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Developments in the clinical understanding of rheumatoid arthritis

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Abstract

New treatments and, more specifically, a fresh perspective on the disease's clinical features in relation to therapeutic advancements have been part of the rheumatoid arthritis (RA) field's evolution during the last ten or twenty years. Disease activity controls the progression of joint damage, composite disease activity indices are useful for patient follow-up, and disability includes several components, one of which is joint damage. Additional findings include the following: the destruction of joints is more likely to progress if any state of disease activity other than remission (or, at most, low disease activity) is sought after; early detection and appropriate treatment of RA are critical components of the overall strategy for optimal clinical control of the disease; and tight control using composite scores aids in optimizing therapeutic approaches. The development of new treatments has made remission a possibility, and treatment algorithms that take into account all of the aforementioned factors will help us reach our lofty goals, both now and in the future.

People with arthritis and rheumatologists who have been around for the last 20 years have seen advances in our clinical knowledge of rheumatoid arthritis (RA) that most people would have thought were out of this world if someone had anticipated them. The following (r)evolutionary changes have occurred: (a) in the reporting of clinical trial results; (b) in the recognition of time as an important element in both the progression of RA and our treatment strategies, particularly in regards to early therapeutic interference and swift switching of therapies; (c) in the profoundness of the response to novel therapies and therapeutic strategies; and (d) in the possibility of influencing all major characteristics associated with the disease, including signs and symptoms, joint damage, disability, quality of life, and other important outcomes like comorbidity and economic consequences. These developments may be considered almost iconoclastic as they have necessitated major shifts in thinking. For that reason, we will break down this study into sections for each of these four innovations.

A. Influencing major characteristics of the disease

A new look at assessing active disease

Clinical fact 1

Composite indices are the best depicters of disease activity. The degree of disease activity at the start of a disease-modifying therapy is a major determinant of the disease activity attainable in treatment.

Background and evidence

Pain, swelling (from synovial thickening and effusion), and joint stiffness are hallmarks of polyarticular synovitis, the central clinical presentation of rheumatoid arthritis (RA). At first, clinical practitioners relied on individual symptoms like morning stiffness or swelling joint counts as well as laboratory variables like erythrocyte sedimentation rate or C-reactive protein (CRP) to track their patients' disease activity. However, it was the joint efforts of clinical researchers in the US and Europe, as well as committees from the American College of Rheumatology, the European League Against

Rheumatism, and the International League against Rheumatism, that led to the realization that only a small number of variables were reliable and change-sensitive, and that composite indices based on such a narrow spectrum of disease characteristics would capture disease activity the most accurately. True, various parts of these "core sets" represent various RA features. As an illustration, a swollen joint

ACR70% = a 70% improvement in symptoms according to the American College of Rheumatology criteria; CDAI = Clinical Disease Activity Index; CRP = C-reactive protein; DAS28 = disease activity score using 28 joint counts; DMARD = disease-modifying anti-rheumatic drug; HAQ = health assessment questionnaire; IL = interleukin; MTX = methotrexate; RA = rheumatoid arthritis; SDAI = Simplified Disease Activity Index; SF-36 = short form-36; TNF = tumor necrosis factor.

counts and acute-phase reactants are best associated with joint damage [10-12], even though the correlation between swollen joint counts and acute-phase response is relatively weak. In contrast, functional impairment is best associated with tender joint counts [10,12]. These few examples show that composite indices encapsulate variables that relate to the spectrum of RA and that they also comprise information provided by the evaluator, the patient, or both and often an 'objective' laboratory variable as well [13]. Consequently, changes in these scores, response criteria using these instru- ments, or disease activity states employing these indices to categorize the extent of disease expression have provided important information about the relation of the range of disease activity with intermediate and long-term outcomes and have been pivotal in our evaluation of therapeutic success in clinical trials [5,7,8,13]. Importantly, however, it appears that the degree of disease activity at any point in time, such as at the beginning of a new treatment course, is an important predictor, on the group level, of disease activity in the longer term, even with effective therapy [14].

Disease activity is the driver of joint damage

> Clinical fact 2
> Joint damage is a consequence of the inflammatory process (disease activity over time). Joint space narrowing and erosions by radiography depict related but distinct components of joint damage that may develop separately.

Background and evidence

The hallmark of RA that distinguishes it most from all other arthritides is the damage elicited in the joints. The RA synovial membrane directly invades bone, entailing osteoclast activation to carry out this job [15,16]. Likewise, the products activated in the course of the inflammatory response, whether originating from synovial cells or chondrocytes, lead to degradation of the cartilage matrix [17,18]. All of these events are a consequence of the activation of many cell populations and, ultimately, of the upregulation of proinflammatory cyto- kines [19,20]. By whichever means they themselves become activated, they induce a plethora of inflammatory products, including degradative enzymes, which mediate most if not all of the total phenotypic expression of RA, including joint destruction. The fact that CRP is induced by the proinflam- matory cytokine interleukin-6 (IL-6) and the observation that CRP levels over time correlate with joint damage [10,21] indirectly link joint damage to the inflammatory cytokine levels. However, as indicated before, the correlation of CRP with joint destruction is lower than that of swollen joint counts but higher than that of tender joint counts.

It has been unequivocally shown that the relationship of time averaged disease activity, and its change in response to herapy, as assessed by various composite indices, corre- lates well with the extent of radiographic joint damage or the degree of inhibition of its progression, respectively [1,8,21,22]. These correlations pertain to both cartilage damage, as reflected radiologically by joint space narrowing, and bone destruction, as depicted by erosions, which can be captured reliably and validly using respective scores [23]. Recent data suggest that these two processes may be related but distinct and can be separated by detailed analyses and even by specific therapies [24,25].

Disability is a multifarious feature

> Clinical fact 3
> Disability comprises an activity-related component that is fully reversible and a destruction-related component that is irreversible. Clinical trial design needs to account for this complexity. Interference with disease activity will reverse the activity-related segment and prevent the accrual of the damage-related part.

Background and evidence

Failure of functioning is the most critical endpoint for an organ or an individual. In RA, physical functioning is the major outcome of interest given the impact of its impairment on the person, the family, and society. Various instruments have been developed to capture disability and its consequences on quality of life, and the most frequently used ones in RA are the health assessment questionnaire (HAQ) disability index and the short form-36 (SF-36), including its physical compo- nent subscale [26,27]. However, disability is a complex feature: it comprises disease-specific as well as non-disease- specific elements. Among the latter, psychological well-being (which may or may not be related to RA), comorbidities (which may or may not be related to RA or its treatment), and age constitute important determinants [28]. However, the disease-specific portion has at least two components since pain and stiffness impair physical function even in the absence of joint damage (such as in very early active disease), while patients with severely destroyed joints may suffer from disability even in the absence of any disease activity. Indeed, several studies have directly or indirectly provided evidence of this bicomponential nature of the HAQ index [29-31]. Importantly, however, with increasing joint destruction, there is an increase in irreversible disability, even in states of stringent clinical remission [31]. Thus,

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in these patients, the floor that can be reached rests at a higher level. Therefore, irreversible disability can be averted only by prevention of joint destruction, which (as discussed above) is a consequence of disease activity. Since joint damage is also related to the duration of the disease, similar associations of reversibility and irreversibility can be found for disease duration [31] and similar findings can be made using a more

generic quality-of-life instrument such as the SF-36. Impor- tantly, however, these observations have a bearing on the response to therapy: in clinical trials of patients with long- standing disease, the functional improvement may be limited to an extent that does not allow one to discern active effective medication from placebo [32]; this indicates the importance of careful clinical trial design that accounts for the potential irreversible disability. Importantly, instruments enabling clinicians and trialists to predict the degree of reversibility of functional impairment would be desirable.

Inter-relationship of disease activity and disability with various secondary outcomes characteristic of rheumatoid arthritis, such as comorbidity, mortality, and costs

Clinical fact 4

The reduction in life expectancy as well as comorbidities associated with rheumatoid arthritis (RA), such as cardiovascular disease and lymphoma, and economic consequences, including loss of working capacity, are associated primarily with the severity of RA as manifested by chronic high disease activity and long-term irreversible disability.

Background and evidence

Mortality is increased in patients with RA. This reduction in life expectancy has been shown unequivocally to be related to the chronic active disease process and the associated disability [33-37]. However, mortality is due primarily to comorbidities, and among those conditions cardiovascular events are particularly relevant [38,39]. Importantly, cardio- vascular disease is highly related to the inflammatory response [40,41]. Likewise, the prevalence of lymphoma is increased in RA and has been shown to be associated with the degree of inflammation and thus, again, chronic active disabling disease [38,42].

RA also leads to multiple economic consequences. While addressing health economics in a broader sense is beyond the scope of this article, it needs to be mentioned that direct medical costs comprise not only costs for drugs but also those for other medical attention (including joint surgery) and that, with increasing HAQ scores, joint replacement surgery and use of other health care resources increase dramatically [43-45]. Among the many indirect costs, work disability constitutes an important economic consequence of RA. Within 10 years, up to 60% of RA patients may be fully or partly work-incapacitated [46-48]. Again, this is directly related to HAQ scores [46,48,49]. Thus, active disabling disease is generally associated with higher direct and indirect costs in RA [45,50,51]. Therefore, disease activity, as a sequel to the inflammatory events, directly or indirectly steers all of the characteristics and consequences of RA (Figure 1

Inter-relationship of disease activity and outcomes in rheumatoid arthritis: a spinning wheel.

which in turn have partial influence on each other as further detailed in this commentary.

B. The importance of appropriate disease activity reporting

It's the state, not just the change

Clinical fact 5

Therapy for rheumatoid arthritis needs to aim at least to achieve low disease activity by composite scores and, ideally, remission. Clinical trial reporting has to account for both improvement and disease activity categories, and the latter also needs to be evaluated during

follow-up in clinical practice.

Background and evidence

Disease activity is rarely a dichotomous quality (active versus inactive) but, like temperature, constitutes a continuum. Composite disease activity indices, but also visual analogue scales or joint counts, are like a thermometer, reflecting this by providing a continuous measure. Nevertheless, to under- stand the impact of disease activity on the vast arrays of outcomes in RA, to select patients for clinical trials, to interpret laboratory findings or results from basic scientific

investigations, to judge the indication or the necessity to change therapy, and to define the most appropriate thera- peutic aims, categorical criteria are helpful. Therefore, cate- gories or states of high, moderate, and low disease activity as well as remission have been identified for the most commonly used indices: the disease activity score (DAS), disease activity score using 28 joint counts (DAS28), Simplified Disease Activity Index (SDAI), and Clinical Disease Activity Index (CDAI) [13]. Indeed, the lower the disease activity category that can be attained under therapy, the lower the progression of joint damage [12,22].

On the other hand, in clinical practice and clinical trials, response to or improvement of therapy has been the center of attention [5,52]. Improvement or response, however, relates primarily to absolute or relative changes of disease activity, and actual activity at the endpoint will depend on the baseline values. Thus, response criteria do not account, or at least do not sufficiently account, for the disease activity state to be aimed for. This is further supported by observations that a symptom state acceptable to patients requires greater amounts of improvement as baseline disease activity increases. This reveals that the achievement of a particular state is the major desirable goal for patients [53]. Indeed, patients with an approximately 50% or higher improvement of their disease activity will suffer from continuing profound joint destruction if their disease activity is not brought into at least the low disease activity category [54]. Furthermore, even in states of low disease activity, there is a smoldering progression of joint damage with therapies like methotrexate (MTX), and therefore only remission leads to the arrest of joint damage [22].

On the basis of the above, achieving remission ought to be the ultimate goal when treating RA. The definition of remission, however, is still under debate and many rheumatologists would like to see remission defined as a state of no residual disease activity [12]. Nevertheless, some of the composite scores allow for significant residual disease activity and currently the most stringent remission criteria appear to be those defined by the SDAI and CDAI. Indeed, only when remission by these criteria is fulfilled will patients stop destroying their joints and reduce their functional impairment maximally and thus possibly to normality [54], regardless of their level of improvement.

These and other insights mandate a change in clinical trial reporting by requesting the provision of information on cate- gories of disease activity attained in the course of a trial and at the endpoint rather than just providing levels of improve- ment [55]. Indeed, the first randomized double-blind controlled trial using a state as the primary endpoint has recently been published [56]. Thus, assessing disease activity has under- gone major changes and has become both standardized and the standard of care. Such assessment is also important in clinical practice.Time and timing as well as appropriate follow-up are important facets of rheumatoid arthritis and the care for rheumatoid arthritis

Early recognition and therapy are mandates

Clinical fact 6

Early recognition of rheumatoid arthritis is important for early institution of disease-modifying anti-rheumatic drug therapy, which is more efficacious than delayed treatment.

Background and evidence

The destructive process of RA starts within the first few weeks or months of disease, and by 2 years the majority of patients have damaged joints [57,58]. Indeed, there is evidence from experimental arthritis that osteoclast activation may occur even before the onset of clinical symptoms [59]. Several trials have revealed that early institution of disease- modifying anti-rheumatic drug (DMARD) therapy, when compared with late start, improves the outcome of RA [60- 62]. The major gain is twofold: it appears that the more established disease may be somewhat less responsive to the same drugs when compared with early disease [62] ('window of opportunity'). The second asset is the earlier prevention of accrual of damage and thus an overall reduction in joint destruction and risk of irreversible disability. However, early therapy requires early diagnosis. Alas, current criteria for the classification of RA are based on patients with long-standing RA and criteria for early RA are needed and awaited [63].

Regular tight follow-up and change of therapy are important

Clinical fact 7

Tight follow-up examinations (every 3 months) and appropriate switch of therapy after a maximum of 3 to 6 months in patients who do not achieve low disease activity or remission are important constituents of modern therapeutic approaches to rheumatoid arthritis.

Background and evidence

Another aspect of time relates to the observation that chronic active disease, despite therapy, will lead to increasing joint damage (see above). Therefore, treatment that does not reduce disease activity to a low state should be switched rapidly. Since in clinical trials maximal therapeutic responsive- ness can be seen within 3 to 6 months and since disease activity at 3 to 6 months is an excellent predictor of activity at 12 months [14], all necessary decisions can be made at that time, for the sake of the patient and consequently for society. However, this requires tightly timed control examinations and definitions of thresholds for switching insufficiently effective

therapies. Indeed, following such an algorithm has allowed for better

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outcomes [64-66].

C. New therapies and therapeutic strategies have revolutionized clinical developments

Tumor necrosis factor inhibitors plus methotrexate lead to profound clinical responses and uncouple the close relationship between disease activity and joint damage

Clinical fact 8

Remission has become a highly achievable goal with the advent of biological therapies. Moreover, tumor necrosis factor inhibitors plus methotrexate significantly retard joint damage, even in patients who do not respond well clinically, thus reducing the propensity to accumulate irreversible disability with active disease.

Background and evidence

As indicated before, achieving low disease activity and remission need to be the ultimate therapeutic goals in RA in order to affect all of its attributes, which comprise destruction of bone and cartilage and accumulation of irreversible disability. The introduction of tumor necrosis factor (TNF) inhibitors, particularly in combination with MTX, has revolutionized the scene in this regard: never before have response rates been so profound, with ACR70% (a 70% improvement in symptoms according to the American College of Rheumatology criteria) improvement criteria fulfilled in up to about 40% of patients [67]. While proportions of patients with 'DAS28 remission' often exceed ACR70% response rates, stringent remission according to the SDAI criteria has been observed at the end of a 1-year trial of a TNF inhibitor plus MTX in more than 20% of patients, whereas less than 15% of patients remained in the high disease activity category; in contrast, almost 30% of patients treated with MTX monotherapy still resided at high disease activity levels and approximately 12% had attained remission at 1 year [22]. In clinical practice, this success can be surpassed: in our clinic, about 25% of patients are in SDAI remission and only about 5% are in high disease activity [68]; this is in line with findings that most patients in today's clinical practice do not fulfill entry criteria for clinical trials [69]. A scenario in which 1 in 4 patients has reached remission and only 1 in 20 resides in high disease activity is a dream that probably no rheumatologist would have dared to entertain just few years ago – a novel reality challenging us to aim for more.

One of the most surprising findings in the decade since the introduction of TNF inhibitors was the observation that TNF inhibitors in combination with MTX would arrest or at least significantly retard progression of joint damage even in patients with highly active RA despite anti-TNF plus MTX treatment and even in those who had no clinical benefit at all

[70]. This indicated that TNF blockade plus MTX uncoupled the tight linkage between clinical disease activity and joint damage, and these findings were confirmed in other studies [71]. Although the underlying mechanisms responsible for these findings have not been worked out, they may have to do with threshold levels of bioactive TNF [72]. Importantly, in contrast to MTX monotherapy, the combination with MTX arrested progression of joint damage in patients who achieved low disease activity rather than remission and retarded it significantly even in those who had moderate or high disease activity [22]. Nevertheless, also with TNF inhibitor plus MTX therapy, progression of joint destruction increased with increasing disease activity, albeit at a lower level and slope [22].

Extinction of extra-articular manifestations and amyloidosis

Clinical fact 9

Effective therapy, in particular with methotrexate (MTX) and more pronounced with biologicals plus MTX, has abolished the bulk of extra-articular manifestations and amyloidosis, has reduced disease-related comorbidity such as cardiovascular disease and lymphoma, and has essentially normalized life expectancy.

Background and evidence

Extra-articular manifestations and complications have been major causes of death in RA. These abnormalities concerned mainly the occurrence of vasculitis, secondary amyloidosis, malignancy, infections, and cardiac events. All of them have been related to the severity of the disease [73-75]. Already with its appropriate use (that is, by rapid escalation and employing high enough doses [76,77]), MTX was found to interfere with disease activity and thus to reduce the levels of rheumatoid factor and acute-phase reactants. In particular, vasculitis and amyloidosis became rare due to the better control of disease activity. Moreover, the incidences of lymphoma and cardiovascular disease have declined signifi- cantly, leading to increased survival rates [42,78]. The improvement in all of these outcomes appears to have been uniformly expanded by the advent of TNF inhibitors, which allowed clinicians to further reduce the clinical and serological disease activity [79,80], resulting in further improved survival - at least in observational studies [81,82].

The novel therapies allow for a modification of treatment strategies and have significant economic consequences

Clinical fact 10

Novel algorithms that encompass regular disease activity assessment, change or modification of therapy upon insufficient

response defined as a lack of achievement of low disease activity or even remission, and the use of glucocorticoids and biological agents may allow for rapid achievement of optimal therapeutic responses in the vast majority of patients. This will not only improve quality of life but also lead to a reduction in the need for joint surgery and to the preservation of working ability.

Background and evidence

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The arsenal for treating RA has been greatly enhanced with the availability of biological agents that include not only IL-1 and TNF inhibitors, but also a B-cell-depleting agent, a co-stimulation inhibitor, and (at least in Japan, but soon globally) an IL-6 receptor antibody [67]. Based on the findings that patients with RA should be closely monitored using composite indices and controlled, that switching therapy has a significant impact if predefined low disease activity criteria are not met, and that long-term efficacy can be predicted within the short term after treatment starts, treatment algorithms have been developed that could potentially improve RA outcomes even further. The combination of synthetic DMARDs with glucocorticoids has substantial effectiveness that may approach that of the combination of DMARDs with biological agents, according to further data from clinical studies [66,84-87]. The value of synthetic DMARD combinations that do not include glucocorticoids, on the other hand, remains unclear [66,88].

There are significant monetary ramifications to the innovative treatment techniques' (e.g., biological agents') impact on disease activity, joint degradation, physical function, and quality of life. One the one hand, these agents aren't cheap and won't work for everyone. Conversely, additional direct and indirect expenses should be reduced as a result of successful treatment. There is a noticeable decrease in costs. Joint replacement surgery, for instance, has become less necessary as new treatments have become available. For instance, in Sweden, where the prevalence of inflammatory arthritis accounts for about 530 annual total hip joint replacements, this number has been steadily declining this decade, reaching about 300 in 2006, in contrast to the rise in osteoarthritis [89]. Equally encouraging is the fact that employment rates and employability rise throughout successful treatment [49], which may indicate that patients' working capacities are restored or maintained, the rate of early retirement is reduced, and patients' quality of life is improved or preserved.

Collectively, our knowledge of RA from a clinical perspective has grown substantially in the last ten years. The design of clinical trials and clinical trials in general have been, or will soon be, profoundly affected by these innovations.

References

The validity of individual factors and composite indices for assessing disease activity in rheumatoid arthritis was examined by van der Heijde DM, van't Hof MA, van Riel PL, van Leeuwen MA, van Rijswijk MH, and van de Putte LB. Annual Review of Rheumatology, 1992, 51:177–181.

Revised disease activity scores with 28-joint counts were developed by Prevoo MLL, van't Hof MA, Kuper HH, van de Putte LBA, and van Riel PLCM. Design and testing in a prospective longitudinal study of RA patients. Article published in Arthritis Rheumatoid Disease in 1995, volume 38, pages 44–48.

3.Consensus Study Group of the European Workshop for Rheumatology Research: Disease activity in rheumatoid arthritis: preliminary report. (Scott DL, Panayi GS, van Riel PL, Smolen J, van de Putte LB). Clinical Experimental Rheumatology 1992, 10:521-525.

A preliminary core set of disease activity measures for rheumatoid arthritis developed by the American College of Rheumatology. 4. Felson DT, Anderson JJ, Boers M, Bombardier C, Chernoff M, Fried B, Furst D, Goldsmith C, Kieszak S, Lightfoot R, Paulus H, Tugwell P, Weinblatt M, Widmark R, Williams HJ, Wolfe F. Clinical Trials for Rheumatoid Arthritis Outcome Measures Committee. Rheumatoid Arthritis 1993, 36:729-740.

Preliminary definition of progress in rheumatoid arthritis by the American College of Rheumatology. 5. Felson DT, Anderson JJ, Boers M, Bombardier C, Furst D, Gold-smith C, Katz LM, Lightfoot R Jr, Paulus H, Strand V, Tugwell P, Weinblatt M, Williams HJ, Wolfe F, Kieszak S. Rheumatoid Arthritis 1995, 38:727-735.

Core objectives for symptom-modifying antirheumatic medicines in rheumatoid arthritis clinical trials: a review by Boers M, Tugwell P,

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Vol-11 Issue-04 Dec 2023

Felson DT, van Riel PL, Kirwan JR, Edmonds JP, Smolen JS, Khaltaev N, and Muirden KD: World Health Organization and International League of Associations for Rheumatology. The citation is from the Journal of Rheumatoid Surgery, Volume 41, Supplemental Pages 86–89, 1994.
A study conducted by van Gestel AM, Prevoo MLL, van't Hof MA, van Rijswijk MH, van de Putte LBA, and van Riel PLCM was conducted to develop and validate response criteria for rheumatoid arthritis. The criteria were compared with the preliminary World Health Organization/International League Against Rheumatism Criteria and the American College of Rheumatology! Article cited in Arthritis Rheum 1996, 39:34–40.
A streamlined disease activity index for RA for clinical use: 8. Smolen JS, Breedveld FC, Schiff MH, Kalden JR, Emery P, Eberl G, van Riel PL, Tugwell P. Oxford Journal of Rheumatology, 2003, 42:244-257.
9.Goldsmith CH, Boers M, Bombardier C, Tugwell P: Development, scoring, and assessment of rheumatoid arthritis patients and trial profiles: criteria for clinically relevant improvements in outcomes. Joint Journal 1993, 20: 561–565.

10. The association between outcome measures and process factors in early rheumatoid arthritis was studied by van Leeuwen MA, Van der Heijde DM, van Rijswijk MH, Houtman PM, van Riel PL, van de Putte LB, and Limburg PC. Imaging findings, functional limitations, joint counts, and acute phase reactants compared. J Journal of Rheumatology, 1994, 21: 425-429.
Smolen JS, Van Der Heijde DM, St Clair EW, Emery P, Bathon JM, Keystone E, Maini RN, Kalden JR, Schiff M, Baker D, Han C, Han J, Bala M; Active-Controlled Study of Patients Receiving Infliximab for the Treatment of Rheumatoid Arthritis of Early Onset (ASPIRE) Study Group: 11. In early RA patients treated with high-dose methotrexate alone or in combination with infliximab, what factors are associated with joint damage? Findings from the ASPIRE study. Rheumatology (2006), 54:702-710.

Twelve. Aletaha D, Machold KP, Nell VPK, and Smolen JS: Rheumatologists' views on RA core set assessments. Survey findings. Journal of Rheumatology, 2006, 45: 1133-1139.
Elettaha D. and J. Smolen: Inflammatory rheumatic disease: a definition and measuring guide. Medical Condition Published in 2006 by North American, volume 32, pages 9–44.
Aletaha D, Funovits J, Keystone EC, and Smolen JS (2014) found that rheumatoid arthritis patients' disease activity during treatment predicted their response to therapy one year later. Joint Research 2007, 56:3226-3235.
15.Gravallese EM, Harada Y, Wang JT, Gorn AH, Thornhill TS, Goldring SR: Identification of cell types responsible for bone resorption in rheumatoid arthritis and juvenile rheumatoid arthritis. The source is the American Journal of Pathology, volume 152, pages 943–951.
Joint destruction caused by tumor necrosis factor alpha requires osteoclasts (16) Redlich K, Hayer S, Ricci R, David JP, Tohidast-Akrad M, Kollias G, Steiner G, Smolen JS, Wagner EF, Schett G. Article published in the Journal of Clinical Investigation in 2002, volume 110, pages 1419–1427.
"Molecular and cellular mechanisms of joint destruction in rheumatoid arthritis: two cellular mechanisms explain joint destruction?" (17) Gay, Gay, and Koopman (WJ) presented their findings. This information is sourced from the Ann Rheum Dis 1993 article, volume 52, supplement 1, pages S39–S47.
18.Firestein GS: Evolving ideas of rheumatoid arthritis. The publication title is Nature, 2003, 423:356-361.
The function of tumor necrosis factor alpha and interleukin-1 in inflammatory arthritis (19. Feldmann M, Brennan FM, Foxwell BM, Maini RN). Annual Review of Immunology 2001, 3:188-199.
The paradigm of IL-6: from fundamental research to medicine (Naka T, Nishimoto N, Kishimoto T, p. 20). In: Arthritis Research, 2002, vol. 4, no. 3, pp. 233–242.
Elettaha et al. (2021) validated a clinical activity score for rheumatoid arthritis and found that acute phase reactants did not significantly increase

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Vol-11 Issue-04 Oct 2023

composite disease activity indices. R796–R806 in Arthritis Research and Therapy, 2005.
Radiographic changes in RA patients achieving different disease activity states with methotrexate monotherapy and infliximab plus methotrexate: the impacts of remission and TNF-blockade (22. Smolen JS, Han C, Van der Heijde DM, Emery P, Bathon JM, Key-stone E, Maini RN, Kalden JR, Aletaha D, Baker D, Han J, Bala M, St Clair EW). The American Journal of Rheumatology, 2008, July 7. Published online before print.
23. a roundtable discussion on how to publish radiographic data in randomized clinical trials in rheumatoid arthritis: van der Heijde D, Simon L, Smolen J, Strand V, Sharp J, Boers M, Breedveld F, Weisman M, Weinblatt M, Rau R, and Lipsky P. Published in 2002 in the journal Arthritis Rheumatoid, volume 47, pages 215-218.
24-Smolen JS, Aletaha D, Xu S, Han J, Baker D, St Clair EW: Radiographic joint damage progression in rheumatoid arthritis: independent of erosins and joint space narrowing. Journal of the American Rheumatology Association, 2008, October 28. Published online before print.
Denosumab Rheumatoid Arthritis Study Group; Cohen SB, Dore RK, Lane NE, Ory PA, Peterfy impact of disease activity and radiologic damage over time on the long-term course and result of functional ability in rheumatoid arthritis. In 1999, the article was published in Arthritis Rheum and with the reference number 42:1854-60.
The correlation between RA disease activity, joint destruction, and functional ability during the illness's progression (Welsing PM, van Gestel AM, Swinkels HL, Kiemeney LA, van Riel PL, page 30). Article published in Arthritis Rheumatoid Disease in 2001, volume 44, pages from 2009 to 2017.
Reversible and irreversible components of rheumatoid arthritis: a functional assessment (Aletaha D, Smolen J, Ward MM, 31). Arthritis Rheum 2006, 54:2784-2792. 32. Aletaha D, Ward MM: The amount of functional improvement in clinical trials is affected by the duration of rheumatoid arthritis. The article "Ann Rheum Dis 2006, 65:227-233" provides more accurate information.
Poor clinical condition predicts early death in RA (33. Pincus T, Callahan LF). The published CG, Sharp JT, van der Heijde D, Zhou L, Tsuji W, Newmark R; Denosumab Rheumatoid Arthritis Study Group: Twelve-month, multicenter, random-ized, double-blind, placebo-controlled, phase II clinical trial on the effects of denosumab treatment on structural damage, bone mineral density, and bone turnover in rheumatoid arthritis. Journal of Arthritis and Rheumatoid Diseases, 2008, 58:1299-1309.
Holman HR, Kraines RG, Spitz P, and Fries JF: Evaluation of arthritis patient outcomes. Rheumatoid Arthritis 1980, 23:137-145.
27. Ware The MOS-36, a 36-item short-form health survey, was developed by JE J and CD Sherbourne. Part I. Theoretical structure and data collection protocols. Clinical Care 1992, 30:473-483.
28. The relationship between aging, health hazards, and

long-term impairment. Journal of the National Library of Medicine, 1998, 338(1038), 1035–1041. 29. Drossaers-Bakker KW, de Buck M, van Zeben D, Zwinderman AH, Breedveld FC, Hazes JM: The

publication is Bull Rheum Dis 1992, volume 41, pages 1–4.
Pincus T, Brooks RH, and Callahan LF (2017) conducted a study on the use of a short questionnaire and joint count measurements to predict long-term mortality in RA patients. Published in 1994 in the Annals of Internal Medicine, volume 120, pages 26–34.
The long-term effects of RA (35. Isomaki H). Scientific Reports in Rheumatology, 1992, 95 (Suppl): 3-8.
Research by Wolfe, Michaud, Gefeller, and Choi on the prediction of death in RA patients (36). This information is sourced from the 2003 edition of Arthritis Rheum, volume 48, pages 1530–1542.
Yelin et al. 37: Functional status and its change over 18 years as a predictor of death in RA patients. Journal of Rheumatology, 2002, 29: 1851–1857.
Comorbidities in RA (Michaud K, Wolfe F, et al., 2008).
Johns Hopkins University Press, 2007; 21(11): 885–90.

ISSN: 1832-5505
Vol-11 Issue-04 Dec 2023

First cardiovascular events are less common in rheumatoid arthritis patients who use tumor necrosis factor blockers, according to a study by Jacobsson LT, Turesson C, Gülfe A, Kapetanovic MC, Petersson IF, Saxne T, and Geborek P. Volume 32, Issue 12, Pages 1213–1218, Journal of Rheumatology, 2005.
40.Ridker PM, Hennekens CH, Buring JE, Rifai N: C-reactive protein and other indicators of inflammation in the prediction of cardio- vascular disease in women. Article published in the New England Journal of Medicine in 2000, volume 342, pages 836–843.
Newby LK and Shah SH: C-reactive protein as a potential indicator of cardiovascular risk. Heart Journal, 2003, 11: 169–179.
Research conducted by Baecklund et al. found an elevated risk of lymphoma in rheumatoid arthritis patients associated with chronic inflammation rather than the treatment of inflammation itself (42). The article was published in Arthritis Rheumatoid Manual 2006, volume 54, pages 692–701.
The impact of health-related quality of life on the reported use of health care resources in individuals with osteoarthritis and rheumatoid arthritis: a longitudinal study. 43. Ethgen O, Kahler KH, Kong SX, Reginster JY, Wolfe F. Publication date: 2002 in the Journal of Rheumatology, volume 29, pages 1147–1155.
Elin E, Wanke LA: The effect of impaired function and functional decline on the yearly and long-term direct costs: an evaluation. Published in 1999 in the journal Arthritis Rheumatoid, volume 42, pages 1209-1218.
The direct cost of rheumatoid arthritis was published by Ward MM, Javitz HS, and Yelin EH in 45. Volume 3, Issue 2, Pages 243–252 of Value Health in 2005.
Pincus T, Callahan LF, Sale WG, Brooks AL, Payne LE, and Vaughn WK: A nine-year study of 75 individuals with rheumatoid arthritis found that there were significant functional losses, job impairment, and higher death. Presented in the 1984 issue of Arthritis Rheumatoid Disease, volume 27, pages 864–872.
Work incapacity in rheumatoid arthritis ten years after diagnosis (Sokka et al., 2007). Journal of Rheumatology 1999, 26: 1681-1685.
Wolfe FE, Hawley DJ: Rheumatoid arthritis and its long-term effects. A prospective 18-year study of 816 people on work disability. Journal of Rheumatology, 1998, 25: 2108-2117.
Researchers Smolen, Han, van der Heijde, and Emery conducted the study. People with early-stage rheumatoid arthritis who take infliximab are able to keep their jobs, according to research by Bathon, Key-stone, Kalden, Schiff, Bala, Baker, Han, Maini, and St. Clair. Arts and Rheumatism 2006, 54:716-722. 50. Fries JF: Problems with the efficacy, cost, and safety of disease-modifying anti-rheumatic medications in RA. Journal of the American Rheumatism Society, 1999, 58 Suppl 1: I86-I89. 51. The toll of RA and its complications, by Kobelt G and Jönsson B