der Heijde DM, van Riel PL, Nuver-Zwart IH, Gribnau FW, van de Putte LB. Effects of hydroxychloroquine and sulphasalazine on progression of joint damage in rheumatoid arthritis. Lancet 1989;1:1036–8.
[7] 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.
[8] 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.
[9] 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 concomi-
tant methotrexate therapy: a randomized, placebo-controlled, 52-week trial. Arthritis Rheum 2004;50:1400–11.
[10] Weisman MH. Progress toward the cure of rheumatoid arthritis? The BeSt study. Arthritis Rheum 2005;52:3326–32.
[11] van Vollenhoven RF. Switching between biological agents. Clin Exp Rheumatol 2004;22:819–36.
[12] Smolen JS, Aletaha D, Weisman MH, Emery P. New therapies for treatment of rheumatoid arthritis. Lancet 2007;370:1861–74.
[13] Kievit W, Fransen J, Oerlemans AJM, Kuper HH, vd Laar MAFJ, de Rooij DJRAM, et al. The efficacy of anti-TNF in rheumatoid arthritis, a comparison between randomized control trials and clinical practice. Ann Rheum Dis 2007;66:1473–8.
[14] Sokka T, Pincus T. Eligibility of patients in routine care for major clinical trials of anti-tumor necrosis factor alpha agents in rheumatoid arthritis. Arthritis Rheum 2003;48:313–8.
[15] Zink A, Strangfeld A, Schneider M, Herzer P, Hierse F, Stoyanova-Scholz M, et al. 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 2006;54:3399–407.
[16] Wolfe F, Michaud K. Towards an epidemiology of rheumatoid arthritis outcome with respect to treatment: randomized controlled trials overestimate treatment response and effectiveness. Rheumatology (Oxford) 2005;44:18–22 (Suppl 4): iv.
[17] Kremer JM, Gibofsky A, Greenberg JD. The role of drug and disease registries in rheumatic disease epidemiology. Curr Opin Rheumatol 2008;20:123–30.
[18] Valesini G, Montecucco C, Cutolo M. Anti-TNF treatment for rheumatoid arthritis. Clin Exp Rheumatol 2006;24:413–23.
[19] Askling J, Dixon W. The safety of anti-tumor necrosis factor therapy in rheumatoid arthritis. Curr Opin Rheumatol 2008;20:138–44.
[20] Desai SB, Furst DE. Problems encountered during anti-tumor necrosis factor therapy. Best Pract Res Clin Rheumatol 2006;4:757–90.
[21] Bongartz T, Sutton AJ, Sweeting MJ, Buchan I, Matteson EL, Montori V. Anti-TNF antibody 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;295:2275–85.
[22] Tubach F, Ravaud P, Salmon-Ceron D, Petitpain N, Brocq O, Grados F, et al. Emergence of Legionella pneumophila pneumonia in patients receiving tumor necrosis factor-alpha antagonists. Clin Infect Dis 2006;43:95–100.
[23] Zein NN. Etarnercept Study Group. Etanercept as an adjuvant to interferon and ribavarin 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.
[24] 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.
[25] Carmona L, Descalzo MA, Perez-Pampin E, Ruiz-Montesinos D, Erra A, Cobo T, et al. All-cause and cause-specific mortality in rheumatoid arthritis are not greater than expected when treated with TNF antagonists. Ann Rheum Dis 2007;66:680–5.
[26] Jacobsson LT, Turesson C, Nilsson JA, Petersson IF, Lindqvist E, Saxne T, et al. Treatment with TNF blockers and mortality risk in patients with rheumatoid arthritis. Ann Rheum Dis 2007;66:670–5.
[27] 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.
[28] Atzeni F, Doria A, Carrabba M, Turiel M, Sarzi-Puttini P. Potential target of infliximab in autoimmune and inflammatory diseases. Autoimmun Rev 2007;6:529–36.
[29] Genovese MC, Bathon JM, Martin RW, Fleischmann RM, Tesser JR, Schiff MH, et al. Etanercept versus methotrexate in patients with early rheumatoid arthritis: two-year radiographic and clinical outcomes. Arthritis Rheum 2002;46:1443–50.
[30] 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.
[31] 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.
[32] van der Heijde D, Klareskog L, Rodriguez-Valverde V, Codreanu C, Bolosiu H, Melo-Gomes J, et al. Comparison of etanercept and methotrexate, alone and combined, in the treatment of rheumatoid arthritis: two-year clinical

and radiographic results from the TEMPO study, a double-blind, randomized trial. Arthritis Rheum 2006;54:1063–74.

[33] Taylor PC, Steuer A, Gruber J, McClinton C, Cosgrove DO, Blomley MJ, et al. Ultrasonographic and radiographic results from a two-year controlled trial of immediate or one-year-delayed addition of infliximab to ongoing methotrexate therapy in patients with erosive early rheumatoid arthritis. Arthritis Rheum 2006;54:47–53.

[34] Allaart C, Breedveld F, Dijkmans B. Treatment of recent-onset rheumatoid arthritis: lessons from the BeSt study. J Rheumatol 2007;34(Suppl 80):25–33.

[35] Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, van Zeben D, Kerstens PJ, Hazes JM, et al. Comparison of treatment strategies in early rheumatoid arthritis: a randomized trial. Ann Intern Med 2007;146: 406–15.

[36] Grigor C, Capell H, Stirling A, McMahon 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.

[37] Smolen JS, Han C, van der Heijde D, Emery P, Bathon JM, Keystone E, et al. Infliximab treatment maintains employability in patients with early rheumatoid arthritis. Arthritis Rheum 2006;54:716–22.

[38] Hjardem E, Ostergaard M, Podenphant J, Tarp U, Andersen LS, Bing J, et al. Do rheumatoid arthritis patients in clinical practice benefit from switching from infliximab to a second tumor necrosis factor alpha inhibitor? Ann Rheum Dis 2007;66:1184–9.

[39] Quinn MA, Conaghan PG, O'Connor PJ, Karim Z, Greenstein A, Brown A, et al. 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 2005;52:27–35.

[40] P. Sarzi-Puttini, M. Antivalle, A. Marchesoni, E.G. Favalli, R. Gorla, M. Fillipini, et al. Efficacy and safety of anti-TNF agents in the Lombardy Rheumatoid Arthritis Network (LORHEN). Reumatismo in press.

Pregnancy outcome in systemic lupus erythematosus complicated by anti-phospholipid antibodies.

Pregnant women affected by SLE have been associated with high risk of gestational hypertension and pre-eclampsia (32-50%). The risk is particularly elevated if antiphospholipid antibodies (aPLs) are high . However maternal-fetal outcomes are widely variable, the main reason for that is the presence of different influencing therapeutic strategies implemented. In a recent study performed by **Mecacci F. et al. (Rheumatology (Oxford) 2008)**, a retrospective description of the maternal-fetal outcomes of different groups of SLE pregnant patients was performed after clustering them by diverse risk factors: Patients affected by APS treated with a combination of low-dose aspirin (LDA) and low-molecular weight heparin (LMWH), nulliparous patients with high aPL treated by LMWH and SLE patients with no aPL administered no treatment during pregnancy. They found no statistically significant difference after comparring fetal and maternal outcomes of the three groups despite differences in SLE activity: SLE aPL-positive pregnancies were associated with a higher incidence of nephritis and chronic hypertension than pregnancies treated for APS or not presenting with the added risk factor. The incidence of pre-eclampsia was 15% in aPL positive, 12.5% in APS and 14.7% in no aPL pregnancies, respectively. The authors concluded that LMWH is rather a possible option of prophylaxis for SLE aPL-positive pregnancies with potential maternal-fetal outcomes similar to aPL-negative patients or to standard treated APS.

Antineuronal antibodies in Parkinson`s disease.

The autoimmune origin of the postinfectious movement disorders, such as Sydenham's chorea has been related with the presence of certain autoantibodies such as the antineuronal antibodies (ANAs). However, their relevance in other movement disorders–in the absence of infectious triggers–remains largely unclear. In addition, the autoimmune origin of neurodegenerative diseases is stll an uncertainty and discussion. In a recent study performed by **van de Warrenburg BP. et al. (Mov Disord 2008; 23:958-63)**, the frequency of ANAs in idiopathic Parkinson's disease (IPD) and an exploration on whether a specific phenotype is likely associated with the presence of ANAs was done. They recruited 76 IPD patients, 9 patients with genetic Parkinsonism, and 10 with one of the Parkinson-plus syndromes. A comprehensive clinical review was assessed in the all patients. In addition, 50 patients with non-extrapyramidal neurological disease and 30 healthy blood donors were employed as a control population. Blood samples were tested for the presence of ANAs with Western blotting, using recombinant proteins of the three putative antigens (aldolase C, neuron-specific enolase, and pyruvate kinase M1). They found these antibodies in 11.8% of the 76 IPD patients, which differed significantly from healthy controls (0%, P = 0.043), but non-significantly from patients with genetic Parkinsonism (11.1%), with a Parkinson-plus syndrome (10%), or from neurological disease controls (4%). With respect to relevant disease characteristics, IPD patients with or without ANAs were indistinguishable, except for atypical disease features (mainly early falls or freezing and marked Pisa syndrome), which were more frequent in the ANA-positive IPD group. The authors concluded that ANAs appear not to play a role in the majority of patients with IPD, but might be relevant in the pathogenesis of IPD with atypical features.