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Frailty in the Rheumatology Clinic: Current Approaches to Assessment and Management

Alexandra Legge, MD, MSc.

Clinical Cases

To illustrate frailty in the context of rheumatic disease, we will consider two women, both 65 years of age who have been living with rheumatoid arthritis (RA) for the past 15 years.

Case #1: Rita is a retired lawyer. Her RA has been well-controlled, having remained in remission for the past 5 years on a combination of low-dose methotrexate and a tumour necrosis factor (TNF) inhibitor. She is otherwise healthy, with no comorbid medical conditions and no additional prescription medications. She lives independently with her husband and enjoys attending group fitness classes at the recreation centre in her neighbourhood.

Case #2: Alice lives alone in a rural area. She previously worked as a waitress but has been unable to work for the past 10 years due to chronic mechanical low back pain. Her RA has led to significant joint damage and remains moderately active despite treatment with hydroxychloroquine, sulfasalazine, and chronic low-dose prednisone. She also has a history of diabetes, heart failure, and depression, for which she takes six additional medications. Following a couple of falls last year, she now uses a walker at home. Alice has difficulty leaving the house due to poor mobility along with poor vision. Her neighbour helps with groceries and medical appointments.

Although these two women are chronologically identical in age, their health trajectories and risks for adverse outcomes differ substantially. Frailty provides a framework for understanding this heterogeneity.

Why Frailty Matters

These cases demonstrate how individuals of the same chronological age can vary considerably in their current health status and future life expectancy. It was this unmeasured variability in the risk of death among people of the same age that originally gave rise to the term "frailty" in the medical literature nearly 50 years ago.[1] Since then, the concept has been broadened to describe the greater susceptibility to adverse outcomes experienced by certain individuals.

Frailty can be defined as an age-related process characterized by reduced physiological reserve, greater vulnerability to stressors, and an increased risk of adverse health outcomes.[2] It reflects impaired homeostatic regulation and a diminished capacity to recover from physiological insults. Consequently, frail individuals are more likely to experience functional decline, loss of independence, or death in response to health stressors (e.g., infection or surgery), while robust (non-frail) individuals possess sufficient intrinsic capacity to recover more rapidly and fully under similar circumstances.[2,3]

Although strongly associated with chronological age, frailty reflects more than simply the passage of time. It represents a measure of biological aging, capturing individual differences in physiological reserve and vulnerability not explained by chronological age alone. Frailty is also conceptually related to, yet distinct from, both disability and multimorbidity.[2,3] Multimorbidity refers to the presence of two or more chronic medical conditions, while disability describes impairments in physical or mental function that limit daily activities. Although these constructs often overlap and interact, they represent distinct aspects of health status. Notably, frailty may be present even in the absence of multimorbidity or disability, reflecting a unique dimension of vulnerability that cannot be fully accounted for by chronic disease burden or functional impairment alone.[2,3]

Frailty is becoming an increasingly important consideration for Canadian rheumatologists as our population continues to age. Between 2017 and 2037, the number of Canadians aged 65 years and older is projected to increase by 68%, exceeding 10 million individuals by 2037.[4] As a result, rheumatologists will care for a growing population of older adults with rheumatic diseases, many of whom will also be living with multimorbidity, polypharmacy, and geriatric syndromes, including frailty. Consequently, caring for people living with rheumatic diseases in the context of these age-related conditions is increasingly becoming the norm rather than the exception, making the recognition and assessment of frailty an essential component of contemporary rheumatology practice.

Measuring Frailty in the Rheumatology Clinic

While broad agreement exists on the conceptual definition of frailty, there remains considerable debate regarding the optimal approach for its measurement. Theoretically, a definitive diagnosis of frailty can only be established retrospectively by observing a disproportionately poor response to a physiological stressor. However, to be useful clinically, alternative strategies are needed to identify frailty prospectively (i.e., prior to an inciting event) and to allow opportunity for intervention before any negative health consequences occur.

Most existing frailty assessment tools are grounded in one of two conceptual frameworks: phenotypic frailty[5] or deficit accumulation.[6] Some instruments, however, incorporate features of both approaches.[7,8] Many tools are available to measure frailty in rheumatic disease populations, some of which are disease agnostic[5,9] while others have been developed for use in specific rheumatic disease populations.[7,10,11] Examples of commonly used approaches for measuring frailty are shown in **Table 1**.

Phenotypic frailty, most commonly operationalized using the Fried phenotype, views frailty as a distinct biological syndrome characterized by specific clinical features that can be directly measured: slowness, weight loss, exhaustion, weakness, and decreased physical activity.[5] This approach may be particularly useful for identifying candidates for interventions targeting physical frailty. Although the Fried phenotype is relatively quick to administer, it requires direct assessment of grip strength and gait speed, which may limit feasibility in some settings and preclude its application in existing health datasets. As the phenotypic approach focuses primarily on physical frailty, separate assessment of other health domains (e.g., cognition, mental health, comorbidities) is required to fully characterize vulnerability. Importantly, in patients with active rheumatic

Frailty instrument	Description	Advantages	Limitations
Fried Frailty Phenotype	Five directly measured or patient-reported clinical criteria **3+ criteria** = frail **1–2 criteria** = pre-frail **0 criteria** = robust	• Biologically plausible • Relatively quick and easy to use in clinic • Useful to evaluate interventions that target physical frailty	• Requires specialized equipment and trained assessors • Difficult to apply in existing datasets • Requires separate evaluation of non-physical domains
Frailty Index	At least 30 items spanning multiple domains (e.g., function, comorbidities, lab results, among others) Exact item list and data sources may vary (e.g., patient-reported, medical record, or direct measurement)	• Single measure of vulnerability across multiple domains • Flexibility to adapt to existing datasets • Suitable for large, population-based datasets	• Challenging to implement in clinical settings due to large number of variables and complex calculation
Clinical Frailty Scale	9-point pictorial scale based on subjective clinical judgment	• Rapid and easy to implement as a screening tool in clinical settings • Requires minimal resources or training	• Potential variability between raters • Susceptible to implicit bias

Table 1. Selected approaches for the measurement of frailty among people living with rheumatic diseases in clinical and research settings; *courtesy of Alexandra Legge, MD, MSc.*

disease, manifestations such as fatigue and joint pain may interfere with frailty assessment.[12] In certain populations, modifications to the Fried phenotype may be required, such as using chair sit-to-stand time rather than hand grip strength in people with active hand arthritis or joint deformities.[13]

In contrast, the deficit accumulation approach conceptualizes frailty as a multidimensional risk state arising from the cumulative burden of age-related health deficits (e.g., comorbidities, functional limitations, and geriatric syndromes) across multiple domains.[6] This approach is commonly operationalized using a frailty index,[14] calculated as the proportion of deficits present from a predefined list. Advantages of the frailty index include its flexibility and suitability for use in large, pre-existing datasets (e.g., administrative databases), facilitating population-level frailty measurement. However, unless it is automatically derived within electronic medical records,[15] the complexity of the frailty index may limit its use in routine clinical care.

The Clinical Frailty Scale (CFS) has gained widespread use due to its simplicity and clinical feasibility. The CFS is a 9-point pictorial scale that categorizes individuals according to their baseline level of functioning using clinical judgment.[16] Because it requires minimal time and resources, the CFS may be particularly useful as a point-of-care frailty screening tool in busy rheumatology clinics. However, its reliance on subjective assessment by individual clinicians raises concerns regarding inter-rater reliability and susceptibility to implicit biases.

Despite substantial methodological differences, most frailty instruments demonstrate comparable ability to predict adverse health outcomes. Direct comparisons generally reveal only fair-to-moderate agreement between tools, indicating that different instruments identify overlapping but not identical groups of individuals as frail.[17] Moving forward, harmonizing frailty measurement approaches across rheumatic disease populations is therefore a research priority

to improve interpretability and generalizability of study results.

Currently, no single frailty measurement tool can be considered universally superior. Selection should depend on the intended purpose of the frailty measurement and the feasibility of the tool in the specific clinical or research context. For example, population-based studies may favour electronically derived frailty indices, whereas clinical settings may benefit from more practical tools such as the CFS or patient-facing phenotypic assessments.

Frailty in Rheumatic Disease Populations

Frailty is particularly relevant in the context of rheumatic diseases. Multiple studies have demonstrated that frailty occurs more frequently and at younger ages among people with inflammatory rheumatic diseases when compared to the general population.[7,10,18] Several mechanisms may contribute to the relationship between frailty and rheumatic disease, which may be bidirectional. One hypothesis relates to the concepts of immunosenescence and inflammaging, which respectively describe the immune dysregulation and chronic low-grade systemic inflammation that are observed in association with aging.[19,20] On the one hand, age-related immune dysregulation could predispose individuals to develop autoimmune disease. On the other hand, chronic inflammation associated with immune-mediated rheumatic diseases may accelerate biological aging and promote the premature development of frailty. Clarifying the temporal relationship between these processes remains an important area for future investigation.

Muscle loss and physical deconditioning represent additional contributors to the development of frailty among people living with rheumatic diseases. Chronic pain, fatigue, joint damage, and mobility limitations can reduce physical activity, leading to sarcopenia. Finally, increased medication burden also likely plays a role, in particular via the health risks associated with polypharmacy and glucocorticoid exposure.

Frailty is a powerful predictor of health outcomes in rheumatic disease populations. Across a range of rheumatic diseases, studies consistently demonstrate that frailty is associated with an increased risk of adverse outcomes, including functional decline, organ damage accrual, hospitalizations, and mortality.[10,18,21,22] Importantly, frailty frequently improves risk prediction beyond traditional prognostic factors, enhancing our understanding of why patients with apparently similar rheumatic disease characteristics can experience markedly different health outcomes.

Frailty assessment can help address the impact of ageism on rheumatology care by shifting clinical decision-making away from chronological age and toward a more individualized evaluation of physiologic vulnerability.[23] Reliance on chronological age alone can contribute to both over- and under-treatment of older adults with rheumatic diseases, as assumptions about aging may not accurately reflect a patient's true health status. In contrast, frailty provides a more clinically meaningful measure of susceptibility to adverse outcomes, including treatment-related harms such as the risk of serious infections associated with the use of biologic disease-modifying antirheumatic drugs.[24] Incorporating frailty assessment into routine care for frail individuals can support safer prescribing and facilitate more personalized risk-benefit discussions. At the same time, it may help prevent the under-treatment of robust older adults whose care might otherwise be limited by unfounded concerns about treatment-related harms based on their chronological age.[23]

Routine frailty assessment should be considered for all adults with rheumatic diseases, particularly those aged 50 years and older or those with other risk factors for frailty, such as multimorbidity or polypharmacy. As active rheumatic disease can confound frailty measurement,[12] frailty should ideally be measured during periods of low disease activity or stable disease. Longitudinal assessment of frailty—such as at each clinic visit, or at least once annually—may be more informative than measurement at a single timepoint. Emerging evidence suggests that frailty trajectories provide additional prognostic information[25] and may facilitate earlier identification of at-risk individuals who could benefit most from interventions to prevent frailty progression.

Managing Frailty in People Living with Rheumatic Diseases

Unlike chronological aging, frailty is a dynamic and potentially reversible process. An individual's frailty status may worsen, stabilize, or improve over time, presenting opportunities for prevention and treatment (**Table 2**). The first step in managing frailty among patients with

Treatment Strategies
1. Ensure adequate control of rheumatic disease activity.
2. Consider evidence-based strategies for mitigating health risks associated with frailty in community-dwelling older adults, especially multicomponent interventions. ***Physical activity*** • Multimodal programs including aerobic, strengthening, flexibility, and balance exercises, especially in a group setting • Adequate sleep (7–9 hours/night) ***Vaccinations*** • Annual high-dose influenza vaccination • Shingles and pneumococcal vaccinations ***Medication optimization*** • Regular medication review by a physician or pharmacist ***Social interaction*** • Group-based social activities and educational support groups • Remote digital solutions, local community resources ***Dietary interventions*** • Maintain adequate hydration • Ensure adequate protein intake • Vitamin D supplementation
3. If frailty is identified through routine screening, consider referral for further evaluation with comprehensive geriatric assessment.
4. For individuals with severe frailty, consider prioritizing short-term symptom management strategies over interventions designed for longer-term benefit.
5. Further research is needed to clarify the optimal strategies for rheumatic disease management in the context of frailty.

Table 2. Strategies for the prevention and treatment of frailty among people living with rheumatic diseases; *courtesy of Alexandra Legge, MD, MSc.*

rheumatic disease is optimizing control of the underlying inflammatory condition, which may reduce inflammation-driven aging processes, improve physical function, and potentially delay frailty progression. In some cases, treatment of active rheumatic disease may itself improve frailty status.[12,26] However, for the majority of frail individuals, rheumatic disease control alone is unlikely to be sufficient, and more comprehensive and holistic management plans are needed.

Currently, data supporting interventions to prevent and treat frailty specifically in rheumatic disease populations remains limited. However, extrapolating from the available evidence for community-dwelling older adults, several low-risk therapeutic interventions may be considered for the prevention and treatment of frailty in this patient population. The Canadian Frailty Network's AVOID Frailty framework[27] outlines various evidence-based strategies for mitigating the health risks associated with frailty in older adults, including physical activity,[28] dietary interventions,[29] vaccinations, social interaction,[30] and medication optimization.[31] Multicomponent interventions targeting more than one of these domains may be particularly effective. Importantly, given the strong link between frailty and mortality risk in rheumatic disease populations, the presence of severe frailty may warrant prioritizing short-term symptom relief over interventions intended to yield long-term benefits that patients may not live long enough to experience.

Given the heterogeneity and complexity of frailty, a "one size fits all" approach to management is unlikely to be effective. Screening alone is insufficient; identifying frailty should prompt further evaluation to understand its underlying contributors and guide interventions. One approach is referral for comprehensive geriatric assessment (CGA), a structured,

multidimensional diagnostic and therapeutic process used to establish a holistic picture of an individual's health status.[32] CGA facilitates the identification of modifiable risks (e.g., falls, malnutrition, polypharmacy) and the creation of personalized treatment plans developed through shared decision-making and aligned with patient values and goals of care.[32] Evidence from oncology demonstrates that integrating CGA into treatment planning for older adults improves quality of life, reduces treatment-related toxicity, and lowers rates of unplanned hospitalizations.[33,34] Similar approaches may be beneficial in rheumatology, particularly when considering high-risk therapies for conditions such as systemic vasculitis. Ultimately, effective implementation will require multidisciplinary care pathways involving rheumatologists, geriatricians, primary care providers, and allied health professionals.

The optimal approach to treating rheumatic disease in the context of frailty remains uncertain, and it is unclear whether management strategies should differ from those used in non-frail individuals. A major challenge is that randomized controlled trials in rheumatology frequently exclude individuals with complex medical and psychosocial needs, including frail older adults, limiting the applicability of existing evidence to this patient population.[35] Consequently, rheumatologists currently have limited data to guide individualized treatment decisions for frail patients. Addressing this evidence gap is a research priority, with an urgent need for studies that evaluate the relative benefits and risks of different therapeutic approaches for rheumatic diseases in the context of frailty.

Conclusions

Frailty is increasingly recognized as an important clinical construct in rheumatology, distinct from chronological age, multimorbidity, and disability. Given its high prevalence among people living with rheumatic diseases and its strong association with adverse health outcomes, frailty carries important prognostic implications. Importantly, frailty is not an inevitable consequence of chronological aging or chronic disease but rather a dynamic and potentially reversible process. As such, routine screening for frailty in the rheumatology clinic, coupled with targeted interventions and risk mitigation strategies, represents an important opportunity to improve patient outcomes and support more personalized and holistic care. Ongoing research is needed to refine approaches to frailty assessment and management and to better understand how frailty should inform treatment decision-making for rheumatic diseases.

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Why Rheumatologists Should Know About Nociplastic Pain

Mary-Ann Fitzcharles, MD
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Introduction

The story of nociplastic pain in rheumatology practice begins with fibromyalgia (FM). More than three decades ago, rheumatologists played a leading role in establishing criteria for FM, with early criteria requiring examination of tender points.[1] With increasing knowledge that FM encompassed more than pain alone, along with evidence that the tender point examination showed poor reliability, the American College of Rheumatology developed updated criteria. These updates eliminated tender point assessment and instead incorporated the concept that FM was a syndrome that included "central" symptoms of fatigue, unrefreshed sleep, and cognitive dysfunction, as well as associated conditions such as headaches, abdominal pain, and depression.[2] At that time, the concept of pain sensitization as an explanation for "invisible pain" was being actively studied by basic scientists, but had not yet translated into the clinical domain. The wide range of subjective symptoms experienced by patients with FM were difficult to explain, with many believing that symptoms were exaggerated or primarily psychiatric in origin. With growing recognition, it is now understood that nervous system sensitization is a plausible explanation for "invisible" pain that cannot be sufficiently explained by tissue abnormality. This mechanism

is now identified as nociplastic pain, the third pain phenotype alongside nociceptive and neuropathic pain.[3] Nociplastic pain is common and often unrecognized in patients with rheumatic diseases (**Table 1**).

Why Should Rheumatologists Acquire Knowledge About Pain Mechanisms?

Over the past decade, FM has served as the flagship condition for nociplastic pain. As FM has increasingly shifted outside of rheumatology practice, with patients commonly managed in primary care, the relevance of FM/nociplastic pain within rheumatic disease has become an important element in rheumatology practice. Many patients with inflammatory rheumatic conditions deemed well controlled by recognized parameters continue to experience persisting pain. Early studies described this phenomenon as "remaining pain" in patients with clinically controlled rheumatoid arthritis (RA), but without a precise understanding of the operative mechanisms.[4] It is now recognized that overlapping pain phenotypes, particularly prominent nociplastic pain, likely account for these findings, with over three quarters of patients with "well-controlled" RA reporting inadequate pain control.[4]

Nociplastic pain occurs across a range of musculoskeletal conditions including those of soft tissues and myofascia (i.e., shoulder tendonitis), degenerative and inflammatory arthritis, and spinal disease.[5] While the population prevalence of FM is estimated at 2–8%, the prevalence of FM/nociplastic pain in rheumatic diseases is considerably higher. Pooled prevalence estimates range from 18–24% in RA, 14–16% in axial spondyloarthritis, and 18% in psoriatic arthritis, to name just a few.[6] When FM co associates with rheumatic disease, patients experience considerably greater pain severity, higher measured disease activity, reduced functional capacity, and poorer quality of life. Of critical importance is that unrecognized nociplastic pain can lead to erroneous management strategies that focus on controlling the underlying rheumatic condition, rather than addressing the underlying pain mechanism (**Table 2**).

Understanding Pain Mechanisms

Traditionally nociceptive pain has been viewed as arising from disturbances of tissue structure, mediated by localized inflammatory processes that activate peripheral primary afferent neurons. In this context, pain intensity is typically proportional to the nociceptive input. In contrast, nociplastic pain is a disorder of pain processing with resulting upregulation of nociception, termed pain sensitization.[3] In nociplastic pain states, pain is perpetuated by enhanced neuronal function and is no longer directly coupled to the noxious input. Instead, it becomes a self-sustaining, dysfunctional response to normally non-painful sensory inputs.[7] Pain sensitization is a complex process that occurs at multiple levels in the nervous system. Alterations in excitatory neurotransmitter signalling can induce changes in nervous system gene expression, leading to neuronal hyperexcitability, with changes at multiple levels across the spinal cord and brain regions. These central nervous system changes are associated with symptoms of fatigue, sleep disturbances, and cognitive changes.[8] A downstream effect is disinhibition of descending inhibitory pathways (the descending analgesic system), resulting in increased pain signalling within the spinal cord.[7]

Why Do Some Patients Develop Nociplastic Pain?

Musculoskeletal nociplastic pain typically begins with a persistent anatomical noxious input, such as chronic joint inflammation or anatomical abnormality—that induces nervous system hyperresponsiveness and is influenced by a multitude of biopsychosocial factors, leading to a combination of pain mechanisms sometimes termed 'overlapping pain'.[9] Predisposing factors for the development of nociplastic pain include a genetic predisposition, with studies pointing to a polygenic trait, as well as background psychological and physical stressors, previous pain experiences, precipitating physical events, and social disadvantage.[10,11] At its core, central sensitization represents a detrimental form of neuroplasticity.

How to Recognize Nociplastic Pain

Nociplastic pain may be generalized, as in FM, or regional, and cannot be accurately confirmed by objective bedside tests, biomarkers or imaging studies. The pain is not binary, but exists along a continuum. Some individuals exhibit minimal amplification of nociceptive input, others demonstrate the ability to naturally

Pain Type	Mechanism	Key Features	Clinical Relevance
Nociceptive	Peripheral tissue inflammation/damage	Proportional to structural abnormality, localized	Responds to anti-inflammatory and analgesic treatments
Neuropathic	Lesion/disease of somatosensory nervous system	Burning, electric, dermatomal distribution	Requires specific neuropathic agents
Nociplastic	Upregulation of nervous system pain processing, termed pain sensitization.	Disproportionate intensity, widespread, fluctuating, with fatigue/sleep/cognitive symptoms	Poor response to conventional analgesics; requires biopsychosocial approach

Table 1. Key Concepts of Pain Phenotypes; *courtesy of Mary-Ann Fitzcharles, MD and Hance Clarke, MD.*

Condition	Estimated Prevalence of FM/Nociplastic Pain	Clinical Impact
Rheumatoid Arthritis	18–24%	Higher pain, ↑ disease activity scores, ↓ function
Axial Spondyloarthritis	14–16%	Persistent pain despite controlled inflammation
Psoriatic Arthritis	18%	Worse quality of life and function
General Inflammatory Arthritis	20%	Risk of overtreatment of inflammation

Table 2. Prevalence of Nociplastic Pain in Rheumatic Diseases; *courtesy of Mary-Ann Fitzcharles, MD and Hance Clarke, MD.*

inhibit nociceptive signalling, while still others experience marked nociceptive magnification. These differences are influenced by factors such as expectations, attentional processes, and psychological characteristics.

The Clinical History

Identifying nociplastic pain begins with a clinical history that explores the pain characteristics and associated symptoms. Nociplastic pain does not conform to traditional concepts of pain; it is often reported as severe, fluctuating in intensity, and can occur without clear provocation, or be influenced by environmental factors such as temperature, stressors, and psychological status. Pain is typically more widespread than expected, and is usually associated with subjective symptoms of fatigue, sleep disturbance, cognitive difficulties, depression, or hypervigilance.[12] Patients may also report other pain complaints such as migraine headaches, irritable bowel syndrome, or bladder symptoms. Patients may complain of heightened sensitivity to touch, with discomfort elicited by normally non-painful stimuli, such as clothing with a rough texture, or a gentle caress that gives an unpleasant sensation. Gentle pressure, such as a child sitting on the lap, may induce pain. Pain can be aggravated by environmental factors of heat, cold, or stress, and additional associated comorbidities including hypervigilance to light, sound, or smell, sleep disturbances, fatigue, myriad gastrointestinal and genitourinary symptoms, or cognitive difficulties. Collectively, these subjective yet valid experiences point to the phenomenon of central sensitization (**Table 3**).

Physical Examination

Physical examination will reveal features of the underlying musculoskeletal condition, which for an inflammatory condition could appear clinically quiescent (**Box 1**). In addition, signs of pain hypersensitivity can be identified by a few simple bedside manoeuvres. These may include tactile allodynia to light touch/brushing, mechanical hyperalgesia following application of pressure, hyperalgesia related to cold or warm stimuli, and persistence of after sensations,

Assessment Component	Tools, Findings
History	Pain more widespread, complaints often vague, fatigue, sleep disturbance, depression, hypervigilance, other pain complaints (e.g., migraine, irritable bowel symptoms)
Physical examen	Excessive sensitivity to non painful stimuli: allodynia, hyperalgesia, temporal summation
Questionnaires	FSQ, painDETECT, CSI
Advanced testing	QST (PPT, TS, CPM) currently in the research setting

Table 3. Clinical Assessment of Nociplastic Pain; *courtesy of Mary-Ann Fitzcharles, MD and Hance Clarke, MD.*

Abbreviations: CPM: conditioned pain modulation; **CSI:** Central Sensitization Inventory; **FSQ:** Fibromyalgia Survey Questionnaire; **PPT:** pressure pain threshold; **QST:** quantitative sensory testing; **TS:** temporal summation

described as an echo of the stimulus, for a few seconds following a sensory input.[13] Temporal summation, characterized by progressively increasing pain in response to repeated, identical (low-level) noxious stimuli (a sharp object) rather than accommodation or extinction, is a hallmark feature of central sensitization. Although further validation is required, these simple clinical steps can guide clinicians toward a diagnosis of nociplastic pain and overlapping pain mechanisms.

Clinical Features of Nociplastic pain
Pain characteristics: severe, diffuse, non-anatomical distribution, fluctuating, disproportionate to tissue damage.
Triggers: underlying rheumatic condition, stress, temperature, emotional factors.
Sensory symptoms: allodynia, hyperalgesia, after-sensations.
Associated symptoms: fatigue, sleep disturbance, cognitive dysfunction.
Comorbidities: depression, anxiety, hypervigilance.

Box 1. Clinical features of nociplastic pain; *courtesy of Mary-Ann Fitzcharles, MD and Hance Clarke, MD.*

Additional Testing

Although not commonly used in clinical practice, quantitative sensory testing (QST) in research settings can identify sensitivity of the somatosensory system to nociceptive input, providing information on abnormal pain processing. Findings from QST have greatly strengthened the concept of nociplastic pain associated with musculoskeletal conditions, particularly through measures such as the pressure pain threshold, temporal summation, and conditioned pain modulation. Several questionnaires can support the identification of nociplastic pain, with the Fibromyalgia Survey Questionnaire most commonly used in the context of rheumatic diseases.[2] Other questionnaires applicable to clinical practice include the painDETECT questionnaire and the Central Sensitization Inventory, both easily self-administered.

Consequences of Nociplastic Pain in the Musculoskeletal Context

Across all inflammatory arthritis, the prevalence of nociplastic pain is approximately 20% and is associated with higher pain scores, overall reduced function, more global suffering, and elevated scores on standard questionnaires to assess disease activity. This latter finding is of critical importance as the inflammatory disease could be misjudged as inadequately controlled, leading to inappropriate adjustments of disease modifying agents (**Box 2**). Nociplastic pain is also a risk factor for poor outcomes following interventions, including surgery. Notably, up to 20% of those with nociplastic pain experience chronic, persistent pain after knee replacement, with consequences of decreased function, lower satisfaction, and poorer mental health outcomes.[14] While non-pharmacological supports, such as

cognitive behavioural therapy and exercise, should be integrated early into the clinical care pathway in any chronic pain condition, it is of utmost importance for patients presenting with nociplastic pain.

Although degenerative changes of the spine may involve multiple anatomical structures, there is a poor correlation between pain severity, imaging, and anatomically-directed interventions such as injections. Nearly one third of patients with low back pain exhibit nociplastic features, which are associated with poorer physical and psychological functioning, greater disability, and reduced responsiveness to procedures. Even in conditions affecting the hand, such as trigger finger, carpal tunnel syndrome, and osteoarthritis, the coexistence of fibromyalgia is associated with higher healthcare utilization and increased surgery rates.

Consequences of Unrecognized Nociplastic pain
Misinterpretation of disease activity.
Overtreatment, polypharmacy.
Increased risk of persistent pain after surgery.
Increased utilisation of the healthcare system.

Box 2. Consequences of unrecognized nociplastic pain; *courtesy of Mary-Ann Fitzcharles, MD and Hance Clarke, MD.*

Treatment Recommendations for Musculoskeletal Nociplastic Pain

Treatments for nociplastic pain generally reflect those recommended for FM, beginning with a stepwise, multimodal approach that incorporates non-pharmacological strategies as a cornerstone, with additional drug therapy when indicated. Comorbid mental health conditions such as anxiety, depression, and post traumatic stress disorder should be addressed. Pharmacologic treatments are not a panacea, are often associated with adverse events, and generally provide only modest benefit, with few patients experiencing remarkable improvement.[15,16] Traditional management strategies that address nociceptive pain, including analgesic or anti-inflammatory medications, or anatomically-focused interventions, are less successful and should be discouraged (**Table 4**).

Non-pharmacological Treatments

Education should emphasize the biopsychosocial model that promotes active patient participation and discourages reliance on passive practitioner-administered treatments. Often overlooked are recommendations for good lifestyle practices such as sufficient physical activity, attention to diet, strategies to control stress, pacing of activities, and setting realistic outcome goals. Integrating psychological measures that include cognitive behavioural therapy (often available on-line), acceptance/mindfulness-based therapies, and attention to stress can improve treatment effects.[17] Mind-body interventions, such as yoga, support care by harmonizing physical and psychological factors.

Regular and sufficient physical exercise (at least 150 minutes per week of moderate activity) is recommended. However, individuals with nociplastic pain are more likely to respond to a graded exercise approach in a pain-contingent manner combined with pacing of activities.[18] Patients should be encouraged to choose forms of physical activity that are easily accessible and enjoyable, with no specific exercise recommended.

Although patients frequently request advice about the ideal diet, there is no single dietary intervention with sufficient evidence to be recommended. Overall the less healthy Western diet, high in fat and sugar and low in fibre content, should be adjusted to incorporate whole foods that are prepared in the home. Studies examining various whole-food dietary interventions report modest reductions in pain, but no single diet has shown excellent or consistent benefit. The gut microbiome dysbiosis plays a role in the modulation of chronic pain by acting at the interface between the neuroimmune-endocrine system and the microbiome-gut-brain axis. Strategies aimed at restoration of the gut microbiota, including probiotic supplementation and more recently fecal microbiota transplantation, have been explored with preliminary but promising-results.

Neuromodulation techniques that deliver electrical or magnetic stimulation to the central or peripheral nervous system are being studied, with the aim of facilitating neuroplasticity and modulating pain. Although these studies are generally small and carry a high risk of bias, short-term reductions in pain have been reported.

Intervention	Key elements
Non-pharmacologic	
Education	Biopsychosocial model, active participation
Exercise	≥150 min/week, graded approach
Psychological therapies	CBT, mindfulness, acceptance
Lifestyle	Sleep, diet, stress management
Neuromodulation	Modulate neuroplasticity
Pharmacologic	
Antidepressants	Moderate benefit (for some)
Anticonvulsants	Small benefits, side effects
Analgesics, NSAIDs	Ineffective
Opioids	Discouraged

Table 4. Treatment Recommendations; *courtesy of Mary-Ann Fitzcharles, MD and Hance Clarke, MD.*

Abbreviations: CBT: cognitive behavioural therapy; **NSAIDs:** nonsteroidal anti-inflammatory drugs

Pharmacologic Treatments

Drug treatments, although often expected by patients, offer only a modest benefit for some. The strongest available evidence, largely derived from studies in FM, is for the use of antidepressants and anticonvulsants, although the strength of this evidence remains contentious. Medications should be prescribed cautiously, as patients with nociplastic pain often exhibit heightened sensitivity to adverse effects. When used at low to moderate doses, these medications may offer meaningful effects for some and can have synergistic effects. However, routine escalation to maximal doses can have deleterious effects both in the short- and long-term for quality of life and functional outcomes.

Centrally-acting medications, such as tricyclic antidepressants (TCAs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and α2δ ligands are considered agents of choice, although central nervous system side effects may limit their use.[18] Whereas gabapentinoids are not recommended by guidelines for arthritis or spine pain, clinicians frequently prescribe low doses, especially at night, to primarily promote sleep and with some benefit for nocturnal pain.

Antidepressants increase concentrations of serotonin and norepinephrine in the presynaptic cleft and thereby modulate descending inhibitory pathways. Both the older TCAs and more recent SNRIs have been best studied, demonstrating short- to medium-term improvements in pain and quality of life. However, among these agents, duloxetine is the only medication identified as moderately effective across all outcomes at standard doses. Anticonvulsants primarily depress dorsal horn sensitivity via calcium channel regulation, leading to decreased release of pain-inducing neurotransmitters such as glutamate, substance P, and others, also exert effects on descending inhibitory mechanisms. Within the gabapentinoid class, studied largely in FM, pregabalin has shown a small benefit in reducing pain and improving sleep, but with high dropout rates and a number needed to harm of approximately 13.

Conventional pain-management agents, including acetaminophen, nonsteroidal anti-inflammatory drugs and opioids, have shown no benefit in nociplastic pain and are not recommended. Given the well-recognized risks inherent with the use of opioids, their use should be strongly discouraged. Although some studies do show a small reduction in pain and improved physical functioning with opioids, problematic use has been reported for over one third of patients. Given the personal and societal risks associated with opioid use, even small modest gains in pain reduction are currently viewed as unacceptable trade-offs. Cannabinoid-based products are

promoted as pain modulators, especially for nociplastic pain; however, high-quality clinical trials to support their effectiveness are lacking.

A range of novel pharmacologic and interventional treatments are currently under investigation for nociplastic pain, but none have sufficient evidence to recommend universal use. These include agents with N-Methyl-D-Aspartate antagonist properties, such as ketamine, dextromethorphan, memantine, and magnesium, as well as nutritional supplements such as N-acetyl cysteine and alpha lipoic acid. Paradoxically, low-dose naltrexone (an opioid antagonist) has shown some efficacy in select nociplastic conditions such as irritable bowel syndrome and FM. In addition, suzetrigine, a NaV1.8 blocker, currently indicated only for acute pain, may have promising potential for managing chronic pain.

Conclusion

Nociplastic pain is a pain phenotype that commonly overlaps with nociceptive pain across all rheumatic conditions and leads to substantial reductions in quality of life. Key clinical messages are summarized in **Box 3**. Recognition requires a heightened clinical alertness, prompted by the unique clinical characteristics of the pain, the presence of associated "central" symptoms such as fatigue, sleep disturbance, cognitive difficulties, and hypervigilance, along with physical findings suggestive of pain sensitization, in the absence of an objective biomarker to confirm diagnosis. Treatments should adopt a biopsychosocial approach, with emphasis on non-pharmacological strategies, and using pharmacologic therapies cautiously, as no single medication provides substantial benefit for the majority of patients.

Key Clinical Messages
Nociplastic pain is common and must be routinely considered in the context of rheumatic diseases.
Nociplastic pain commonly overlaps with underlying nociceptive pain (which is a trigger to pain sensitization).
Clinical reasoning is important because there are no biomarkers.
Non-pharacological treatments should be prioritized.

Box 3. Key clinical messages; *courtesy of Mary-Ann Fitzcharles, MD and Hance Clarke, MD.*

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The Emerging Role of IgG4 in Rheumatology

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Immunoglobulin G4 (IgG4) is the least abundant IgG subclass and possesses unique structural and functional properties, including Fab-arm exchange, weak complement activation, and reduced Fc receptor binding. These features confer a predominantly immunomodulatory profile that distinguishes IgG4 from other IgG subclasses. Historically associated with allergic responses and immune tolerance, IgG4 has gained increasing attention following the recognition of IgG4-related disease (IgG4-RD), a systemic fibroinflammatory condition characterized by tumefactive lesions, IgG4-positive plasma cell infiltration, and storiform fibrosis.

Beyond IgG4-RD, IgG4 responses have also been described in several rheumatic diseases, including rheumatoid arthritis, systemic lupus erythematosus, anti-neutrophil cytoplasmic autoantibody-associated vasculitis, and Sjögren disease. In these diseases, IgG4 may function as a marker of chronic immune activation, an immunomodulatory adaptation, or contribute to disease pathogenesis; however, its precise role remains poorly understood. Elevated serum IgG4 levels or tissue infiltration by IgG4+ plasma cells lacks disease specificity and should be interpreted within an appropriate clinical and histopathologic context.

This review summarizes the biological features of IgG4, its established association with IgG4-RD, and its emerging significance across rheumatic diseases. Understanding the context-dependent role of IgG4 may improve diagnostic interpretation and advance our understanding of immune-mediated disease in rheumatology.

Introduction

Immunoglobulin G (IgG) antibodies are divided into four subclasses: IgG1, IgG2, IgG3, and IgG4, each with distinct structural and immunologic functions. Among these subclasses, IgG4 is the least abundant, accounting for approximately 3–6% of total serum IgG.[1] Historically, IgG4 was considered a benign and anti-inflammatory immunoglobulin due to its poor ability to activate complement, weak Fc receptor binding, and limited ability to form stable immune complexes.

Interest in IgG4 was initially focused on allergic conditions and parasitic infections. Over the last two decades, however, evidence has shifted attention toward systemic autoimmune disorders following the recognition of IgG4-related disease (IgG4-RD).[2,3] Beyond IgG4-RD, accumulating evidence suggests that IgG4 responses are also present in a range of other conditions such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), anti-neutrophil cytoplasmic antibody-related vasculitis (AAV), and Sjögren disease (SjD).[4] Nevertheless, the precise role of IgG4 in these entities remains unclear—whether as a pathogenic driver, biomarker of chronic immune stimulation, or immunologic epiphenomenon. This review explores the biology of IgG4 and its expanding significance across rheumatology.

Biology of IgG4: Why Is It Different?

Structural and Functional Features

IgG4 is structurally and functionally distinct from other IgG subclasses due to its ability to undergo Fab-arm exchange, a dynamic process in which half-molecules are exchanged between antibodies, generating bispecific, functionally monovalent molecules.[1,5] This structural feature reduces effective cross-linking of antigens and limits immune complex formation. As a result, IgG4 demonstrates weak binding to activating Fc receptors and a limited ability to activate complement via C1q. Collectively, these properties

render IgG4 as the least pro-inflammatory IgG subclass.

Compared with IgG1 and IgG3, IgG4 has a limited capacity to mediate antibody-dependent cellular cytotoxicity or activate the classical complement pathway, further contributing to its "non-inflammatory" profile.[1] Functionally, IgG4 antibodies are considered "blocking antibodies" that are capable of competitively inhibiting antigen–antibody interactions and dampening effector immune responses rather than amplifying inflammation.

Immunological Context

IgG4 class switching is driven by T helper 2 (Th2) and T follicular helper (Tfh2) cells, with key mediators including interleukin (IL)-4, IL-10, and IL-21.[4] IL-4 and IL-13 promote class-switch recombination toward IgG4, while IL-10 and IL-21 further support plasma cell differentiation and IgG4 production. Regulatory T cells may also promote IgG4 production during chronic antigen exposure, supporting immune tolerance and limiting tissue injury.

A prevailing hypothesis proposes that IgG4 develops as an adaptive response to persistent antigen stimulation, such as chronic allergen exposure or infection, in which immune dampening may be beneficial.[6] In this model, the immune system gradually shifts toward a less inflammatory phenotype to limit tissue damage associated with persistent immune activation.

However, in IgG4-RD, the activation of Tfh cells and plasmablast populations suggest a dysregulated immune activation rather than a simple protective immune tolerance. This highlights the dual nature of IgG4: an antibody adapted to suppress inflammation that is also paradoxically associated with fibroinflammatory disease. Within rheumatology contexts, IgG4 is interpreted as a marker of chronic immune activation and immune dysregulation rather than a direct driver of inflammation.

IgG4-Related Disease: The Prototype

Clinical Overview

IgG4-RD is a systemic fibroinflammatory disorder characterized by immune activation, tumefactive lesions, and progressive organ damage. It is a rare condition typically affecting patients in the sixth decade of life, with male predominance. The incidence is 1.2 per 100,000 persons-year.[7] Commonly involved organs include pancreas and the biliary tree (48%), salivary glands (38%), lacrimal glands (26%), orbits (7%), kidneys (16%), lungs (14%), retroperitoneum (16%), lymph nodes (28%), and aorta (10%).[8] Multiorgan involvement is common, affecting two or more organ systems simultaneously in two thirds of the cases.[9]

Patients often present with subacute, painless swelling or enlargement of affected organs. Four clinical phenotypes have been described to encompass the usual presentations: **1)** pancreato-hepato-biliary, **2)** retroperitoneum and aorta, **3)** head and neck—limited, and **4)** Mikulicz syndrome and systemic.[8] Patients with IgG4-RD have a two-fold increase in mortality compared to the general population and remain at risk for chronic organ damage including pancreatic insufficiency, renal dysfunction, or development of arteria aneurysms.[7]

IgG4-RD frequently mimics infections, malignancy, or other inflammatory or infiltrative conditions, making diagnosis particularly challenging.

Histopathology and Diagnosis

Histopathologically, IgG4-RD is defined by a triad of dense lymphoplasmacytic infiltrates, storiform fibrosis ('cartwheel-shaped'), and obliterative phlebitis. Eosinophilic infiltration might also be present. Immunostaining demonstrates IgG4+ plasma cells, although different threshold counts apply depending on the specific tissue. An IgG4+/IgG plasma cell ratio ≥0.4 further supports the diagnosis.[10]

Importantly, neither the presence of IgG4-positive plasma cells in the tissue nor elevated serum IgG4 levels is specific for IgG4-RD. Similar infiltrates may occur in malignancy, vasculitis, infection, and other immune-mediated diseases. In addition, up to 30–40% of patients with biopsy-confirmed IgG4-RD may have normal serum IgG4 concentrations.[8] Elevated serum IgG4 levels may also be observed in allergic, infectious, and other autoimmune diseases. Therefore, serum IgG4 should be viewed as a supportive finding rather than a diagnostic marker.

Circulating plasmablasts can serve as biomarkers for disease activity and treatment response in IgG4-RD. Unfortunately, access to this test remains outside of routine clinical practice. Among patients with elevated baseline serum IgG4, changes in levels may help predict treatment response or disease flares, although less

consistently than plasmablast counts. Ultimately, diagnosis relies on histopathological confirmation in an appropriate clinical and radiologic context.[10] Although originally designed for research purposes, the 2019 American College of Rheumatology/European Alliance of Associations for Rheumatology (ACR/EULAR) classification criteria offer a good framework to exclude other mimicking conditions.[11]

Immunopathogenesis

The pathogenesis of IgG4-RD involves complex interactions among B cells, plasmablasts, T cells, and macrophages.[12] Antigen presentation in the germinal centres by Tfh lymphocytes and follicular dendritic cells initiates the immune response. However, only a limited number of these antigens have been identified. Subsequent B cell activation promotes plasma cell differentiation and immunoglobulin class switching toward IgG4 and Immunoglobulin E (IgE) production. Oligoclonal expansion of plasmablasts and CD4+ cytotoxic T lymphocytes (CTLs) is observed in peripheral blood and tissues.

Tissue injury and fibrosis arise by different mechanisms. CD4+ CTLs may contribute directly to tissue damage through cytotoxic pathways. CD4+ CTLs, macrophages, and plasma cells promote fibroblast activation and extracellular matrix deposition through profibrotic cytokine signalling.

The Role of IgG4: Marker or Mediator?

Despite its central role in the IgG-RD nomenclature, the exact pathogenic contribution of IgG4 remains unclear. Limited *in vitro* data support a direct pathogenic role for IgG4 itself. B cell depletion therapy has shown clinical improvement and marked plasmablast population reductions, yet serum IgG4 levels may remain elevated.[11] This temporal dissociation favours the possibility that IgG4 reflects ongoing immune activation as an epiphenomenon, rather than serving as the main driver of the disease.

From a clinical perspective, acknowledging the limitations of serum IgG4 is essential. Both tissue and serum IgG4 findings must be interpreted cautiously within the appropriate clinical, radiographic, and histologic context.

IgG4 in Other Rheumatic Diseases

Although IgG4 is strongly associated with IgG4-RD, increasing evidence suggests that IgG4 responses also occur across a broader spectrum of rheumatic diseases (**Table 1**).

Rheumatoid Arthritis

RA is a chronic autoimmune disease characterized by synovial inflammation, autoantibody production, and progressive joint destruction. Anti-citrullinated protein antibodies (ACPAs) and rheumatoid factor (RF) are RA's immunological hallmarks. While IgG1 is the most abundant form of ACPAs and RF, a significant portion of these autoantibodies belongs to the IgG4 subclass.[1] The role of IgG4 in RA remains controversial, as conflicting evidence supports both pathogenic and immunomodulatory effects.

On one hand, elevated IgG4-ACPA levels have been associated with higher disease activity, increased inflammatory markers, and more severe radiographic progression.[13] Furthermore, serum IgG4 levels in RA correlate with interleukin 6 levels.[14] These findings suggest that IgG4 may reflect persistent immune stimulation within chronic RA, potentially having a pathogenic role. On the other hand, persistent exposure to citrullinated antigens may promote Th2- and regulatory T cell-mediated cytokine signalling, thereby favouring IgG4 class switching. IgG4-ACPAs demonstrate a limited ability to activate complement because of weak C1q binding and reduced Fc receptor affinity compared to IgG1-ACPAs. Subclass switching to IgG4 in RA may represent an adaptive or compensatory immunoregulatory response that develops during chronic immune dysregulation and prolonged antigenic stimulation.[13] Consequently, the precise pathogenic role of IgG4-ACPAs remains uncertain.

Systemic Lupus Erythematosus

SLE is characterized by autoantibody production, immune complex deposition, and complement-mediated tissue injury.[15] In contrast to IgG1 and IgG3 autoantibodies, which strongly activate complement, IgG4 autoantibodies exhibit limited pro-inflammatory effector functions.

IgG4 anti-double-stranded DNA (anti-dsDNA) antibodies have been identified in patients with SLE, especially among those with lupus nephritis. Some studies suggest that, because IgG4 binds

Disease	IgG4 Findings	Clinical Relevance
IgG4-Related Disease	Elevated serum IgG4 levels; abundant IgG4+ plasma cells in affected tissues	Hallmark disease feature, although IgG4 likely reflects underlying immune dysregulation more than pathogenicity
Rheumatoid Arthritis	IgG4-ACPAs, IgG4-RF, and elevated serum IgG4 levels reported in some patients	Associated with chronic antigenic stimulation; may correlate with greater disease activity and structural damage
Systemic Lupus Erythematosus	IgG4 anti-dsDNA antibodies, particularly in lupus nephritis	May have a protective role because of limited complement activation, overall clinical significance remains uncertain
ANCA-Associated Vasculitis	IgG4 MPO-ANCA, PR3-ANCA, and occasional IgG4-rich tissue infiltrates	May contribute to disease activity; important source of diagnostic overlap with IgG4-RD
Sjögren Disease	Occasional IgG4+ plasma cells in salivary glands; serum IgG4 levels are usually normal	Major diagnostic mimic of IgG4-RD; clinicopathologic correlation is therefore essential
Other Rheumatic Diseases (*systemic sclerosis, inflammatory myopathies*)	Sporadic reports of elevated serum IgG4 levels and tissue infiltration	Likely reflects chronic inflammation and fibrosis rather than a disease-specific mechanism

Table 1. Clinical Relevance of IgG4 Across Rheumatic Diseases; *courtesy of Sinthiha Krishnan, MD and Andreu Fernández-Codina, MD.*

Abbreviations: ACPA: Anti-Neutrophil Cytoplasmic Antibody; **ANCA:** anti-neutrophil cytoplasmic antibodies; **dsDNA:** double-stranded deoxyribonucleic acid; **IgG4:** Immunoglobulin G 4; **IgG4-RD:** IgG4-related disease; **MPO:** Myeloperoxidase; **PR3:** Proteinase 3; **RF:** Rheumatoid factor

poorly to C1q, IgG4-containing immune complexes may generate less tissue inflammation within the skin, kidneys, and vasculature.[16] These observations have led to the hypothesis that IgG4 anti-dsDNA may represent an adaptive response to mitigate chronic immune activation in SLE. However, it remains to be established whether IgG4 contributes to disease modulation or merely simply reflects ongoing immune dysregulation.

Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis

AAV encompasses a group of necrotizing small vessel vasculitides characterized by the presence of anti-neutrophil cytoplasmic antibodies (ANCAs) in the serum. A subset of both anti-myeloperoxidase and anti-proteinase-3 ANCA belong to the IgG4 subclass. AAV includes granulomatosis with polyangiitis (GPA), eosinophilic granulomatosis with polyangiitis (EGPA), and microscopic polyangiitis.[17]

Experimental studies have shown that IgG4-ANCA can activate neutrophils and contribute to oxidative burst responses, suggesting a potential role in vasculitic injury.[18] However, the specific pathogenic contribution of IgG4-ANCA compared with other ANCA subclasses remains incompletely understood. In EGPA, elevated serum IgG4 concentrations may also reflect the underlying Th2-predominant immune response associated with asthma, eosinophilia, and allergic disease.[19] Thus, while the classical biologic properties of IgG4 suggest predominantly immunomodulatory functions, some observations support a potential pro-inflammatory role in selected settings.

The possibility of an overlap between AAV and IgG4-RD deserves particular consideration. Both diseases share similar anatomical sites, including the sinuses, orbits, lungs, or retroperitoneum.[20] Some patients with GPA exhibit increased IgG4-positive plasma cell infiltration in sinus and periorbital biopsy specimens, creating diagnostic challenges. Shared organ involvement and histopathologic findings must therefore be interpreted alongside distinguishing features such as necrotizing vasculitis and granulomatous inflammation, which are characteristic of AAV but not of IgG4-RD. Interestingly, both groups of diseases respond well to glucocorticoids and B cell depletion. True overlap syndromes have been reported, although their exact nature remains debated.

Importantly, the ACR/EULAR classification criteria explicitly exclude patients with AAV features.[11] Consequently, the presence of elevated serum IgG4 levels or tissue IgG4-positive plasma cells should not be considered sufficient evidence for IgG4-RD in the absence of compatible clinical and pathologic findings.

Sjögren Disease

SjD and IgG4-RD share several overlapping features, particularly involving the salivary and lacrimal glands. Both disorders may present with gland enlargement, and less often, interstitial nephritis. In contrast to IgG4-RD, patients with SjD will typically present with sicca symptoms, vasculitic manifestations, positive TROVE2/Ro60 and/or La autoantibodies, and normal or decreased serum IgG4 levels.[21] Furthermore, IgG4-RD lesions might affect other organs, such as the pancreas or retroperitoneum, which are not typically affected in SjD.

Histopathologic overlap may also occur. Salivary gland biopsies may occasionally demonstrate some IgG4+ plasma cells along with lymphocytic infiltrates in SjD. In IgG4-RD, however, IgG4+ plasma cells are usually more abundant, although storiform fibrosis and obliterative phlebitis might be absent in lacrimal and salivary glands specimens.[22] This reinforces the concept that IgG4+ plasma cell infiltration is not disease-specific. Instead, IgG4 responses may emerge across multiple chronic inflammatory states involving persistent immune activation and tissue remodelling.

Other Rheumatic Conditions

Elevated serum IgG4 levels and increased IgG4-positive plasma cell infiltrates have also been described in systemic sclerosis and inflammatory myopathies.[23] These findings are generally thought to reflect chronic inflammation and fibrosis rather than a specific pathogenic role for IgG4. However, the available evidence remains limited and does not allow definitive conclusions.

Future Directions

Future research on IgG4 should focus on the contexts in which it acts as an immunomodulatory molecule versus those in which it may contribute to disease pathogenesis across different rheumatic conditions. Advanced molecular techniques and a better understanding of B cell responses might help address this question. Additionally, reproducible and accessible biomarkers are needed to diagnose and monitor IgG4-RD. The emergence of B-cell targeted therapies such as inebilizumab and obeleximab will likely reshape the management of IgG4-RD while providing new insights into disease-pathogenesis.[24,25]

Conclusion

IgG4 emerges as an immunological adaptation during chronic antigen exposure and immune activation. Although IgG4 is closely associated with IgG4-RD, IgG4 responses have also been observed across a range of other rheumatic diseases. In most contexts, this response remains regulatory, whereas in others it might trigger inflammation and tissue damage. Understanding this duality remains key to interpreting the role of IgG4 across rheumatology.

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Background: *Large vessel vasculitis (LVV), encompassing giant cell arteritis (GCA) and Takayasu arteritis (TAK), causes granulomatous inflammation of large- and medium-sized arteries with potentially devastating ischemic complications. Glucocorticoids remain first-line therapy but carry significant long-term morbidity.*

Methods: *This narrative review synthesizes current evidence on the classification, diagnosis, monitoring, and management of LVV, incorporating data from randomized controlled trials, meta-analyses, and international guidelines.*

Results: *Advances in vascular imaging have improved diagnostic accuracy and increasingly supplement or replace temporal artery biopsy. In GCA, phase 3 trials have demonstrated that tocilizumab and upadacitinib have superior remission rates and glucocorticoid-sparing effects. In TAK, tumour necrosis factor inhibitors remain the preferred biologic for refractory disease, with emerging evidence supporting Janus kinase (JAK) inhibition and novel disease-modifying anti-rheumatic drug combinations.*

Conclusion: *Targeted therapies have transformed LVV management, though reliable biomarkers for disease activity and consensus on optimal treatment duration remain unmet needs.*

Keywords: *large vessel vasculitis, giant cell arteritis, Takayasu arteritis, tocilizumab, upadacitinib, glucocorticoid-sparing, JAK inhibitors*

Updates on the Treatment and Management of Large Vessel Vasculitis

Stephanie Garner, MD, MSc, FRCPC

Introduction

Large vessel vasculitis (LVV) is characterized by granulomatous inflammation of large- and medium-sized arteries and manifests as giant cell arteritis (GCA) and Takayasu arteritis (TAK). GCA affects individuals over the age of 50 years, and is the most common systemic vasculitis in Western populations, with an incidence of approximately 25 cases per 100,000 persons aged ≥50.[1] TAK predominantly affects young women, often of Asian or Latin American descent, with a global incidence of approximately 1.1 per million per year (95% confidence interval [CI] 0.70–1.76), though prevalence is substantially higher in Asian populations (up to 40 per million in Japan).[2]

Although GCA and TAK share a common basis of granulomatous arterial inflammation, they differ in genetic susceptibility, pathogenesis, and vascular manifestations.[3,4] Resultant vascular injury can lead to stenosis, aneurysm formation, and ischemic complications.[5] In GCA, prompt diagnosis and treatment are essential to prevent irreversible vision loss and stroke.[6] Glucocorticoids have long been the cornerstone of therapy for both conditions, but long-term use carries substantial adverse effects, including osteoporosis, diabetes, cataracts, cardiovascular disease, and weight gain.[7,8]

Over the past decade, management strategies have increasingly shifted toward glucocorticoid-sparing regimens, driven by advances in understanding disease pathogenesis, the availability of targeted biologics, and growing recognition of the harm caused by corticosteroids.

This review offers a clinically relevant, evidence-based update on LVV management, diagnostics, disease monitoring, pharmacological advances, and future therapeutic directions.

Classification and Pathophysiology

The American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) 2022 classification criteria for GCA and TAK incorporate modern imaging modalities (positron emission tomography [PET], ultrasound), weighted scoring systems, and revised age thresholds.[9,10] For GCA, the updated criteria markedly increase the sensitivity for extracranial disease from 24% to 92%.[11] In TAK, the age threshold was raised to ≤60 years, acknowledging that onset after age 40 occurs in 9–32% of patients.[10] Imaging evidence of large vessel vasculitis is now a mandatory entry requirement, along with patterns of arterial involvement.[10,12] Although not intended for diagnosis, accurate classification remains clinically important because treatment protocols and prognoses differ.

The pathophysiological differences between GCA and TAK have direct therapeutic implications. In GCA, the human leukocyte antigen (HLA) class II/CD4+ T-cell/IL-6 axis underlies the efficacy of tocilizumab and Janus kinase (JAK) inhibitors, while in TAK, the HLA class I/CD8+ T-cell/tumour necrosis factor (TNF)-α axis in TAK explains the clinical effectiveness of TNF inhibitors, which have not demonstrated similar benefit in GCA.[3,5]

Diagnosis and Disease Assessment

Clinical Presentation

GCA classically presents with new-onset headache, scalp tenderness, jaw claudication, and visual symptoms in patients aged over 50 years.[5,13] Visual complications are broad and can include arteritic anterior ischemic optic neuropathy, amaurosis fugax, and diplopia.[14] Early ophthalmology involvement is critical. Systemic features (fever, weight loss) are common, and polymyalgia rheumatica co-occurs in 40–60% of cases.[15] Jaw claudication has the highest positive likelihood ratio (+LR 4.90) for predicting GCA, though diagnostic delay is frequent given the often non-specific symptom profile.[16]

In contrast, TAK presents insidiously, with constitutional symptoms, limb claudication, asymmetric blood pressures, diminished pulses, bruits, and hypertension.[5,12] Diagnostic delays are common, particularly given the younger demographic, and the disease is often discovered incidentally on imaging.

Biomarkers and Laboratory Assessment

C-reactive protein (CRP) and erythrocyte sedimentation rate are standard surrogate markers for disease activity in LVV. A normal CRP provides the strongest negative likelihood ratio (−LR 0.40; 95% CI 0.29–0.56) for excluding GC.[16] In TAK, however, active disease can occur despite normal inflammatory markers. Disease activity determined solely by clinical assessment and acute-phase reactants correlates poorly with histopathologic activity, and new arterial lesions have been observed in 61% of patients considered clinically inactive.[12,17] Notably, CRP is unreliable for monitoring in patients receiving interleukin (IL)-6 inhibitors, as CRP production is directly IL-6–dependent.

Temporal Artery Biopsy

Temporal artery biopsy (TAB) has a sensitivity of approximately 85–95% in clinically suspected GCA, though diagnostic yield is diminished by short segments, skip lesions, and extracranial disease.[6] Contrary to traditional teaching, the 2-week window for biopsy following steroid initiation is not supported by evidence. A prospective study of follow-up biopsies in treated patients demonstrated unequivocal vasculitis in 70% at 3 months, 75% at 6 months, and 44% at 12 months after treatment initiation,

with lymphocytic infiltrates persisting even as granulomatous features diminished over time.[18] Additional studies have shown that biopsies are consistently positive for at least 6 weeks after treatment initiation.[19] Glucocorticoids should never be delayed while awaiting biopsy. Although imaging has an increasing role in diagnosis, biopsy-confirmed GCA has been associated with higher rates of visual loss (9.7% vs 2.4%).[20]

Imaging in LVV

Imaging has increasingly replaced TAB and is recommended over other imaging modalities for diagnosing GCA.[21] Ultrasound of the temporal and axillary arteries demonstrating the "halo sign" (hypoechoic mural edema) achieves sensitivity and specificity comparable to biopsy.[21] "Fast Track" ultrasound clinics using this approach have been implemented in several centres to reduce diagnostic delay and support point-of-care diagnostics.[22]

PET offers excellent sensitivity for large vessel involvement in both GCA and TAK and is increasingly used for diagnosis and monitoring.[21] Magnetic resonance imaging/magnetic resonance angiography (MRI/MRA) is preferred for aortic and branch-vessel assessment in TAK, given its spatial resolution and avoidance of ionizing radiation in a younger population. computed tomography angiography (CTA) remains valuable for emergency evaluation and structural vascular complications. Temporal artery MRA (TAMRA) shows promise, particularly as a rule-out test, but uptake is limited by the availability of 3T MRA and radiologist expertise.[21]

Currently, no standardized guidelines exist for the frequency of monitoring using imaging in these populations; therefore, decisions should be made on an individual basis.

Investigative Algorithms

Given the heterogeneous presentation of GCA, pre-test probability tools have been developed to improve diagnostic accuracy. The halo count-GCA (HAS-GCA) algorithm combines the giant cell arteritis probability score (GCAPS) clinical score with temporal artery ultrasound (TAUS) to classify 74% of patients as either low or high probability, thereby reducing the need for additional testing (**Figure 1**).[23]

Treatment of Giant Cell Arteritis

Glucocorticoids

High-dose glucocorticoids remain the first-line treatment for GCA: oral prednisone 40–60 mg/day without visual involvement, or intravenous methylprednisolone (500–1000 mg/day for 3 days) when visual loss or ischemic complications are present, followed by oral therapy.[6] Traditional tapering over 12–18 months carries high relapse rates (40–50%), and cumulative steroid exposure drives significant morbidity.[24,25] Vision loss during treatment is uncommon (2.2%); new visual symptoms should prompt a broad evaluation, including consideration of corticosteroid-related causes such as cataracts and glaucoma.[26]

Steroid-Sparing Agents

Steroid-sparing therapies are now considered the standard of care for patients with GCA, with current treatment options outlined in **Table 1**. The ACR guidelines suggest starting steroid-sparing therapies in all patients.[6]

Other targeted therapies remain under investigation. Abatacept demonstrated improved relapse-free survival in a small, randomized trial of GCA, supporting the role of T-cell co-stimulation in disease pathogenesis, although evidence remains limited compared with that for IL-6 and Janus kinase (JAK) inhibition.[27]

Data from the GiACTA and SELECT-GCA extension studies support the concept that GCA requires prolonged immunosuppression (prednisone, steroid-sparing agents) in many patients.[28,29] Current guidelines recommend individualized decision-making regarding treatment duration, with some patients discontinuing after 1–2 years while others require indefinite therapy to prevent relapse.[6]

Treatment of Takayasu Arteritis

Conventional Immunosuppression

Glucocorticoids (1 mg/kg/day; maximum 60 mg/day) remain the cornerstone of initial treatment for TAK; however, relapse rates of 50–80% during dose tapering necessitate the early addition of a steroid-sparing agent.[6,30]

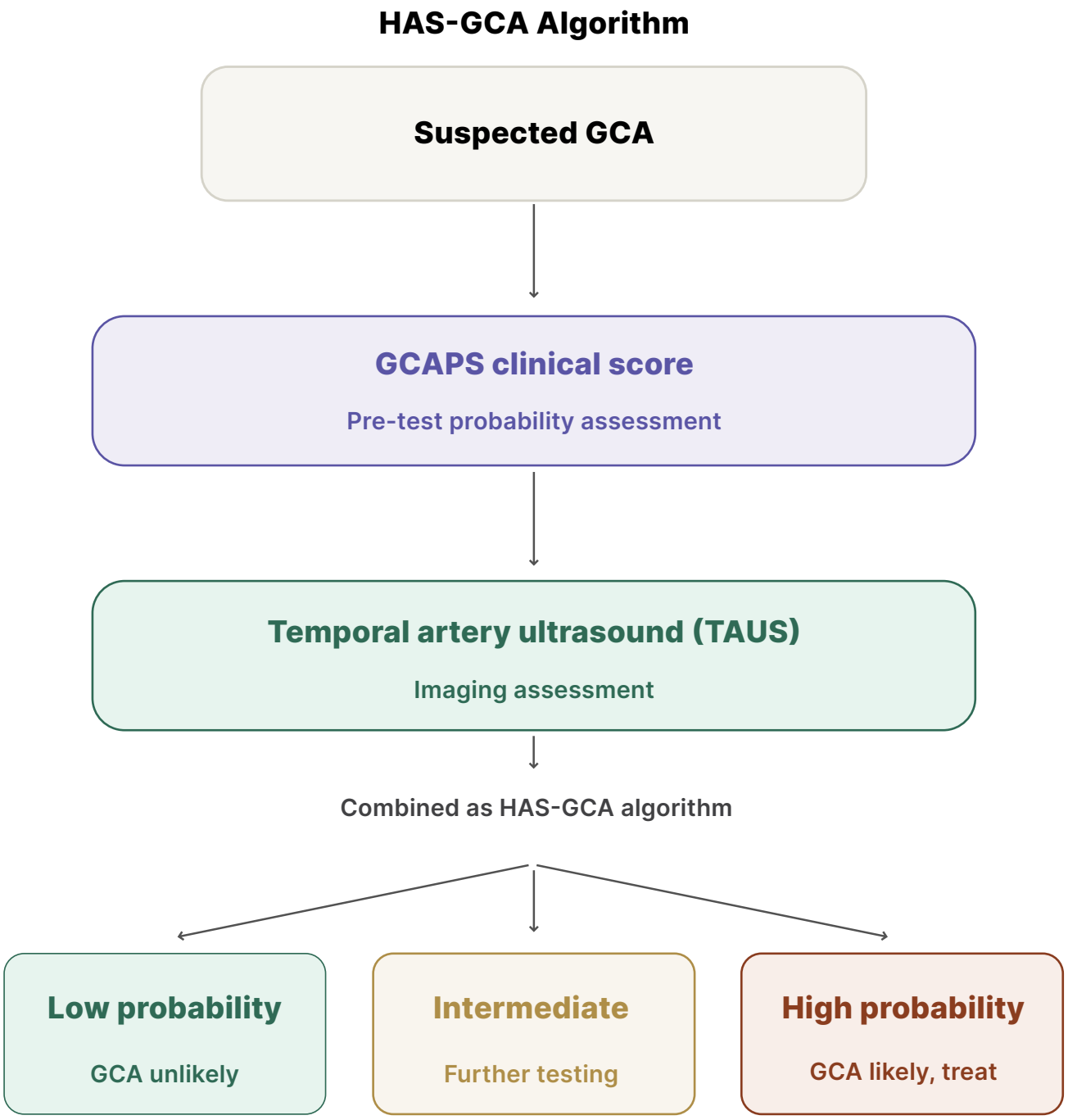

Figure 1. HAS-GCA Algorithm; *adapted from Sebastian, 2024.*[23]

Abbreviations: GCA: Giant Cell Arteritis; **GCAPS:** Giant Cell Arteritis Probability Score

Feature	Tocilizumab	Upadacitinib	Methotrexate	Leflunomide
Drug class	Anti-IL-6R monoclonal antibody	Selective JAK inhibitor	Conventional DMARD (antimetabolite)	Conventional DMARD (pyrimidine synthesis inhibitor)
Route	SC (162 mg weekly)	Oral (15 mg daily)	Oral/SC (10–25 mg weekly)	Oral (10–20 mg daily)
Landmark trial	GiACTA (phase 3, n=251)	SELECT-GCA (phase 3, n=428)	3 RCTs (n=21–98); IPD meta-analysis	Observational studies only
Sustained remission at 52 weeks	56% vs 14% placebo (P=0.001)[28]	46.4% vs 29.0% placebo (P=0.002)[29]	Modest relapse reduction (HR 0.65, P=0.04)[38]	~60% achieved at least partial remission (meta-analysis of 7 studies)[11]
GC-free remission	42% maintained drug-free remission over a 2-year extension	50.2% vs 19.6% at week 52 (P0.001)[29]	HR 2.8 vs placebo (P=0.001)[38]	53% discontinued GCs entirely[11]
Median cumulative GC dose (52 weeks)	1,862 mg vs 3,296 mg placebo[28]	1,615 mg vs 2,882 mg placebo[29]	−1.1 g reduction at 96 weeks (20–44% reduction)[38]	Mean reduction of 15.6 mg/day[11]
GC taper in trial	26-week taper[28]	26-week taper[29]	Variable (concurrent with GCs)[38]	Variable[39]
Key safety concerns	Infections, GI perforation, hyperlipidemia; masks CRP[40]	Herpes zoster, theoretical MACE/VTE (none observed in trial)[29,37]	Hepatotoxicity, cytopenias, nausea,	GI symptoms, hepatotoxicity, 19–25% discontinuation rate[11]
CRP monitoring reliability	Unreliable (IL-6 pathway suppressed)	Partially suppressed but more reliable than TCZ[37]	Reliable	Reliable
Level of evidence	High (phase 3 RCT + 3-year extension)[28,36]	High (phase 3 RCT + extension ongoing)[29,37]	Moderate (3 small RCTs with mixed results)[38]	Low (observational only; phase 3 RCT recruiting)[41]
Guideline positioning	First-line steroid-sparing agent[6]	Alternative to TCZ	Option if biologics inaccessible/contraindicated	Alternative if MTX is not tolerated

Table 1. GCA Treatment Options; *courtesy of Stephanie Garner, MD, MSc, FRCPC.*

Abbreviations: CRP: c-reactive protein; **DMARD:** disease-modifying anti-rheumatic drugs; **GC:** glucocorticoid; **GCA:** giant cell arteritis; **GI:** gastrointestinal; **HR:** hazard ratio; **IL:** interleukin; **IPD**: individual participant data; **JAK:** Janus kinase; **MACE:** major adverse cardiac events; **MTX:** methotrexate; **RCT:** randomized controlled trial; **SC:** subcutaneous; **TCZ:** tocilizumab; **VTE:** venous thromboembolism

Conventional disease-modifying anti-rheumatic drugs (DMARDs) remain first-line, with methotrexate most frequently used.[6] In a recent randomized trial (n=111), mycophenolate mofetil plus methotrexate was superior to cyclophosphamide/azathioprine (overall response 55% vs 32% at 52 weeks, P=0.022), providing the first high-quality evidence favouring a specific conventional DMARD combination in TAK.[31]

Biologic DMARDs are recommended for refractory or severe disease. TNF inhibitors have the strongest supporting evidence and are preferred in the 2021 ACR guidelines[6], with a large multicenter study (n=209) demonstrating 3-year relapse-free survival of 90.9% versus 58.7% with conventional DMARDs.[32] Tocilizumab showed benefit in the TAKT trial extension despite failing its primary endpoint, and a 2023 meta-analysis reported comparable efficacy between TNF inhibitors and tocilizumab.30 JAK inhibitors are an emerging option, though long-term data remain limited.[5,30,33]

Vascular Interventions

Surgical and endovascular interventions, including angioplasty, stenting, and bypass grafting, may be required for hemodynamically significant stenoses or occlusions in TAK. These procedures should be performed during disease remission, when possible, to reduce the risk of restenosis, with perioperative glucocorticoid coverage and postoperative surveillance.

Monitoring of Disease Activity

In GCA, ongoing imaging monitoring is indicated primarily for those with documented large-vessel disease to identify stenoses, aneurysms, or structural progression.[6] FDG-PET can assess inflammatory burden and identify large vessel involvement; however, findings are not specific to active inflammation and require clinical correlation.[6,34] The 2026 French recommendations propose Doppler ultrasound as the first-line imaging modality for suspected relapse and structural monitoring, with FDG-PET, MRI, and CT as alternative options.[34]

A caveat to this is that monitoring disease activity during tocilizumab therapy is challenging because CRP, no longer a reliable marker, and PET findings often show clinical-radiographic dissociation. Complete PET normalization occurs in only a minority of patients, even in clinical remission.[35] Treatment decisions should therefore be guided by clinical assessment and structural imaging rather than isolated PET findings in asymptomatic patients.

For TAK, regularly scheduled non-invasive imaging (MRA, CTA, or FDG-PET) is conditionally recommended in addition to clinical assessment, as vascular changes can occur during clinically quiescent disease.[6] Follow-up imaging frequency ranges from every 6 to 24 months, depending on disease activity, with shorter intervals early in the disease course.[5]

Special Considerations

Glucocorticoid Toxicity Mitigation

All patients initiated on glucocorticoid therapy for LVV should receive concurrent prophylaxis for glucocorticoid-induced osteoporosis, along with blood pressure monitoring, glycemic surveillance, and ophthalmological follow-up. Lipid profiles, bone mineral density assessment, and vaccinations (pneumococcal, influenza, and herpes zoster) should be addressed at disease onset.

Pregnancy and LVV

TAK disproportionately affects women of reproductive age, and pregnancy in the setting of active or recently active vasculitis carries elevated maternal and fetal risks, including hypertension, preterm delivery, and small-for-gestational-age infants. Close collaboration among rheumatology, obstetric medicine, and maternal-fetal medicine is essential.

Conclusion and Future Directions

The management of LVV has evolved substantially with advances in imaging, disease classification, and targeted therapies. In GCA, IL-6 and JAK inhibition have significantly reduced glucocorticoid exposure while improving disease control. In TAK, biologic therapies, particularly TNF inhibitors, have expanded treatment options for patients with refractory disease.

Despite these advances, important challenges remain, including the lack of reliable biomarkers for disease activity, uncertainty regarding optimal treatment duration, and the need for better decision-making tools to monitor vascular inflammation and damage. Future research will focus on precision medicine approaches, novel targeted therapies, and improving long-term outcomes while minimizing treatment-related toxicity. Continued advances in

immunopathogenesis and imaging are expected to further refine the diagnosis and management of both GCA and TAK.

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Vaccination in Adult Patients with Rheumatic Diseases: A Practical Guide for Canadian Rheumatology Practice

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Introduction

Vaccination remains one of the most effective interventions to reduce morbidity and mortality in patients with rheumatic and musculoskeletal diseases. Individuals with autoimmune inflammatory rheumatic diseases face an increased risk of infection due to both immune dysregulation and immunosuppressive therapy.[1]

This article summarizes current recommendations on the vaccination of patients with rheumatic diseases put forth by the National Advisory Committee on Immunization (NACI).[2] NACI is a national advisory committee that develops recommendations for the use of vaccines in Canada. These recommendations are reviewed and implemented by provincial and territorial public health authorities; thus, publicly funded schedules may differ between jurisdictions. It is recommended that all practitioners review their local guidelines prior to administration of vaccines.

In addition, this article incorporates recommendations from the Canadian Rheumatology Association[1] and American College of Rheumatology[3] where they align with NACI guidance.

General Principles

Non-live vaccines are recommended for most immunocompromised patients; however, the efficacy of these vaccines may be decreased as a result of immunosuppression.

- Live-attenuated vaccines should generally be deferred in patients receiving significant immunosuppression given the risks for infectious complications (see **Table 1**).[3]
- Methotrexate may be held for 2 weeks after influenza vaccination if disease activity permits; methotrexate has been found to significantly blunt immunogenicity of the influenza vaccine.[3]
- Most other immunosuppressive medications can be continued around the time of non-live vaccination.[3]
- Patients taking B-cell depleting therapies (most commonly rituximab, but also ocrelizumab, ofatumumab, and obinituzumab) should ideally time vaccination for when the next rituximab dose is due, and then hold rituximab for at least 2 weeks after vaccination.
- Individualized decision-making is essential to balance disease control and vaccine response.

Live Attenuated Vaccines Available in Canada
MMR(V): measles, mumps, rubella, (varicella)
Varicella (chickenpox)*
Influenza (nasal spray only)
Rotavirus
Yellow fever
Typhoid (oral only)
Tuberculosis: BCG (Bacillus Calmette-Guérin)

Table 1. Canadian Rheumatology Association: Live Attenuated Vaccines Available in Canada.[1]

Influenza

Annual influenza vaccination is recommended for all individuals aged 6 months and older. Influenza immunization is particularly important for individuals who are immunocompromised or who have chronic health conditions that are associated with increased risk of influenza-related complications.[4]

COVID-19

Moderately to severely immunocompromised individuals should receive two COVID-19 vaccine doses per year. mRNA vaccines are preferred in immunosuppressed patients.

Vaccine response may be reduced in patients receiving anti-CD20 therapy, mycophenolate, glucocorticoids, abatacept, Janus kinase inhibitors, and antimetabolites. Supplemental doses improve immunogenicity in many patients.

Vaccination should proceed regardless of prior infection.[4]

Herpes Zoster (Shingrix®)

Recombinant zoster vaccine (RZV) is strongly recommended for immunocompromised individuals aged 18 years and older, and is administered 2–6 months apart.

Ideally, the series should be completed at least 14 days before initiating immunosuppressive therapy. If needed, the second dose can be administered at a minimum of 4 weeks after the first dose.[4]

RZV should be offered to individuals who have been exposed to varicella-zoster virus through either previous varicella infection or vaccination. For individuals known to be susceptible to varicella infection, providers should refer to current varicella vaccine recommendations in the Canadian Immunization Guide[4] for further guidance. Live vaccines including varicella vaccine are contraindicated for many immunocompromizing conditions.[5]

Pneumococcal Vaccination

A single dose of pneumococcal conjugate vaccine (Pneu-C)-20 or Pneu-C-21 is recommended for adults 65 years and older and for adults under 65 with certain current or previous immunocompromizing conditions. One dose of either Pneu-C-20 or Pneu-C-21 should be administered regardless of pneumococcal vaccination history with Pneu-C-13, Pneu-C-15, or Pneu-P-23.[4]

Human Papillomavirus (HPV)

HPV vaccination is recommended for all individuals 9 to 26 years of age and is recommended for individuals 27 years of age and older who are at ongoing risk of exposure to HPV. Immunocompromised individuals require a 3-dose schedule.[4]

Respiratory Syncytial Virus (RSV)

A single RSV vaccine dose is recommended for adults 75 years and older and may be considered on an individual basis for those aged 50–74 years after discussion between the patient and their health care provider.[4]

Measles (MMR – Live Vaccine)

Live-attenuated vaccines should generally be deferred in patients on immunosuppressive therapy.

During outbreaks, vaccination recommendations may expand. If immunization status is unknown, vaccination is preferred over serologic testing.[4]

Tetanus / Td / Tdap

Adults should complete a primary tetanus series and receive Td booster doses every 10 years. One single does of Tdap is recommended in adulthood if not previously administered.[4]

Conclusion

Vaccination is a core component of preventive care in rheumatology. When appropriately timed, most recommended vaccines are safe for use in immunocompromised patients. Depending on the nature of the rheumatologic condition or immunosuppressive therapy, additional doses of vaccination may be required to achieve sufficient immunogenicity.

Proactive vaccine review, medication coordination, and patient education significantly reduce preventable infectious morbidity in patients with rheumatic diseases.

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