**International Journal of Advances in Rheumatology** is supported by an unrestricted educational grant from Abbott Immunology

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**ISSN 1478-856X**
Measures of inflammation in formal clinical trials

Many measures have been used to assess inflammation in rheumatoid arthritis (RA), derived from physical examination of the joints, laboratory tests, and patient self-report. None of these measures can provide a "gold standard" for assessment of every individual patient. Therefore, an index of 3–7 measures is used in clinical assessment, based on a core dataset of seven measures including three from a health professional (swollen joint count, tender joint count, and global estimate of status), one from a laboratory (erythrocyte sedimentation rate [ESR] or C-reactive protein [CRP]), and three from a patient (physical function, pain, and patient global estimate of status). The earliest use of an index was defined by the American College of Rheumatology (ACR) as a 20%, 50%, or 70% improvement in swollen and tender joint count plus three of the other five measures (patient’s assessment of pain on a visual analogue scale [VAS], patient’s global assessment of disease activity [on a VAS], physician’s global assessment of disease activity [on a VAS], patient’s assessment of physical function, and acute-phase reactant level). These are known as ACR20, ACR50, and ACR70 responses, respectively [1,2]. The ACR criteria measure change relative to baseline, rather than absolute status. Therefore, a 50% improvement can be achieved when tender and swollen joint counts decrease from 20 to 10, or when joint counts decrease from four to two (provided that three of five other ACR core dataset measures also improve by 50%).

Inflammatory activity can be assessed according to absolute indices of efficacy or disease “state”, which may be defined as a measurable, cross-sectional level of disease activity. The most prominent index is the disease activity score (DAS or DAS based on 28-joint count [DAS28]), which includes swollen joint count, tender joint count, ESR or CRP, and patient global estimate, calculated using a specific website or DAS calculator [3,4]. DAS28 has been shown to be an ideal measure on a group level but not so in individual patients [5,6]. The DAS28 index ignores inflammation in ankles and feet.

Different disease activity indices with a continuous scale can be used to assess absolute efficacy. Remission, and low, moderate, and high disease activity, represent “states” of disease activity. According to the European League Against Rheumatism (EULAR)/ACR recommendations, both disease activity “state” and “response” should be reported in clinical trials [7].

“Disconnect” of inflammatory activity, damage, and outcomes

Clinical trials are designed to analyze the efficacy of the agent under study compared with a control treatment. In contemporary clinical trials of biological agents, approximately 60%, 40%, and 20% of patients, respectively, achieve a 20%, 50%, and 70% response according to ACR criteria. Similar or even better results
TREATMENT GOALS OF RA AND HOW TO REACH THEM

Rheumatologists have spoken of “remission” and “remission-inducing therapy” in RA for many years [14], much as oncologists speak of “no evidence of disease” in patients with neoplastic disease [15]. However, sustained remissions in RA were unusual with traditional DMARDs [16]. The term remission in RA includes continuing therapy, and not a drug-free remission. In ACR remission criteria, five of the six following requirements have to be fulfilled for at least two consecutive months: duration of morning stiffness not exceeding 15 min, no fatigue, no joint pain, no joint tenderness or pain in motion, no soft tissue swelling in joints or tendon sheaths, and an ESR <30 mm/h for a female or 20 mm/h for a male [14].

In certain clinical trials, the primary outcome has involved a target value of a DAS28 of 2.6 [17–19], or a DAS of 1.6 [20] as a surrogate for remission. The FIN-RACo trial was the first trial that employed remission – as identified by stringent ACR criteria [14] – as the endpoint. In this trial, work disability rates were significantly lower in patients who had received combination methotrexate, sulfasalazine, hydroxychloroquine, and prednisolone versus patients who received single DMARD therapy with or without prednisolone, although the primary determinant was evidence of remission, regardless of the therapeutic group [12]. The TICORA (Tight Control of RA) study documented that a strategy of intensive tight control of RA led to a significantly better status compared with traditional therapeutic strategies in articular, functional, and radiographic outcomes over 18 months [20]. These data provide strong evidence that a “target control value” or remission is associated with better outcomes than ACR20 or ACR50 responses.

In theory, the goal of treatment of any disease is a “cure” or “remission”. As noted, a cure is not yet possible in diseases characterized by dysregulation of normal mechanisms, such as RA, hypertension, diabetes, and most other chronic non-infectious disease, as the mechanisms of dysregulation remain poorly understood [21]. Nonetheless, although the dysregulation cannot be cured, “tight control” of its consequences through long-term (lifetime) therapy results in lesser vascular damage in diabetes [22], increased survival in hypertension [23], and improved survival in RA [24,25]. In other diseases, control of 20% or perhaps of 50% of a dysregulation appears inadequate to prevent long-term damage.

Improved outcomes before the era of biological agents

In clinical care, the treatment goal for RA is to prevent consequences of the disease such as joint deformity, work disability, comorbidities, and early death. These outcomes are generally not feasible to be studied in a clinical trial setting for ethical and logistical reasons.

Evidence from clinical cohorts and from standard monitoring of consecutive patients who receive routine care indicate improved clinical status of RA patients at this time compared with previous decades, concomitantly with active
likelihood of achieving remission [47]. Even a short delay of therapy of 4 months reduces the risk of severe joint damage [28]. Early treatment may prevent development of RA [46] while minimizing side effects of contemporary DMARDs [45]. However, the risks of “side effects” of RA are substantially less than the long-term consequences of either DMARDs or non-steroidal anti-inflammatory drugs (NSAIDs) [45].

General principles of drug therapy for RA to achieve treatment goals

The contemporary approach to the management of patients with early arthritis is based on identification of patients with early RA, early use of available therapies [35] in suspected cases to control inflammation as completely as possible, using methotrexate as the anchor drug [36,37], and tight control according to quantitative monitoring in order to prevent long-term consequences [37].

Early treatment

Drug treatment for early inflammatory polyarthritis should be initiated before a patient meets classification criteria for RA [37], as ACR 1987 classification criteria do not differentiate between patients with early RA from other types of recent-onset inflammatory polyarthritides [38,40]. Each of the laboratory tests, which are emphasized traditionally by general physicians and even rheumatologists at the “front lines” of diagnosis, are normal in about 30–40% of patients with RA, including measures of ESR, CRP, rheumatoid factor, and anti-cyclic citrullinated peptides (CCP) [41,42]. At the same time, a substantial fraction of patients with very early arthritis may have a spontaneous remission [43,44]. Nonetheless, any patient with polyarthritis for longer than 2–4 weeks should be evaluated by a rheumatologist.

A “preventive” effort to reduce or prevent damage through control of inflammation with DMARDs should begin as soon as there is evidence of joint swelling upon clinical examination. In capable hands, ultrasonography or magnetic resonance imaging may be utilized to detect synovitis. Causes other than RA such as infection, crystal arthropathy, and reactive arthritis should be excluded. Some patients may be treated unnecessarily using a preventive approach, similar to that which occurs in hypertension, hypercholesterolemia, and many infections. However, the risks of “side effects” of RA are substantially greater than side effects of contemporary DMARDs [45]. Early treatment may prevent development of RA [46] while even a short delay of therapy of 4 months reduces the likelihood of achieving remission [47].

Methotrexate as an “anchor drug”

The “anchor drug” for most patients with RA is weekly, low-dose methotrexate [36,37,48]. It is among the DMARDs with the lowest level of toxicities, particularly with use of concomitant folic acid. Long-term continuation of methotrexate treatment is considerably greater than for other traditional DMARDs, indicating a good efficacy and tolerability profile of the drug [49–51]. Weekly low-dose methotrexate for RA (weekly dose <30 mg) is anti-inflammatory [52], in contrast to high-dose methotrexate, which is cytotoxic and associated with far higher levels of adverse events.

A large fraction of patients have disease that is controlled adequately by methotrexate (plus prednisone) or methotrexate in combination with traditional DMARDs such as sulfasalazine and/or hydrochloroquine; they do not appear to require biological agents [53]. Although a systematic review failed to prove the superiority of methotrexate in the treatment of RA [54,55], many randomized controlled trials with biological agents indicate that methotrexate is as effective as monotherapy with a biological agent in patients with early, severe RA [19,56].

Tight control

Therapy to control inflammation should be directed to achieving tight control, with a goal of prevention of joint damage and other undesirable consequences. An improvement at a level of 20% (ACR20) versus placebo is sufficient for approval of marketing through the US Food and Drug Administration (FDA), but this level of control is usually not sufficient to prevent long-term damage, with more extensive control of inflammation required in most patients.

Several studies provide strong evidence that “target control” or remission is associated with better outcomes than ACR20 or ACR50 responses, as discussed above [12,20]. A treatment goal of low DAS levels has been shown to be beneficial in clinical practice [57]. Computer assisted monitoring helped to reach remission in the CAMERA (Computer Assisted Management for Early RA) trial [58]. It is clear that the good results of the BeSt (Behandelstrategieën voor Reumatoide Artritis) trial are, at least in part, due to a treatment goal of low disease activity [59]. The goal of total remission is desirable, although a low-disease-activity status may be acceptable for many patients, as a gold standard measure of remission does not exist.

Mapping of RA disease activity and outcomes in clinical care: QUEST-RA

A major limitation in knowledge concerning treatment goals and results for RA is the absence of quantitative data on...
disease activity and outcomes in the majority of rheumatology units worldwide.

A Quantitative Standard Monitoring of Patients with RA (QUEST-RA) program was established in 2005 to promote quantitative assessment in usual clinical care at multiple sites, and to develop a database of RA patients seen in regular care in multiple countries. By July 2008, the program included 6004 patients from 69 sites in 25 countries [34]; these were: Argentina, Brazil, Canada, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Kosovo, Latvia, Lithuania, The Netherlands, Poland, Russia, Serbia, Spain, Sweden, Turkey, the United Arab Emirates, the UK, and the USA.

Among the 6004 patients, significant variation in mean DAS28 was seen between countries, ranging from approximately 3.0 in The Netherlands, Greece, and Finland to 5.5 in Lithuania and Argentina, and about 6 in Serbia and Kosovo (p<0.001) [34]. Remission according to the ACR criteria was essentially absent in five countries, and in 10 countries fewer than 10% of patients were in DAS28 remission [60].

The QUEST-RA data extend previous observations that most patients at some clinical sites would not be eligible for most RA clinical trials due to low disease activity [61,62]. However, >50% of patients had DAS28 >5.1, indicating high disease activity, in Hungary, Latvia, Poland, Lithuania, Serbia, Kosovo, and Argentina.

Data from QUEST-RA may contribute to our understanding of current RA status in a global perspective as QUEST-RA is the first study to document current RA inflammatory activity and outcomes simultaneously in many countries. The observations may be viewed as fulfilling a vision of Fries in the 1970s – that standardized databases concerning patients with rheumatic diseases could enhance more rational care and improve patient outcomes [63,64].

**Future directions toward improved outcomes of patients with RA**

Many clinicians have suggested that it is not possible to acquire outcomes data in standard rheumatology clinical care. There are certainly complexities of performing a rigorous, formal quantitative joint count in each patient. However, it is simple to collect a short patient questionnaire from each patient at each visit in the waiting room, as a component of the infrastructure of clinical rheumatology settings [65,66]. This procedure can be easily implemented in any rheumatology clinical setting using the same questionnaire for each patient. Patient questionnaire data may be the best (and perhaps only) measure that can allow optimum analysis of quality management in RA [67], and patient questionnaires should be incorporated into standard rheumatology care [65,66]. Solutions have been developed using current technology, to extend routine clinical monitoring of patients with RA [68] and to provide a method to collect real-time data from each patient, assist clinical decision-making, and improve quality of clinical care. The patient is asked to arrive in the clinic 15 min prior to the scheduled visit to complete an expanded self-report health questionnaire on the touch-screen. Data are stored in a central server. Patient self-report of clinical status is available for the health professional as calculated scores and as raw data to scan (“eye-ball”) before the patient enters the room and to facilitate a focused discussion. Physicians record tender and swollen joints by pointing to each of the joints with positive findings on a homunculus on the screen, which provides immediate scores for disease activity on the DAS28. Disease activity, patient-reported outcomes, and the use of DMARDs over time also are shown in time-oriented graphics.

Computerized data management systems could be used to improve the quality of rheumatology care, by acquisition of data previously not available from the medical record and to the facilitation of retrieval of this information. Even in offices in which joint count data (from physicians) and questionnaire data regarding physical function, pain, global status, and fatigue (from patients) might be available, retrieval often requires review of medical records that are several inches thick. Similarly, numerous screens of electronic medical records cannot depict patient status to accurately assess the quality of structure, process, or outcomes in the absence of computerized data-management systems.

**Conclusion**

The contemporary approach to patients with RA is to control inflammation as completely as possible. Tight control according to quantitative monitoring may help to prevent long-term consequences of RA in many countries.

**Acknowledgement**

The authors would like to thank Dr Theodore Pincus for his helpful comments.

**Disclosures**

The authors have no relevant financial interests to disclose.

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Rheumatoid arthritis (RA) is a chronic inflammatory disease with a worldwide prevalence of 0.7%, mostly affecting synovial joints. Although its clinical course is variable, joint destruction can occur rapidly and early in the course of the disease. Erosion of joints can be detected by magnetic resonance imaging as early as 4 months after symptom onset [1] and as many as 93% of untreated patient sustain radiographic damage by 2 years [2]. Within 5–10 years of diagnosis, half of RA patients will be unable to work [3,4].

Advances in treatment and treatment strategies over the past decade have greatly revolutionized the approach to this disease. Early, aggressive intervention has become the mainstay of RA treatment. Combination therapy of two or more conventional disease-modifying antirheumatic drugs (DMARDs) has been shown to be superior to monotherapy in slowing clinical and radiographic progression [5–11]. The advent of biological agents has revolutionized RA therapy and offers safe and more effective treatment options.

The objective of this article is to review the evidence from randomized, controlled clinical trials of the efficacy and safety of common combinations of DMARDs as well as of biological agents used as monotherapy and in combination. Int J Adv Rheumatol 2009;6(4):120–9.

**American College of Rheumatology recommendations**

In June 2008, the American College of Rheumatology (ACR) released treatment recommendations for the use of non-biological and biological DMARDs [12]. Recommendations for initiation and resumption of treatment in a DMARD-naïve population were included. However, recommendations for switching agents in the population of DMARD-treated patients with suboptimal control were not included. Initiation of a biological agent is only recommended for patients who have failed on non-biological DMARDs. The recommendations propose algorithms for choosing appropriate treatment regimens based on the stratification of patients by duration and activity of disease as well as by prognosis. These algorithms often recommend 3–4 possible treatment options, which may be confusing to the physician in clinical practice.

**Common combinations of non-biological DMARD therapy**

According to the ACR recommendations [12], monotherapy with any conventional DMARD other than methotrexate is only recommended for patients without poor prognostic indicators (defined as high joint counts, erosive disease, positivity for rheumatoid factor [RF] and/or cyclic citrullinated peptides [CCP], elevations in erythrocyte sedimentation rate [ESR] and/or C-reactive protein [CRP], older age, female sex, and tobacco use). Combining certain DMARDs has been shown to be more effective than monotherapy in reducing disease activity and slowing radiographic progression [5–11]. The rationale for combination therapy is to simultaneously target different inflammatory pathways that mediate the pathogenesis of RA.

**Sulfasalazine and methotrexate**

In the COBRA (Combinatetherapie BIJ Reumatoide Arthritis) trial, triple therapy with sulfasalazine, methotrexate, and
prednisolone was compared with sulfasalazine alone [5]. Prednisolone was discontinued by 28 weeks. At week 28, a 20% and 50% improvement in ACR criteria for RA (ACR20 and ACR50 responses) was achieved by significantly more patients receiving combination therapy, and joint destruction progressed at a slower rate in this group. However, the advantages of combination therapy were no longer apparent after withdrawal of prednisolone. By week 56, both clinical efficacy and radiographic damage measures were not significantly different between the two groups suggesting that the positive initial results may have been due to the effect of prednisolone. Additionally, adverse events (AE) such as infection, gastrointestinal (GI) complaints, and cardiovascular disorders were more frequent in the combination group.

Sulfasalazine, methotrexate, and hydroxychloroquine

Three trials have evaluated the combination of sulfasalazine, methotrexate, and hydroxychloroquine. O’Dell et al. showed this triple therapy to be superior to a combination of two conventional DMARDs or to single agent therapy in two separate trials [9,10]. The first compared this regimen with combination sulfasalazine plus hydroxychloroquine and with methotrexate alone in patients unresponsive to DMARD therapy [9]. In the second study, a combination of sulfasalazine, methotrexate, and hydroxychloroquine was compared with methotrexate plus hydroxychloroquine or methotrexate plus sulfasalazine over a 2-year period [10]. Triple therapy resulted in the greatest improvement with an ACR20 response of 78%, 60%, and 49% for each group, respectively.

In the open-label FIN-RACo (Finnish RA Combination Therapy) trial, patients were randomized to triple therapy or sulfasalazine with or without prednisolone for 2 years, after which treatment became unrestricted [6]. At 2 years, clinical remission according to the ACR criteria was achieved in 40% of patients receiving triple therapy compared with 18% receiving monotherapy. Radiographic improvement was seen in the combination therapy group. Although remission rates at 5 years were comparable between the two groups (28% and 22%, respectively), radiographic damage continued to be significantly lower with combination therapy.

In all studies, AEs and discontinuations because of AEs were comparable between the groups. GI distress was the most commonly reported AE.

Leflunomide and methotrexate

In a 24-week trial of patients with inadequate response to methotrexate, the addition of leflunomide was compared with methotrexate monotherapy [7]. An ACR20 response was achieved by 46% of patients on combination therapy compared with 20% of patients receiving methotrexate alone. Abnormal liver function tests (LFTs) were more common in patients receiving leflunomide plus methotrexate. There was a significant increase in incidence of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) level elevations to greater than three times the upper limit of normal (ULN) in patients receiving combination therapy. However, all elevated enzyme levels greater than 1.2-times the ULN normalized to 1.2-times the ULN or below during or by the end of the study. Other AEs occurring more frequently in the leflunamide plus methotrexate group were diarrhea, nausea, headaches, dizziness, and alopecia. The use of methotrexate and leflunomide together requires close monitoring.

Tumor necrosis factor inhibitors

There are two major types of tumor necrosis factor (TNF) biological inhibitors approved for RA: soluble TNF receptors (etanercept) [13] and monoclonal antibodies against TNF (infliximab and adalimumab) [14,15].

Etanercept

A 24-week trial evaluated the addition of etanercept to methotrexate in patients with active disease despite methotrexate therapy [16]. Significantly higher ACR20/50/70 response rates were observed for the patients in the combination group (71/39/15%) than in the patients receiving methotrexate alone (27/3/0%; p<0.001). In the ERA (Early Erosive RA) trial, etanercept 25 mg twice weekly resulted in greater clinical response and halted radiographic progression significantly better than etanercept at a 10-mg dose and methotrexate in patients with early RA (<1 year) at 12 months [17]. The long-term, open-label extension showed sustained efficacy at 3 years in patients on etanercept 25 mg weekly monotherapy. Seventy percent of patients randomized to the 10-mg etanercept group had achieved an ACR20 response at baseline of the open-label extension and 81% achieved an ACR20 response rate by 1 year after switching to the etanercept 25 mg dose. Forty-eight percent of patients originally randomized to the methotrexate monotherapy group had achieved an ACR20 response rate at baseline of the open-label extension, and 72% achieved an ACR20 response rate by 1 year after switching to or adding etanercept 25 mg twice weekly.

An important efficacy trial for etanercept, TEMPO (Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes), compared the combination of etanercept plus methotrexate, etanercept alone, and methotrexate alone in patients with active RA despite therapy with a DMARD other than methotrexate [18]. After 1 year of therapy,
significantly higher ACR20/50/70 response rates were observed for the combination group (85/69/43%) than the methotrexate (75/48/19%) or etanercept group (76/48/24%). In addition, the proportion of patients achieving remission (disease activity score [DAS] <2.6) was similarly greater in the combination group (35%) compared with the methotrexate group (13%) and etanercept group (16%). The combination was also more efficacious than methotrexate or etanercept alone in improving functional disability (as measured by the Health Assessment Questionnaire [HAQ]) and retardation of radiographic progression [18]. At 52 weeks, 80% of patients receiving the combination showed no radiographic progression compared with 68% and 57% with etanercept and methotrexate monotherapy, respectively. ACR responses, remission rates, HAQ improvement, and radiographic findings were sustained for up to 3 years [19–21]. During a 52-week, open-label extension period, 227 patients were treated with combination etanercept and methotrexate with a primary clinical efficacy outcome of remission, defined as a DAS <1.6. The results revealed that continued treatment showed further improvement in outcomes. More patients treated with combination methotrexate and etanercept achieved remission after 4 years (50%) than after 3 years (38%). Furthermore, patients who added etanercept to methotrexate and those who added methotrexate to etanercept also showed improved outcomes and higher rates of remission, compared with the results at 3 years.

Improvement in disability seen with the use of etanercept is especially pronounced when used early in the course of the disease. In a post hoc analysis of patients with recent-onset (mean duration of 1 year) versus late disease (mean duration of 12 years) [22], the difference in mean percentage improvement between the groups was seen within 2 weeks of etanercept therapy and was sustained throughout the duration of the study. At 3 years, more patients with early disease (26%) achieved a HAQ score of zero than did patients with long-standing disease (14%).

The recently published COMET (Comparison of Methotrexate Monotherapy with a Combination of Methotrexate and Etanercept in Active, Early, Moderate to Severe RA) trial is the first TNF inhibitor study to look at remission as its primary endpoint [23]. Patients with early (<24 months), moderate-to-severe RA who were methotrexate-naïve received either methotrexate alone or in combination with etanercept. At week 53, half of the patients receiving combination therapy achieved remission (defined as DAS <2.6) compared with 28% of patients receiving methotrexate monotherapy. Radiographic non-progression (defined as a modified total Sharp score [mTSS] of ≤0.5) was achieved by 21% more patients in the etanercept plus methotrexate group. A significant improvement in the degree of disability was also seen in the combination group compared with the monotherapy group. More patients receiving methotrexate alone (24%) had to stop working during the course of the study than patients receiving etanercept plus methotrexate (9%).

Evaluations of safety in all trials presented reveal comparable rates of AEs and discontinuations because of AEs across all treatment groups. In the TEMPO trial, serious adverse events (SAEs) were more common in the monotherapy groups than in the combination group (8% of the combination group, 12% of the methotrexate group, and 11% of the etanercept group) [18]. Similarly, in the COMET trial, more patients in the methotrexate group had serious infections than in the combination group, including one patient in the methotrexate group who had opportunistic herpes zoster [23]. No cases of tuberculosis (TB), multiple sclerosis, or other central demyelinating diseases were reported. Mild injection site reactions were more commonly reported for the combination and etanercept monotherapy than the methotrexate monotherapy group (incidences from TEMPO study were 10%, 21%, and 2%, respectively).

The incidence of malignancies was comparable. In the TEMPO trial, three cases of carcinomas (one in each group) and one case each of breast cancer, rectal cancer, and melanoma in the etanercept group were reported [18]. In the COMET trial, there were eight reported malignancies: three breast cancer cases and one prostate cancer in the methotrexate group, and one case each of chronic lymphocytic leukemia, epidermoid cancer of the tongue, basal-cell carcinoma, and Bowen’s disease in the combined treatment group [23].

Infliximab
The addition of infliximab to existing methotrexate therapy was evaluated in patients with an inadequate response to methotrexate in the ATTRACT (Anti-TNF Therapy in RA) trial [24,25]. At 2 years, ACR20/50/70 response rates were significantly higher for patients receiving infliximab plus methotrexate compared with those receiving methotrexate alone. The addition of infliximab to existing methotrexate therapy resulted in significant improvement in quality of life measures (by HAQ and Short Form-36 [SF-36] physical component summary scores) as well as in halting progression of damage. Significantly greater reductions in erosion score and in joint-space narrowing score from baseline to week 102 were observed for the infliximab plus methotrexate group, compared with methotrexate alone. This was particularly pronounced among a subgroup of patients with early disease (<3 years), in which the mean
change from baseline in total erosion score for the infliximab plus methotrexate group was greater than for the methotrexate group, further reinforcing the benefits of early intervention [26].

After 52 weeks of therapy in the ATTRACT study, similar rates of discontinuations as a result of AEs were observed across all groups [23]. SAEs were also comparable between the various dosing groups of infliximab plus methotrexate (9–13%) and methotrexate alone (16%). However, the frequency of any infection requiring antimicrobials was significantly higher for the 10-mg/kg dose of infliximab (64–73%) than for methotrexate alone (40%).

The ASPIRE (Active-Controlled Study of Patients Receiving Infliximab for the Treatment of Early-Onset RA) trial evaluated the efficacy of the combination of infliximab 3 or 6 mg/kg plus methotrexate and methotrexate alone in methotrexate-naive patients with early active RA [27]. Although the differences between the numbers of ACR20/50/70 responders in the combination groups were relatively small compared with the methotrexate group at 54 weeks, the number of patients showing radiographic benefit was significantly higher with either dose of infliximab plus methotrexate compared with methotrexate monotherapy.

Mild infusion reactions were more commonly reported in combination groups in both trials (10–20%), compared with methotrexate alone (3–10%). In the ATTRACT trial, antibodies to double-stranded DNA (anti-dsDNA) were reported in 16% of infliximab-treated patients versus none in the methotrexate alone group. One patient receiving the 10-mg/kg dose of infliximab developed drug-induced lupus syndrome characterized by a rash, a rising anti-nuclear antibody (ANA) titer from 1:40 to 1:80, and a low complement component C4 level (but no anti-dsDNA). Between weeks 54 and 102 of the study, there was an increase of 13% in the proportion of patients with ANA in the infliximab plus methotrexate group and an increase of 5% in the percentage of patients with anti-dsDNA antibodies, compared with increases of 6% and 0%, respectively, for the methotrexate group. No additional cases of lupus-like syndrome were observed in the second year of the study, and only one patient experienced a lupus-like reaction during the entire study.

**Adalimumab**

The efficacy and safety of adding adalimumab to insufficient DMARD therapy was evaluated in three trials: ARMADA (Anti-Tumor Necrosis Factor Research Study Program of the Monoclonal Antibody Adalimumab in RA), DE019 (A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of the Human Anti-TNF Monoclonal Antibody Adalimumab in RA Patients Currently Receiving Treatment with Methotrexate), and PREMIER (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 RA who were Methotrexate Naive) [28–32].

In the ARMADA trial, addition of adalimumab 20, 40, and 80 mg every other week to existing methotrexate therapy was evaluated [28]. Response to therapy was seen as early as 1 week after initiation of therapy, and the percentage of patients achieving a response increased from week 1 to 24. At week 24, significantly greater ACR20/50/70 response rates were achieved by the groups receiving adalimumab plus methotrexate compared with those receiving methotrexate alone. Clinical measures of improvements for fatigue (Functional Assessment of Chronic Illness Therapy [FACIT]) and quality of life (SF-36) also favored adalimumab plus methotrexate over methotrexate alone. Similar numbers of patients in the adalimumab plus methotrexate group withdrew from the study because of AEs (5/209 patients) compared with the methotrexate group (2/62 patients). The number of treatment-related AEs was also similar between the combination group and the methotrexate group. Higher rates of mild or moderate injection site reactions were reported for the adalimumab plus methotrexate group (15%) compared with the methotrexate group (3%). Anti-dsDNA antibodies were reported in 3.9% of adalimumab plus methotrexate-treated patients versus none in the methotrexate monotherapy group.

The DE019 trial evaluated adalimumab 20 mg once weekly and 40 mg every other week in combination with methotrexate in patients with an inadequate response to methotrexate [31]. Similar to reported observations from the ARMADA trial, a significantly higher percentage of patients receiving adalimumab plus methotrexate achieved ACR20/50/70 responses after 52 weeks of therapy, compared with patients receiving methotrexate alone [31]. There was also significantly less radiographic progression in the combination group than in the methotrexate monotherapy group. Similarly, reductions in HAQ scores were significantly greater in the combination group than in the methotrexate monotherapy group.

Discontinuations related to AEs occurred in 10% of adalimumab-treated patients, compared with 7% for methotrexate-treated patients. However, significantly higher rates of serious infections were reported for the adalimumab combination group than for the methotrexate group. Rare cases of TB, histoplasmosis infection, herpes zoster, non-skin cancers, and central demyelinating illness were reported for adalimumab-treated patients. Injection site reactions were comparable for the adalimumab plus methotrexate (22–26%) and methotrexate monotherapy (24%) groups.
At week 52, 12% of adalimumab-treated patients and 9% of methotrexate-treated patients were positive for ANA.

In a subsequent analysis, the effect of combination therapy was examined by disease duration [30]. Patients with early disease (<2 years) had a significantly greater benefit than patients with late disease (>2 years). In patients receiving adalimumab 40 mg every other week, ACR20/50/70 responses were 70%, 59%, and 41% in the group with early disease and 62%, 36%, and 18% in patients with long-standing disease. HAQ improvement was also higher for combination-treated patients (0.79 vs. 0.57, respectively).

The PREMIER study compared the safety and efficacy of adalimumab 40 mg every other week plus methotrexate combination therapy with methotrexate alone or adalimumab alone in methotrexate-naïve patients with recent-onset RA [29]. At 2 years, ACR50/70 responses were significantly higher in the combination group compared with either methotrexate or adalimumab. The proportion of patients achieving remission, as defined by DAS <2.6, was also significantly higher in the combination group (50%) than in the methotrexate or the adalimumab monotherapy groups (25%). Radiographic outcomes were also significantly better in the combination group than the monotherapy groups after 2 years of therapy. The frequencies of AEs were comparable among all three groups.

**Anakinra**

Approved for use in RA in 2001, anakinra is a recombinant human interleukin-1 (IL-1) antagonist [33]. The benefits of adding anakinra to methotrexate therapy in patients with inadequate response to methotrexate were evaluated in a 24-week study [34]. Although the ACR20/50/70 response rates were statistically significantly greater for patients receiving anakinra 1 and 2 mg/kg than for patients receiving methotrexate, response rates in all groups were low. The ACR20/50/70 response rates were 35%, 17%, and 7% in the 2 mg group, 42%, 24%, and 10% in the 1 mg and 23%, 4%, and 0% in the methotrexate alone group. Withdrawals as a result of AEs were higher in the 1- and 2-mg/kg anakinra plus methotrexate groups (14-15%) than methotrexate alone (4%). Mild and moderate injection site reactions were the most frequent AEs reported for anakinra (63% for the 2-mg/kg group compared with 28% for the methotrexate control group). Abdominal pain was reported more frequently for patients receiving anakinra plus methotrexate (6%) than for patients receiving methotrexate alone (1%). Five of 345 patients (1%) receiving anakinra plus methotrexate developed leukopenia. No serious infections were noted.

In the 990145 (A Multicenter, Double-blind, Randomised, Placebo-Controlled Trial of Anakinra, a Recombinant IL-1 Receptor Antagonist, in Patients with RA Treated with Background Methotrexate) study, patients with active RA despite current treatment with methotrexate received either anakinra 100 mg daily or methotrexate for 24 weeks [35]. Similar to the previous study, a statistically significant difference in ACR response was seen between the treatment and placebo groups, but response rates were low in all groups. ACR20/50/70 responses were 38%, 17%, and 6% for the treatment group versus 22%, 8%, and 2% for the placebo group. Safety profiles for anakinra were similar to those reported in the earlier trial, with more mild-to-moderate injection site reactions reported for anakinra than placebo (65% vs. 24%). The number of withdrawals because of injection site reactions was greater in the anakinra plus methotrexate groups (8%) compared with the methotrexate alone group (<1%). Rates of SAEs were comparable (4% anakinra plus methotrexate vs. 3% methotrexate alone). SAEs leading to study withdrawal included reported gangrene of a limb, fracture, and prostate cancer in the methotrexate group and interstitial lung disease and pulmonary fibrosis in the anakinra group. Rates of infectious events were comparable for both groups (33% anakinra vs. 26% methotrexate).

The use of anakinra together with etanercept has also been studied [36]. A significant increase in infection was seen in the combination group (7.4% incidence of SAE in combination groups vs. 0% in etanercept alone group) without any increased efficacy. As a result, this combination is not recommended for clinical use.

**Abatacept**

Abatacept was approved by the US Food and Drug Administration (FDA) in 2005 for use in adults with moderate-to-severe RA and inadequate response to one or more DMARD. It modulates the co-stimulatory signal required for T cell activation. It is a recombinant fusion protein comprised of the extracellular portion of the cytotoxic T lymphocyte antigen-4 (CTLA-4) receptor fused to the Fc portion of immunoglobulin G1, and has been modified to avoid complement fixation. Abatacept mimics the action of CTLA-4, blocking the binding of CD28 to CD80/86 and, in turn, the co-stimulatory signal required for activation of T cells.

The AIM (Abatacept in Inadequate Response to Methotrexate) study was a 1-year, placebo-controlled trial of abatacept 10 mg/kg every 4 weeks in patients who had failed methotrexate [37]. Improvement compared with placebo was seen in all three primary outcomes: ACR response at 6 months (ACR20/50/70 for abatacept vs. placebo of 68/29/20% vs. 40/17/6%), functional capacity according to HAQ-Disability Index (HAQ-DI), and radiographic progression of disease at
1 year. In addition, a statistically larger proportion of patients in the abatacept group achieved remission (DAS28 <2.6). Progression of structural damage was reduced by 50% in the abatacept group after the first year and an even greater reduction was seen in the second year. A long-term, open-label extension of AIM revealed sustained response of all outcomes at 3 years.

The ATTAIN (Abatacept Trial in the Treatment of Anti-TNF Inadequate Responders) compared abatacept with placebo in RA patients with TNF-inhibitor failure [38]. In the 6-month follow-up period, an ACR20, 50, and 70 response was achieved in a significantly greater proportion of patients in the abatacept group than the placebo group (50/20/10% vs. 19/4/1.5%, respectively). Significant improvements in HAQ-DI were also seen. The interpretation of these findings is complicated by the mandatory washout period. Subjects had stopped TNF antagonists a minimum of 3 months prior to entry into the trial; this may have resulted in disease flares and falsely enhanced the apparent efficacy of abatacept.

This question was addressed in a sub-analysis of the open-label study ARRIVE (Abatacept Researched in RA Patients with an Inadequate anti-TNF Response to Validate Effectiveness) [39]. A comparison was made between patients whose last dose of TNF antagonist was more than or less than 2 months prior to the initiation of abatacept. Clinically meaningful improvements in DAS28 and HAQ-DI were seen equally in both groups.

One of the limitations in using this medication is its delayed time to response. Although statistically significant responses were seen as early as 15 days in both the AIM and ATTAIN trials, the maximal percentage of responders was only reached at 90 days [37,38]. In a head-to-head comparison entitled ATTEST (Abatacept or Infliximab versus Placebo, the Trial for Tolerability, Efficacy and Safety in Treating RA), clinical improvement was similar in both groups; however, the onset of ACR20 response was significantly later in the abatacept group, only reaching similar response rates by day 85 [40].

The safety profile of abatacept is similar to that of other biological agents. The AIM trial showed comparable incidence of AEs but a higher rate of SAEs in the abatacept group. However, in the ATTAIN trial, SAEs were similar in both groups. Both trials revealed a higher risk of infection with abatacept compared with placebo (3.9% vs. 2.3% in AIM and 38% vs. 32% in ATTAIN). Infections were mostly mild including upper respiratory tract infections (URTIs) and nasopharyngitis. The AIM trial also described a higher incidence of severe infection with abatacept (2.5% vs. 0.9% with placebo) including one case of aspergillosis. Infusion reactions, though more frequent in the abatacept group in all studies, were mild (most commonly headaches and dizziness).

The safety of abatacept in combination with other DMARD and/or biological agents was studied in the ASSURE (Abatacept Study of Safety in Use with Other RA Therapies) trial [41]. Patients on at least one DMARD or biological agent (11% were on biological agents) were randomized to abatacept 10 mg/kg every 4 weeks or placebo for 1 year. The incidences of AEs, SAEs, or discontinuation of medication due to AEs were almost identical in both groups. However, subgroup analysis of patients on biologics showed more SAEs (22% vs. 11–12%). Due to the higher rates of SAEs and infections with abatacept plus other biologics subgroups, it is recommended that these combinations not be used. Serious infections were mostly URTIs and did not include any cases of TB or other opportunistic infections. Notably, patients with a previous diagnosis of chronic obstructive pulmonary disease who received abatacept reported more AEs (43.2% vs. 23.5%) and SAEs (27% vs. 5%) than similar patients in the placebo group.

**Rituximab**

Rituximab is a selective B-cell-depleting biological agent recently introduced for use in combination with methotrexate for refractory RA. This chimeric monoclonal antibody against CD20 is selectively expressed on mature B cells but not on plasma or stem cells. Several mechanisms for the mode of action of rituximab have been proposed including cell-mediated cytotoxicity, complement dependent cytotoxicity, and induction of B cell apoptosis.

The DANCER (Dose-Ranging Assessment: International Clinical Evaluation of Rituximab in RA) trial is a three-arm study evaluating rituximab 500 mg/1000 mg for two doses, 2 weeks apart, added to methotrexate compared with placebo in patients with inadequate response to DMARDs and/or biological agents [42]. Each of the three groups additionally received either intravenous methylprednisolone premedication followed by 2 weeks of oral steroids, intravenous methylprednisolone premedication alone, or placebo. Significantly more patients achieved the primary outcome of ACR20 at 24 weeks in both rituximab groups compared with placebo (55%, 54%, and 28%, respectively) but efficacy was comparable between doses. Statistically and clinically significant improvements were also seen in all secondary outcomes including ACR50/70, DAS28, European League Against Rheumatism (EULAR) responses, and patient-reported health-related quality of life measures. Response was seen early on in treatment, with 30% of patients achieving an ACR 20 response by 4 weeks. Of note, glucocorticoid dosing did not contribute to efficacy outcomes.

The REFLEX (Randomized Evaluation of Long-Term Efficacy of Rituximab in RA) trial compared 1000 mg of
rituximab plus methotrexate with methotrexate alone in inadequate responders to TNF agents [43]. Similar to the DANCER study, at 24 weeks, significant improvement were seen in primary and secondary outcomes. This study additionally evaluated progression of radiographic disease. Although there was no significant difference in change from baseline in the Genant modified sharp scores at 24 weeks, in the open-label extension at 1 and 2 years rituximab-treated patients had slower progression of structural damage. Patients who had received repeated courses of rituximab achieved comparable efficacy to their original treatment. An ACR20 response was achieved by 70.9% after the first course, 72.6% after the second, and 73.2% after a third course of the drug. Furthermore, remission rates increased with subsequent courses.

Rituximab is generally safe and well tolerated. In both the DANCER and REFLEX trials, a similar proportion of patients reported AEs and SAEs in all groups with most related to infusion reactions [42,43]. Acute infusion reactions described as pruritis, pyrexia, rigors, throat irritation, angioedema, and bronchospasm were more common with the first infusion and were significantly reduced with the use of premedication glucocorticoid infusion. In the DANCER trial, the incidence of acute reaction without premedication glucocorticoids in the placebo, 500 mg, and 1000 mg groups was 14%, 32%, and 37%, respectively, while the incidence with premedication was 19%, 19%, and 29%, respectively. Addition of 2 weeks of oral steroids did not significantly reduce the incidence of these reactions.

Infections occurred slightly more often in the rituximab groups (incidence in the rituximab vs. placebo groups was 35% vs. 25% and 41% vs. 38% in DANCER and REFLEX, respectively). Infections were generally mild with URTIs and nasopharyngitis being most commonly reported. Serious infections were infrequent in all studies. Common AEs included GI toxicity with complaints of nausea and epigastric pain as well as skin manifestations with dermatitis and pruritis. In the TOWARD trial, the infection incidence was 37% in the tocilizumab group and 32% in the placebo group with 1% and 3% of the placebo groups in OPTION and TOWARD, respectively. Tocilizumab was also found to produce rapid and sustained improvements in acute phase reactants, ESR, CRP, and hemoglobin. Blocking of IL-6’s effect on hepcidin, which normally acts to restrict iron availability may explain the rise in hemoglobin seen with tocilizumab use.

The AMBITION (Actemra versus Methotrexate Double-Blind Investigative Trial in Monotherapy) trial compared tocilizumab monotherapy with methotrexate in a DMARD/biologic-naïve population [47]. Patients receiving tocilizumab monotherapy achieved higher ACR responses than those on methotrexate (ACR20/50/70 of 70/53/44% and 34/28/15% in the tocilizumab and placebo groups, respectively).

In the SAMURAI (Study of Active Controlled Monotherapy used for RA, an IL-6 Inhibitor) trial, patients with RA for less than 5 years who were non-responsive to at least one DMARD (excluding biological agents) were randomized to tocilizumab monotherapy or standard DMARD therapy [48]. At week 52, 56% of patients receiving tocilizumab had no radiographic progression compared with 39% of those on placebo. The authors argue that perhaps these differences would be even more impressive with addition of methotrexate to tocilizumab.

AEs were slightly higher but comparable in the tocilizumab group in all trials. Common AEs included GI toxicity with complaints of nausea and epigastric pain as well as skin manifestations with dermatitis and pruritis. In the TOWARD trial, the infection incidence was 37% in the tocilizumab group and 32% in the placebo group with serious infections occurring in 2.7% and 1.9%, respectively [46]. Five serious infections led to study withdrawal including one opportunistic infection with *Mycobacterium avium* intracellulare in a patient who had received 4 mg/kg of tocilizumab. Infusion reactions were mild-to-moderate and were infrequent in all studies.

The use of tocilizumab is associated with a number of unique safety concerns. Elevations in LFTs have been well described. In the TOWARD trial, transient elevations in ALT were seen in 45% of patients in the tocilizumab group. Patients exhibiting elevations of greater than three-fold the
response to methotrexate \[50\]. The GO-AFTER (Golimumab and methotrexate alone in patients with an inadequate 50/100 mg combined with methotrexate, golimumab alone Active RA Despite Methotrexate) compares golimumab patients \[49\]. GO-FORWARD (Golimumab For Subjects with methotrexate to methotrexate alone in methotrexate-naïve different populations, are currently in progress. GO-BEFORE evaluating the safety and efficacy of this agent in three different populations. Three trials, Golimumab is a fully humanized anti-TNF agent which has the advantage of every 4 week dosing. Three trials, evaluating the safety and efficacy of this agent in three different populations, are currently in progress. GO-BEFORE (Golimumab Before Employing Methotrexate as the First-line Option in the Treatment of RA of Early-onset) compares golimumab monotherapy or in combination with methotrexate to methotrexate alone in methotrexate-naïve patients [49]. GO-FORWARD (Golimumab For Subjects with Active RA Despite Methotrexate) compares golimumab 50/100 mg combined with methotrexate, golimumab alone and methotrexate alone in patients with an inadequate response to methotrexate [50]. The GO-AFTER (Golimumab After Former anti-TNF Therapy Evaluated in RA) has randomized patients with inadequate response to another TNF inhibitor to golimumab or placebo [51]. Certolizumab, a pegylated TNF antagonist is currently being evaluated in the RAPID (RA Prevention of Structural Damage) I and II trials [52,53]. Patients were randomized to certolizumab 400 mg monotherapy, certolizumab 200 mg/400 mg combination therapy with methotrexate, or methotrexate alone. The initial results are promising with significant improvements in clinical outcomes, health quality of life measures, and slowing of radiographic progression.

**Conclusion**

Combinations of two or more DMARDs or a DMARD and a biological agent are often superior to monotherapy for improving the clinical signs and symptoms of the disease in addition to reducing the rate of joint damage in patients with early RA. Although they slow disease progression and may even result in clinical remission, combinations of conventional DMARDs do not always result in inhibition of joint destruction. DMARDs are slower acting than corticosteroids or biological therapy and are associated with an increased incidence of therapy discontinuations because of AEs and lack of efficacy.

Biological agents overcome some of the limitations of conventional DMARD therapy. They have a relatively rapid onset of action and long-term sustained effects. Many of these agents inhibit radiographic progression by effectively reducing synovitis. The concern with these agents is related to their safety profiles, the increased risk of infection they impose, and their cost-effectiveness. The annual cost of biological agents is substantially higher than traditional DMARDs. However, in assessing the cost-effectiveness of these agents consideration must be given to the high healthcare costs of this chronic musculoskeletal disease, including the direct costs associated with medical visits, laboratory testing, hospitalizations, and acquisition of medications, as well as the indirect cost associated with disability and unemployment. By inhibiting or halting progression of joint damage, therapy with biological agents may improve quality-adjusted life years and, despite their price, may provide a cost-effective, long-term approach for the treatment of RA.

In conclusion, clinical trials of combination therapy with DMARDs or DMARD plus biological agent combinations have demonstrated that an aggressive approach to RA early in the disease process, coupled with careful monitoring of patient response and appropriate optimization of the treatment regimen, can lead to favorable long-term outcomes. New targeted therapies have greatly raised expectations for treatment outcomes. Current biological

ULN were described in the OPTION, TOWARD, and RADIATE trials at incidence rates for tocilizumab-treated patients versus placebo of 2–10% versus 1–4% [44–46]. Of note, these elevations were asymptomatic, not associated with clinical hepatitis, and not sustained. No association could be made between LFT abnormalities and combination of tocilizumab with any one particular DMARD. Cases of GI perforation, though rare, have been reported more often in the tocilizumab-treated patients than in those receiving placebo. Eleven events have been described in five pivotal RA studies. Events have involved both the upper and lower GI tracts and have occurred mostly in patients treated with the 8 mg/kg dose. Of note, most patients were receiving concomitant therapy with nonsteroidal anti-inflammatory drugs and/or steroids.

Elevations of total cholesterol, low-density lipoprotein (LDL), triglycerides, high-density lipoprotein (HDL), and total cholesterol:HDL ratio have been described with the use of tocilizumab. In the OPTION trial, 21% of patients receiving tocilizumab met criteria for initiation of a statin versus 3% of patients receiving placebo. Similarly in TOWARD, elevations of total cholesterol to >240 mg/dL were seen in 26% and 6% of patients receiving tocilizumab and placebo, respectively. These abnormalities appropriately responded to statin use and were not associated with an increased incidence of cardiovascular events during the duration of the trial.

The presence of the IL-6 receptor on the cell surface of neutrophils likely accounts for the neutropenia associated with this agent. In the RADIATE trial, the incidence of transient neutropenia was 28% in the tocilizumab-treated patients versus <1% in the placebo group. Most were grade 1 or 2, but grades 3 and 4 neutropenia were reported in 10 patients. A similar incidence of neutropenia was reported in other trials. No events of neutropenia were temporally related to infection.

**Agents on the horizon**

Golimumab is a fully humanized anti-TNF agent which has the advantage of every 4 week dosing. Three trials, evaluating the safety and efficacy of this agent in three different populations, are currently in progress. GO-BEFORE (Golimumab Before Employing Methotrexate as the First-line Option in the Treatment of RA of Early-onset) compares golimumab monotherapy or in combination with methotrexate to methotrexate-naïve patients [49]. GO-FORWARD (Golimumab For Subjects with Active RA Despite Methotrexate) compares golimumab 50/100 mg combined with methotrexate, golimumab alone or methotrexate alone in patients with an inadequate response to methotrexate [50].
treatments, as well as those that are now in development, are likely to dramatically alter the natural history of RA and make severe RA a rarity in clinical practice.

Disclosures
Dr Singer has no relevant financial interests to disclose. Professor Gibofsky is a stockholder with Abbott, Amgen, Bristol-Myers Squibb, Johnson & Johnson, and Pfizer. Professor Gibofsky has also acted as a consultant for Abbott, Amgen, Bristol-Myers Squibb, Roche, and Wyeth; and as a speaker for Abbott, Amgen, Bristol-Myers Squibb, Pfizer, and Wyeth.

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Systemic lupus erythematosus (SLE) is an autoimmune disease that can affect many organs and has a range of clinical and immunological manifestations. The incidence of SLE varies according to the characteristics of the population studied, for example age, gender, and ethnic background. Similarly, the prevalence of the disease in the general population has been found to vary, with factors such as a changing definition of SLE over time affecting prevalence rates. The present review considers the epidemiology of SLE and evaluates the factors that impact upon the incidence and prevalence of the disease. Specific focus is given the Euro-Lupus Cohort – a prospective registry of 1000 SLE patients followed since 1991 – which has provided key data on SLE. Int J Adv Rheumatol 2009;6(4):130–6.

Incidence and prevalence in the general population

Incidence

The incidence of SLE varies according to the characteristics of the population studied, i.e. age, gender, race, ethnic and national origin; the period of time considered; and the diagnostic criteria used [1–39]. In Europe, the annual incidence ranges between 2.2 cases per 100 000 persons per year in Asturias, Spain [2], and 5.8 cases per 100 000 persons per year in Iceland [3]. In the US, the annual incidence of SLE has been estimated in several studies, with incidence rates ranging from 2.2 cases per 100 000 persons per year in the rural area of Rochester, MN [4], to 7.6 cases per 100 000 in the city of San Francisco, CA (Table 1) [5]. Due to the relative rarity of SLE, precise incidence estimates are difficult to produce, and although point estimates from many of these studies differ, the confidence intervals (CIs) may overlap.

Prevalence

Studies on the prevalence of SLE in the general population also show marked differences. This variability may result from differences in the methodology of case ascertainment; socioeconomic causes, such as educational level and availability of medical care; or diagnostic issues, such as the changing definition of SLE over time, improved availability of tests, and increased awareness of SLE as a disease entity. Moreover, since the prevalence of SLE varies by sex and age group, the age and sex distribution of a given population can lead to variation in the overall prevalence of SLE. However, true geographic differences cannot be excluded, and may result from differences in genetic or environmental factors (Table 2).

In 1982, Hochberg et al. reported a prevalence of SLE of 12.5 cases per 100 000 women in England and Wales overall,
and a prevalence of 17.7 cases per 100,000 among those aged 15–64 years [6]. More recently in the UK, Hopkinson et al. reported a prevalence of 24.6 cases per 100,000 persons in Nottingham [7], and Johnson et al. demonstrated a prevalence of 27.7 cases per 100,000 persons in Birmingham [8]. A higher prevalence has been reported in Sweden, at 36.3 cases per 100,000 persons [9]. However, as mentioned previously, methodological differences may explain this variation. The prevalence of SLE in the US has been reported to range between 14.6 cases per 100,000 persons in New York and 78.5 cases per 100,000 in Wisconsin [4,10,11].

Again, as SLE is relatively uncommon, precise incidence estimates are difficult to generate, and though point estimates from many of these studies differ, the CIs around them may overlap.

### Patterns of disease expression in specific subsets

An important question that has been raised by several authors is whether age at onset, gender, or other factors can modify disease expression and possibly define some specific SLE subsets. A significant amount of information on this topic has been contributed by studies performed within the Euro-Lupus cohort. This cohort is composed of 1000 patients with SLE who have been followed prospectively since 1991. These patients were accrued by a European consortium—the Euro-Lupus Project Group—which includes more than 40 investigators from seven European countries, all with substantial experience in the management of SLE patients. This consortium originated as part of the network promoted by the European Working Party on SLE. The initial general characteristics of the cohort were published in 1993 [12]. A great proportion of patients presented with non-specific symptoms, such as arthritis and fever, which may have led to a delay in establishing the final diagnosis of SLE. The mean age at onset of symptoms was 29 years, and the mean age at final diagnosis of SLE (according to the American College of Rheumatology [ACR] criteria) was 31 years.

The prevalence of major clinical features during the evolution of the disease in this cohort was comparable to that reported in previous studies (Table 3). Arthritis, malar rash, photosensitivity, nephropathy, serositis, neurological involvement, and thrombocytopenia were common manifestations. In addition, other manifestations that are not specified in the ACR criteria were also frequently found, including fever, Raynaud’s phenomenon, sicca syndrome, livedo reticularis, thrombosis, and lymphadenopathy.

The frequency of the major immunological features of SLE in this series was also comparable to that in other reports (Table 4). Antinuclear antibodies (ANA) were detected at some time during the course of the illness in the majority of patients, and high titers of anti-double-stranded DNA (anti-dsDNA) antibodies were found in 78%. Other autoantibodies (anti-extractable nuclear antigen [anti-ENA], antiphospholipid antibodies [aPL], and rheumatoid factor [RF]) were less commonly found.

### Effects of age

Age-specific incidence rates have been estimated in several studies of SLE, and peak incidence rates have been described in women of reproductive age, including the age groups 15–44 years [10], 20–39 years [13], 25–44 years [4], and...
Age-specific incidence rates in men are difficult to interpret because of the small numbers of reported cases, although some studies have suggested that SLE appears in males at an older age than in women – 50–59 years of age [6] or >65 years of age [10]. Regardless, SLE can appear at all ages, from pediatric onset of the disorder (<15 years), which occurs in 8–15% of SLE patients, to initial presentation at older ages (>55 years), which occurs in a similar percentage of cases to pediatric onset [12,16–18].

In several studies, it has been suggested that the clinical and immunological characteristics of SLE may differ according to the age at symptom onset. In the Euro-Lupus cohort, 76 patients (8% of the cohort) developed the disease before the age of 14 years [12]. In the pediatric-onset group, the female-to-male ratio was 7:1; this is slightly less than the female-to-male ratio of 10:1 seen in the adult-onset SLE patients in the cohort. Pediatric patients are more likely to present with severe organ involvement than adult-onset patients. This may be because the milder manifestations of SLE are unlikely to be noticed in the pediatric population. In the Euro-Lupus sample, initial diagnosis in the childhood-onset group was delayed for a mean of 5 years, possibly because doctors did not recognize initial symptoms or because clinicians may be reluctant to diagnose SLE in childhood. Over time, disease patterns appear to be quite similar in childhood-onset versus adult-onset patients.

Although SLE has traditionally been considered a disease of young women, several reports have described it in elderly populations [12,16]. In the Euro-Lupus cohort, 90 patients (9% of the cohort) developed initial manifestations of the disease aged >50 years. Although some authors have found no difference in the female-to-male ratio across age groups, observations in the Euro-Lupus cohort suggest that the female predominance of the disease is not so pronounced in the elderly onset group, with a female-to-male ratio of 5:1. Manifestations in older-onset patients may resemble drug-induced SLE, primary Sjögren’s syndrome, or polymyalgia rheumatica [16]. In the Euro-Lupus cohort, typical SLE manifestations, such as malar rash, photosensitivity, arthritis, and nephropathy, were less common in the older age group than in younger patients. In contrast, sicca syndrome was frequent in the older age group, possibly because the prevalence of sicca syndrome increases with age, regardless of whether SLE is present or not.

Although the explanation for the age-related variability in the expression of SLE is still unclear, differences in genetic predisposition or responsiveness of aging immune systems may be implicated. Specifically, it has been proposed in previous studies that older patients may have different genetic determinants of disease, and may respond to different triggering mechanisms than younger patients. Alternatively, the milder expression of SLE both clinically and immunologically in older patients may reflect senescence of the immune system [16].

### Sex differences
Clinical studies have consistently demonstrated female predominance in SLE. In the largest US series, which
incidence and prevalence rates of SLE in the Asian compared with the white population [20]. The age-adjusted an excess in the prevalence of SLE among Asian individuals women. Some data from Leicester, UK, have demonstrated Caribbean women, and a median age of 41 years in white groups, with a median age of 34.5 years in Afro-Caribbean origin than in white individuals [8]. The prevalence of nephropathy, neurological involvement, thrombocytopenia, vasculitis, and serositis was similar in the two groups. In addition, no significant immunological differences were found between men and women.

Effects of ethnic and social factors
Greater incidence and prevalence rates of SLE have consistently been found in black people compared with white people [10]. A study in Birmingham, UK, found a higher age-adjusted incidence and prevalence in those of Afro-Caribbean origin than in white individuals [8]. The incidence rates (age-adjusted) were 25.8 and 4.3 per 100,000 persons per year in Afro-Caribbean and white people, respectively, and the corresponding prevalence rates were 112 and 21 per 100,000 persons. The age distribution of incidence cases also differed significantly between the two groups, with a median age of 34.5 years in Afro-Caribbean women, and a median age of 41 years in white women. Some data from Leicester, UK, have demonstrated an excess in the prevalence of SLE among Asian individuals compared with the white population [20].

The age-adjusted incidence and prevalence rates of SLE in the Asian population were 20.7 and 46.7 cases per 100,000 persons, respectively, while these rates were 4.3 and 20.7 cases per 100,000 persons in the white population. Epidemiological data on SLE in African subjects are scarce.

Genetic factors
Studies involving relatives of SLE patients, particularly homozygous twins, have revealed a higher than expected incidence of the disease, suggesting the importance of genetic factors [21]. Nonetheless, the frequency is still relatively low, ranging 3–18%. Recent studies indicate little clinical difference between SLE patients who have relatives affected with the disease (familial SLE) and those who do not (sporadic SLE) [21].

Effects of the autoantibody pattern

ANA-negativity
Although the majority of SLE patients demonstrate a positive ANA test at some point in time, a proportion of patients – usually around 5% – are persistently ANA-negative. In the Euro-Lupus cohort, the clinical and immunological characteristics of 37 patients (4% of the cohort) who were persistently ANA-negative were analyzed [12]. Compared with ANA-positive patients, no differences were noted in age at onset; however, ANA-negative patients were more likely to have discoid cutaneous lesions and thrombosis, and less likely to have arthritis as a first symptom. During follow-up, the ANA-negative patients also had an increased prevalence of discoid lesions and livedo reticularis.

High anti-dsDNA antibody titer
A high titer of anti-dsDNA is considered the best marker of disease activity in SLE [1]. In the Euro-Lupus cohort, this marker was associated with a higher prevalence of nephropathy, hemolytic anemia, and fever; however, patients with high titer of anti-dsDNA antibodies had a lower prevalence of thrombosis and sicca syndrome than those without this marker [12].

Anti-ENA antibodies
Anti-Ro/SSA antibodies, and/or anti-La/SSB antibodies are present in 20–30% of SLE patients. Anti-Ro/SSA antibodies are associated with a higher prevalence of subacute cutaneous lesions and sicca syndrome, but a lower prevalence of thrombocytopenia [12]. Anti-La/SSB antibodies are associated with malar rash, subacute cutaneous lesions, photosensitivity, arthritis, serositis, and thrombosis [12]. Anti-ribonucleic protein (RNP) antibodies may also have clinical significance in SLE. The prevalence of anti-U1-snRNP in the Euro-Lupus cohort was 13%. Patients with these antibodies had a higher incidence of Raynaud’s
phenomenon, myositis, and lymphadenopathy. Anti-Smith antibodies occurred in 10% of patients, and were more prevalent in those with oral ulcers and myositis but less prevalent in those with sicca syndrome [12].

Rheumatoid factor positivity
The presence of RF was found in 18% of patients in the Euro-Lupus cohort. Interestingly, these patients had a higher prevalence of sicca syndrome, but a lower prevalence of nephropathy, compared with RF-negative subjects [12]. This may be an incidental finding related to the fact that both RF positivity and sicca syndrome increase with age.

Antiphospholipid antibodies
In the Euro-Lupus cohort, positive levels of aPL were found to be strongly associated with clinical manifestations of the anti-phospholipid syndrome, including thrombosis, spontaneous fetal loss, and thrombocytopenia. A significant association between the presence of immunoglobulin M anti-cardiolipin antibodies and hemolytic anemia was also found.

Mortality studies
Over the last 40 years, there has been significant improvement in the survival of patients with SLE [40–61]. While in 1955 the 5-year survival rate was reported to be <50% [41], more recent US studies indicate that 93% of patients with SLE survive for 5 years, and 85% survive for 10 years [42–44]. In the Euro-Lupus cohort, the authors observed an even higher survival rate – 95% at 5 years following entry into the study [45], and 93% at 10 years (Table 5) [46]. This is probably due to the more recent observation period (1990–2000), as well as the more homogenous healthcare system in Europe compared to previous studies.

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<td>Active SLE</td>
<td>18 (26.5)</td>
<td>13 (28.9)</td>
<td>5 (21.7)</td>
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<td>Multi-system</td>
<td>5 (7.4)</td>
<td>4 (8.9)</td>
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<td>6 (8.8)</td>
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<tr>
<td>Cardio-pulmonary</td>
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<td>3 (6.7)</td>
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<td>Hematological</td>
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<tr>
<td>Neurological</td>
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<td>1 (2.2)</td>
<td>2 (8.7)</td>
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<tr>
<td>Infections</td>
<td>17 (25)</td>
<td>13 (28.9)*</td>
<td>4 (17.4)†</td>
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<td>Bacterial sepsis</td>
<td>15 (22.1)</td>
<td>11 (24.4)</td>
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<td>Fungal</td>
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<td>Viral</td>
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<td>Thromboses</td>
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<td>Cerebral</td>
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<tr>
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<td>Malignancies</td>
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<td>Lung</td>
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<td>Lymphoma</td>
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<td>Gastric bleeding</td>
<td>2 (2.9)</td>
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<td>Obstetric</td>
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<td>7 (15.6)</td>
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SLE: systemic lupus erythematosus.
*In six patients, the cause of death was attributed to infection plus other factors (active SLE in five and thrombosis in one); **In two patients, the cause of death was attributed to gastric bleeding plus other factors (active SLE in one and infection in one); †In one patient, the cause of death was attributed to infections plus active SLE.
with the US. It may also imply an improvement in the management of SLE patients (earlier diagnosis, more appropriately used anti-SLE therapies, and advances in medical therapy in general). Despite these promising results, when SLE patients are compared with the general population, some studies have found that their overall mortality is four- to five-fold increased [45].

The improved survival rate of patients with SLE has been associated with an alteration in the patterns of mortality (changes in the main causes of death). The Euro-Lupus study findings indicate that complications of therapy and thrombotic manifestations are increasingly the cause of death in these patients [46]. For instance, aPL-related thrombotic events were responsible for 26.7% of deaths in the cohort. However, it is important to stress that determination of cause of death can be difficult in SLE patients. The often complex nature of this disease may mimic, or be mimicked by, other conditions. Additionally, many patients present with multisystem SLE involvement in their last days of life (e.g. renal, cardiac, pulmonary, and hematological involvement), as well as with other combined complications, such as infections.

Prognostic studies and investigation of variables affecting mortality in SLE have identified a wide range of significant factors. In the Euro-Lupus study, only nephropathy was found to have prognostic significance in terms of survival probability; however, 92% of patients with nephropathy at the beginning of the study survived the 5-year follow-up period [45]. Other studies performed in the US demonstrated that black patients (who have a higher prevalence of renal disease) and those with worse socioeconomic conditions have a more aggressive disease course and a greater rate of mortality [47].

**Final Remarks**

Epidemiological studies, notably those involving the Euro-Lupus cohort, have vastly our understanding of the incidence and prevalence of SLE, the patterns of disease expression in specific subsets, and the mortality rates of patients. However, although much has been learned in the past few decades, much remains to be elucidated.

**Disclosures**

The author has no relevant financial interests to disclose.

**References**


CLINICAL REVIEWS
Commentary and Analysis on Recent Key Papers

Clinical reviews were prepared by Tom Huizinga, MD, Peter Nigrovic, MD, Eric Ruderman, MD, and Hendrik Schulze-Koops, MD

PROGNOSIS AND ASSESSMENT

Remission and rheumatoid arthritis: data on patients receiving usual care in twenty-four countries
Sokka T, Hetland ML, Mäkinen H et al.; Questionnaires in Standard Monitoring of Patients With Rheumatoid Arthritis Group.

In this evaluation of a large, multinational cohort of rheumatoid arthritis patients, remission rates varied from 8.6% to 19.6% depending on the definition of remission applied.

As treatment for rheumatoid arthritis (RA) has improved, the clinical status of RA patients has also improved, and remission is becoming an increasingly viable target for treatment response. However, there is no “gold standard” definition for remission, which can make it difficult to compare results of different treatment trials and different treatment strategies.

In this manuscript, the authors compared seven different criteria for remission in RA using data from a multinational cross-sectional cohort of 5848 patients with the disease. The definitions of remission used were: American College of Rheumatology (ACR) definition, 28-joint count disease activity score (DAS28), Clinical Disease Activity Index, clinical remission using 28 and 42 joints (Clin28 and Clin42), the Routine Assessment of Patient Index Data 3 (RAPID3), and physician report of absence of disease activity (MD remission).

Remission rates varied in this cohort depending on the criteria used, from 8.6% using the ACR definition of remission to 19.6% using the DAS28 definition of remission. In addition, the range of remission rates varied widely between the countries included in the cohort. Independent of the definition of remission, male gender, higher education, shorter disease duration, fewer comorbidities, and regular exercise were all statistically associated with remission. Remission rates were higher for men, regardless of the definition used.

The authors conclude that, because of the wide variability in remission rates, any studies or reports of remission should include a rationale for the choice of definition, so that the results can be properly interpreted. Moreover, since all current definitions for remission favor men, the authors suggest that none may be an optimal definition.

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The importance of reporting disease activity states in rheumatoid arthritis clinical trials
Aletaha D, Funovits J, Smolen JS.

In patients with rheumatoid arthritis, functional and radiographic outcomes differ depending on the disease activity category, even if the same level of response is achieved. This finding indicates the importance of reporting disease activity categories.

To date, the response to treatment in rheumatoid arthritis (RA) has generally been assessed by the frequency of patients who meet the American College of Rheumatology (ACR) 20%, 50%, or 70% response criteria, only requiring a relative improvement from baseline, irrespective of the disease activity at baseline or at the endpoint. Disease activity categories (remission, low, moderate, and high), as defined according to measures such as the 28-joint count Disease Activity Score (DAS28) and the Simplified Disease Activity Index (SDAI), have gained interest since the availability of therapies allowing the achievement of low disease activity and even remission. In order to ascertain whether it is sufficient to evaluate treatment effects by looking at improvement, or whether information on the achieved disease activity state is necessary, the investigators evaluated data from recent clinical trials in RA.
For 629 patients from methotrexate monotherapy arms who had active disease at baseline, the frequencies of ACR20, ACR50, and ACR70 responders as well as endpoint disease activity states were assessed for a 1-year treatment period. The findings of this analysis were validated using the same types of analyses in patients treated with a combination of tumor necrosis factor (TNF) inhibitors plus methotrexate. For statistical analysis, physical function determined by the Health Assessment Questionnaire-Disability Index (HAQ-DI), and radiographic progression defined by changes in modified Sharp/van der Heide scores, were used as external standards to evaluate the merits of response and state analysis.

Within the ACR50 and ACR70 responder groups, physical function and radiographic progression were significantly different among the subgroups of patients with different disease activity states (remission, low, and moderate), indicating that outcomes are different in patients depending on the disease activity category, even if they reach the same level of ACR response. Using a generalized linear model, the investigators demonstrated that the impact of disease activity category on HAQ-DI scores, which increase with higher level of activity, are independent of the response level achieved. The results found in the patients treated with methotrexate alone were replicated in those treated with methotrexate plus TNF inhibitors, except that with TNF inhibition, the significant differences between different activity states with regard to radiographic outcome disappeared due to the complete absence of or low level of radiographic progression.

The authors acknowledge the limitations of this secondary study; however, they conclude that the disease activity state provides additional important insights with regard to the outcome of disability and joint damage, and should therefore be an integral part of clinical trial data reporting.

Validation of a prediction rule for disease outcome in patients with recent-onset undifferentiated arthritis: moving toward individualized treatment decision-making


A prediction rule was recently developed to identify – from within the pool of the patients with undifferentiated arthritis (UA) – those likely to develop rheumatoid arthritis (RA). This study investigates the accuracy of this prediction rule in three independent cohorts of patients with UA. The early initiation of methotrexate in undifferentiated arthritis (UA) patients has been shown to be effective in slowing the progression to rheumatoid arthritis (RA) and in reducing the level of joint damage. However, only one-third of patients with UA will develop RA. The rate of spontaneous remission of UA is considerable (up to 40–50%). Therefore, to avoid the overtreatment (with toxic drugs) of UA patients whose synovitis will remit spontaneously, and equally to avoid the undertreatment of those with RA, these authors developed a rule for the prediction of RA onset in patients with UA [1]. In the current study, its accuracy was assessed. In three cohorts of patients with recent-onset UA, from the UK, Germany, and The Netherlands, the prediction score and the corresponding likelihood of developing RA were calculated. A total of 99 patients with UA were recruited into the Birmingham, UK, Early Arthritis cohort (EAC). For this cohort, patients were included if they had synovitis in at least one joint and a duration of symptoms (inflammation-related joint pain, swelling, or morning stiffness) of ≤3 months. For the Berlin EAC (Germany), a total of 155 patients were enrolled. These patients were included if they had synovitis in at least two joints and a duration of symptoms of between 4 weeks and 12 months. The third validation cohort consisted of 34 Dutch patients included in the placebo arm of the PROMPT (Probable Rheumatoid Arthritis: Methotrexate Versus Placebo Treatment) trial. The original prediction rule was re-derived with the duration of morning stiffness used as a substitute for severity of morning stiffness (not available for all cohorts). These data were compared with the observed disease outcome after 1 year of follow-up. Positive predictive values (PPVs) and negative predictive values (NPVs) were calculated and the overall discriminative ability of the prediction rule was assessed using area under the receiver operating characteristic curves (AUCs). The AUC for this rule was 0.88 (standard error of the mean [SEM] 0.015). For each validation cohort, the AUC was 0.83 (SEM 0.041), 0.82 (SEM 0.037), and 0.95 (SEM 0.031) in the British, German, and Dutch cohorts, respectively. The NPVs in these three cohorts were 83%, 83%, and 86%, respectively; the PPVs were 100%, 93%, and 100%, respectively. Thus, the recently derived prediction rule has an excellent discriminative ability for assessing the likelihood of progression to RA. Application of this rule will allow individualized treatment decision-making for patients with UA.


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Recognition of inflammatory back pain and ankylosing spondylitis in primary care
Jois RN, Macgregor AJ, Gaffney K.

An early diagnosis is essential in the treatment of ankylosing spondylitis (AS). Considerable inconsistencies in the current diagnosis and management of AS in primary care dictate a need to improve education and to provide a diagnostic algorithm to improve the outcome of AS.

An early diagnosis of inflammatory back pain (IBP) and ankylosing spondylitis (AS) is essential for successful treatment. The present authors therefore investigated how current diagnostic criteria are used in primary care by general practitioners (GPs) to assess patients with IBP and also how they initially manage AS. Using a postal questionnaire, all GPs in Norfolk, UK, were assessed for their ability to identify symptoms of IBP, in patients with back pain, for their consideration of other clinical features of spondyloarthopathies (SpA), and for their awareness of the usefulness of features such as positive family history, human leukocyte antigen-B27 (HLA-B27) status, and spinal radiography in diagnosis of AS. Additionally, GPs were questioned about the initial management of AS and unmet needs.

Out of a total of 300 questionnaires, 186 (62%) were completed and returned. Only 5% of GPs could identify all eight known features indicative of IBP (from most to least frequently identified: morning stiffness >30 min, insidious onset, pain relieved by nonsteroidal anti-inflammatory drugs [NSAID], symptom duration >3 months, nocturnal pain, pain improved with exercise, pain not relieved by rest, and alternating buttock pain); 78% identified between four and eight, and 17% of GPs identified fewer than four features. Only 6% of GPs considered all clinical features of SpA (from most to least frequently considered: psoriasis, inflammatory bowel disease, uveitis, genitourinary/gut infection, enthesitis, and dactylitis) and 17% of GPs did not look for any of them. The utility of inflammatory markers and physiotherapy in patients with suspected IBP was deemed to be extremely important by 49% and 32% of GPs, respectively; the utility of spinal X-ray and HLA-B27 by 26% and 24% of GPs, respectively; and the utility of family history by 10% of GPs. However, only 17.2% of GPs commonly checked HLA-B27, 32.2% sometimes, 32.7% rarely did so, and 17.7% never checked HLA-B27 in routine clinical practice. With regard to initial treatment, 93% of GPs considered NSAIDs to treat IBP. Only 26% of GPs mentioned anti-tumor necrosis factor therapy, whereas the remainder was unaware of any new treatments. Unmet needs were described by 54.8% of GPs: 32% recognized physiotherapy as an unmet need; for 22%, it was diagnosis and treatment of AS; education was identified as the principal unmet need by 16%; and 9% cited delayed hospital appointment to rheumatologists.

The authors conclude that inconsistencies in the diagnosis of IBP and management of AS exist that warrant a necessity to develop a common algorithm for early identification and referral of patients with AS in the UK.

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Perioperative testing for joint infection in patients undergoing revision total hip arthroplasty
Schinsky MF, Della Valle CJ, Sporer SM et al.

Pain in the prosthetic hip is a difficult clinical problem because infection is only one of many potential causes. These investigators evaluated the predictive value of common clinical assays employed in this setting, and defined optimal cutoff values to help intraoperative assessment of the likelihood of infection.

The painful prosthetic hip presents a diagnostic challenge, since the differential diagnoses include aseptic loosening, component failure, and soft tissue syndromes as well as infection. To determine the optimal testing strategy to identify infection in the setting of revision arthroplasty, the authors of this study performed a standardized evaluation at the time of surgery, including serum erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels, intraoperative hip aspiration, three sets of intraoperative cultures, and intraoperative frozen section, as well as subsequent permanent pathological tissue examination for infiltrating neutrophils. Infection was defined as two of three of the following: positive culture, gross purulence, and positive histopathological findings. Of 201 evaluable hips, 55 (27.4%) were found to be infected, most commonly with Staphylococcus aureus or Staphylococcus epidermidis. Receiver–operator curve analysis found that among all patients, a joint fluid white blood cell count (WBC) of 4200 cells/mL optimally identified infected hips. In patients with an elevation in both ESR (>30 mm/h) and CRP (>10 mg/dL), a WBC of 3000 cells/mL and a differential cell count of 80% neutrophils optimally identified infected hips, while in those with either ESR or CRP elevation the optimal cutoff was 9000 cells/mL. The sensitivity, specificity, and accuracy of these cutoffs varied but generally approximated 90%. No hip was infected in patients whose perioperative ESR and CRP levels were both less than specified values. These results require validation in an independent
Prognostic model based on nailfold capillaroscopy for identifying Raynaud's phenomenon patients at high risk for the development of a scleroderma spectrum disorder: PRINCE (prognostic index for nailfold capillaroscopic examination)

Ingegnoli F, Borachi P, Gualtierotti R et al.

In patients with Raynaud's phenomenon (RP), nailfold capillary changes are a marker of risk for progression to an associated systemic rheumatic disease. This group performed a prospective study of nailfold capillary changes in >200 adults with apparently isolated RP in order to develop a quantitative measure of this risk.

Disorders including scleroderma and dermatomyositis are associated with changes in the nailfold capillaries, such as giant loops and capillary dropout, presumably reflecting associated vascular injury. In patients with apparently isolated Raynaud's phenomenon (RP), such changes suggest that a connective tissue disorder may be just over the horizon. To quantitate the prognostic significance of nailfold capillaroscopy in this population, these authors performed a careful prospective examination of nailfolds in two series of 104 and 100 patients to derive and then validate a risk index, respectively. Adult patients presenting at a single center with RP but without associated clinical features of connective tissue disease were subjected to digital video-capillaroscopy of all 10 fingers. Images were examined by an investigator blinded to patient history, and scored for the presence of giant loops, microhemorrhages, enlarged loops, branching loops, capillary disorganization, and the density of capillaries per millimeter. Patients were subsequently followed clinically, and associations were identified between baseline findings and clinical course. In each group, approximately 30% of patients progressed to an associated connective tissue condition, usually a disease in the scleroderma family. Among the phenotypes examined, giant loops, microhemorrhages, and reduced capillary density were found to correlate positively with progression, and a graphical scoring system (Prognostic Indicator for Nailfold Capillary Examination (PRINCE)) was developed to help estimate the risk of progression over a 5-year term. Since laboratory values (such as antinuclear antibodies and anticientromere antibodies) were not included in the index, the contribution of PRINCE in the context of all the variables considered by the clinician remains uncertain.

Synovial fluid is a site of citrullination of autoantigens in inflammatory arthritis

Kinloch A, Lundberg K, Wait R et al.

The authors report that the citrullination of proteins in rheumatoid arthritis (RA), previously noted to occur in synovial tissue, appears to take place in synovial fluid as well. They also suggest that RA-specific antibodies to the candidate autoantigen α-enolase may help to explain the chronic autoimmune response in RA joints.

Citrullinated proteins are formed when arginine residues are deiminated by the enzyme peptidylarginine deiminase (PAD), which has five human variants. While the process of citrullination is generally associated with inflammation, antibodies to citrullinated proteins have been described as highly specific for rheumatoid arthritis (RA), as well as predictive of disease severity in RA. In practice, the assay for antibodies to cyclic citrullinated peptide 2 (CCP2) uses synthetic citrullinated peptides as its substrate, rather than naturally occurring citrullinated peptides.

The authors of this study have previously characterized an autoantibody to human citrullinated α-enolase peptide-1 (CEP-1), which correlates with anti-CCP1 and is highly specific for RA. In this manuscript, they examine synovial fluid from patients with RA, spondylarthritis (SpA), and osteoarthritis (OA) for the presence and production of citrullinated proteins, including CEP-1, along with antibodies to these proteins.

Synovial fluid was obtained from 20 patients with RA, 20 with SpA, and 20 with OA. Citrullinated proteins, including α-enolase, were present in the synovial fluid from the patients with RA and SpA, but not in the OA synovial fluid. Antibodies to CEP-1 were detected in 12 of 20 RA synovial fluid samples, but only in one of the OA samples and none of the SpA samples. All 12 patients with anti-CEP-1 antibodies had synovial fluid antibodies to CCP2 as well. PAD-2 was detected in 18 of 20 RA synovial fluids, 16 of 20 SpA fluids, and none of the OA fluids, suggesting that the extracellular synovial fluid may be a site of protein citrullination in inflammatory arthritis. However, the antibody data described in this manuscript...
supports previous reports suggesting that antibody formation against these citrullinated proteins is unique to RA.

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**Disease activity of rheumatoid arthritis during pregnancy: results from a nationwide prospective study**

de Man YA, Dolhain RJ, van de Geijn FE et al.


In this first prospective study of rheumatoid arthritis (RA) in pregnancy to use a validated instrument to measure disease activity, the results were similar to prior prospective and retrospective studies, although disease improvement and flares were somewhat less frequent than previously described.

Rheumatoid arthritis (RA) is widely presumed to remit during pregnancy and flare during the post partum period. However, only one large, prospective study has examined this issue, and the data collected was limited to late pregnancy and the post partum period [1]; moreover, the study did not use validated criteria for scoring disease activity and remission. In this study, known as PARA (pregnancy-induced amelioration of RA), 276 Dutch women planning to become pregnant, or early in their pregnancies, were recruited and followed through the course of their pregnancy and 6 months after delivery.

The participants in the study were assessed at home six or seven times during the course of the study; before conception (when possible), during the first, second, and third trimesters, and 6, 12, and 26 weeks after delivery. Disease activity was measured by a research physician or nurse using the 28-joint count disease activity score (DAS28) assessment. Improvement was defined using the European League Against Rheumatism (EULAR) response criteria for RA, and post partum flares were defined using the “reverse” of these criteria. After excluding women who did not become pregnant during the study period and those without adequate follow-up data, 84 women were available for analysis.

Overall, the subjects’ mean disease activity decreased during pregnancy and increased post partum. These changes were most pronounced in those with moderate or high disease activity during the first trimester, with 48% of those with at least moderate disease activity in the first trimester having a good or moderate response by the third trimester. The presence of rheumatoid factor, anti-cyclic citrullinated peptide antibodies, or erosions did not affect the course of disease activity. Despite profound changes in medication use (such as no methotrexate use during or immediately prior to pregnancy), the percentage of patients in remission according to DAS28 criteria increased from 17% during the first trimester to 27% during the third trimester, then decreased to 18% at 12 weeks post partum. Between week 6 and week 12 or 26 post partum, 39% of the subjects had a disease flare. Steroid dose, which was not pre-specified during the study, was stable during pregnancy, increased at 6 weeks post partum, then decreased at 12 and 26 weeks post partum.


**Association of body fat with C-reactive protein in rheumatoid arthritis**

Giles JT, Bartlett SJ, Anderson R et al.


C-reactive protein (CRP) is a marker of systemic inflammation incorporated into the 28-joint count disease activity score index of rheumatoid arthritis (RA) activity. These authors studied the role of body habitus on CRP levels in patients with RA. They found that increasing truncal fat correlated with higher CRP levels independent of RA disease activity, but that this correlation held in women only.

C-reactive protein (CRP) is a pentraxin, serving in innate immune defense as an opsonin and activator of complement. It is synthesized by hepatocytes in response to inflammatory cytokines, most importantly interleukin-6 (IL-6). In rheumatoid arthritis (RA), the synovium is one important source of such cytokines, resulting in elevated CRP levels. However, adipose tissue can also produce IL-6, and population studies have demonstrated an association between body fat and CRP levels. These authors studied whether such an effect also occurs in RA, potentially confounding the interpretation of CRP in patient assessment. They employed data obtained in the ESCAPE RA (Evaluation of Subclinical Cardiovascular Disease and Predictors of Events in RA) trial, which enrolled RA patients without a history of cardiovascular events. Dual X-ray absorptiometry scanning was used to measure body fat (whole and regional) and lean mass. Body mass index (BMI) and weight and hip circumference were also measured. RA disease activity was assessed by a trained examiner. Patients (118 women and 78 men) were aged 45–84 years. Among women, a strong linear relationship between body fat
Clinical Reviews

(particularly truncal fat) and log-transformed CRP was observed, translating into a difference of 4.79 mg/L between women at the 80th and 20th percentiles of truncal fat (31 mg/L between the individuals with the highest and lowest amount of truncal fat). Similar associations were noted for BMI and waist circumference, and also when substituting serum IL-6 levels for CRP. The association remained robust despite adjustment for disease activity, such that highly active RA did not seem to obscure the effect of truncal fat. Interestingly, no correlation between fat mass and CRP was observed in men, though among men with high levels of RA activity an inverse association appeared, with higher truncal fat mass correlating with lower CRP. The reasons for the observed gender differences remain uncertain. These results suggest that in women with RA, adiposity may complicate the interpretation of inflammatory markers such as CRP, particularly in those in whom habitus renders the physical examination of the joints most challenging.

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Epidemiology

Geographic variation in rheumatoid arthritis incidence among women in the United States

Costenbader KH, Chang SC, Laden F et al.
Arch Intern Med 2008;168:1664–70.

The causes of rheumatoid arthritis (RA) are genetic, environmental, and stochastic. In recent years, a tremendous growth in our insight into genetic causes has been established, whereas smoking remains the only well-established environmental factor. In this large study from the US, it was observed that the risk of RA is highest in eastern parts of the country – the region with the highest levels of air pollution. Although this may be a coincidental finding, it adds support to the suggestion that environmental factors in the air (akin to smoking) can trigger the immune system to initiate an autoimmune disease such as RA.

In this investigation, the geographic variation in rheumatoid arthritis (RA) incidence in the US was studied in a prospective cohort of women, the Nurses’ Health Study. Information on state of residence was collected when the study began in 1976 (when participants were aged 30–55 years) and on the state of residence of the women at birth, at age 15 years, and at age 30 years. Among 83,546 participants who reported their residence for all four time points, 706 incident RA cases were confirmed. Compared with women in the western regions of the US, women in the eastern states of New England had a 37–45% elevated risk of RA after controlling for confounders.

In analyses of women who lived in the same region at birth and at the ages of 15 and 30 years, living in the Midwest was associated with a greater risk of RA (relative risk [RR] 1.5, 95% confidence interval [CI] 1.1–2.1), as was living in New England (RR 1.4, 95% CI 1.0–2.0). Compared with living in the West at birth, age 15 years, and age 30 years, the RA risk was higher in the East. Thus, significant geographic variation in the incidence of RA seems to exist. Potential explanations for this include regional variation in behavioral factors, climate, environmental exposures, RA diagnosis, and genetic factors.

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Cardiovascular Risk

Chronic arthritis aggravates vascular lesions in rabbits with atherosclerosis: a novel model of atherosclerosis associated with chronic inflammation

Largo R, Sánchez-Pernaute O, Marcos ME et al.

In a rabbit model in which both atherosclerosis and chronic antigen-induced arthritis were induced, systemic and femoral inflammation were more pronounced than in animals that had either atherosclerosis or chronic antigen-induced arthritis alone.

Cardiovascular (CV) events are a leading cause of morbidity and mortality in patients with chronic inflammatory diseases. In rheumatoid arthritis (RA) and other inflammatory disorders, an association between disease activity and CV risk has been found. However, the mechanisms by which inflammation might induce atherosclerosis are not fully understood. The present authors reproduced systemic inflammation in rabbits in order to study inflammation-related mechanisms of vascular lesions.

Atherosclerosis (AT) was induced by feeding a hypercholesterolemic diet to the animals and by the induction of endothelial lesions in both femoral arteries. Chronic antigen-induced arthritis (cAIA) was induced by the...
injection of ovalbumin intradermally and into the knee joints. The combination of both diseases (cAIA–AT) was generated by hypercholesterolemic diet, the induction of endothelial lesions, and injection of ovalbumin. The studies were carried out with 15 white rabbits (with disease) per group and 15 untreated rabbits as healthy controls. Serum biochemistry included analyses for high-density lipoprotein (HDL)-cholesterol and triglycerides as well as C-reactive protein (CRP), interleukin-6 (IL-6), and prostaglandin E₂ (PGE₂). Tissue sections of femoral arteries, thoracic aorta, and synovial membranes were stained with hematoxylin and eosin and for infiltrating macrophages. Femoral arteries and synovial membranes were also used for the assessment of cyclooxygenase-2 (COX-2) proteins. RNA extracted from peripheral blood mononuclear cells (PBMCs) was used for the evaluation of COX-2 and CCL2 expression.

The hyperlipidemic diet in the AT group and in the cAIA–AT group resulted in an increase in total serum cholesterol and triglycerides and reduced levels of HDL-cholesterol. Levels of CRP, IL-6, and PGE₂ were significantly higher in sera from the cAIA–AT group in comparison with healthy controls. CRP and IL-6 were also increased in the AT group versus healthy controls and there was an increase in levels of the two markers in rabbits with both cAIA and AT compared with animals with cAIA alone. Gene expression of COX-2 and CCL2 was upregulated in PBMCs of the cAIA–AT group versus healthy control rabbits. CCL2 was also upregulated in the cAIA–AT group when compared with the AT-alone group. In comparison with healthy controls, there was a greater nuclear factor-κB (NF-κB) binding activity in the cAIA–AT group compared with that in non-inflammatory rheumatic disorders. These drugs contribute to the overall risk of MI.

The risk of myocardial infarction (MI) is increased in rheumatoid arthritis (RA) patients compared with the general population. In order to guide the care of RA patients, assessment of the factors causing this increase in risk is necessary. In this case–control study, it was found that common cardiovascular risk factors and the use of corticosteroids were risk factors. Since corticosteroid use itself may be a marker of disease activity, it may well be that the observed association can be explained by an effect of disease severity. Thus, in the care of RA patients, an emphasis on reducing common risk factors, disease severity, and corticosteroid use would appear to be beneficial in reducing the risk of MI.

In this study, a total of 17 738 patients with rheumatoid arthritis (RA) and 3001 patients with non-inflammatory rheumatic disorders were assessed at 6-month intervals between January 1999 and July 2006 for the occurrence of myocardial infarction (MI). The adjusted risk of a first MI in RA patients versus that in the control subjects was 1.9 (95% confidence interval 1.2–2.9). In the RA patients, MI was predicted by age, sex, education level, hypertension, smoking, exercise, prior MI, diabetes, relevant comorbidity, the use of aspirin and anti-lipemic agents, RA severity and treatment variables, and corticosteroid use. In general, predictors of an MI were of similar strength in RA and non-inflammatory rheumatic disorders. Notably, the increased risk of MI in RA compared with that in non-inflammatory rheumatic disorders lessen when corticosteroid users were excluded. The use of corticosteroids was associated with future development of diabetes and hypertension, which indicates that (by virtue of their effect of increasing the risk of diabetes and hypertension) these drugs contribute to the overall risk of MI.
Adalimumab with or without methotrexate in juvenile rheumatoid arthritis


Antagonism of tumor necrosis factor is an established strategy for the treatment of patients with severe juvenile idiopathic arthritis (JIA). This study demonstrates that adalimumab is effective, both with and without background methotrexate, in children with polyarticular JIA.

While juvenile idiopathic arthritis (JIA) is nominally divided into seven major subgroups, diagnostic category is far less important than disease course in the selection of appropriate therapy. This multicenter, randomized controlled trial tested the anti-tumor necrosis factor (anti-TNF) agent adalimumab in children aged 4–17 years with active polyarticular (at least five active joints) JIA of any onset type who had previously failed nonsteroidal anti-inflammatory drug (NSAID) therapy. Adalimumab doses were initially tailored (24 mg/m²) but subsequently dichotomous (20 mg for those <30 kg, otherwise 40 mg subcutaneously every 2 weeks; these preparations are commercially available). The study design included a 16-week lead-in open-label phase during which all patients received adalimumab, a 32-week randomized withdrawal phase, and finally an open-label extension phase. Only patients who achieved an American College of Rheumatology Pediatric 30 response (ACR Pedi 30; 30% improvement in at least three of the six JIA core set variables and 30% worsening in not more than one of the six JIA core set variables) were enrolled in the withdrawal phase. The primary endpoint was arthritis flare during withdrawal. Patients receiving methotrexate were randomized separately from patients off methotrexate, such that the study in fact consisted of two parallel trials of a similar design.

Of 171 patients entered into the open-label phase, an ACR Pedi 30 response was observed in 94% on concomitant methotrexate and 74% who were not. Subsequently, 75 patients on methotrexate and 57 not on methotrexate completed the randomized withdrawal phase. In both groups, flares were observed at a significantly higher frequency in patients on placebo (methotrexate group: 65% placebo, 37% adalimumab, p=0.02; no methotrexate group: 71% placebo, 43% adalimumab, p=0.03). Responses were sustained through to the end of the extension phase at 104 weeks, at which point 40% of patients exhibited complete clinical remission. Interestingly, anti-adalimumab antibodies were detected in 26% of patients not receiving methotrexate versus 6% on methotrexate, although no correlation with efficacy or side effects was observed. Fourteen patients on adalimumab experienced adverse events, including seven infections. Together, these results show adalimumab to be a generally tolerable and effective therapy for polyarticular juvenile rheumatoid arthritis, though not necessarily one free of risk.

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Assessment of anti-TNF-alpha efficacy in rheumatoid arthritis: is 3 months sufficient?


In this retrospective cohort study of rheumatoid arthritis patients who received anti-tumor necrosis factor-α (anti-TNF-α) treatment, more than half of those who remained on anti-TNF-α after failing the 3-month assessment achieved a response at 6 months. This finding supports longer trial periods in future.

Antagonists to tumor necrosis factor-α (TNF-α), an inflammatory cytokine that is overexpressed in the synovium of patients with inflammatory arthritis, can be an effective treatment in patients who failed to respond to first-line disease-modifying antirheumatic drug (DMARD) therapy. However, some patients do not show an improvement or develop side effects to anti-TNF-α medication. Only patients with a high disease activity, indicated by a 28-joint count disease activity score (DAS28) of ≥5.2, are eligible for this treatment according to the 2007 guidelines of the National Institute for Health and Clinical Excellence (NICE) in the UK. NICE defines an adequate response to anti-TNF-α treatment as an improvement in DAS28 of ≥1.2. But how long should patients remain on anti-TNF-α treatment before it is considered as ineffective? Various guidelines recommend that an improvement should be demonstrated either at 3 months or at 6 months.

To determine whether the undertaking of a 6-month therapeutic trial would be of more benefit than a 3-month investigation, the present authors compared the efficacy of anti-TNF-α medication at 3 and 6 months in a retrospective study. They evaluated the proportion of patients on anti-TNF-α treatment that did not achieve a response at 3 months but who did respond at 6 months. The aim was to assess whether trials of a longer duration would be beneficial, and also to investigate potential predictive factors for a late response.
A total of 196 rheumatoid arthritis (RA) patients who underwent anti-TNF-α treatment from June 2002 to March 2007 were reviewed retrospectively, with data collected on DAS28 values at baseline, 3 months, and 6 months. The response at 3 and 6 months was defined according to the 2007 NICE guidelines and subdivided into partial response (DAS28 improvement 0.6–1.2) and poor response (DAS28 improvement <0.6). Potential predictive factors were the anti-TNF-α agent employed, disease severity at onset, dose escalation of anti-TNF-α, and switching from a previous anti-TNF-α agent.

Information on the DAS28 response at 3 months was available for 189 patients, of whom 21 had no response at 3 months but continued to receive therapy for a further 3-month period. A substantial proportion of those 21 patients (12 patients; 57%) who failed to achieve a response at 3 months did respond at 6 months, supporting the application of a longer trial period. The small group size did not allow statistical analysis of predictive factors for a late response. However, no patient had any changes in their anti-TNF-α dosing regimens, and in both 6-month responders and non-responders, there were patients who switched and patients who had not-switched anti-TNF-α agents.

The most costly outcome of rheumatoid arthritis (RA) is loss of employment. Given the effectiveness of anti-tumor necrosis factor (anti-TNF) agents, it is hoped that they will reduce work disability. In this observational study of patients from clinical practices in the US, it was observed that the use of methotrexate early in the clinical care of RA patients increased from <5% in 1980 to >90% in 2004. Over this period, substantially improved outcomes were observed. Intriguingly, most of the improvement in outcome (especially disability assessed using the health assessment questionnaire) and pain antedated the introduction of biological agents.
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These changing prescription patterns were associated with a better outcome over time. The data emphasize the positive effects of prescribing methotrexate as the anchor drug in RA. At the same time, they illustrate the need for rapid referral programs such as early arthritis clinics – given the benefit of rapid initiation of methotrexate.

Imatinib mesylate treatment of nephrogenic systemic fibrosis
Kay J, High WA.

In this analysis, it was found that imatinib mesylate decreased fibrosis and mediated a relatively rapid and steady improvement in skin changes and knee joint contractures in two patients who had stage 5 chronic kidney disease and nephrogenic systemic fibrosis (the latter was associated with prior exposure to gadolinium-containing contrast media during magnetic resonance imaging). Clinical signs and side effects, and histology of skin biopsies before and after treatment, were assessed.

Two patients with stage 5 chronic kidney disease and nephrogenic systemic fibrosis (NSF) were initially treated with oral imatinib mesylate at a dosage of 400 mg/day for up to 15 weeks. Both patients displayed a progressive reduction of skin thickening and tethering, with a decrease in the modified Rodnan skin thickness score (MRSS), with therapy. One of the patients (patient 1) had knee joint contractures and, upon treatment, achieved increased knee extension with passive range-of-motion exercises. This patient discontinued imatinib mesylate treatment at 15 weeks. At between 5 and 9 weeks after discontinuation, this patient experienced a recurrence of the skin changes. The improvement of the knee joint flexion contractures persisted during the first 5 weeks of discontinuation, but disappeared after 9 weeks of discontinuation of imatinib mesylate treatment. On the request of patient 1, treatment was re-started and within 5 weeks of 400 mg/day imatinib mesylate treatment, the MRSS decreased again from 33 to 10 and remained within that range with continued treatment.

In the second patient, after 12 weeks of treatment, the imatinib mesylate dosage was increased to 600 mg/day, with the aim of achieving further improvements in the skin; however, 2 weeks later, this patient discontinued treatment because of repeated hospitalizations (for chronic gastrointestinal bleeding, repair of an abdominal hernia, and difficulty in controlling his international normalized ratio). Patient 2 declined to restart imatinib mesylate except for a brief 2-week period. He experienced persistence and slight progression of his skin thickening and tethering during the subsequent 20 weeks.

With the exception of fluid retention, which was successfully corrected by dialysis treatment, neither patient experienced any adverse effect related to imatinib mesylate. The skin biopsy specimen obtained from patient 1 before and after 15 weeks of treatment with imatinib mesylate revealed reduced fibrosis and reduced staining for type I procollagen. Furthermore, fewer type I procollagen-positive cells were present in the upper dermis. Of interest, the amount of gadolinium in the affected skin was unchanged between the specimens before and after imatinib mesylate treatment.

The results suggest that imatinib mesylate improves fibrosis, skin changes, and joint contractures in patients with stage 5 chronic kidney disease and NSF, despite the persistence of gadolinium in the tissues. Discontinuation of the treatment causes worsening of these signs; however, the necessary duration of treatment remains undetermined.

Comparison of methotrexate monotherapy with a combination of methotrexate and etanercept in active, early, moderate to severe rheumatoid arthritis (COMET): a randomised, double-blind, parallel treatment trial
Emery P, Breedveld FC, Hall S et al.

This study shows that methotrexate alone or in combination with etanercept are both highly effective at producing disease remission at 1 year, but that remission is more likely with combination therapy.

As treatments for rheumatoid arthritis (RA) improve, the goal of treatment has advanced, so that remission has
become a viable target. In this study of early RA patients treated with methotrexate alone or in combination with etanercept, the two primary outcomes were remission and radiographic non-progression at 52 weeks.

Enrolled patients had RA for <2 years (mean 9 months) and had not previously been treated with methotrexate or a tumor necrosis factor (TNF) antagonist. Enrollment criteria included a 28-joint count disease activity score (DAS28) ≥3.2 and an elevated sedimentation rate or C-reactive protein (92% actually had severe disease at baseline, with a DAS28 ≥5). Of the 542 patients included, 268 were assigned to receive methotrexate at a weekly dose escalated to 20 mg/week by 8 weeks, and 274 were assigned to receive combination therapy with etanercept 50 mg weekly and methotrexate (same dose titration as the monotherapy arm). Stable doses of nonsteroidal anti-inflammatory drugs and steroids at a dose ≤10 mg prednisone, but no additional disease-modifying antirheumatic drugs other than methotrexate, were allowed. Treatment groups were well matched for disease activity and demographic characteristics.

At 52 weeks, the proportion of patients in remission was 28% in the methotrexate group vs. 50% in the combination therapy group. This difference in remission rates was significant by week 2. Radiographic non-progression, defined as a modified total Sharp score ≤0.5, was also seen more frequently in the combination therapy arm (80% vs. 59%). Function, as measured by the health assessment questionnaire, and work productivity, also improved more in the combination therapy arm (80% vs. 59%). Function, as measured by the health assessment questionnaire, and work productivity, also improved more in the combination therapy arm (80% vs. 59%).

This study shows that both remission and radiographic non-progression are achievable therapeutic goals in early RA. Abatacept consists of cytotoxic T lymphocyte-antigen-4 (CTLA-4) fused to human immunoglobulin G1, and functions by blocking stimulation of CD80 on T cells by CD80 or CD86 molecules on antigen-presenting cells. These authors designed a withdrawal trial to test the efficacy of this molecule in patients with polyarticular-course juvenile idiopathic arthritis (JIA) who had responded inadequately to at least one disease-modifying antirheumatic drug (DMARD). A total of 190 patients were studied. Two-thirds of patients remained on concomitant methotrexate, although other DMARDs were prohibited. Abatacept was dosed at 10 mg/kg intravenously (maximum 1000 mg) on days 0, 14, and 28, and then every 4 weeks thereafter. All 190 patients received the drug for 16 weeks during the run-in period, to identify potential responders. Patients who exhibited at least an American College of Rheumatology Pediatric 30 response (ACR Pedi 30 response; 30% improvement in at least three of the six JIA core set variables and 30% worsening in not more than one of the six JIA core set variables), 65% of the initial population, were then randomized to placebo or active drug for 6 months.

The primary endpoint, flare of arthritis, was reached by 53% of patients receiving placebo but only 20% receiving abatacept (p=0.0033). An improvement of ≥90% was achieved by 40% on abatacept compared with 16% of control subjects (p=0.006). No opportunistic infections or other serious adverse events were reported, although 6% of patients developed new antibodies against double-stranded DNA. Of note, while anti-tumor necrosis factor failure represents the most likely “window” for the use of abatacept in children, of the 57 patients in this category in the open-label phase, only 22 (39%) experienced the 30% response required to enter the randomized phase. These results add abatacept to the list of agents of potential utility in the treatment of polyarticular-course JIA.

**Taking Home Points**

**Abatacept in children with juvenile idiopathic arthritis: a randomized, double blind, placebo controlled withdrawal trial**


Abatacept is an effective therapy for adult arthritis, but what about pediatric disease? These authors performed a randomized controlled withdrawal trial in 190 patients with polyarticular-course juvenile idiopathic arthritis who had failed at least one disease-modifying antirheumatic drug, and found that abatacept has clear efficacy with good tolerability in this population.

**Tumor necrosis factor antagonist responsiveness in a United States rheumatoid arthritis cohort**


Data from this large practice registry of rheumatoid arthritis patients suggests that those treated with tumor necrosis factor antagonists in clinical practice have a lower disease activity and are less likely to respond to the treatment than those in clinical trials.

Large controlled trials of new therapies are generally designed to generate the data required for regulatory

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approval of the product, and are frequently criticized for not being representative of the types of patients that will ultimately be treated with the product. Trials of tumor necrosis factor (TNF) antagonists typically include patients with high disease activity and demonstrate notable improvements with therapy. In this article, the authors examine patients from a large rheumatoid arthritis (RA) cohort and assess their responsiveness to initial biological therapy with a TNF antagonist.

Patients were selected from the CORRONA ( Consortium of Rheumatology Researchers of North America) registry and included 465 biologic-naïve patients being started on their first TNF antagonist. Subjects in this prospective registry come from a mix of private and academic sites and are entered sequentially, without regard to therapy or disease activity.

All patients selected had clinical outcome measurements collected; 129 had concurrent sedimentation rates available with which to calculate American College of Rheumatology (ACR) response rates, while 336 patients were assessed using a modified ACR response scale that did not require evaluation of an acute phase reactant.

The authors reviewed the potential eligibility of the patients in this cohort for three previously published, controlled TNF antagonist trials [1–3] and found that the percentage of patients who would have qualified for trial inclusion ranged from just 5.4% to 19.4%. The cohort subjects who met trial inclusion criteria had predominantly high disease activity, while the overall cohort was more heterogeneous, with as many as half having low disease activity, suggesting that TNF antagonist therapy was, in practice, initiated in patients with milder disease.

Response to the TNF antagonist therapy was measured using the conventional ACR response criteria in the 129 patients for whom acute phase reactant levels were measured and a modified version for those without available acute phase reactant levels. The response rate following initiation of therapy in those meeting trial inclusion criteria was approximately 55% for ACR20 (range 52.3–63.6%) and about 37% for ACR50 (range 30.8–45.5%). The response rates within the trial-ineligible patients were approximately 18% and 10% using the ACR20 and ACR50 criteria, respectively.

The authors raise questions about the generalizability of RA clinical trial data, since only a small percentage of subjects in this cohort of “real world” practice patients would have met disease activity criteria for a clinical trial, and those who did not had a much more limited response to therapy. These findings may have important implications for reimbursement, as more and more payors are requiring evidence of clinical response for reapproval of biological therapy.

The value of synovial cytokine expression in predicting the clinical response to TNF antagonist therapy (infliximab)


In this “negative” study, synovial cytokine expression was not predictive of response (according to American College of Rheumatology [ACR] criteria) to tumor necrosis factor antagonist therapy. Similar changes in post-treatment biopsies from both ACR responders and non-responders suggest a mechanism for reduced structural damage with this therapy, even in the absence of clinical response.

Despite the profound impact that tumor necrosis factor (TNF) antagonists have had on the management of rheumatoid arthritis (RA), one of the ongoing challenges has been the difficulty in predicting which patients will respond to these agents and which will not. Demographic information has not been helpful, nor, so far, have genomic analyses. In this study, the authors examined pre-treatment synovial biopsies taken from patients receiving infliximab, along with a smaller number of post-treatment biopsies, in order to determine whether the synovial histology was predictive of response to therapy.

Arthroscopic synovial biopsies were obtained from 51 patients prior to treatment with infliximab 3 mg/kg. Biopsies were assessed using a semiquantitative scoring system for the presence of T cells (marked by CD3) and macrophages (marked by CD68) in the synovial tissue, as well as for immunohistochemical staining for TNF-α, lymphotxin-α, interleukin-1α (IL-1α), IL-1β, IL-1 receptor antagonist, and IL-6. In addition, 32 patients underwent post-treatment biopsies 16 weeks after starting infliximab, which were assessed in the same manner.

Of the original 51 patients, 24 (47%) achieved a 20% improvement in American College of Rheumatology criteria for RA (ACR20 response), and 27 (53%) did not. There were no differences in CD3 populations, CD68 populations, TNF-α staining, or in any of the measured cytokines between responders and non-responders. Post-treatment biopsies were obtained from 17 responders and 15 non-
Angiotensin converting enzyme inhibitors delay the occurrence of renal involvement and are associated with an increased risk of disease activity in patients with systemic lupus erythematous – results from LUMINA (LIX): a multiethnic US cohort


Inhibitors of angiotensin-converting enzyme (ACE) are routinely employed in lupus patients with established renal disease, but could they prevent renal involvement in the first place? These authors interrogated the LUMINA (Lupus in Minority Populations: Nature vs. Nurture) registry and observed an association between ACE inhibitor use and reduced de novo nephritis.

Angiotensin II is a potent vasoconstrictor, but has been observed to have pro-inflammatory effects at a cellular level. The authors of this study hypothesized that angiotensin-converting enzyme (ACE) inhibition might forestall nephritis in patients with lupus who have no history of renal disease. To investigate this issue, they employed data from the LUMINA (Lupus in Minority Populations: Nature vs. Nurture) registry, a prospective, observational study of lupus patients from several ethnic backgrounds. In the study, information including medication history was collected at baseline, twice over the next year, and then on a yearly basis. Within this cohort, the investigators identified 378 patients without nephritis at baseline, of whom 21% were on ACE inhibitors for another reason, usually hypertension. ACE inhibitor users were less likely to develop renal involvement over the course of observation than non-users (renal involvement at 10 years: 12% of users vs. 25% of non-users; p=0.0099). In a multivariate analysis including age, gender, and ethnicity, ACE inhibitor use was associated with increased time to renal involvement (hazard ratio [HR] 0.27, 95% confidence interval [CI] 0.09–0.78). Furthermore, using each patient as his or her own control, the authors found that lupus flare was slightly less likely in intervals at which patients reported receiving ACE inhibitors than in those without (HR 0.56, 95% CI 0.34–0.94). While these findings are intriguing, questions of confounding by indication inevitably trouble observations such as these. Might ACE inhibitor use not be a proxy for a hidden confounder? For example, these drugs are teratogens and would be likely prescribed in women of reproductive age only if compliance with contraception were considered likely. Frustratingly, the authors do not supply data that would enable direct comparison of users and non-users along demographic and clinical variables, rendering the findings difficult to interpret. Given these concerns, extrapolations to a potential therapeutic benefit of ACE inhibitors are challenging, and the authors’ conclusion that “ACE inhibitor use delays the development of renal involvement…in SLE” is hardly justified by the evidence presented. However, the study raises interesting findings worthy of further investigation.

MISCELLANEOUS

Kidney transplantation in lupus patients: a case-control study from a single centre


The prognosis of renal disease in systemic lupus erythematous (SLE) is still not optimal, with approximately one-fifth of subjects progressing to end-stage renal disease. In this case–control study, it was observed that graft survival after kidney transplantation is inferior in SLE compared with control patients. However, the overall outcome is satisfactory, with similar patient survival rates.

In this study, 26 patients with systemic lupus erythematous (SLE) who received kidney transplants were compared with 26 patients who received a kidney transplant for renal failure unrelated to SLE. The control group was matched for gender, source of donor, age, and time of kidney transplantation. The graft survival rate for SLE patients was 88% at 1 year, 67% at...
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5 years, and 38% at 10 years compared with respective control group graft survival rates of 92%, 92%, and 84% (p=0.004). Patient survival in the SLE group was similar to that in the control group. The survival rate in the SLE group was 92% at 1 year, 77% at 5 years, and 77% at 10 years versus 96%, 92%, and 92%, respectively, in the control subjects (p=0.26). Chronic allograft nephropathy was the major cause of graft loss; recurrent lupus nephritis was detected in two patients but only one led to graft failure. This study emphasizes that kidney transplantation is a successful treatment modality in SLE patients with renal failure.

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Replication of the tumor necrosis factor receptor-associated factor 1/complement component 5 region as a susceptibility locus for rheumatoid arthritis in a European family-based study


Several new susceptibility genes for rheumatoid arthritis (RA) have recently been recognized. It is anticipated that this finding will lead to the identification of new pathways in RA and aid the subsequent development of new targets and drugs to treat RA. Novel candidate genes have been identified in association studies comparing cases and control subjects. This study design may be hampered by artifacts if the frequencies in the control population are not correct due to coincidental inclusion of subjects from a different ethnic background. This can be circumvented by the undertaking of family-based studies in which the influence of genetic risk factors can be identified within the same family.

In the present study, a total of 1356 Western European white individuals from 452 “trio” families were genotyped for a marker in a region of tumor necrosis factor receptor-associated factor 1 (TRAF1) and complement factor 5 (C5). This region has been found to be associated with RA in a number of independent studies.

Evidence of an association was identified in this analysis, with an overtransmission of the rs10818488 A allele to RA patients compared with their healthy sibling (p=0.036). Moreover, in an analysis of the parents, an increased frequency of the risk allele was found in affected versus unaffected parents (p=0.015). Thus, in this family-based study, evidence for an association of the TRAF1/C5 region with RA was identified.

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Previous family-based analyses have confirmed human leukocyte antigen and protein tyrosine phosphatase, non-receptor type 22 as genetic risk factors for rheumatoid arthritis (RA). In the present family-based study, the tumor necrosis factor receptor-associated factor 1/complement factor 5 region was also confirmed as a genetic risk factor for RA.
The 15th Paediatric Rheumatology European Society (PReS) Congress (14–17 September 2008) was held at University College London, London, UK, and co-organized by the PReS Scientific and Organizing Committees and the British Society for Paediatric and Adolescent Rheumatology (BSPAR). The meeting was well attended (>500 delegates) and featured integrated clinical, scientific, and allied health professional sessions on all aspects of pediatric rheumatology. Abstracts can be found at: http://www.ped-rheum.com/supplements.

**Therapeutic goals in pediatric rheumatology**

The main PReS congress was based around four main areas: juvenile idiopathic arthritis (JIA), juvenile dermatomyositis (JDM), vasculitis, and pain. Key overviews saw Gordon Duff (University of Sheffield, Sheffield, UK) emphasize the need for “good, new, safe medicines at the prices we can afford” and Berent Prakken (University Medical Center Utrecht, Utrecht, The Netherlands) outlining the challenging goals of developing biomarkers, providing immune regulation not suppression, tailor-made therapy, and ultimately, achieving long-lasting drug-free remission – a cure. The safety of treatment remains of critical importance, given the potential risk of infections or cancer resulting from immunosuppressive treatment. Long-term observational studies (LOS) have some advantages over randomized controlled clinical trials, namely large numbers, a wide variety of patients, and the opportunity for very long-term follow-up – even from childhood to old age. However, LOS are not controlled, and the patients not randomized.

**The advent of biologics in juvenile idiopathic arthritis**

Methotrexate remains a first-choice disease-modifying antirheumatic drug (DMARD) in JIA, having a good long-term efficacy and safety record, but is being increasingly supplemented by a variety of biologics, where efficacy data are encouraging. With data for >5000 patient-years, etanercept alone or in combination with methotrexate appears to be a safe, long-term therapy.

Data from the Paediatric Rheumatology International Trials Organization (PRINTO; Genoa, Italy) showed that 11 of 19 patients with systemic JIA (sJIA) achieved a 50% improvement in modified American College of Rheumatology pediatric criteria by day 15 after a single dose of canakinumab (an anti-interleukin-1β [anti-IL-1β] agent). The PRINTO open-label extension of a Phase III trial of 128 JIA patients on adalimumab (anti-tumor necrosis factor-α [TNF-α]) showed improvements of 90% in active joint count by week 56. Shumpei Yokota (Yokohama City University, Yokohama, Japan) described sustained clinical improvement in sJIA patients after Phase II and III clinical trials of tocilizumab (anti-IL-6).

However, serious adverse events remain a risk factor and Michael Levin (Imperial College London, London, UK) described mechanisms for tuberculosis emergence with anti-TNF-α treatment. Recent genetic studies have shown patients with mutations in interferon-γ (IFN-γ) or IL-12 pathways had impaired TNF production, impaired macrophage activation, and were more susceptible to mycobacterial infection. Studies of whole blood from RA patients post anti-TNF-α treatment demonstrated reduction in factors vital for granuloma formation and for the containment of mycobacteria (i.e. IL-8, macrophage inflammatory protein-1α [MIP-1α], MIP-1β, and monocyte chemoattractant protein-1). Anti-TNF-related tuberculosis may be due to inhibition of TNF-dependent chemokine gradients, subsequently disrupting cellular migration.
Moreover, biological agents that interfere with the IFN-\(\gamma\)/IL-12/TNF pathway may impair immunity to intracellular pathogens.

**Auditions for novel regulatory cells**

While biological therapies target specific pathways, regulation of disease via certain cell populations remains an area of active research. There are several phenotypes of human macrophages and Johannes Roth (University Hospital of Munster, Munster, Germany) discussed “regulatory macrophages or mRegs,” a monocytic phenotype induced by glucocorticoids. Macrophages were treated with glucocorticoids for 16 h and gene expression microarray performed. Key findings were that glucocorticoids inhibit respiratory burst and stimulate phagocytosis and migration; thus, glucocorticoids induce a specific phenotype in macrophages and the induction of anti-apoptotic genes. The survival of anti-inflammatory monocytes, which would die spontaneously in the absence of appropriate stimuli, may be a general mechanism to control inflammation.

Data were presented on mesenchymal stem cell (MSC) therapy in murine arthritis. Joost Swart (VU University Medical Center, Amsterdam, The Netherlands) showed a protective effect of a single systemic dose of MSC on established proteoglycan-induced arthritis. Francesco Dazzi (Imperial College London) proposed that IFN-\(\gamma\) induces MSC to extravasate and become “licensed” for a protective role when high levels of IFN-\(\gamma\) are present; however, this was not the case when MSC were transferred before disease induction or at a late time point. MSC are protective in acute, severe, collagen-induced arthritis (CIA) whereas they accelerate onset and severity of chronic CIA. Whether these findings will translate to patients is not yet known.

**Developments in juvenile dermatomyositis**

Several large JDM patient cohorts exist, including a study of 490 JDM patients across five countries (C Ferrari, Italian Pediatric Rheumatology Study Group, Italy) and the JDM National Registry and Repository of UK and Ireland (Lucy Wedderburn, Institute of Child Health, University College London [UCL], London, UK). International collaboration has developed core set variables to measure disease activity (International Myositis Assessment and Clinical Studies [IMACS] Group and PRINTO). The first randomized controlled trial of rituximab (anti-CD20) in JDM is underway.

In the UK cohort, reductions in JDM mortality rate over time have been reported, from a 30% mortality rate in the pre-steroid era to 10% post-steroids to <1% at present (two out of 245 patients) (S Smith, Institute of Child Health, UCL). Specific autoantibodies in JDM may allow the identification of particular phenotypes within the clinical spectrum. Harsha Gunawardena (Royal National Hospital for Rheumatic Diseases, Bath, UK) reported a serological screen of 162 JDM children revealing a 140-kDa protein as a major target for autoantibodies. Anti-p140 is detected in JDM only (in 27% of JDM subjects) and not in JDM overlap syndromes or in control subjects. One possible pathogenic mechanism in myositis is the IFN pathway. Type I IFN is increased in myositis patients and plasmacytoid dendritic cells that secrete IFN are present in DM muscle and skin. After incubation with sera containing Jo-1 antibody, normal peripheral blood mononuclear cells were shown to secrete type I IFN (Frederick Miller, National Institutes of Health, Bethesda, MD, USA).

**New advances in vasculitis**

Research by Dorothee Viemann (University Hospital of Munster, Munster, Germany) may explain the poor benefit of glucocorticoid treatment in primary endothelial inflammation. She described an innate resistance of endothelial cells to glucocorticoids. The cytosolic receptor for glucocorticoids (GR) was expressed in both human umbilical vein endothelial cells (HUVEC) and monocytes, but while monocytes treated with glucocorticoids showed nuclear translocation of GR, HUVEC GR did not. Therefore, a new treatment strategy may be required for a lasting benefit in vasculitis.

Lindsey Clarke (Institute of Child Health, UCL) described that damage to, or activation of, endothelial cells may lead to release of microparticles or mature cells; this is increased in patients with active disease and therefore circulating microparticles or mature cells may represent a biomarker for disease severity. Children with active vasculitis had higher levels of circulating endothelial cells (CEC)/mL compared with febrile and healthy control children. Moreover, levels of CEC increased upon disease flare.

Until recently, Kawasaki disease (KD) patients without cardiac involvement were thought to have a good prognosis. Surjit Singh (Postgraduate Institute of Medical Education and Research, Chandigarh, India) showed data from 20 KD children without coronary abnormalities who had significantly increased QT-interval dispersion compared with age-matched healthy controls. These findings may represent an increased risk of developing ventricular arrhythmia.

**Young Investigators meeting**

Held prior to the main congress, the Young Investigators meeting (YIM) was the largest to date (>100 delegates). Prize winning YIM abstracts were: Patricia Hunter (Institute of Child Health, UCL), for basic science, who described predictors of extension of disease severity in JIA, where a T cell:B cell ratio from synovial fluid cells was shown to have a 90% prognostic value, and Roman Jurerncák (University of...
Toronto, Toronto, ON, Canada), for clinical science, who described ethnic differences in autoantibody profiles in pediatric systemic lupus erythematosus and showed that cohorts can be clustered into different groups based on autoantibody serology that have links with different disease outcomes. Anti-U1RNP was associated with 24% of Caucasians and 62% of non-Caucasians, and seropositive patients had a severe disease outcome with the highest frequency of nephritis, renal failure, and hemolytic anemia.

Allied Health Programme
The Allied Health Programme was integrated into the main conference sessions to encourage interdisciplinary learning and practice. Prior to the congress an allied health study day was attended by 40 delegates and provided a valuable opportunity to build links with other professionals.

Physical fitness and activity levels
Physical activity levels (PAL) and physical fitness of children and adolescents with JIA continues to be a key focus. Otto Lelieveld (University Medical Center Groningen, Groningen, The Netherlands) showed that PAL were markedly reduced in adolescent JIA patients compared with healthy controls. Interestingly, PAL were not associated with disease activity. This study resulted in development of the “Rheumates programme” to increase physical activity in JIA patients aged 8–12 years, comprising education, group exercise, internet resources, and individual physical activity programmes.

Advanced clinical treatment
Julie Payne (Institute of Child Health, UCL) highlighted the importance of early input of hand therapists and surgeons in the management of JIA with hand involvement. Radiography was described as an important tool in guiding clinical therapy, particularly to assess joint space and potential for increasing range of movement. Furthermore, the importance of obtaining appropriate hand X-rays prior to beginning a therapy programme was underscored. Gay Kuchta (Vancouver, BC, Canada) described sleep fragmentation frequency and its effect on fatigue levels in JIA patients. Web-based educational resources were available to equip families and therapists to manage fatigue symptoms.

Pain and improving quality of life
Increasing proportions of children with non-inflammatory pain syndromes are seen in rheumatology clinics, with high economic costs. A study of Dutch adolescents showed that JIA patients had an under-representation of positive thoughts of achievement; these patients have a reduced quality of life. There was a recommendation for a realistic approach to limitations rather than raised expectations. Susan Maillard (Institute of Child Health, UCL) reviewed the physiotherapy treatment of these patients in her presentation “function despite pain”. Addressing biomechanical changes through specific muscle strengthening and working with patients and parents to develop meaningful goals were identified as key strategies. Encouragingly, children had a favorable outcome with approximately 40% back to school fulltime after 3 months of rehabilitation (Jacqui Clinch, University of Bath, Bath, UK).

Collaboration
With relatively rare diseases, large international consortia have provided new opportunities to perform well-powered genetic or biological studies, and have therefore increased our understanding of disease mechanisms and ultimately helped to achieve therapeutic goals. As the treatment model moves towards personalized treatment (e.g. with biologics) resulting in smaller patient subgroups, cooperation will remain essential to ensure data compatibility between cohorts and so maximize the benefits of international collaborative research. The PReS international meeting is now an established part of the scientific calendar within pediatric rheumatology, and continues to provide many opportunities for collaborative networking.

Acknowledgement
Dr Halima Moncrieffe is funded by a grant from SPARKS UK.

Disclosures
The authors have no relevant financial interests to disclose.
The recent American College of Rheumatology/Association of Rheumatology Health Professionals (ACR/AHRP) annual scientific meeting, held on October 24–29, 2008, in San Francisco, CA, USA, attracted a record-breaking number of around 15,000 attendees from >100 countries. Almost 12,000 scientific registrants presented over 2100 abstracts and were able to choose from >150 scientific sessions to attend. There were many highlights and each attendee will certainly have had his or her own list of favorites. The selection provided in this report is not intended to be exhaustive. Rather, a personal selection of exciting abstracts has been made, with those containing important new information of value to clinicians and which could influence daily clinical practice specifically discussed. In addition to reports from large biological trials providing successful long-term efficacy and safety updates, innovative recent data were also presented at the meeting, and are summarized here.

Since the ultimate goal of treating patients with inflammatory joint disease is the prevention of disability, special emphasis is given to the effects of biological therapy on radiographic progression (as a surrogate measure of disability) in rheumatoid arthritis (RA) and ankylosing spondylitis (AS) patients. In addition, data on new therapeutic options in the treatment of RA, psoriatic arthritis (PsA), gout, and systemic lupus erythematosus (SLE) are discussed.

Comorbidities
The use of DMARDs/methotrexate is not significantly associated with the development of obstructive lung disease/pneumonitis
In a large population-based study, investigators from the Mayo Clinic (Rochester, MN, USA) confirmed that RA patients are at higher risk of developing obstructive lung disease than non-RA patients (hazard ratio [HR] 1.54) [1]. Significant risk factors for developing obstructive lung disease were male sex, smoking, the presence of rheumatoid factor (RF), elevated erythrocyte sedimentation rate (ESR), disease-modifying antirheumatic drug (DMARD) use, and corticosteroid use. Among RA patients with obstructive lung disease, a higher mortality risk was significantly associated with age at onset of obstructive lung disease (1.94 increase in HR per 10-year increase in age) and functional capacity (level 3–4 vs. level 1–2: HR 3.16) whereas it was not significantly related to treatment with DMARDs such as methotrexate (HR 1.12) or corticosteroids (HR 1.84).

In another study, the incidence of pneumonitis as a serious pulmonary side effect of low-dose methotrexate was prospectively studied [2]. All 164 patients in the study had a forced vital capacity (FVC) of >1.0 L and were started on 10 mg of methotrexate and followed for 2 years of methotrexate therapy (dose range 2.5–30 mg/week). Interestingly, only one patient developed methotrexate-related pneumonitis, which suggests an incidence of 0.63% overall at 1 year (n=164), and of 0.42% at 2 years (n=120). The results of this trial suggest that methotrexate pneumonitis does not occur as frequently as was previously thought.

Treatment strategies in early RA
In early RA, patients with a good initial response to methotrexate monotherapy continue to have excellent clinical outcomes during the first year of therapy
The SWEFOT (Comparison of Methotrexate+Anti-Tumor Necrosis Factor [anti-TNF] to Methotrexate+Conventional
In patients with early RA who fail on initial methotrexate, the addition of anti-TNF yields better ACR and EULAR responses than the addition of conventional DMARDs

In a second presentation by Dr van Vollenhoven and colleagues, the two therapeutic strategies employed in the SWEFOT study were compared in patients who had not achieved a DAS28 <3.2 with methotrexate monotherapy after 3–4 months [4]. The 258 patients were randomized to one of two treatment arms:

- Sulfasalazine 1000 mg twice daily plus hydroxychloroquine 400 mg daily (n=130): arm A.
- Infliximab 3 mg/kg given at 0, 2, and 6 weeks, and then every 8 weeks (n=128): arm B.

Patients were allowed to switch therapy once (from sulfasalazine plus hydroxychloroquine to cyclosporine A, and from infliximab to etanercept) if they were unable to tolerate their treatment. Significantly more patients in arm B experienced a European League Against Rheumatism (EULAR) good response at 12 months than in arm A (42% vs. 26%; p<0.01). Similarly, a greater proportion of patients in arm B experienced a 20% improvement in ACR criteria for RA (ACR20 response), and ACR50 and ACR70 responses, than those in arm A; the difference in ACR70 response was not statistically significant between the two arms [4].

Based on the results, the investigators concluded that addition of anti-TNF therapy to methotrexate monotherapy is superior to sulfasalazine plus hydroxychloroquine in patients who have an inadequate response to methotrexate monotherapy.

**Kinase inhibitors: new treatment options for RA patients**

CP-690,550, an oral JAK inhibitor, is a well-tolerated and effective long-term treatment for patients with moderate-to-severe RA

Janus kinase-3 (JAK3), which is restricted to immune cells, is critical for signaling by several cytokines that have been implicated in the pathogenesis of RA, including interleukin-2 (IL-2), IL-4, IL-7, IL-9, IL-15, and IL-21. CP-690,550 is an orally active inhibitor of JAK3 that was initially designed as an immunosuppressive agent in transplantation but that was later demonstrated to have a potent anti-inflammatory effect.

The first results of a 6-month, open-label, Phase II study investigating the efficacy and safety of CP-690,550 were reported by Joel Silverfield and colleagues (Tampa Medical Group, Tampa, FL, USA) [5]. A total of 129 patients with moderate-to-severe RA (86% continued on background methotrexate and 53% on glucocorticoids) were given 5 mg of the agent twice daily for a median treatment duration of 109 days. Mean DAS28 scores were 3.60 and 3.47 at 1 and 6 months, respectively, with five patients discontinuing treatment due to lack of efficacy. There were 93 mild, 64 moderate, and three severe adverse events (SAE), with the most commonly reported AE being urinary tract infection (by eight patients) and diarrhea (by five patients). The investigators concluded that CP-690,550 is well tolerated and effective over 6 months for the treatment of patients with moderate-to-severe RA.

**TASKI-1 trial**

Syk, a protein tyrosine kinase that is expressed in epithelial cells and in hematopoietic cells, can be relatively selectively inhibited by the investigational drug R788 (Rigel Pharmaceuticals, San Francisco, CA, USA), which has been demonstrated to suppress arthritis in animal models, suggesting utility in the treatment of RA.

The Phase II, double-blind TASKI-1 (Treatment of Arthritis with Syk Kinase Inhibition) trial, presented by
Michael Weinblatt (Brigham and Women’s Hospital, Boston, MA, USA), included 189 patients receiving chronic methotrexate therapy for active RA who were randomly assigned to R788 at a dose of 50, 100, or 150 mg (all twice daily), or placebo [6]. The ACR20 response rates at 12 weeks (primary endpoint) were significantly higher in the 100 mg twice daily and 150 mg twice daily groups at 65% and 72%, respectively, compared with 32% in the 50 mg twice daily group and 38% in the placebo group. Similar findings were observed for ACR50 and ACR70 response rates and DAS remission rates (Table 1). The investigators reported that the clinical effect was noted as early as week 1, and that 47% of patients treated at the highest dose were in remission after 3 months of treatment. Of note, diarrhea (45%), dizziness (11%), and neutropenia (15%) were the major AE; however, these were dose-related and reversible.

Although larger studies (which are in progress) are needed to define the optimal dose with an acceptable toxicity profile, the investigators concluded that the rapid improvement of arthritis indicates that inhibition of Syk kinase is a viable target for the treatment of RA.

This presentation, and that by Dr Silverfield and colleagues [5], demonstrates the utility of kinase inhibitors in modulating signaling pathways involved in inflammation in the treatment of RA patients. The advantages of these drugs in comparison to current biologics are that they are given orally and that manufacturing costs are lower. However, in the future, larger randomized controlled trials will need to demonstrate that they are as effective as current biologics and have an acceptable toxicity profile.

Radiographic progression in RA studies: LITHE and PREMIER

The LITHE study confirms that tocilizumab inhibits structural joint damage in RA patients with an inadequate response to methotrexate

Tocilizumab is an anti-IL-6 receptor antibody that inhibits signaling through IL-6 – a key cytokine in RA pathogenesis.

Joel Kremer (Albany Medical College, Albany, NY, USA) and colleagues presented the 12-month interim results of the LITHE (Tocilizumab Safety and the Prevention of Structural Joint Damage) study, which assessed the efficacy of tocilizumab plus methotrexate in preventing structural joint damage and improving patient function in RA patients with an inadequate response to methotrexate (methotrexate-IR) [7].

In this Phase III, double-blind, randomized controlled trial, methotrexate-IR patients with moderate-to-severe, active RA (n=1190) received methotrexate once weekly plus tocilizumab 4 or 8 mg/kg, or placebo intravenously every 4 weeks for 1 year. At week 52, patients who received tocilizumab experienced significant inhibition of radiographic progression from baseline compared with placebo recipients (p<0.0001). In addition, the Health Assessment Questionnaire Disability Index (HAQ-DI) score significantly improved in patients in the tocilizumab groups. ACR response (ACR20, ACR50, and ACR70) and DAS28 remission rates were significantly higher in the tocilizumab 8 mg/kg cohort when compared with the control group (DAS28 remission rates 47% vs. 8%; p<0.0001). The results are summarized in Table 2.

The safety profile was consistent with previous studies and did not change from 6 to 12 months. The most common SAE were serious infections (tocilizumab 8 mg/kg 3.0%, tocilizumab 4 mg/kg 2.5%, and control 1.5%), whereas significant infusion events were reported only in the 4 mg/kg tocilizumab group (four anaphylactic and two hypersensitivity reactions).

The authors concluded that tocilizumab therapy resulted in improved rates of disease remission and improved functional ability.

Initial combination of adalimumab and methotrexate leads to better long-term inhibition of radiographic progression in early RA

In the PREMIER (Comparator with Adalimumab and Methotrexate versus Methotrexate in Subjects with Early...
RA) study, 799 patients with early RA (<3 years) were randomized to methotrexate, adalimumab, or a combination of the two for 2 years. Previously reported results demonstrated that after 2 years, the combination of adalimumab and methotrexate was the optimal treatment regimen in terms of signs and symptoms of disease, functional ability, and radiographic progression [8]. Patients who completed the blinded part of the study were allowed to continue receiving adalimumab in a long-term, open-label extension study [9]. The treating physicians adjusted treatments from years 2 through 5, and overall use of medications became similar among groups after the blinded phase. In spite of this, radiographic outcomes were better among patients initially randomized to the combination of adalimumab and methotrexate. The percentage of patients with no radiographic progression was 54% in the combination group, compared with 33–34% in each of the monotherapy groups. Data on parameters of radiographic damage are provided in Table 3.

These results are in line with those of the BeSt (Behandel Strategieen) trial showing that although clinical responses over 5 years across all groups were similar, differences were observed with regard to radiographic progression favoring the initial combination of a TNF inhibitor and methotrexate [10].

**Ankylosing spondylitis**

No inhibition of radiographic progression in AS patients treated with adalimumab over 2 years compared with a historical control group

In a presentation on the third day of the meeting, Désirée van der Heijde (Leiden University Medical Center, Leiden, The Netherlands) presented the results of an analysis of the long-term effects of adalimumab on radiographic progression in patients with active AS [11]. The investigators compared radiographs of the lateral cervical and lumbar spine obtained at baseline and after 2 years of two Phase III clinical studies of adalimumab, M03-606 (A Phase 3, Multicenter Study of the Safety and Efficacy of Adalimumab in Subjects with Active AS; n=82) and ATLAS (Adalimumab Trial Evaluating Long-Term Efficacy and Safety in AS; n=315) with radiographs from the OASIS (Outcome in AS International Study) cohort of AS patients naïve to TNF antagonist therapy (as a control). Baseline modified Stoke AS spinal scores (mSASSS) as a measure for radiographic damage were comparable between groups, whereas disease activity indices were greater for the patients treated with adalimumab than for OASIS participants.

After 2 years of therapy, there was no statistically significant difference in the mean change in mSASSS for...
adalimumab-treated patients compared with the OASIS cohort control patients (0.8 vs. 0.9; p=0.771). Similarly, when the investigators compared adalimumab-treated subjects with only those 77 patients in the OASIS cohort who had baseline disease characteristics comparable to those of patients enrolled in the adalimumab trials, the mean changes in mSASSS after 2 years were 0.8 and 0.9 respectively (p=0.744).

The investigators concluded that despite providing substantial and significant improvements in clinical efficacy, adalimumab therapy did not lead to inhibition of radiographic progression in AS patients treated for 2 years. Further, they conclude that these findings are comparable to observations for etanercept and infliximab in AS. However, in all of these studies, including those discussed here, the theoretical appropriate control was missing as historical controls were used. Multiple publications have demonstrated that TNF antagonists are effective in the long-term suppression of inflammation and result in improvement of spinal mobility in AS. Longer term, controlled studies with balanced baseline characteristics between the study groups are needed to convincingly demonstrate the effect of TNF blockers on radiographic progression.

### Psoriatic Arthritis

**First-ever treatment recommendations for PsA by GRAPPA**

Given the wide range of clinical manifestations, which are often difficult to manage, the treatment of PsA is complicated. Thus, there is a need for treatment guidelines. The International Group for Research and Assessment of Psoriasis and PsA (GRAPPA) presented comprehensive recommendations for the treatment of the key clinical manifestations of PsA (peripheral arthritis, axial disease, skin disease, enthesitis, and dactylitis) at the meeting [12].

After consideration of evidence obtained from a systematic review of the literature and from the consensus expert opinion of 70 rheumatologists and dermatologists, 19 recommendations were drafted (with >80% agreement on 16 of these). The strength of the recommendations was graded from A (strongest) to D (weakest); these are detailed in Table 4. The authors propose that their recommendations should serve as the basis for treatment guidelines. The recommendations are aimed at helping the clinician reach treatment decisions for individual patients with different disease manifestations, based on thorough assessments of the specific areas. It is anticipated that periodic updates, using this useful framework as a basis, will take place as new data become available.

### Gout

**Pegloticase: promising for subjects with treatment-failure gout**

In a small percentage of patients, the most commonly used anti-gout medication, allopurinol, fails to be effective or is contraindicated; therefore, alternative treatment options are in demand. While most gout treatments work by either blocking uric acid production (e.g. xanthine oxidase inhibitors) or enhancing its excretion (e.g. uricosuric agents), pegloticase, a recombinant pegylated form of the enzyme urate oxidase acts by breaking down uric acid.

At the meeting, the results from duplicate Phase III, double-blind, randomized controlled trial – referred to as GOUT1 (Gout Outcome and Urate Therapy 1; n=104) and GOUT2 (n=108) – which assessed the efficacy and safety of pegloticase in patients with treatment-failure gout (TFG) were reported by John Sundy (Duke University Medical Center, Durham, NC, USA) and colleagues [13]. All patients were considered to have TFG if they had at least three flares of gout in the prior 18 months, or at least one tophus or gouty arthropathy and failure of the maximum medically appropriate dose of allopurinol, or a contraindication to allopurinol. At baseline, participants conformed with the typical profile of patients with gout: 82% were male, the mean age was 55 years, and many had comorbidities such as hypertension (71%), chronic kidney disease (43%), and diabetes (22%).
A total of 212 patients were randomized to 6 months of double-blind treatment with 8 mg pegloticase intravenously every 2 weeks (n=85), every 4 weeks (n=84), or placebo (n=43), followed by open-label extension for a further 12 months. The primary endpoint in the intention-to-treat analysis was a reduction in plasma uric acid to below 6.0 mg/dL 80% of the time at 3 and 6 months. In GOUT1 and GOUT2, 47% and 38% of patients given pegloticase every 2 weeks, respectively, met the primary endpoint of uric acid reduction, (both p<0.001); similarly, 20% and 48% of those given the agent every 4 weeks met the primary endpoint compared with none in the placebo group (p=0.044 and p<0.001, respectively). Among the significant secondary efficacy findings, the researchers reported an improvement in resolution of tophi, quality of life, and physical function, and a reduction in the number of tender joints for the two dose groups compared with placebo. Of note, AE leading to treatment discontinuation were more common with pegloticase (19% every 2 weeks and 20% every 4 weeks vs. 2% placebo; p<0.05). The most frequent AE were gout flares (not significantly different to placebo) and infusion reactions (26% every 2 weeks and 40% every 4 weeks vs. 5% placebo; p<0.003). This probably reflects the immunogenicity of the agent, as antibodies against pegloticase were common (89%) and were associated with loss of treatment efficacy and an increased risk of infusion reactions. Even more concerning were the eight serious cardiac AE and one death that occurred in those on the study drug; in the placebo group, no deaths or severe cardiac events occurred. However, determining whether these events were related to the study medication or rather reflected the underlying medical problems of these patients is important, as emphasized by David Fox (University of Michigan Medical Center, Ann Arbor, MI, USA), a moderator at the plenary session. Obviously, additional data from longer follow-up periods are needed to clarify whether the use of pegloticase provides an acceptable risk–benefit ratio for patients with TFG.

Systemic lupus erythematosus

Efficacy and safety of rituximab in patients with moderately to severely active SLE: results of the EXPLORER study

B cells play an important role in the pathogenesis of systemic lupus erythematosus (SLE); therefore, these cells are potential therapeutic targets. Rituximab, an anti-CD20 chimeric monoclonal antibody that induces peripheral B cell depletion, has been anecdotally used in the management of patients with SLE resistant to traditional regimens. Although small uncontrolled case series have suggested the efficacy of rituximab in SLE patients, there have been no randomized controlled trials evaluating its use in these individuals.

The EXPLORER (A Study to Evaluate the Efficacy and Safety of Rituximab in Patients with Severe SLE) trial, a double-blind, multicenter, Phase II/III study, assessed the efficacy and safety of rituximab in patients with SLE and active extra-renal disease [13]. SLE patients satisfying at least four of 11 ACR Lupus Classification Criteria with British Isles Lupus Assessment Group (BILAG) disease activity scores of A (>1) or B (>2) despite receiving at least one immunosuppressive drug were included in the study. Patients were randomized in a 2:1 ratio to receive rituximab 1000 mg or placebo on days 1, 15, 168, and 182. Baseline immunosuppressive drugs were continued and prednisone (0.5–1 mg/kg/day) was added at entry to treat active disease and then tapered per protocol.

There were no significant differences between the rituximab and placebo groups in terms of any of the primary endpoints (response defined by improvement and maintenance of BILAG activity over 12 months):

- Major clinical response rate (12.4% vs. 15.9%).
- Partial clinical response rate (17.2% vs. 12.5%).
- No clinical response (70% vs. 71.6%).

Moreover, none of the secondary endpoint measures were met; these included the number of patients with a major or minor clinical response at week 52, the number of patients who achieved BILAG C or better in all domains at week 24, the time to moderate or severe flare over 52 weeks, change in Short Form-36 Health Survey from baseline to week 52, and the number of patients who achieved a major clinical response with <10 mg daily prednisone from week 24–52. Rates of SAE were not statistically different between the two groups (rituximab 38% vs. placebo 36%), although all four patients who experienced serum sickness and all six patients who experienced neutropenia were in the rituximab group. Further studies will have to be conducted in order to prove whether rituximab is of clinical benefit in patients with moderate-to-severe SLE, particularly in light of the limited array of conventional treatment options.

Disclosures

The authors have no relevant financial interests to disclose.

References


# Reader Survey – Let Us Know What You Think!

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<td>c) The information was presented clearly:</td>
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<td>d) The leading articles provided new information regarding the understanding and treatment of rheumatological disease:</td>
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<td>e) The literature analysis was helpful and I would like to see analyses in future issues:</td>
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| 2. | Did you learn anything from the *International Journal of Advances in Rheumatology* that will change the way you practice? | Yes | No |
|---|---|
| If so, what? | ............................................................................................................................................................................................................ |

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<th>3.</th>
<th>What specific topics do you think should be covered in future issues?</th>
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| 4. | Have you ever visited our website [www.advancesinrheumatology.com](http://www.advancesinrheumatology.com)? | Yes | No |
|---|---|
| If yes, is there anything you think we could do to improve it? | ................................................................................................................................................................................................................................ |

| 5. | Would you like to recommend the *International Journal of Advances in Rheumatology* to a colleague? | Yes | No |
|---|---|
| My colleague’s email is: | ............................................................................................................................................................................................................ |

Name ............................................................................................................ Job title ..........................................................
Institution ...........................................................................................................
Address ............................................................................................................
Country ......................................................................................................... Post/zip code ...........................................
Email ..............................................................................................................