




NOTES FROM THE FIELD

Damage Accrual in Rheumatoid Arthritis: Evaluating the Joint and Beyond

George E. Fragoulis,¹  Katerina Chatzidionysiou,² Elena Nikiphorou,³  Andrew Cope,³ and
Iain B. McInnes⁴ 

The clinical, personal, and societal impact imposed by rheumatoid arthritis (RA) has transformed in the last decade. The likelihood of a more favorable disease course is increasing, being associated, more recently, with less articular damage and an improved long-term prognosis (1,2). This has been driven largely by a substantially revised treatment paradigm, comprising earlier diagnosis, treatment, and application of treat-to-target strategies, together with the advent of selective immune-targeted therapeutic strategies based on pathogenesis-driven principles.

However, rates of remission of RA remain low, especially “drug-free” remission (2). In a large RA study, remission rates ranged between 8.6% and 19.6%, depending on the medical center where data were obtained and the definition of remission used (3). Some individuals remain partial responders whereas a significant minority of patients are truly “difficult to treat.” An important consequence of the unmet needs of these “difficult-to-treat” RA patients is irreversible damage and a substantial residual loss of quality of life. Difficult-to-treat RA poses the greatest challenges to rheumatologists and also has a wider societal impact driven by various factors, including higher health care utilization, social isolation, and work disability.

Rheumatoid arthritis is not simply a disease of the joints. It is a multifaceted, chronic, systemic disorder that is characterized by additional classic extraarticular RA-related features such as interstitial lung disease (ILD). Uncontrolled inflammation can also result in notable comorbidities of disease, such as osteoporosis, increased cardiovascular risk, recurrent infections, and substantial cognitive dysfunction (4). Moreover, some of these conditions may be the consequence of treatments, such as glucocorticoids. Thus, the disease impact in patients with RA may be limited to articular manifestations only (a less likely scenario) but could also involve extraarticular manifestations, such as complications due to therapies, or comorbidities. The latter scenarios are more

representative of “real-life” conditions and pose additional challenges for complex disease management strategies designed to optimize outcomes. The poorer prognosis associated with these complex scenarios in RA, especially multimorbidity, necessitates a revision of the current treatment strategy that should stimulate the research agenda.

What is irreversible damage in RA?

Irreversible damage in RA, whether of the joints or of other organs, necessitates attention, both in routine clinical practice and in clinical research. Conventionally, the phrase “irreversible damage in RA” is used in the context of articular damage that can subsequently lead to deformity, loss of function, and chronic pain. Although orthopedic surgery has been studied as a surrogate marker of end-stage joint destruction (5), radiographic damage using validated scores, such as the Larsen or Sharp/van der Heijde scores, are now the standard in assessing this type of damage (6,7). Though widely used in academic context and in trials, the use of these validated scores in everyday practice is limited, and it is self-evident that they quantify only a small component of the damage burden placed on the patient.

The damage seen in RA reflects chronic inflammation, immune-mediated tissue injury, and accelerated comorbidity; it may also be iatrogenic. Potentially any organ/tissue can be affected and may result in multisystem disease, with both physical and psychological manifestations, as described above. Should we now consider the development of usable indices that more widely reflect the damage accrual in patients with RA—such as an index that would include parameters not only in the joints, but also in other tissues? To answer this question, one needs to consider the value of such an index, especially in routine clinical practice. Previous attempts to design clinical damage scores did not receive

¹George E. Fragoulis, MD, PhD: National and Kapodistrian University of Athens and Laiko General Hospital, Athens, Greece, and University of Glasgow, Glasgow, UK; ²Katerina Chatzidionysiou, MD, PhD: Karolinska University Hospital and Karolinska Institutet, Stockholm, Sweden; ³Elena Nikiphorou, MD, PhD, Andrew Cope, MD, PhD: King's College London, London, UK; ⁴Iain B. McInnes, MD, PhD: University of Glasgow, Glasgow, UK.
Drs. Fragoulis and Chatzidionysiou contributed equally to this work.

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Address correspondence to George E. Fragoulis, MD, PhD, Laiko General Hospital, First Department of Propaedeutic Internal Medicine, Agiou Thoma 17 Street, 11527 Athens, Greece. Email: geofragoul@yahoo.gr.

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wide adoption despite being associated with disease activity and other disease-related indices. The Overall Status in Rheumatoid Arthritis (OSRA) is an example. OSRA is a simple measure of overall status that consists of 4 components, with 1 being a disease damage score (8). The Rheumatoid Arthritis Articular Damage (RAAD) score is another example, developed as a clinical method for scoring long-term articular damage in patients with RA (9). Of note, none of these scores have been developed to capture permanent global damage in RA. Moreover, they were published in an era when multimorbidity in RA was underrecognized, which is perhaps why, at least in part, their wider acceptability and implementation was hindered.

What have we learned from other diseases?

There are 2 important concepts to consider when we attempt to define damage: chronicity and reversibility. For many immune-mediated inflammatory diseases, such as systemic lupus erythematosus, Sjögren's syndrome, and vasculitis, disease damage indices have been developed in order to measure irreversible organ damage and to better describe treatment efficacy and disease prognosis (10–12). These tools have been important for measuring permanent injury and have been used in clinical studies as well as translational research studies. These indices use the concept of irreversible damage, as distinct from active and reversible inflammatory processes which would be expected to respond to immunosuppression. In some of these indices, the duration of signs/symptoms aids in the distinction between permanent and temporary damage (10, 11). These indices have found a place in the routine management and monitoring of their respective diseases. Beyond their clinical value, they are also widely used

for research purposes, such as in the study of treatment strategies and disease progression and characteristics, as well as mortality and other potentially preventable adverse outcomes like functional disability and drug-related side effects (13). However, significant limitations have been identified regarding the content of these indices and their implementation in everyday clinical practice (14).

Envisioning a global damage index in RA

Thus far, a global damage index comprising all possible causes of permanent damage, such as articular, extraarticular, comorbid systemic involvement, and iatrogenic damage, does not exist. We envision a damage index that consists of the following domains: 1) articular and extraarticular manifestations, 2) comorbidities, and 3) iatrogenic damage (Figure 1). Each domain in turn will be characterized by relevant aspects of the “fields” of disease related to that domain. These characteristics could include, for example, neurologic manifestations, ILD, and radiographic damage for articular and extraarticular manifestations; cardiovascular disease and mental health disorders for comorbidities; and demyelination for iatrogenic damage. Fields may be scored in a weighted manner. The sum score of the fields of each domain can provide the domain score. The sum of the domain scores can provide a score for the damage index. To derive such a score, a working group comprising experts in the field from various relevant disciplines (rheumatologists, health care providers in rheumatology, epidemiologists, and statisticians) should be included in the development of this index. Patient participation in this project will be of paramount importance to obtain input via focus groups and face-to-face meetings and by online surveys distributed by patients' organizations.

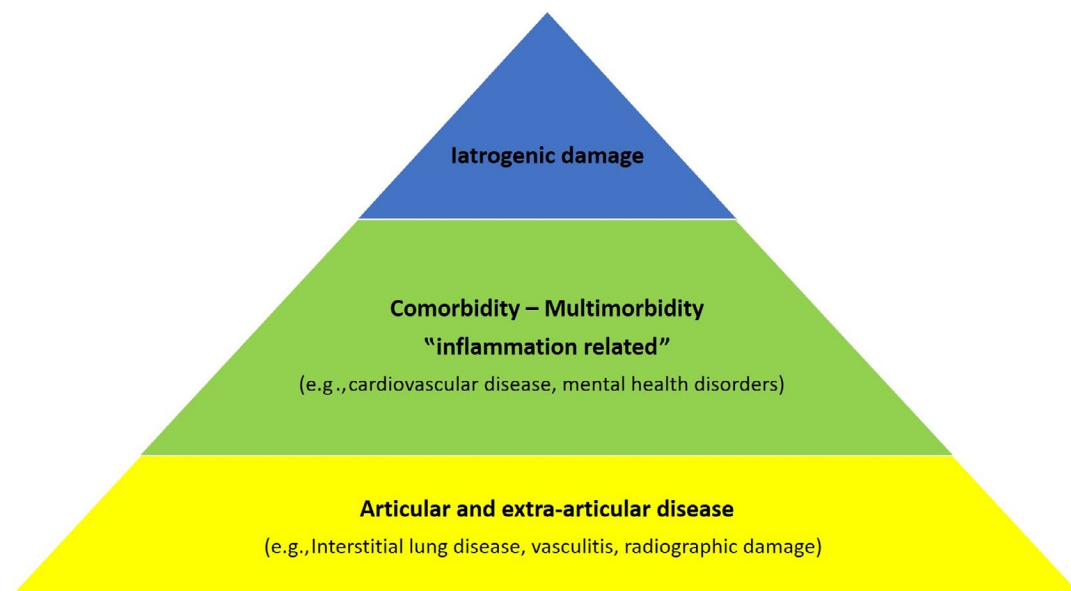


Figure 1. Domains and fields proposed for a new rheumatoid arthritis damage index. Different layers represent the domains of the index, with examples provided for fields that can be included in each domain.

A damage index would serve as a useful tool in clinical practice and in research, although the needs between these areas might differ. In terms of clinical practice, we seek holistic care in RA management. First, it appears that certain subgroups of RA patients are undertreated or overtreated using existing therapeutic adjustment tools (for example, treat-to-target principles that do not include multimorbidity in treatment algorithms) (15). Concerning residual and irreversible damage, redefining our targets and treatment strategies in RA would be helpful in improving outcomes. Second, such an index could help define a subgroup of patients in whom damage is more readily accumulated. These individuals could be either patients who have irreversible damage (i.e., erosions or ILD) at the time of symptom onset/disease diagnosis or patients who, during their disease course, quickly accumulate significant damage. Regardless, patients who continue to accrue damage despite achievement of effective control of inflammation (as determined by clinical and laboratory measures) would be promptly recognized with this proposed damage index. Third, mortality is still increased in RA mainly due to comorbidities and extraarticular manifestations. These disease features are at least partly preventable, and therefore, it is vital to understand what drives irreversible damage in RA. A novel global damage index in RA may have value in this respect.

In addition to the above points, an RA damage index could be very useful for clinical research in RA. It could be utilized to compare different interventions in preventing damage, enabling comparisons to be made between patients with similar disease burden (i.e., comorbidities, extraarticular manifestations, and drug-related damage). Besides, a known problem is that there are discrepancies between results demonstrated in randomized controlled trials (RCTs) and data obtained from real-world medical practice. This is partly because of the strict inclusion/exclusion criteria of RCTs, which tend to exclude patients with significant comorbidities and/or extraarticular manifestations and complications.

Such an index is expected to have high clinical and research impact. Accordingly, several aspects need to be considered. One would have to think carefully about the sensitivity of the analyses in terms of the criteria for risk stratification of the patients and weighing of the data. One should also acknowledge that construction of such an index would necessitate a careful and stepwise approach to ensure its value, such as, for example, in preventing further damage in a patient once the patient is identified as having irreversible damage, and especially in the preservation of function and quality of life in these patients. The need for a minimum severity grade for a feature to be included in such an index or the need for a range of severity grades and different scoring would have to be discussed. Additionally, direct and obvious relation to RA should be taken into consideration, with the caveat that certain comorbidities might be unrelated to RA. The sensitivity of such an index to identify those individuals who might benefit from more aggressive preventative treatment or those individuals who are overtreated would also need to be considered.

Conclusions

Although joint damage is the prominent feature of damage accrual in RA, it is certainly not the only one. The available joint damage scores have high academic value but are not widely used in clinical settings. Several organs can be irreversibly damaged in RA due to autoimmune mechanisms and chronic inflammation, comorbid acceleration, and drug toxicity. A clinical index that involves different domains apart from joint damage is needed as a more realistic reflection of the global impact of disease on patients we treat in real-world settings. Such an index should have high clinical value, enabling rheumatologists to “summarize” damage and stratify patients according to the severity of the global damage, identify more aggressive disease, and predict progression and poor outcomes in terms of both higher morbidity and mortality. A global damage index for RA could guide more individualistic disease management, improve treatment decisions, and lead to more patient-centric and holistic care.

AUTHOR CONTRIBUTIONS

All authors drafted the article, revised it critically for important intellectual content, and approved the final version to be published.

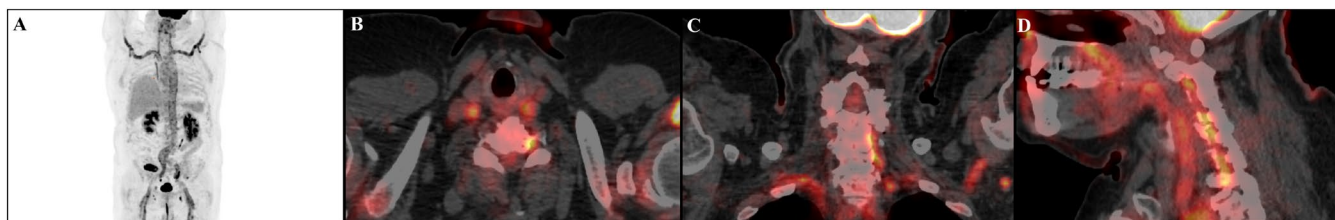
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Clinical Images: Cerebral vertebral artery vasculitis presenting as neck pain and fever



The patient, a 64-year-old man, was admitted to our hospital with a 6-week history of intermittent neck pain, posterior headaches, fever (39°C), and inflammatory syndrome (persistently elevated C-reactive protein level [~200 mg/liter]). Because of a dry cough, bronchopneumonia was initially suspected; however, antibiotics were not effective. He had not experienced vision loss or jaw or limb claudication and was not experiencing any headache at the time of admission. He had been diagnosed as having polymyalgia rheumatica (PMR) 3 years prior, which was still being treated with methotrexate. Because of the immunosuppressive drugs, we initially suspected infectious spondylodiscitis, but magnetic resonance imaging (MRI) of the neck showed only cervical arthrosis. Blood cultures were sterile. ^{18}F -labeled fluorodeoxyglucose positron emission tomography with computed tomography (^{18}F -FDG-PET/CT)-derived maximum intensity projection (**A**) showed pathologic uptake in the vertebral, supraclavicular, and mammary arteries and the aortic wall (fused axial PET/CT [**B**], coronal PET/CT [**C**], and sagittal PET/CT [**D**]). Large vessel vasculitis (LVV) consistent with giant cell arteritis (GCA) was diagnosed. Previous treatment was discontinued, and treatment with prednisone and tocilizumab (anti-interleukin-6 receptor monoclonal antibody) was initiated, greatly improving neck pain and inflammatory syndrome. Posterior headaches can be symptomatic of LVV-like GCA or Takayasu arteritis. Inflammation of vertebral arteries and structural damage are more specifically observed in GCA (1). GCA should be suspected in patients >50 years old with unusual headaches, associated PMR, and prolonged inflammatory syndrome. Temporal artery biopsy must be performed to confirm the diagnosis, even though the sensitivity of the histologic signs is only ~77% (2). In the Giant Cell Arteritis Clinical Research Study, new criteria were proposed, including morphologic signs of vasculitis, such as thickening of the aortic wall (on CT or MRI) or pathologic ^{18}F -FDG uptake in large vessels (on ^{18}F -FDG-PET/CT). In the case of a negative temporal artery biopsy finding, pathologic ^{18}F -FDG uptake in the vertebral arteries seems to be highly specific for LVV (3) and could be associated with ischemic manifestations (4).

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Jonathan Broner, MD
Benjamin Chambert, MD
Erik Arnaud, MD
CHU Nîmes
and University of Montpellier
Nîmes, France
Radjiv Goulabchand, MD 
CHU Nîmes
and University of Montpellier
Nîmes, France
INSERM U1183
Montpellier, France