Complexities in defining remission in rheumatic diseases

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ABSTRACT

The rheumatology community has devoted increasing attention to the subject of remission over the past 2 decades, on the basis of greater appreciation of the long-term severity of inflammatory rheumatic diseases and availability of new therapies and approaches to improve outcomes. Nonetheless, description of remission in rheumatic diseases is complex, compared to many nonrheumatic diseases. Recognition of remission requires a set of measures or an index rather than a single "gold standard." Spontaneous remission is not infrequent in people with early inflammatory arthritis, including some who may meet criteria for rheumatoid arthritis (RA) over less than a few months, and may be confused with a drug-induced remission. Remission may be transient in many patients over short periods, and the length of time required to maintain remission status varies in different reports. Maintenance of a state of remission in autoimmune diseases that result from dysregulatory processes, rather than invasion of foreign cells or toxins, generally requires ongoing therapy indefinitely. Patients who have organ damage or functional disability may be described as "in remission," although they are free of disease activity only, but not necessarily free of disease consequences. A status of "low disease activity" or "near remission" with 70% to 90% of the features of an ideal remission may be adequate for many people with rheumatic diseases to avoid risks that may be required to reach 100% remission status. Thus, the subject of remission remains under active discussion in the rheumatology community.

Introduction

A clear indicator of dramatic changes in the therapeutic approach to patients with rheumatic diseases in recent years is the growth of interest in and reports concerning the term "remission" (1-24). Certainly, remission has always been a goal of the treating rheumatologist. However, most remissions were transient, and sustained remission was rarely observed (25). When remission was seen, it as likely represented natural variation in underlying disease processes as a result of any specific therapeutic intervention.

At this time, remission is appropriately regarded as the goal of contemporary treatment of rheumatoid arthritis (RA) (1-3, 26), and increasingly so for other rheumatic diseases. Several important developments over the past 2 decades underlie this notable change in treatment strategies, in which the goal of therapy has shifted to *prevention of*, rather than *response to*, long-term damage (27): 1) The severity of long-term outcomes of rheumatic diseases, including premature mortality (28), has been increasingly recognised, with a growing awareness of the unmet needs left by traditional therapies to address adequately these conditions. 2) There has been appreciation that partial control of inflammation, as had been acceptable traditionally, often does not prevent long-term damage (29). 3) Based on progress in defining the immunopathophysiologic bases of rheumatic diseases, combined with important developments in biopharmaceutical production, new medications and combinations with greater efficacy, effectiveness, and tolerability, as well as lower toxicities than previous disease modifying antirheumatic drugs (DMARDs), have become available, with capacity to achieve complete or near-complete control of disease processes (30). 4) Evidence that severe outcomes of organ damage, such as joint destruction in RA (31) or progressive renal failure in systemic lupus erythematosus (SLE) (32) or scleroderma (33), are preventable with early aggressive intervention.

In certain situations, a status of "remission" is obvious to the patient and the clinician as "no evidence of disease" (3), a phrase long used in oncology.

However, the status of remission in rheumatic diseases may be less clear, depending not only on the disease in question but also its duration and attendant sequelae. "Remission" may not be complete in terms of recovery of function, permanent, free of organ damage, and/or free of a need to continue long-term medications to maintain remission status. Therefore, a definition of remission in rheumatic diseases can be quite complex, as presented in the 18 chapters in this supplement. This introductory chapter presents a brief summary of some of these complexities:

1. *Absence of single "gold standard" measurement – the need for multiple measures or indices*

Quantitative assessment of rheumatic diseases is constrained by the absence of a single "gold standard" measure, not only to establish a diagnosis, but perhaps more importantly to estimate prognosis, and to assess and monitor disease activity and response to treatment. Thus, there is not a single measure analogous to blood pressure in hypertensive patients, serum cholesterol in hyperlipidemic patients for diagnosis, monitoring, prognosis, and outcomes (34). Lacking a single measure, multiple measures or pooled indices (35) are used to determine if patient status is improved or worsened, or to define remission (16).

Classification criteria for RA (36), as well as the initial ACR remission criteria involve multiple measures (37). More recently, indices for assessment of RA (38-40), osteoarthritis (41), SLE (42), ankylosing spondylitis (43), vasculitis (44, 45), and psoriatic arthritis (46) have been developed, which may address inflammatory activity, or organ damage, or both activity and damage (a damage index is not available in RA other than radiographic scores). The need for multiple measures or indices is an important matter in approaches to remission in rheumatic diseases.

2. *Spontaneous remission is not uncommon in patients who present with early arthritis*

As long ago as the 1960s, it was recognised that people who met criteria for RA in population-based studies often did not meet these criteria 5 years later, and many had no disease at all at 5-year review (47, 48). In the Tecumseh cohort, a re-examination of 66 subjects who had met criteria of likely or probable RA 3 to 6 years earlier indicated 19 (29%) who continued to meet criteria for RA, 12 (18%) who met criteria for "possible RA" (49), 9 (14%) who had positive rheumatoid factor only, and 26 (39%) who had no signs of the disease (47). In the Sudbury study, a re-examination of 40 subjects 3 to 5 years after baseline indicated that only 21 (53%) of subjects who had met American Rheumatology Association (ARA) criteria for definite RA, and only 11 (15%) of those who had met criteria for probable RA, still had evidence of disease (48). At least a few subjects, perhaps the majority, who did not meet criteria for RA at the second evaluation had experienced an apparent spontaneous remission, probably as a result of recovery from a transient viral or posttraumatic arthritis, misclassification at baseline, or other basis.

Recent data from early arthritis clinics support the notion of spontaneous remission as a not infrequent event in people who have early inflammatory arthritis (50). Development of RA was more likely after 1 year. Anticyclic citrullinated protein (anti-CCP) antibodies and the shared epitope are major risk factors for persistent disease (23, 50). Among the first 1,000 patients in the Leiden early arthritis clinic, 10% met criteria for RA, and one third presented with an undifferentiated arthritis (51). Among 1,064 patients with early arthritis, 330 were in remission after 1 year of follow-up and were discharged from the clinic (52). Similar results were seen in other early arthritis cohorts (53). In the Norwich Arthritis Register (NOAR), 42% of 358 patients with early arthritis had "natural remission" after 2 years of follow-up (54). In Birmingham, 55% of 112 patients with undifferentiated arthritis had a natural remission after 1 year of observation. In Leeds, 13% of patients were in remission after 1 year of follow-up (55).

These data suggest that spontaneous remission may be seen in 13% to 55% of individuals with undifferentiated arthritis and even among people who have clinical features of RA. It is not possible to perform placebo-controlled trials in patients who might have RA, as ethical considerations cannot permit damage (56), which may occur with a delay of 3 months (8; 57). However, it may be different in very early undifferentiated arthritis, even if disease of some of the patients might develop into RA. In these individuals, a placebo control might not be unethical and may even be necessary, since there is a high rate of spontaneous remissions. Many patients with early arthritis in whom a diagnosis of RA cannot be established would not receive DMARDs but rather symptomatic therapy and/or low-dose glucocorticoids. Indeed, many of these patients might not even be seen by a rheumatologist but are recruited in the context of early arthritis actions or clinics. We cannot appreciate sufficiently the possible risks of over-treatment versus those of under-treatment at this time. Otherwise, any interpretation of remission in patients with early arthritis, particularly when attributed to interventions, would have to recognise (and actually estimate) a certain, though unknown and potentially high, level of spontaneous remission.

3. *What is the time-frame required to designate remission status?*

A time-frame for remission is important. The term "remission-inducing drugs" was derived originally from evidence that some patients entered into apparent remission status when treated with traditional DMARDs, such as gold salt injections or penicillamine. However, most of the apparent remissions did not last longer than a few months, as only 2% of remissions were sustained over 3 years or longer (25).

Many patients with RA and other inflammatory diseases may experience a disease-free status without medication for 3, 6, or even 12 months, but usually not indefinitely (58, 59). As noted, such "honeymoon" phases tend to be more common and longer among patients with early disease. Furthermore, women with RA and several other rheumatic diseases, such as psoriatic arthritis,

may experience an apparent remission during a pregnancy, which generally is transient, as postpartum flares are common (60, 61).

Controversy exists about the length of time a patient must maintain a status free of disease activity to be designated as "remission." A definition of sustained remission depends in part on the frequency of disease activity assessment itself, as sustained remission would be more likely to be reported on the basis of annual, compared to monthly, assessments. The period required to meet criteria for remission has been suggested to be as short as 2 months or as long as 2 years.

4. *Can one have remission in the absence of medication?*

The prototypical drug treatment in the minds of the public, including most people with rheumatic diseases and even many health professionals, involves antibiotic treatment of infections. In such situations, the patient is a host to an invading microorganism which can cause severe symptoms and even death. The treatment paradigm calls for administration of appropriate antibiotic therapy, and when the patient recovers, no further drug therapy is needed. This concept of a disease-free and drug-free state is widely regarded as an appropriate goal.

Treatment of cancer generally does not involve a self-limited process (unless immune surveillance is an ongoing phenomenon). However, a patient may enjoy a disease-free status after completion of courses of chemotherapy (and possibly radiation) without a need for further medication. Again, this remission status, with no symptoms and no medication, appears ideal.

Rheumatic diseases do not involve abnormal cells, as in infections and cancer, but rather a dysregulation of normal cells with abnormal signals to overproduce or underproduce appropriate amounts of proteins, such as cytokines. Many other chronic diseases, such as hypertension or diabetes, result from dysregulation rather than foreign cells or toxins. Treatments available at this time for dysregulatory diseases are not directed to correct the cause of the dysregulation, which remains poorly understood, but rather to the consequences of the dysregulation, such as inflammation in RA, or hyperglycemia, hypertension, or hyperlipidemia.

"Tight control" of activity in dysregulatory diseases, such as diabetes, hypertension, and hyperlipidemia and inflammatory rheumatic diseases, prevents organ damage and prolongs survival (32, 33, 62-66). Nonetheless, a "cure", without a need for medication, is not available, and may require a therapy directed to correcting the dysregulation itself. It is possible that only a therapy directed at the cause of the dysregulation could effectively provide a "cure".

In autoimmune diseases, such a cure may not even be possible, as the inciting stimulus that caused a genetically susceptible host to experience autoimmune reactivity may no longer be etiologogically relevant. By antigenic drift, normal host antigens may be sufficient to sustain an aberrant immune response and its subsequent dysregulation. Therefore, the idea of "cure" of an inflammatory rheumatic disease at this time with drug-free and disease-free status may be unrealistic.

As noted, many patients with inflammatory rheumatic diseases may experience a disease-free status without medication for 3, 6, or even 12 months, but usually not indefinitely (58, 59). The dysregulation apparently recurs as the diathesis has not been corrected. A powerful example of this problem is the recurrence of disease activity following ablative doses of chemotherapy, essentially ablating the host immune system, followed by stem cell transplant. Until therapies effectively directed to the dysregulation become available, it may be unlikely that most patients with RA or other rheumatic or other type of dysregulatory diseases will experience remission without medications.

5. *Can remission occur in the presence of damage as a result of prior inflammation?*

An important distinction in management of patients with rheumatic diseases involves differences in symptoms that result from inflammatory activity versus those that result from organ damage (67). In an ideal situation, a state of remission would involve the absence of both activity and damage (68). However, many patients already have damage when first seen, including many with RA and the majority with ankylosing spondylitis. Indeed, as pointed out by Zochling and Braun in this supplement (69), the current diagnosis of ankylosing spondylitis requires evidence of radiographic damage. In patients with SLE, even therapy that is highly effective at alleviating inflammation may not reverse the proteinuria consequent to renal damage.

Therefore, an unresolved matter for the rheumatology community is whether a patient can be in remission if damage is present. It is possible that, for example, levels of relatively modest American College of Rheumatology 20% improvement (ACR20) responses of 60% to 70%, rather than 90% to 100%, with biologic agents in clinical trials (70) may reflect that some patients have significant joint damage, with scores forfunctional disability, pain, and global status, that do not respond to even the most effective anti-inflammatory therapies (68). Patients may have no signs of inflammation, with no swollen or tender joints, normal erythrocyte sedimentation rate (ESR), and a patient global score of 0, but nonetheless have substantial deformity and limited motion on physical examination and radiographic damage.

Defining a state of remission has an inherent duality in patients with RA, and is therefore a complex concept. This complexity has been addressed in other diseases, such as SLE, by development of a variety of validated indices to assess either activity or damage (71-73). Occasional patients may experience full clinical remission regarding SLE activity but continue to experience increased creatinine levels or proteinuria as a consequence of prior renal damage, which was treated too late to be prevented or reversed. Similar situations occur in patients with RA, in whom the joints rather than the kidneys are the "organ" involved.

6. *Is "near remission" or low disease activity state a reasonable goal for many patients, rather than a full remission?*

Although a complete remission may appear optimal for all patients, many patients are content to have a response of being free of 70% to 90% of their symptoms, functional disability, pain, and global status, while being able to work, carry on most recreational activities, family activities, etc. (73). This situation may represent an application of the "Pareto principle" or the "80/20" rule, which suggests that 80% of results can be achieved with 20% of the effort and the final 20% of results may require 80% of the effort. In the case of patients with RA, an 80% response may be seen with 20% of the risk of therapies, while an effort to eradicate the final 20% of symptoms to gain a complete remission may incur 80% of the of the risk of therapies.

It is certain that the "side effects" of RA (74) and many other inflammatory rheumatic diseases are much more undesirable than the side effects of drugs used to treat these diseases, with an urgent need for intensive intervention. Nonetheless, a reasonable question is whether that intervention requires a 100% response, whether an 70% to 90% response is adequate as a reasonable target (12). Certainly, 20% or even 50% responses in general are not adequate (75), particularly with evidence in the form of radiographic progression and functional disability that may occur over time with these response levels. However, many patients may prefer a 70% to 90% response with lower risk of pharmacologic side effects, rather than 100% response (12).

A 70% to 90% response that has been described as "near remission" or "low disease activity" state (76) will vary for different patients and different physicians. While 100% control of inflammation may be appropriate for certain patients, 70% to 90% control may be satisfactory for others. Perhaps it may be inappropriate for guidelines (26) to necessarily specify that a complete remission is the *only* appropriate goal for *all* patients. Of course, patient preference is a vital component of these decisions. Nonetheless, some important indicators of future disability may not be associated with pain or discomfort, and might therefore not motivate patients to further reduce disease activity, which may require instruction from a physician.

These issues concerning remission illustrate that the matter remains complex. The chapters in this supplement are designed to help clarify these complexities. We hope the supplement meets an important current need for the rheumatology community.

References

1. EMERY P, SALMON M: Early rheumatoid arthritis: time to aim for remission? *Ann Rheum Dis* 1995; 54: 944-7.
2. WEINBLATT ME: Rheumatoid arthritis: Treat now, not later! (editorial). *Ann Intern Med* 1996; 124: 773-4.
3. PINCUS T, STEIN CM, WOLFE F: "No evidence of disease" in rheumatoid arthritis using methotrexate in combination with other drugs: A contemporary goal for rheumatology care? *Clin Exp Rheumatol* 1997; 15: 591-6.
4. PREVOO MLL, VAN GESTEL AM, VAN'T HOF MA, VAN RIJSWIJK HM, VAN DE PUTTE LBA, VAN RIEL PLCM: Remission in a prospective study of patients with rheumatoid arthritis. American Rheumatism Association preliminary remission criteria in relation to the disease activity score. *Br J Rheumatol* 1996; 35: 1101-5.
5. SVENSSON B, SCHAUFELBERGER C, TELEMAN A, THEANDER J: Remission and response to early treatment of RA assessed by the disease activity score. *Rheumatology* 2000; 39: 1031-6.
6. JANTTI J, KAARELA K, KAUTIAINEN H, ISOMAKI H, AHO K: Radiographic remission in seropositive rheumatoid arthritis. A 20-year follow-up study. *Clin Exp Rheumatol* 2001; 19: 573-6.
7. PINCUS T, SOKKA T: Quantitative target values of predictors of mortality in rheumatoid arthritis as possible goals for therapeutic interventions: an alternative approach to remission or ACR20 responses? *J Rheumatol* 2001; 28: 1723-34.
8. MÖTTÖNEN T, HANNONEN P, KORPELA M *et al*.: Delay to institution of therapy and induction of remission using single-drug or combination-disease-modifying antirheumatic drug therapy in early rheumatoid arthritis. *Arthritis Rheum* 2002; 46: 894-8.
9. BALSA A, CARMONA L, GONZALEZ-ALVARO I, BELMONTE MA, TENA X, SANMARTI R: Value of disease activity score 28 (DAS28) and DAS28-3 compared to American College of Rheumatology-defined remission in rheumatoid arthritis. *J Rheumatol* 2004; 31: 40-6.
10. GOSSEC L, DOUGADOS M, GOUPILLE P *et al*.: Prognostic factors for remission in early rheumatoid arthritis: a multiparameter prospective study. *Ann Rheum Dis* 2004; 63: 675-80.
11. PAULUS HE: Defining remission in rheumatoid arthritis: what is it? does it matter? *J Rheumatol* 2004; 31: 1-4.
12. PINCUS T, SOKKA T, KAVANAUGH A: Relative versus absolute goals of therapies for RA: ACR 20 or ACR 50 responses versus target values for "near remission" of DAS or single measures. *Clin Exp Rheumatol* 2004; 22 (Suppl. 35): S50-S56.
13. MAKINEN H, KAUTIAINEN H, HANNONEN P, SOKKA T: Frequency of remissions in early rheumatoid arthritis defined by 3 sets of criteria. A 5-year followup study. *J Rheumatol* 2005; 32: 796-800.
14. VAN DER HEIJDE D, KLARESKOG L, BOERS M *et al*.: Comparison of different definitions to classify remission and sustained remission: 1 year TEMPO results. *Ann Rheum Dis* 2005; 64: 1582-7.
15. ALETAHA D, WARD MM, MACHOLD KP, NELL VPK, STAMM T, SMOLEN JS: Remission and active disease in rheumatoid arthritis. *Arthritis Rheum* 2006; 2625.
16. ALETAHA D, SMOLEN JS: Remission of rheumatoid arthritis: should we care about definitions? *Clin Exp Rheumatol*. In press.
17. EBERHARDT K, FEX E: Clinical course and remission rate in patients with early rheumatoid arthritis: relationship to outcome after 5 years. *Br J Rheumatol* 2006; 1324.
18. FRANSEN J, CREEMERS MCW, VAN RIEL PLCM: Remission in rheumatoid arthritis: agreement of the disease activity score (DAS28) with the ARA preliminary remission criteria. *Rheumatology* 2006; 1252.
19. LANDEWE R, VAN DER HEIJDE D, VAN DER LINDEN S, BOERS M: Twenty-eight-joint counts invalidate the DAS28 remission definition owing to the omission of the lower extremity joints: a comparison with the original DAS remission. *Ann Rheum Dis* 2006; 637.
20. MAKINEN H, KAUTIAINEN H, HANNONEN P, SOKKA T: Is DAS28 an appropriate tool to assess remission in rheumatoid arthritis? *Ann Rheum Dis* 2006; 1410.
21. MOLENAAR ET, VOSKUYL AE, DINANT HJ, BEZEMER PD, BOERS M, DIJKMANS AC: Progression of radiologic damage in patients with rheumatoid arthritis in clinical remission. *Arthritis Rheum* 2006; 36.
22. SESIN CA, BINGHAM III CO: Remission in rheumatoid arthritis: wishful thinking or clinical reality? *Semin Arthritis Rheum* 2006; 185.
23. VAN DER HELM-VAN MIL AHM, BREEDVELD F, HUIZINGA TWJ: Definition of disease states in early arthritis: remission versus minimal disease activity. *Arthritis Res Ther* 2006; 8.
24. VERSTAPPEN SMM, VAN ALBADA-KUIPERS GA, BIJLSMA JWJ *et al*.: A good response to DMARD treatment of patients with rheumatoid arthritis in the first year predicts remission during follow up. *Ann Rheum Dis* 2006; 38.
25. WOLFE F, HAWLEY DJ: Remission in rheumatoid arthritis. *J Rheumatol* 1985; 12: 245-52.
26. AMERICAN COLLEGE OF RHEUMATOLOGY SUBCOMMITTEE ON RHEUMATOID ARTHRITIS GUIDELINES: Guidelines of the management

of rheumatoid arthritis: 2002 update. *Arthritis Rheum* 2002; 46: 328-46.
27. PINCUS T, O'DELL JR, KREMER JM: Combination therapy with multiple disease-modifying antirheumatic drugs in rheumatoid arthritis: A preventive strategy. *Ann Intern Med* 1999; 131: 768-74.
28. CALLAHAN LF, PINCUS T: Mortality in rheumatic diseases. *Arthritis Care Res* 1995; 8: 229-41.
29. PINCUS T, SOKKA T: Quantitative measures and indices to assess rheumatoid arthritis in clinical trials and clinical care. *Rheum Dis Clin N Am* 2004; 30: 725-51.
30. OLSEN NJ, STEIN CM: New drugs for rheumatoid arthritis. *N Engl J Med* 2004; 350: 2167-79.
31. LANDEWE R, VAN DER HEIJDE D: Radiographic progression in rheumatoid arthritis. *Clin Exp Rheumatol* 2005; 23: S63-S68.
32. URAMOTO KM, MICHET CJ JR, THUMBOO J, SUNKU J, O'FALLON WM, GABRIEL SE: Trends in the incidence and mortality of systemic lupus erythematosus, 1950-1992. *Arthritis Rheum* 1999; 42: 46-50.
33. STEEN VD: Scleroderma renal crisis. *Rheum Dis Clin N Am* 2003; 315-33.
34. PINCUS T, SOKKA T: Complexities in the quantitative assessment of patients with rheumatic diseases in clinical trials and clinical care. *Clin Exp Rheumatol* 2005; 23: S1-S9.
35. GOLDSMITH CH, SMYTHE HA, HELEWA A: Interpretation and power of pooled index. *J Rheumatol* 1993; 20: 575-8.
36. ARNETT FC, EDWORTHY SM, BLOCH DA *et al.*: The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988; 31: 315-24.
37. PINALS RS, MASI AT, LARSEN RA *et al.*: Preliminary criteria for clinical remission in rheumatoid arthritis. *Arthritis Rheum* 1981; 24: 1308-15.
38. PINCUS T: The American College of Rheumatology (ACR) core data set and derivative "patient only" indices to assess rheumatoid arthritis. *Clin Exp Rheumatol* 2005; 23: S109-S113.
39. FRANSEN J, VAN RIEL PLCM: The disease activity score and the EULAR response criteria. *Clin Exp Rheumatol* 2005; 23: S93-S99.
40. ALETAHA D, SMOLEN J: The simplified disease activity index (SDAI) and the clinical disease activity index (CDAI): a review of their usefulness and validity in rheumatoid arthritis. *Clin Exp Rheumatol* 2005; 23: S100-S108.
41. BELLAMY N: The WOMAC knee and hip osteoarthritis indices: development, validation, globalization and influence on the development of the AUSCAN hand OA indices. *Clin Exp Rheumatol* 2005; 23: S148-S153.
42. LAM GKW, PETRI M: Assessment of systemic lupus erythematosus. *Clin Exp Rheumatol* 2005; 23: S120-S132.
43. ZOCHLING J, BRAUN J: Assessment of ankylosing spondylitis. *Clin Exp Rheumatol* 2005; 23: S133-S141.
44. LUQMANI RA, BACON PA, MOOTS RJ *et al.*: Birmingham Vasculitis Activity Score (BVAS) in systemic necrotizing vasculitis. *Q J Med* 1994; 87: 671-8.
45. SEO P, MIN Y, HOLBROOK JT *et al.*: Damage caused by Wegener's granulomatosis and its treatment: prospective data from the Wegener's Granulomatosis Etanercept Trail (WGET). *Arthritis Rheum* 2005; 52: 2168-78.
46. KAVANAUGH A, CASSELL S: The assessment of disease activity and outcomes in psoriatic arthritis. *Clin Exp Rheumatol* 2005; 23: S142-S147.
47. MIKKELSEN WM, DODGE H: A four year follow-up of suspected rheumatoid arthritis: the Tecumseh, Michigan, community health study. *Arthritis Rheum* 1969; 12: 87-91.
48. O'SULLIVAN JB, CATHCART ES: The prevalence of rheumatoid arthritis: follow-up evaluation of the effect of criteria on rates in Sudbury, Massachusetts. *Ann Intern Med* 1972; 76: 573-7.
49. ROPES MW, BENNETT GA, COBB S, JACOX RF, JESSAR RA: 1958 revision of diagnostic criteria for rheumatoid arthritis. *Bull Rheum Dis* 1958; 9: 175-6.
50. HUIZINGA TW, AMOS CI, VAN DER HELM-VAN MIL AHM *et al.*: Refining the complex rheumatoid arthritis phenotype based on specificity of the HLA-DRB1 shared epitope for antibodies to citrullinated proteins. *Arthritis Rheum* 2005; 52:3433-8.
51. VAN AKEN J, VAN BILSEN JHM, ALLAART CF, HUIZINGA TWJ, BREEDVELD FC: The Leiden Early Arthritis Clinic. *Clin Exp Rheumatol* 2003; 21: S100-S105.
52. VAN AKEN J, VAN DONGEN H, LE CESSIE S, ALLAART CF, BREEDVELD FC, HUIZINGA TWJ: Comparison of long term outcome of patients with rheumatoid arthritis presenting with undifferentiated arthritis or with rheumatoid arthritis: an observational cohort study. *Ann Rheum Dis* 2006; 65: 20-25.
53. HUIZINGA TWJ, MACHOLD KP, BREEDVELD FC, LIPSKY PE, SMOLEN JS: Criteria for early rheumatoid arthritis. From Bayes' Law revisited to new thoughts on pathogenesis. *Arthritis Rheum* 2002; 46: 1155-1159.
54. HARRISON BJ, SYMMONS DPM, BRENNAN P, BARRETT EM, SILMAN AJ: Natural remission in inflammatory polyarthritis: issues of definition and prediction. *Br J Rheumatol* 1996; 35: 1096-100.
55. QUINN MA, GREEN MJ, MARZO-ORTEGA H *et al.*: Prognostic factors in a large cohort of patients with early undifferentiated inflammatory arthritis after application of a structured management protocol. *Arthritis Rheum* 2003; 48: 3039-45.
56. STEIN CM, PINCUS T: Placebo-controlled studies in rheumatoid arthritis: Ethical issues. *Lancet* 1999; 353: 400-3.
57. PUOLAKKA K, KAUTIAINEN H, MOTTONEN T, HANNONEN P, KORPELA M: Early suppression of disease activity is essential for maintenance of work capacity in patients with recent-onset rheumatoid arthritis: five-year experience from the FIN-RACo trial. *Arthritis Rheum* 2005; 52: 36-41.
58. TEN WOLDE S, BREEDVELD FC, HERMANS J *et al.*: Randomised placebo-controlled study of stopping second-line drugs in rheumatoid arthritis. *Lancet* 1996; 347: 347-52.
59. KREMER JM, RYNES RI, BARTHOLOMEW LE: Severe flare of rheumatoid arthritis after discontinuation of long-term methotrexate therapy. Double-blind study. *Am J Med* 1987; 82: 781-6.
60. OKA M, VAINIO U: Effect of pregnancy on the prognosis and serology of rheumatoid arthritis. *Acta Rheumatol Scand* 1966; 12: 47-52.
61. NELSON JL, HUGHES KA, SMITH AG, NISPEROS BB, BRANCHAUD AM, HANSEN JA: Maternal-fetal disparity in HLA Class II alloantigens and the pregnancy-induced amelioration of rheumatoid arthritis. *N Engl J Med* 1993; 329: 466-71.
62. VETERANS ADMINISTRATION COOPERATIVE STUDY ON ANTIHYPERTENSIVE AGENT: Effects of treatment on morbidity in hypertension: II. Results in patients with diastolic blood pressure averaging 90 through 114 mm Hg. *JAMA* 1970; 213: 1143-50.
63. WILT TJ, BLOOMFIELD HE, MACDONALD R *et al.*: Effectiveness of statin therapy in adults with coronary heart disease. *Arch Intern Med* 2006; 1427.
64. THE DIABETES CONTROL AND COMPLICATIONS TRIAL RESEARCH GROUP: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993; 329: 977-86.
65. KRAUSE D, SCHLEUSSER B, HERBORN G, RAU R: Response to methotrexate treatment is associated with reduced mortality in patients with severe rheumatoid arthritis. *Arthritis Rheum* 2000; 43: 14-21.
66. CHOI HK, HERNÁN MA, SEEGER JD, ROBINS JM, WOLFE F: Methotrexate and mortality in patients with rheumatoid arthritis: a prospective study. *Lancet* 2002; 359: 1173-7.
67. PINCUS T, CALLAHAN LF: Prognostic markers of activity and damage in rheumatoid arthritis: Why clinical trials and inception cohort studies indicate more favorable outcomes than studies of patients with established disease. *Br J Rheumatol* 1995; 34: 196-9.
68. ALETAHA D, SMOLEN J, WARD MM: Measuring function in rheumatoid arthritis: Identifying reversible and irreversible components. *Arthritis Rheum* 2006; 54: 2784-92.
69. ZOCHLING J, BRAUN J: Remission in ankylosing spondylitis. *Clin Exp Rheumatol* 2006; 24 (Suppl. 43): S83-S87.
70. CHUNG CP, THOMPSON JL, KOCH GG, AMARA I, STRAND V, PINCUS T: Are American College of Rheumatology 50% response criteria (ACR50) superior to 20% criteria (ACR20) to distinguish active aggressive treatment in rheumatoid arthritis clinical trials reported since 1997? A metaanalysis of discriminant capacities. *Ann Rheum Dis* 2006; Published online 27 Feb 2006.
71. BENCIVELLI W, VITALI C, ISENBERG DA *et al.*: Disease activity in systemic lupus erythematosus: report of the Consensus Study Group of the European Workshop for Rheumatology Research. III. Development of a computerised clinical chart and its application to the comparison of different indices of disease activity. The European Consensus Study Group for Disease Activity in SLE. *Clin Exp Rheumatol* 1992; 10: 549-54.
72. GLADMAN DD, UROWITZ MB, GOLDSMITH CH *et al.*: The reliability of the Systemic Lupus International Collaborating Clinics/

American College of Rheumatology Damage Index in patients with systemic lupus erythematosus. *Arthritis Rheum* 1997; 40: 809-13.

73. SMOLEN JS, STRAND V, CARDIEL M *et al*.: Randomized clinical trials and longitudinal observational studies in systemic lupus erythematosus: consensus on a preliminary core set of outcome domains. *J Rheumatol* 1999; 26:504-7.
74. PINCUS T, KAVANAUGH A, SOKKA T: Benefit/risk of therapies for rheumatoid arthritis: underestimation of the "side effects" or risks of RA leads to underestimation of the benefit/risk of therapies. *Clin Exp Rheumatol* 2004; 22 (Suppl. 35): S2-S11.
75. SMOLEN JS, HAN C, BALA M *et al*.: Evidence of radiographic benefit of treatment with infliximab plus methotrexate in rheumatoid arthritis patients who had no clinical improvement: a detailed subanalysis of data from the anti-tumor necrosis factor trial in rheumatoid arthritis with concomitant therapy study. *Arthritis Rheum* 2005; 52: 1020-30.
76. WELLS GA, BOERS M, SHEA B, BROOKS PM, SIMON LS, STRAND CV: Minimal disease activity for rheumatoid arthritis: a preliminary definition. *J Rheumatol* 2005; 32: 2016-24.