ReFlections

RGA's Global Medical Newsletter

Volume 56, May 2022

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IN THIS ISSUE

FROM THE EDITORS

Welcome to the May 2022 issue of *ReFlections!* As always, we hope you, your families, and your loved ones continue to be safe and well.

This issue's articles provide updates and insights for a range of conditions. **Dr. Newman Harris**, Consulting Chief Medical Officer, RGA Australia, and a long-time contributor to *ReFlections*, offers an in-depth look at the expanding and evolving understanding of the mechanisms of pain. **Sandeepan Basu**, Deputy Chief Manager, Global Underwriting Research and Manual Development, RGA India, returns to *ReFlections* with a comprehensive review of rheumatoid arthritis. Rounding out the issue is first-time *ReFlections* author **Dr. Preeti Dalawari**, Vice President and Medical Director, U.S. Mortality Markets, whose article focuses on multi-parametric MRI and how it is changing and enhancing prostate cancer diagnostics.

The Longer Life Foundation, RGA's research collaboration with Washington University School of Medicine in St. Louis, is launching a new video series initiative and continues to sponsor its Grand Rounds series. The Foundation's 25th year will be celebrated in 2023 – stay tuned for information about planned activities.

We hope you find this issue interesting and informative. Please don't hesitate to let us know how we can continue to improve *ReFlections* for you.

Dan and Adela

MULTIPARAMETRIC MRI AND PROSTATE CANCER

Abstract

Multiparametric magnetic resonance imaging (mpMRI) is an imaging tool with growing utilization in diagnosis, risk assessment, and management of individuals with prostate cancer. This article examines the current challenges with prostate cancer detection and diagnosis, how the mpMRI tool has been incorporated clinically into the process, and how it is impacting insurance medicine risk assessment. The use of mpMRI overcomes some of the limitations of the prostate-specific antigen (PSA) test and the transrectal ultrasound guided biopsy (TRUS) in prostate cancer's diagnostic pathway.

Introduction

Prostate cancer (PCa) is the second leading cancer diagnosis for men worldwide.[1] In the U.S., it is the leading cancer diagnosis in men and the second leading cause of death.[2] While PCa's overall U.S. five-year survival rate is excellent at 98%, the disease at more advanced stages has a 30% five-year survival rate.[2]

The Prostate Testing for Cancer and Treatment (ProtecT) feasibility study, a randomized controlled trial, found that 95% of men with low and intermediate risk localized prostate cancer do not die of it within 10 years, irrespective of treatment.[3] Because PCa can be slow-growing and indolent, differentiating those cases from the more aggressive prostate cancers that are more likely to lead to mortality is important.

The limitations of the PSA test's sensitivity and specificity as well as indiscriminate use of the test in those who may not benefit from detection, static cutoff values guiding biopsy recommendations, and poor decision-making regarding treatment of low-grade disease, has led to PCa's overdiagnosis and overtreatment, especially in the U.S.[4]

Within the past decade, multiparametric magnetic resonance imaging (mpMRI) has gained traction as a valuable adjunct in PCa risk stratification. While there are many current and potential future indications for its use (staging, therapy selection, local recurrence detection, and active surveillance), this article focuses on its value in the pathway to PCa diagnosis.

Limitations of Traditional Tools for PCa Detection

Total PSA has long been the primary screening test for PCa. It is used in conjunction with a digital rectal exam (DRE) to help determine which patients who may be at risk for prostate cancer to biopsy. Given the operating (sensitivity and specificity) characteristics of the test and the confounding diagnoses that can lead to PSA elevation, the positive predictive value (PPV) of PSA for PCa ranges from 25% to 40%.[5] Secondary tests, including PSA kinetics and derivatives such as PSA velocity and PSA density, biomarkers such as urinary PCA3, and clinical algorithms, have been developed to improve PSA sensitivity and specificity.

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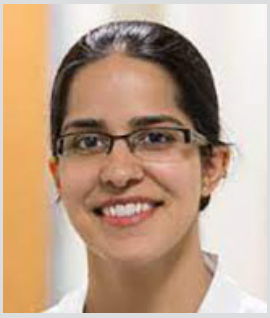

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As Vice President and Medical Director for RGA's U.S. Mortality Markets division, Dr. Preeti Dalawari provides expert case consulting and underwriter education for RGA clients, as well as manual and guideline development within the U.S. market. A board-certified Emergency Medicine physician, she is an experienced clinician and educator, and she continues to serve as a volunteer professor of surgery at Saint Louis University (SLU) School of Medicine.

Dr. Dalawari received her Bachelor of Science (B.S.) degree from Pennsylvania State University and her Doctor of Medicine (M.D.) from Jefferson Medical College in a six-year combined undergraduate and medical school degree program. She completed a three-year residency in emergency medicine at the Christiana Care Health System in Newark, Delaware, and received a Master of Science in public health and epidemiology (M.S.P.H.) from Saint Louis University School of Public Health and Social Justice.

Prior to joining RGA in 2020, Dr. Dalawari had more than 14 years of clinical experience at SLU, including nine years as Research Director in its Division of Emergency Medicine. During that time, she published more than 25 articles and edited an inaugural textbook on Social Emergency Medicine. Dr. Dalawari currently enjoys academic pursuits through The Longer Life Foundation, a collaboration of RGA and Washington University in St. Louis School of Medicine, for which she serves as Deputy Managing Director as well as Director of Member Engagement.

Transrectal ultrasound guided biopsy (TRUS) is currently the standard procedure used for prostate biopsy. A drawback of it, however, is that it is blind, meaning that the ultrasound lacks the capability to distinguish abnormal from normal tissue in order to know exactly where and what to biopsy. A systematic approach is therefore used to obtain three cores from each of the four zones of the prostate. Even so, sampling error can lead to nondetection of 20% to 50% of clinically significant prostate cancer (csPCa) in a first biopsy.[6] Although there is some variation in the literature in defining a csPCa, most studies agree it is a lesion predicted to be Grade Group (GG) of 2 or higher (equivalent to a Gleason score of 3+4=7). Serial TRUS biopsies also do not have an increased cancer detection rate.[4]

Table 1: Equivalent Grade Groups and Gleason Scores

Grade Group	Gleason Score
1	6
2	7 (3+4)
3	7 (4+3)
4	8
5	9-10

At the same time, estimates suggest that approximately 30% of PCa cases when first identified are slow-growing and indolent. Hence, there is the possibility of offering active surveillance rather than treatment for a low-risk subset of patients.[7]

There is also a need to more effectively identify patients who might benefit from a biopsy to detect significant prostate cancers while reducing unnecessary detection and biopsies of indolent cancers.[6]

mpMRI: What It Is

mpMRI combines anatomical sequences of T1- and T2-weighted MRI images with functional sequences (diffusion-weighted and dynamic contrast-enhanced images) in order to obtain three-dimensional images of the prostate.[5, 6] The findings are then classified using the Prostate Imaging-Reporting and Data System (PI-RADS), which is currently in version 2.1 (the original was first released in 2011, and it has had two revisions since then). A higher PI-RADS score indicates higher suspicion of clinically significant malignancy (Table 2). Lesions at higher risk for prostate cancer are then biopsied, using a variety of techniques.

Table 2: Prostate Imaging-Reporting and Data System (PI-RADS) – Classifications

PI-RADS	Likelihood of Cancer
PI-RADS 1	Very Low: clinically significant cancer is highly unlikely
PI-RADS 2	Low: clinically significant cancer is unlikely
PI-RADS 3	Intermediate: clinically significant cancer is equivocal
PI-RADS 4	High: clinically significant cancer is likely
PI-RADS 5	Very High: clinically significant cancer is highly likely

Source: https://www.radiologyinfo.org/en/info/article-prostate-mri-report

mpMRI in the Clinical Diagnostic Pathway

Many studies have shown that mpMRI- and MRI-guided biopsies detect clinically significant prostate cancer (csPCa) and have decreased detection rates for clinically insignificant cases. There is, however, wide heterogeneity in these studies.[4, 8] A 2019 metanalysis, for example, noted that average PPVs for GG ≥2 lesions are 12%, 48%, and 72%, which correlate to PI-RADS scores of 3, 4, and 5, respectively. Another meta-review of 43 studies noted pooled sensitivity and specificity for mpMRI of 91% and 37%, respectively, for GG ≥2 lesions.[6, 8]

The European Association of Urology (EAU) was an early adopter of mpMRI technology for prostate cancer investigation. Currently, practice guidelines from the EAU and the American Urological Association include use of mpMRI as an adjunct in risk stratification for biopsy-naïve patients (pre-biopsy) as well as for those with rising PSA levels or other markers of persistent clinical suspicion following an initial negative TRUS biopsy.[4, 8]

mpMRI- and MRI-guided biopsies detect clinically significant prostate cancer (csPCa) and have decreased detection rates for clinically insignificant cases.

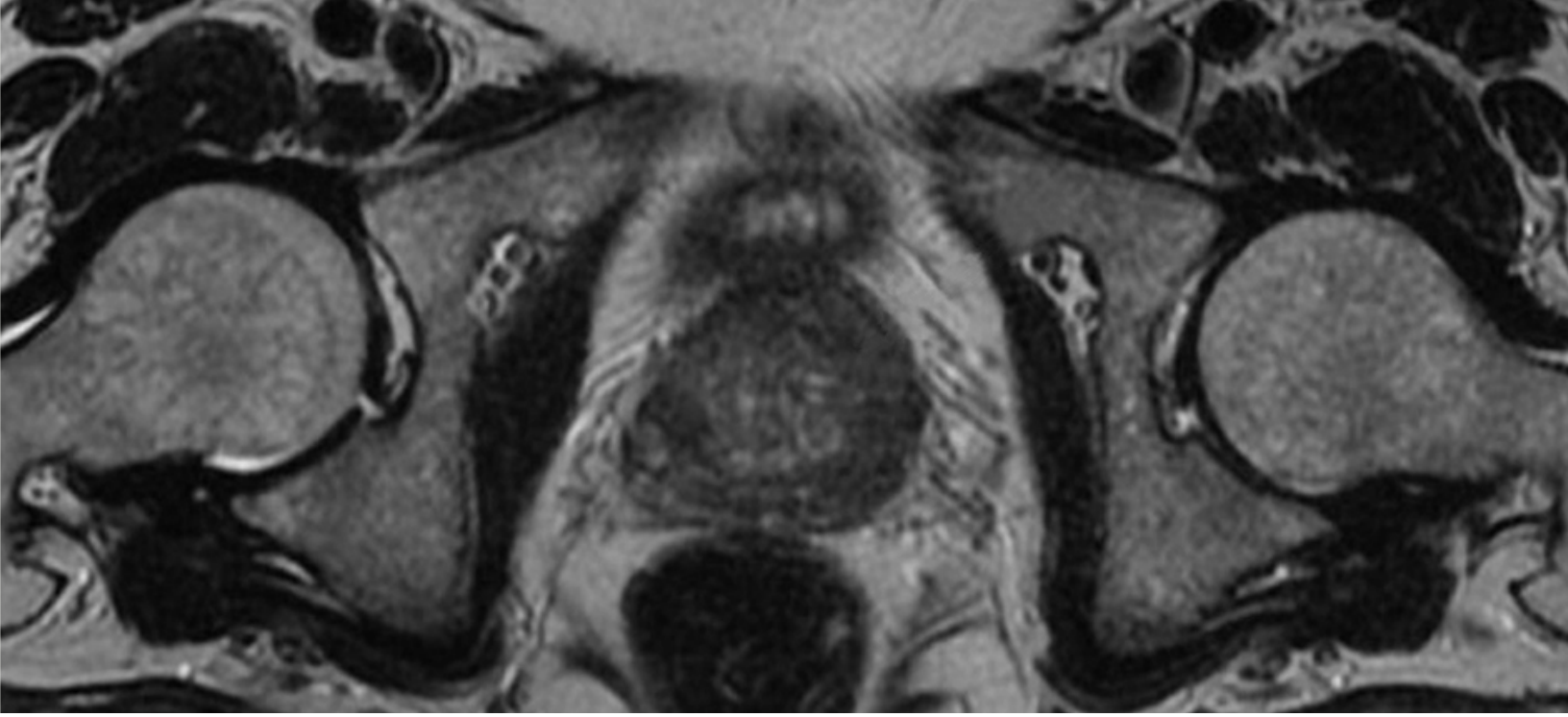
The ability to forego biopsy for those with low risk scores (PI-RADS ≤2) varies by urologic society guidelines, patient characteristics, and ultimately comes down to a decision shared by doctor and patient.

Prebiopsy/Biopsy-Naïve Settings

The three landmark studies commonly cited in favor of the use of mpMRI in prebiopsy/biopsy-naïve patients are: PROMIS (PRostate Magnetic resonance Imaging Study); PRECISION (PRostate Evaluation for Clinically Important disease, Sampling using Image-guidance Or Not?); and the MRI-FIRST trials.

- PROMIS, a prospective multicenter paired-validation cohort study, assessed the efficacy of mpMRI versus that of TRUS-guided systematic 12-core biopsy and the study's reference standard of the template prostate-mapping (TPM) biopsy, in detecting clinically significant prostate cancers and reducing unnecessary biopsies. Study subjects were biopsy-naïve patients in whom there was viable clinical suspicion of PCa (due to elevated PSA levels, abnormal DRE, or a family history of PCa). Of the 576 men who underwent all three tests, 71% had prostate cancers detected by TPM, but only 40% were deemed clinically significant PCa (defined as a Gleason score of ≥4 + 3 [Grade Group 3] or a cancer core length of at least 6 mm). mpMRI tests were found to have a sensitivity of 93% versus 48% for TRUS. Using a broader definition of clinically significant as GG ≥2 or a cancer core length of at least 4 mm, the negative predictive value (NPV) for low-suspicion mpMRI was 74%. The authors concluded that using mpMRI to stratify risk prior to biopsy may reduce unnecessary biopsies by 27%, and that 18% more clinically significant cases of PCa may be detected compared to the TRUS biopsy.[9, 10]
- PRECISION was a noninferiority trial that randomized 500 biopsy-naïve men to either a TRUS systematic (i.e., blind) or a targeted (mpMRI followed by MRI-guided) biopsy in those with clinical suspicion of PCa. The trial sought to determine which method might be more effective for detecting clinically significant (defined as GG ≥2) prostate cancer. Clinically significant PCa was detected in 38% of men in the targeted biopsy cohort compared to 26% of the systematic biopsy cohort, and 13% less clinically insignificant (GG=1) cancer was detected in the targeted cohort. However, 28% (n=71) of the men whose cancers were classified as PI-RADS 1 and 2 were not biopsied, calling into question the mpMRI's NPV of 88.1%, and both targeted and systematic biopsies were not performed in the mpMRI-targeted cohort.[9]
- MRI-FIRST was a prospective multicenter trial designed to investigate whether undergoing an mpMRI before a biopsy might improve csPCa detection in biopsy-naïve patients. The trial determined there was no significant difference in csPCa detection for systematic vs. targeted biopsy, but detection was higher when techniques were combined.[4, 11]

A 2020 systematic review by Sathianathen *et al*. investigating the NPV of mpMRI for csPCa (GG ≥2) in prebiopsy/biopsy-naïve patients noted a NPV of 91%. Still, in approximately 7% to 10% of cases, an mpMRI will fail to detect a csPCa without a subsequent biopsy due to



reading failure, invisibility of lesions on mpMRI, or because the lesion was missed in the targeted biopsy.[8, 12] Because of this, additional clinical indicators such as family history, pretest probability of PCa, and risk calculator scores are combined with lower PI-RADS scores to further stratify the risk. For example, adding a low PSAD (prostate specific antigen density) level (≤0.15 ng/ml/cc) can improve the NPV of the mpMRI.[8]

Repeat Biopsy Setting

mpMRI is recommended for individuals with persistent clinical suspicion (such as rising PSA levels) after a negative TRUS biopsy, if available, to decrease sampling error. For suspicious lesions on an mpMRI (PI-RADS ≥3), for example, a targeted biopsy is recommended that would sample the detected lesions, and there would be questionable value for an added systematic biopsy.[4, 8] In this setting, subsequent mpMRI and targeted biopsy has detected csPCa in approximately 10% to 40% of those who initially had a negative TRUS.[4] Like the biopsy-naïve group with low PI-RADS scores, concurrent indicators can be used to risk-stratify the need for biopsy. Importantly, if biopsy is deferred due to mpMRI findings, continued clinical and laboratory follow-up is indicated.

Limitations and Future Directions

Clinically, efficacy of mpMRI is balanced with its limitations, which include expense, availability, and potential renal impairment and inconvenience of intravenous line placement when contrast is used. Additionally, standardization of radiologist training to ensure consistent interpretation of mpMRI is of paramount importance, as inter-reader reliability can vary.

Currently, biparametric MRI, which uses only two modalities and does not use contrast, is being studied for use in PCa detection. Preliminary studies of biparametric MRI show comparable sensitivity and specificity with multiparametric MRI, but it is unclear if there will be a significant difference in the research setting compared to clinical practice setting.[4, 13]

The wide ranges of PPV and NPV in mpMRI results noted in the literature vary depending on patient populations, prevalence, indication for use, accessory tests, and inherent limitations of study design. For example, prebiopsy mpMRI is not indicated for very low-risk patients (based on clinical, biochemical, and family history information) as the sensitivity would result in a greater number of false positives. As with all tests, the external validity of the study population, or the ability to generalize the conclusions of a study to other populations that were not studied, is important when applying to clinical practice, and thus needs to be considered in insurance medicine and underwriting.

Underwriter Considerations

Given the evolution of indications for the use of mpMRI in PCa diagnosis, underwriters should have some familiarity

with this modality. There are several considerations, however, as more cases will be detected with mpMRI at different stages of the path to a diagnosis.

- mpMRI helps decrease over- and under-diagnosis in prostate cancer, but like other modalities, it has limitations that must be considered. There will still be false negatives and false positives, so pretest probability, or the estimated probability that a person has the disease even before knowing test results, is a paramount consideration.
- mpMRIs yielding PI-RADS scores of 3 through 5 should be biopsied.
- There is no consensus that PI-RADS scores of 1 or 2 for biopsy-naïve patients means they can forgo biopsy.
- mpMRI is just one tool to consider in those with abnormal PSA trends. Look at the overall picture for risk assessment: age, family history of prostate cancer, and data points such as results of a DRE, PSA kinetics, PSA density, prostate health index, risk calculators, and genetic biomarkers (if allowed).
- Standards of care vary from country to country, and indications for use of mpMRI will differ depending upon the geography.

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GLIAL CELLS AND PERSISTENT PAIN: RECENT ADVANCES

Abstract

As technology provides increasingly sophisticated insights into the nature of disease processes within the nervous system, clinical medicine's insight into the nature of persistent pain states has expanded into an understanding of them as manifestations of imbalance and dysfunction at multiple sites of the central nervous system. Not only is there pathology involving the body part generating the pain, but also within the nerves which transmit signals to and from the spinal cord, within the spinal cord itself, and at multiple sites in the brain. Now also known to contribute to experiences of pain are a category of cells known as glial cells, which were formerly thought to be all but inactive within the nervous system. This insight is providing a focus for further research into possible biological approaches to mitigating persistent pain. Importantly, it also supports the concept of persistent or chronic pain as a disease state necessitating an array of therapeutic strategies.

Introduction

For more than 20 years, medical science has seen an explosion of productive research into neuroinflammation (i.e., inflammatory response affecting the nervous system) and its impact on many adverse health conditions including neurodegenerative disorders such as dementias and Parkinson's disease, an array of psychiatric conditions, and persistent pain states. The new knowledge sets aside long-held but apparently incorrect beliefs about the structure and function of the nervous system and related biological processes in the human body.

Inflammation has long been recognized as a process triggered by tissue injury or assault, with the primary purpose of defending against and repairing after the injury or assault. It involves an array of actions that include specific immunological functions of a number of cell types, each with a different set of functions. Some types will ingest and remove substances which threaten the individual experiencing the inflammation. Others will release chemical mediators, of which there are many different types with distinct but sometimes overlapping roles.

Inflammation's processes are integral to the body's survival. They are triggered by infection or injury and are of prominent relevance in conditions such as heart disease, cancer, diabetes, and arthritis. The role of inflammation in both peripheral and central sensitization in pain states has long been recognized. It has also been recognized that, with varying modes, durations, and circumstances, inflammatory activity and its expressions are not always beneficial and indeed may become deleterious, as typified by, for example, rheumatological disease.

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Dr. Newman L. Harris is a specialist in pain medicine and psychiatry, an associate professor, and is trained in rehabilitation medicine. Since joining RGA in 2012, Dr Harris has primarily provided medical underwriting support for RGA's Australia and New Zealand claims teams, and to RGA offices worldwide as needed. He also produces and delivers educational modules and lectures, and contributes his expertise to underwriting and product development initiatives as well.

Dr. Harris's background in pain medicine is substantial: his Master's degree in Pain Medicine is from the University of Sydney, and he is an admitted Foundation Fellow of the Faculty of Pain Medicine of the Australian and New Zealand College of Anaesthetists. He was involved in developing the University of Sydney's Pain Management postgraduate program, and was also previously a director of the Australian Pain Society. He has also served as a New South Wales branch councillor of the Royal Australian & New Zealand College of Psychiatrists.

Currently, Dr. Harris is a member of the elected board of the Faculty of Pain Medicine, a panel member of the Medical Tribunal of New South Wales, and an Associate Professor at Griffith School of Medicine and Gold Coast University Hospital, where he is a senior staff specialist in pain medicine.

Glial Cells and Neuroinflammation

Among the long-held beliefs now being set aside are those related to the glial cells of the central nervous system (CNS). The collective noun for this group of cells originated in the Greek word for "glue" and was applied to a range of CNS cells previously considered essentially inactive, with its only role that of providing scaffolding for the neurons, the active nerve cells of the nervous system. One type of glial cell, the oligodendrocyte, was recognized as providing the very important myelin sheaths around the axons of fast acting nerve cells, but that was all.

Over the last few decades, an understanding has emerged that glial cells do in fact perform a range of the important functions relevant to neuroinflammation within the CNS (see Table 1).

Table 1: Types of Glial Cells, Their Functions, and Implications

Cell Type	Role in Inflammation	Implications in Pain
Microglia	• Respond to pathogens/injury – migrate as required • Removal of damaged cells/ debris • Release cytokines, chemokines, prostaglandins, reactive oxygen species, ATP	Stimulated by repeated exposure to opioids, causing release of inflammatory mediators which amplify pain and distort pain signaling
Astrocytes	• Regulate transmitter release from neurons • Regulate blood-brain barrier • Promote oligodendrocyte activity • Moderate new neuron formation (neuroplasticity)	Involved in response to neuronal stress or injury; can promote nerve destruction as well as nerve repair / rebuilding
Oligodendrocytes	• Myelination of axons – activity dependent	Activity in spinal cord implicated in genesis and maintenance of chronic pain states
Ependymal cells	• Secrete and maintain cerebrospinal fluid • Clearance of waste	Not known as yet

The inflammatory response is not always the same wherever it occurs. It will vary according to several factors, including the nature and site of the injury or assault, its duration, and elements specific to the individual. Neuroinflammation, for example, can have positive or negative impacts. On the one hand, it can be associated with the removal of dangerous elements and reorganization of a repairing nervous system, but on the other, it can be associated with additional damage which can manifest in many ways. Further, neuroplasticity, an important process in recovery from a CNS injury, has been shown to be either enhanced or reduced, depending on different types of neuroinflammatory activity.

Notably, while elevated inflammatory activity has been detected in the CNS in instances of physical adversity, it is also found when there is emotional threat, and has been shown to be associated with adverse mood states such as anxiety. This biological association of mood/anxiety with the inflammation found in conditions such as persistent pain may be an important insight for patients and the practitioners caring for and treating them.[2]

Further to the inflammatory activity of the glial cells themselves, the mediating chemicals they release cause recruitment of inflammatory response cells from the bloodstream. The activity of the latter is facilitated by altered permeability of the blood-brain barrier. That barrier comprises the endothelial cells which line all blood vessels as well as, in the context of the CNS, projections of the astrocytes, the most abundant of the glial cells. It is the astrocytes which are primarily responsible for the altered permeability of the barrier.

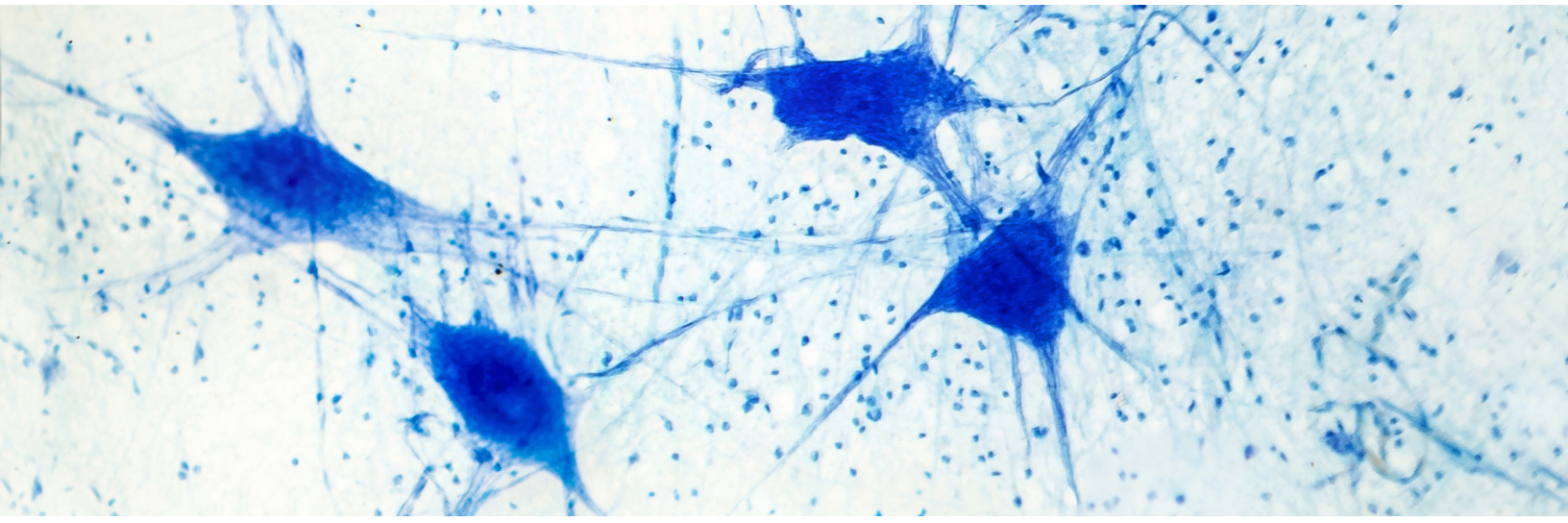
Microglia, a type of glial cell, have two roles – primary immune surveillance and ingestion and removal of unwelcome cells. Comprising 10% to 15% of the cells in the CNS, microglia provide important neuroprotective roles, and as their turnover is slow, they are less susceptible to long-term damage. When confronted by disease and varying with the type of injury or assault, microglia produce inflammatory chemicals which promote the recruitment of other protective cells. Unfortunately, in certain situations, microglial activity can become excessive and/or persistent to the detriment of the individual. Such enhanced activity has been implicated in conditions such as persistent pain states, neurodegenerative conditions, and mental illnesses.[3]

The Glia's Connections

Enmeshed with the advancing knowledge of neuroinflammation is the role of dietary factors. Gut microbiota, the term applied to the microorganisms which colonize the gastrointestinal tract, are known to alter according to a number of variables, not least of which are a person's dietary habits.

Gut microbiota are now increasingly recognized as asserting influence outside of the gastrointestinal tract. This includes the CNS, with established links to cognitive function and immune responses. Research has linked microglial dysfunction, causing chronic neuroinflammation and neurological disorder, to gut microbiome imbalance.[4] The microbiome has also been found to impact hypothalamic-pituitary-adrenal (HPA) activity, which is implicated in the development of neurological and psychiatric disorders as well as of fatigue syndromes.

Glial cells do in fact perform a range of the important functions relevant to neuroinflammation within the CNS.



A bidirectional role for communication between brain and gut is also postulated for the vagus nerve, and numerous studies point to its influence on microglial neuroinflammatory activity.

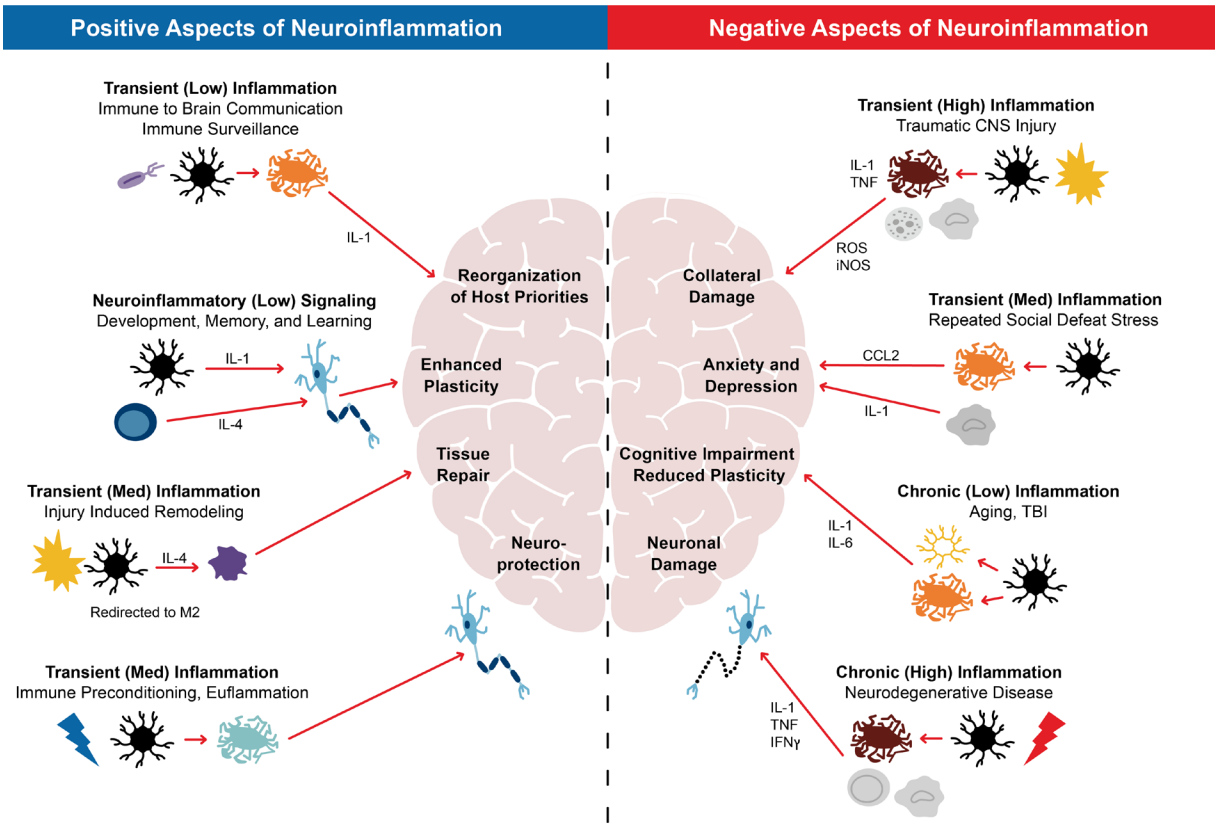
Proinflammatory chemicals are also known to be released by the excessive fat stores carried by overweight individuals, which can increase pain perception and complaint.

Finally, and importantly, there is emerging research on the role of a healthy liver in all of these aspects of pain and its management, which appears to be impacting these systems. The liver-brain axis is recognized as influencing such processes as oxidative stress in the CNS, and other adverse metabolic processes involved with neurodegeneration and central sensitization of pain processing.[7]

The Links to Pain

In relation to pain specifically, there is increasing recognition that two types of glial cells, astrocytes[5] and microglia, have significant roles in the emergence and persistence of amplified pain states, derangement of neuro-organization (as occurs in windup or central pain sensitization), and the reduced efficacy of opiate medications. The activity of these cells involves the release of several inflammatory chemicals as well as modulating chemicals and growth factors, which can lead to derangement of healthy neural structures and networks within the spinal cord and brain. Although these cell types assert little (if any) action in normal pain situations, these cells are involved in changes which cause amplification of pain through these inflammatory actions. Unfortunately, their activation is augmented by persistent opioid use, and the glia themselves demonstrate further increases in activity in response to chronic opiate exposure. The impact is amplification of pain, the spread of pain beyond its original distribution, changes in the type and intensity of pain, and reduced effectiveness of opioid analgesics.

Figure 1: Aspects of Neuroinflammation



Source: Adapted from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5025335/figure/F1/

Implications for Treatment

The most important conclusion to be drawn from the emerging research is that persistent pain states are not usually a disorder of the identified affected body part. While there may be ongoing pathology of the organ or body part, there will also be derangement within the nervous system, particularly in the spinal cord and brain. It is for this reason that persistent pain should perhaps be considered a disease or condition in its own right, beyond the identified affected body part.[6]

Attempts to treat pain with strategies that focus solely on the initial injury or disease are failing to acknowledge and address the nervous system pathology which can ensue, and which can augment and perpetuate the patient's distress and dysfunction.

Research continues to delve into biological approaches to manipulating the mechanisms cited in this article. Some are less specific, such as stimulation of the vagus nerve, while others are more focused attempts to manipulate the activity of centrally acting inflammatory chemicals released by the glia and other implicated cells. This has stimulated interest in the possibility of harnessing these mechanisms with anesthetic and even antibiotic agents, but as yet no solid therapeutic advances have been made.

There are many driving factors which contribute to persistent pain, and all must be recognized and addressed.

The message to patients with persistent pain and their medical caregivers is that there are many driving factors which contribute to persistent pain, and all must be recognized and addressed. As indicated, these include an undue emphasis on treating the presumed source of pain, the ongoing use of opiate medications, and the failure to address psychological factors associated with stress. Ideally, this emerging research should be explained to the patient with a view to promoting insight into persistent pain as a disease state of both the whole nervous system and the whole person. That insight should also be used to encourage clinical adoption of a "whole person" approach to improving the body and brain's proneness to inflammation while reversing the drift to overall deterioration.

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RHEUMATOID ARTHRITIS – THE COMPLEX ARTHRITIS

Abstract

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized primarily by joint swelling and deterioration, leading to increased morbidity and mortality risk. The pathology of RA is complex, and its progression may lead to extra-articular manifestations affecting the skin, the heart, the lungs, and more. Currently, global prevalence of RA stands at between 0.4% and 0.5% and is projected to rise in the next 20 years.

This article aims to strengthen underwriter, claims assessor, and medical director understanding of RA by examining its risk factors, extra-articular manifestations, and treatments, and their corresponding impacts on mortality and morbidity. Additionally, it touches upon a few possible future treatment regimens for RA.

Introduction

Musculoskeletal conditions are becoming a major burden on healthcare systems around the world. They are affecting individuals as well as health and social care systems, with indirect costs a predominant factor. For arthritis alone, more than 100 types are currently known to exist.

Although arthritis has traditionally been considered a disease of older age, diagnosis of individuals between the ages 18 and 64 has been on the rise. It is estimated that more than one-third of all arthritis cases diagnosed from 2015 to 2017 were in this age cohort.[1]

In 2017, 92.1 million adults in the U.S. alone were either already diagnosed with arthritis or were reporting associated symptoms. And with the global population expected to rise by 25% in the next 30 years, further growth in arthritis cases appears imminent.[2]

Rheumatoid arthritis (RA), a progressive form of arthritis with associated inflammation, swelling, and pain in and around affected joints, is a chronic autoimmune disease. RA is commonly associated with progressive disability, systemic complications, early death, and high socioeconomic costs. It is unusual in that it can also affect other organs, such as the skin, blood vessels, heart, and lungs. Its estimated global prevalence is 0.46%, and approximately one in 12 women and one in 20 men are likely to develop RA in their lifetimes.[2, 3]

RA has a highly complex multi-phase pathophysiology which is influenced by risk factors such as the individual's genetics, presence of infectious disease, and habits such as smoking and diet, resulting in progressive erosion and, in the most severe cases, systematic destruction of the affected joint(s).

As RA is an autoimmune disorder, lack of treatment or management may result in a more severe form of the disease, affecting other systemic organs. This aspect is known as "extra-articular involvement," and is generally understood to indicate progression and poorer prognosis.

ABOUT THE AUTHOR

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Sandeepan Basu is Deputy Chief Manager, Research and Manual Development at RGA. Based in Mumbai, India, his focus is on researching medical advances impacting life insurance and incorporating that information in RGA's Global Underwriting Manual.
His experience in life insurance encompasses underwriting, audit, training, and analytics in India, Southeast Asia, and the Middle East, as well as underwriting automation. Sandeepan earned his Bachelor of Pharmacy degree from Manipal College of Pharmaceutical Sciences, Karnataka, India.

Diagnosing RA

Diagnosing RA and distinguishing it from other autoimmune disorders can be challenging. The diagnosis usually involves a holistic assessment that includes:[4]

- Physical examination of affected joints
- Blood tests such as:
  - Rheumatoid factor (RF)
  - Anti-citrullinated protein antibody (ACPA)
  - Erythrocyte sedimentation rate (ESR)
  - C-reactive protein (CRP)
- Imaging studies (e.g., X-Rays, CT scans, MRIs)

Individuals with RA have at least one joint with a clinical diagnosis of synovitis. Synovitis is an inflammation of the synovial membrane, the connective tissue that lines joints such as the hip or knee, which cannot be explained as part of another disease.

The 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) 10-point classification system, detailed in Table 1 (below), requires a score of six or higher to diagnose RA.[5]

High blood titers of RF or ACPA are indicative of poorer functional and radiographic outcomes. However, it is important to understand that none of these tests is specific enough on their own to establish a definitive diagnosis of RA.

Table 1: Scoring and Diagnosing RA

	Score
Joint involvement	
1 large joint	0
2-10 large joints	1
1-3 small joints (with or without involvement of large joints)	2
4-10 small joints (with or without involvement of large joints)	3
>10 joints (including at least one small joint)	5
Serology (at least one test result needed)	
Negative RF and negative ACPA	0
Low-positive RF or low positive ACPA	2
High-positive RF or high positive ACPA	3
Acute-phase reactants (at least one test result needed)	
Normal CRP and normal ESR	0
Abnormal CRP or abnormal ESR	1
Symptom duration	
<6 weeks	0
>6 weeks	1

Source: Aletaha et al. 2010[5]

Comorbidities Associated with RA

RA is associated with several comorbidities and is characterized by many complications. Table 2 (below) summarizes those commonly associated.[2, 6-13]

Table 2: Common Associated Complications

System	Associated Complications
Cardiovascular	• Increased atherosclerosis risk • Endothelial cell damage, which may predispose cholesterol deposition, leading to plaque formation and increased risk of stroke and myocardial infarction (MI). Ischemic heart disease risk is nearly 1.6x higher one to four years after initial RA diagnosis[12] • Endocarditis, pericarditis, left ventricular failure, valvulitis, fibrosis • NSAIDs can increase risk of cardiac complications
Hematologic	• Anemia of chronic disease (ACD) • Thrombocytosis and clotting • Felty's syndrome (rare)
Pulmonary	• Interstitial lung disease (may progress to end-stage lung disease and in severe cases may require a lung transplant) • Fibrosis (possible side effect of methotrexate and leflunomide) • Pleural effusion • Caplan's syndrome (rheumatoid pneumoconiosis) – comparatively rare, seen among RA patients previously exposed to coal dust
Dermatologic	• Rheumatoid nodules (occurs in 30% to 50% of RA cases) • Vasculitis – in severe cases, ulcers may develop on legs and nail beds • Thinning of skin due to corticosteroid use • Skin sensitivity due to NSAIDs and methotrexate use
Ophthalmologic	• Sjogren's syndrome • Episcleritis or scleritis (severe cases can progress to scleromalacia perforans) • Uveitis (inflammation of the eye) – can lead to blindness if untreated • Keratoconjunctivitis sicca (dry eye disease)
Musculoskeletal	• Osteoporosis
Neurologic	• Carpal tunnel syndrome • Mononeuritis multiplex • Myelopathy
Cancer	• Lymphoma (rare) • Non-melanoma skin cancer
Liver and kidney	• Liver failure due to long-term acetaminophen use • Kidney impairments due to use of cyclosporine, methotrexate, NSAIDs
Dental	• Periodontitis (gum disease) can have a direct correlation with RA severity

A study which compared the presence of comorbid disorders among RA individuals to an age- and sex-matched population showed higher odds ratios (ORs) for disorders or diseases of these systems:[14]

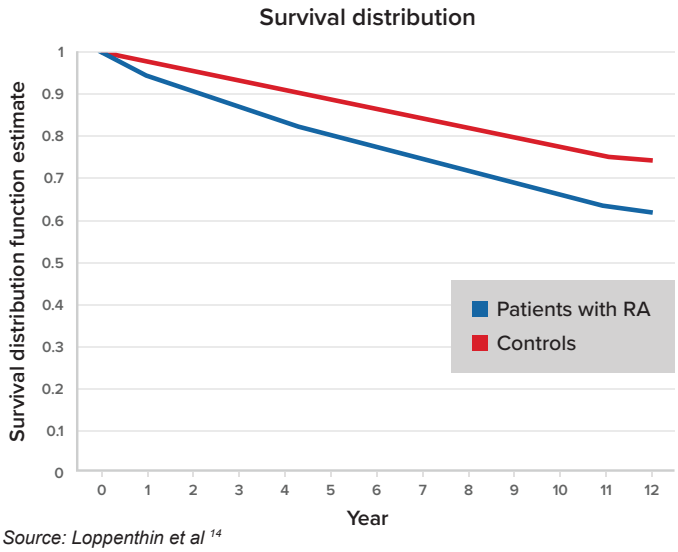
- circulatory (12.7% vs. 9.4%)
- endocrine (4.3% vs. 3.1%)
- respiratory (6.5% vs. 3.8%)

In addition, higher prevalence of diabetes, cardiovascular, and respiratory diseases such as chronic obstructive pulmonary disease (COPD) was noted in individuals prior to their RA diagnoses. This indicates that individuals with RA may develop certain comorbidities before the onset of the disease, perhaps due to associated development of pre-diagnostic inflammatory processes.

Rheumatoid Arthritis and Mortality Trends

RA should be considered a systemic disease rather than one only affecting joints. Its impact on mortality is considerably different from some of the other arthritic conditions.

Figure 1: Survival of RA patients vs. controls



Source: Loppenthin et al [14]

According to Figure 1, a five-year survival rate of 80% (95% CI, 78-81%) was noted for individuals with RA versus 88% (95% CI, 88-89%) for control subjects (age- and sex-matched populations without RA).

Overall survival was persistently lower by less than 10% for RA patients compared with controls. After almost 12 years, the probability of survival among people living with RA was 61% (95% CI, 61-63%) compared to 74% (95% CI, 74-75%) for the controls.

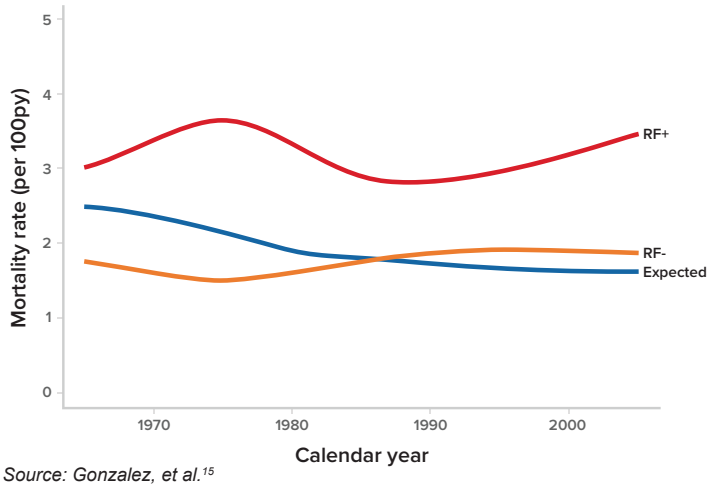
An odds ratio (OR) of 1.41 (95% CI, 1.29-1.64) was observed for the cohort representing RA individuals compared with an age- and sex-matched population.[14]

The Impact of Rheumatoid Factor (RF)

Rheumatoid factors are proteins that are made by the immune system. Their presence or absence can help determine an RA patient's prognosis.[15] Patients with high levels of RF in their blood (more than 20 IU/ml) may be at higher risk of mortality and are prone to poorer prognostic outcomes. It must be understood, however, that high levels may be indicative of other autoimmune disorders such as Sjogren's syndrome.

A study conducted among 603 individuals from the state of Minnesota (U.S.) revealed the difference in mortality between RF positive (RF+) and RF negative (RF-) individuals, benchmarked against expected mortality rates from 1970 to 2000. (See Figure 2, below.)[15]

Figure 2: Mortality comparison – RF+ vs RF-



Source: Gonzalez, et al.[15]

According to the study, the mortality rate for the RF+ cohort was higher than expected compared to RF- cohort. The standardized mortality ratio (SMR) for RF+ individuals was 1.81 (95% CI, 1.6-2.05), whereas the SMR for RF- individuals was similar to the expected mortality for both age and sex matched populations.

Other Factors

In addition to rheumatoid factor, other risk factors which may affect prognosis of RA are:[16]

- **Age:** Those older than age 50 usually have poorer prognoses and higher mortality.
- **Education and socioeconomic levels:** Those with high school diplomas or college degrees had lower mortality rates due to RA than those without,

indicating that better awareness and access to treatment protocols may help in mortality reduction.

- **Other comorbidities:** The presence of angina pectoris and hypertension doubled mortality risk for RA individuals compared to the general population, and impairments such as MI and stroke tripled the risk.
- **Smoking:** Smoking not only increases the risk of RA but is also responsible for excess mortality among RA patients who smoke.

Treatment Modalities

Treatment of RA is often multidimensional. Disease-modifying medicines along with steroids and analgesics are recommended in most cases. Table 3 (below) summarizes the treatments advised for RA.[17, 18]

- **Disease-modifying anti-rheumatic drugs (DMARDs)** are generally the drug(s) of choice for treating RA. They block the effects of chemicals released when the immune system attacks the joints and causes damage to nearby bones, tendons, ligaments, and cartilage.
  - csDMARDs (Conventional DMARDs): These are primarily administered during Phase 1 of an RA treatment regimen. Methotrexate is usually the drug prescribed, often in combination with another csDMARD and a short course of corticosteroids to reduce inflammation and relieve pain. If methotrexate is contraindicated, leflunomide or sulfasalazine may be prescribed.
  - bDMARDs (Biological DMARDs): These are TNF inhibitors, T-cell costimulatory inhibitors, and IL-6 receptor inhibitors. They are usually administered

Table 3: RA Treatments

Treatment Class	Examples
Disease Modifying Anti-Rheumatic Drugs (DMARDs)	Conventional synthetic DMARDs (csDMARDs) • methotrexate, hydroxychloroquine, sulfasalazine, leflunomide, gold salts Biological DMARDs (bDMARDs) • TNF inhibitors – etanercept, adalimumab, golimumab, infliximab • T cell costimulatory inhibitor – abatacept • IL-6 receptor inhibitors – tocilizumab, sarilumab Targeted synthetic DMARDs (tsDMARDs) • JAK inhibitors – tofacitinib, baricitinib, upadacitinib
Analgesics	Non-opioid analgesics Topical agents Opioid analgesics
Anti-inflammatories	Non-steroidal anti-inflammatory drugs (NSAIDS) Glucocorticoids – systemic and intra-articular
Surgical procedures	Arthroscopy Joint replacement surgery
Non-pharmacologic and non-surgical	Patient education Psychosocial interventions Physiotherapy Occupational therapy Orthotic devices Nutritional and dietary counseling Podiatry

Sources: Smolen, et al.[18], Medscape.com[23], Uptodate.com[24]

in Phase 2 of a treatment regimen if Phase 1 treatments have not been adequate or effective.

  - tsDMARDs (Targeted synthetic DMARDs or JAK inhibitors): These newly developed drugs are used in combination in bDMARDs during Phase 2 treatment as well as in different combinations for Phase 3 treatment. These drugs are indicated when bDMARDs fail to achieve desired Phase 2 outcomes.

- **Analgesics** such as NSAIDs are often useful in relieving RA pain while also reducing joint inflammation, although they will not prevent RA from worsening. Long-term NSAID usage may also lead to cardiac complications.
- **Corticosteroids** are usually prescribed for short-term pain relief. They are commonly used as adjuvants – for example, while waiting for DMARD medicines to take effect or during an RA flare-up in Phase 1 treatment. Long-term corticosteroid usage can lead to multiple complications such as osteoporosis and muscle weakening and is advocated only for extreme cases.
- **Surgery** is for cases where joint degeneration is substantial and is limiting a patient's activity in ways that have considerable impact on activities of daily living (ADLs).
- **Physiotherapy and occupational therapy** are frequently recommended to maintain joint range of motion, strength, conditioning, and dexterity.
- **Nutritional supplements** such as calcium and vitamin D may help prevent osteoporosis, and fish oil may reduce joint pain and stiffness.

Remission

The goal of RA treatment is to achieve remission. Various definitions of remission are in use, but the ones listed below, which are based on those used by ACR and EULAR, are the most widely accepted.

- **Comprehensive Disease Control (CDC)**: This is defined as achievement of stringent control of the signs and symptoms of inflammation, according to Disease Activity Score 28 (DAS-28). DAS-28 is an index that measures disease activity in patients based on an examination of their joints, their ESR or CRP results, and an overall assessment of their health.

  CDC is considered to have been achieved when the following criteria are met:[19]

  - A DAS-28 score of <2.6
  - Normal physical function, assessed using the Health Assessment Questionnaire Disability Index (HAQ-DI), and obtaining a score of <0.5.
  - Absence of progression as measured radiographically, and a modified total Sharp erosion score (mTSS) of <0.5.

- **Sustained remission:** The phrase "sustained remission" is another commonly used term to describe remission in RA patients. The more commonly used definition of remission is the ACR/EULAR definition, which depends on DAS28 and uses ESR or CRP results as well as more stringent DAS-based criteria such as the Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI) to measure RA disease activity. A minimum of six months is a designated targeted sustained remission period. However, the definition of sustained remission remains flexible.[20] Indeed, a 10-year follow-up study of RA patients observed that only 14% had achieved sustained drug-free remission.

A Brief Look: Future RA Treatments, Management

Guidelines for RA treatment and management are reviewed periodically by ACR and EULAR. As newer methods, including some alternative therapies, continue to emerge, some traditional methods are being either replaced or restructured.

Recent study findings indicate that:

- Minimizing use of corticosteroids such as prednisone may be beneficial due to deleterious side effects from long-term use.
- Switching between DMARDs is neither advisable nor preferred. If an RA patient starts on a csDMARD, for example, continuing on it long-term showed better prognostic outcomes.
- Using a bDMARD or tsDMARD may be more effective than multiple doses or a triple therapy csDMARD regimen (methotrexate, hydroxychloroquine, sulfasalazine).
- Continuing current medications is also recommended over tapering. Tapering can only be considered for people who have met their treatment goals consistently for at least six months.

Other advances:

- Inflammation is associated with degenerative neurological conditions such as Alzheimer's disease, and research has determined that RA can increase the risk of certain dementias. However, more recent studies have shown that those who took bDMARDs or tsDMARDs had a 17% reduced risk of dementia compared to those taking csDMARDs.
- A new biomarker is improving the ability to predict cardiovascular disease risk in RA patients. UCLA researchers have found that RA patients with the lowest levels of low-density lipoprotein (LDL) had a 2.8 times higher risk of obstructive coronary plaques.[21] This is referred to as the "lipid paradox," as it is contrary to the general understanding of the impact of LDLs on coronary plaque.
- A multi-biomarker disease activity (MBDA) score, also known as a Vectra score, is used to check levels of inflammation beyond CRP or ESR testing and help predict heart disease risk in RA patients.[21]
- A new therapy for complex RA cases focuses on stimulation of the vagus nerve to reduce inflammation. Currently it is being studied in individuals who are not responding well to inflammation-lowering medications. This treatment will require larger study cohorts to better understand its long-term benefits.

New remission approaches:

Definitions of RA remission are constantly being updated. One recent update suggested that if RA patients are using combination therapy (e.g., a csDMARD plus a bDMARD), and if sustained remission was achieved, tapering should be considered for the csDMARD but not the bDMARD.

A Canadian study determined that early RA diagnoses may lead to better prognoses, milder disease, and possible long-term remission. Factors associated with lower remission rates included: female gender; having more comorbidities; being RF+; and smoking. The research underlined the importance of careful monitoring of individuals with RA who are at higher risk for transient (or partial) remission. Over a 24-month follow-up period, the study found that:[22]

- 55% of patients in the study achieved remission
- 47% of patients who achieved remission sustained it for 12 months or more
- 40% sustained remission for up to 24 months

Conclusion

RA is a complex disorder with a myriad of associated risk factors, complications, comorbidities, and extra-articular manifestations. Traditional drugs such as analgesics and DMARDs continue to be treatment mainstays. Research into new therapies is ongoing, but long-term remission remains elusive.

It is essential that underwriters, claims adjudicators, and insurance medical directors understand all aspects of RA's progression as well as what constitutes adequate responses to its treatments, as the holistic risk profile contributes to subsequent morbidity and mortality risk.

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Longer Life Foundation

An RGA/Washington University Collaboration

The Longer Life Foundation (LLF) is a collaboration of RGA and Washington University School of Medicine in St. Louis. Founded in 1998, LLF funds carefully curated investigations of scientific and public health factors predicting and impacting health and wellness.

To learn more, please visit www.longerlife.org or reach out to Dr. Daniel D. Zimmerman, LLF Managing Director, at dzimmerman@rgare.com, or Dr. Preeti Dalawari, Deputy Managing Director, at preeti.dalawari@rgare.com.

SPONSORSHIPS

The Longer Life Foundation has been busy since the year began. 2022 started off with the first of a planned series of LLF-sponsored Grand Rounds for the year. On January 6, LLF alumnus **Dr. Jeffrey Henderson** presented a fascinating talk about his promising research into alternatives to antibiotics and on March 3, LLF was able to share access to a Grand Rounds featuring **Rochelle Walensky, M.D., M.P.H.**, Director of the U.S. Centers for Disease Control and Prevention (CDC). Dr. Walensky discussed the domestic and global challenges facing public health officials as the world emerges from the COVID-19 pandemic. Dr. Henderson's lecture is available here, and Dr. Walensky's discussion, here.

NEW VIDEO SERIES

LLF will be launching a series of videos featuring current and former investigators, which will be available on the LLF website and on a dedicated YouTube channel. The interviews, which are being conducted by Hilary Henly, Global Medical Researcher, RGA, will focus on the researcher's work, its potential impacts on mortality and morbidity, and the importance of the Foundation's support.

LEADERSHIP UPDATES

With the departure of long-time Board Member Robert Musen in December, LLF leadership made the decision to increase the size of the Board from four to five. We recently welcomed the two newest members: **Carmony Wong**, Senior Vice President and Head of Hong Kong and High Net Worth Markets, RGA, and **Dr. John C. Morris**, the Harvey A. and Dorismae Hacker Friedman Distinguished Professor of Neurology at Washington University in St. Louis School of Medicine. Ms. Wong is a proven and influential leader at RGA and in the insurance industry, and Dr. Morris' research and clinical focus is on neurological disorders associated with aging.

Additionally, LLF Deputy Managing Director Dr. Dave Rengachary will be stepping down from that position, as he takes up his new role at RGA as Head of U.S. Mortality Markets Underwriting. He will remain a member of the LLF Advisory Group. Dr. Preeti Dalawari, LLF Director of Member Engagement, will add the role of Deputy Managing Director to her current duties.

2022-2023 GRANT CYCLE

2022 will be another exciting year for grants. The Foundation has received 20 Letters of Intent from applicants representing diverse disciplines such as infectious diseases, immunology, biostatistics, and hematology. The final awards will be announced in September, with funding to begin on October 1, 2022.

MILESTONE CELEBRATION

Planning has begun for the 25th anniversary celebration for the LLF, which will be in 2023. It is both exciting and humbling to realize how long LLF has had a role in the advancement of research to benefit longevity, mortality, and morbidity. Stay tuned for more information!

LLF NEWSLETTER

The April 2022 issue of the LLF Newsletter is available here.

MEDICAL TEAM UPDATE

Dr. Jieun Kim has joined RGA Korea as Chief Medical Officer. A specialist in family medicine, her 15 years of experience in clinical practice and insurance medicine includes the chief medical officer role at Samsung F&M and at DB Insurance, with responsibilities that included medical underwriting, product development, and development of an automated underwriting system.

Dr. SiNing Zhao joins RGA as Regional Medical Director, Asia. Based in Hong Kong, she is a specialist anesthesiologist with further training in critical care medicine and has more than 15 years of clinical experience. Before joining RGA, she was a Medical Director with BUPA for seven years, with a focus on clinical governance and risk, medical underwriting, data driven healthcare management, provider relations, and claims management.

RECENT WEBCASTS

RGA's most recent webcasts, available for viewing at your convenience, focus on topics of interest to underwriters, claims managers, and insurance medical directors.

Liquid Biopsy Technology and Its Impacts on Insurance

Dr. Heather Lund, MBBCh, Regional Chief Medical Officer, Asia; Dr. Daniel D. Zimmerman, DBIM, Senior Vice President, Head of Global Medical; and Andrew Gaskell, FIA, Vice President, Global Actuarial Pricing and Research

Liquid biopsies are revolutionizing oncology by offering increasingly powerful paths to early detection and diagnosis of multiple cancers and more. For insurers, this is ramping up the need for underwriters, claims assessors, and pricing actuaries to be aware of and understand the attendant opportunities and challenges.
https://www.rgare.com/knowledge-center/media/videos/liquid-biopsy-technology-and-its-impacts-on-insurance

Mortality and Morbidity of COVID-19 Survivors

Dr. John Lefebre, FRCPC, Vice President and Senior Global Medical Director, RGA International

Studying the mortality and morbidity trends among COVID-19 survivors can provide vital insights into the insurance implications of the pandemic and its aftermath. Dr. Lefebre, in his recent review of research on the topic, discusses these implications in the context of long COVID (post-COVID syndrome), delving into factors that may increase or decrease risk.
https://www.rgare.com/knowledge-center/media/videos/mortality-and-morbidity-of-covid-19-survivors

Exercise and Your Heart: Can There Be Too Much of a Good Thing?

Dr. Nick Boon, Consulting Medical Officer

Moderate exercise is considered positive for cardiac health, but the hearts of endurance athletes can be their own special cases. Dr. Boon explores the cardiovascular adaptions of the athletic heart, how they compare and can be confused with findings of more concerning pathologic cardiomyopathies.
https://www.rgare.com/knowledge-center/media/videos/exercise-and-your-heart-can-there-be-too-much-of-a-good-thing

A Balancing Act: Vaccination Status and Insurance Pricing

Neil Parkin, Head of Business Development, RGA South Africa

For insurers, whether to use vaccination status as a rating factor in risk assessment is a complex and challenging undertaking that requires many different considerations to be balanced. Neil Parkin explores the pros and cons of adding that factor into the ratings analysis.
https://www.rgare.com/knowledge-center/media/videos/a-balancing-act-vaccination-status-and-insurance-pricing

ReCite

Interesting and relevant articles to the field of insurance medicine recently appearing in the literature...

SARS-CoV-2 is associated with changes in brain structure in UK Biobank

Douaud G, et al.
Nature. 2022 Mar 7.
https://www.nature.com/articles/s41586-022-04569-5

As the SARS-CoV-2 pandemic continues to disrupt the lives of many across the globe, there has been increased focus by scientific and medical communities on longer-term effects on the brain of mild to moderate COVID-19. There is already strong evidence for brain-related abnormalities due to COVID-19, and this study investigated brain changes in 785 UK Biobank participants (ages 51-81). Each participant was imaged twice, and the database included 401 cases who tested positive for infection with SARS-CoV-2 between their two scans, with 141 days on average separating diagnosis and second scan, and 384 controls. (Fifteen of the 401 cases were hospitalized, and findings from those cases were not incorporated.)

The data identified significant longitudinal effects upon the physical brain when comparing the two groups. The effects included: greater reduction in grey matter thickness and tissue-contrast in the orbitofrontal cortex and para-hippocampal gyrus; greater changes in markers of tissue damage in regions functionally connected to the primary olfactory cortex; and greater reduction in global brain size. Infected participants also showed, on average, larger amounts of cognitive decline between the two timepoints.

Editor's Note: *Whether this damaging impact can be partially reversed, or whether these effects will persist in the long term, remains to be investigated and will need to be considered as part of underwriting investigations going forward.*

Risks of mental health outcomes in people with COVID-19: cohort study

Al-Aly Z, et al.
BMJ. 2022 Feb 16; 376.
https://doi.org/10.1136/bmj-2021-068993

This study used data from the U.S. Department of Veterans Affairs to estimate the risks of mental health disorders in survivors of the acute phase of COVID-19 one year later. The study cohort consisted of three groups: the first, the 153,848 who survived their first 30 days of SARS-CoV-2 infection; and two control groups, consisting of a contemporary group with no evidence of SARS-CoV-2 and a historical control group that predated the COVID-19 pandemic.

The data showed increased risk of several mental health disorders, including anxiety disorders, depressive disorders, and stress and adjustment disorders. It also found increased use of antidepressants and benzodiazepines among the survivor cohort. Opioid prescription risk also increased, with rising diagnoses of both opioid use disorders and non-opioid substance use disorders. The first group additionally showed increased risk of neurocognitive decline and sleep disorders. These outcomes were evident even among those not admitted to the hospital and were highest among those admitted during the acute phase of their COVID-19 infection.

Editor's Note: *Understanding mental health disorders among COVID-19 survivors should be a priority for insurers, considering its impacts on both risk assessment and claims.*

Long-term exposure to fine particle matter and all-cause mortality and cause-specific mortality in Japan: the JPHC Study

Sawada N, et al.
BMC Public Health. 2022 March 8; 22: 446.
https://doi.org/10.1186/s12889-022-12829-2

Many studies have found a link between exposure to particulate matter and mortality. However, associations between the two at less dense levels of particulate matter concentration in the atmosphere are not yet well clarified. The Japan Public Health-Center Based Prospective Study (JPHC) evaluated associations between long-term exposure to particulate matter of a diameter less than 2.5 μg/m^3 (PM2.5) and mortality in a Japanese cohort with a relatively low exposure level.

Although in the study, average PM2.5 exposure was not associated with all-cause mortality or cancer and respiratory disease mortality, it was positively associated with cardiovascular disease mortality and, in particular, cerebrovascular disease mortality.

Editor's Note: *Geographical location and exposure to even mild pollution is a strong indicator of increased cardiovascular disease risk, and something to which insurers should pay attention as climate change continues to escalate.*

Gut microbiome–dependent metabolic pathways and risk of lethal prostate cancer: prospective analysis of a PLCO cancer screening trial cohort

Reichard CA, et al.
Cancer Epidemiology, Biomarkers and Prevention. 2022 Jan 11: 31(1): 192-9.
https://aacrjournals.org/cebp/article/31/1/192/675510/Gut-Microbiome-Dependent-Metabolic-Pathways-and

Researchers at Cleveland Clinic in Ohio analyzed blood samples and compared dietary nutrients and gut microbial metabolites for two cohorts of men: those who either did not develop prostate cancer or developed nonlethal prostate cancer (n = 519); and those who later received a prostate cancer diagnosis and died of the disease (n = 173). The data used came from patients enrolled in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial.

Men who had elevated levels of phenylacetylglutamine (PAGln) were found to be approximately two or three times more likely to be diagnosed with lethal prostate cancer. (PAGln is produced when microbes in the gut break down the amino acid phenylalanine.) In addition to PAGln, researchers also found that elevated levels of choline and betaine were linked with increased risk of developing aggressive prostate cancer. The potential implication of this finding is that reducing dietary intake of certain nutrients or pharmacologic targeting of certain pathways could lower the risk of lethal prostate cancer.

Editor's Note: *With more evidence supporting the importance of the microbiome, these markers are likely to become important in the clinical management and risk assessment of prostate cancer.*

RGA THOUGHT LEADERSHIP PUBLICATIONS

RGA's thought leaders publish content on many topics of interest to insurers. Here are links to some articles and white papers published recently on the RGA Knowledge Center.

Genomics Revolution in Life Insurance: Questions and Answers With Insurance Thought Leadership.com

Greig Woodring
Retired Chief Executive Officer, RGA

Checking the Pulse: The Evolving Role of the Insurance Medical Director in 2021

Dr. Sheetal Salgaonkar, DBIM,
Vice President and Medical Director, Global Medical, RGA

Dr. Daniel D. Zimmerman, DBIM,
Senior Vice President, Head of Global Medical, RGA

Leigh Allen
Assistant Vice President, Strategic Survey Research, RGA

Liquid Biopsy II: The RGA Perspective

Dr. Daniel D. Zimmerman, DBIM,
Senior Vice President, Head of Global Medical, RGA

Dr. Georgiana Willwerth-Pascutiu, DBIM,
Vice President and Medical Director, Global Medical, RGA

Dr. John Lefebre, FRCPC,
Vice President and Senior Medical Director, Global Medical, RGA

Dr. Sheetal Salgaonkar, DBIM,
Vice President and Medical Director, Global Medical, RGA

Hilary Henly, FCII,
Global Medical Researcher RGA

Respiratory Outcomes and Lung Transplantation in COVID-19 Patients

Hilary Henly, FCII,
Global Medical Researcher RGA

Screening for Disease and Risk of Disease: Present and Future Considerations, Caveats, and Consequences

Dr. Heather Lund, BBCh, Regional Chief Medical Officer, RGA Asia

Dr. Paul Davis, Chief Medical Officer, RGA Australia

Dr. Karneen Tam, Medical Consultant, RGA Asia

Dr. Sakae Tonoya, Regional Medical Director, RGA Japan

Dr. Jenny Wu, Medical Director, Asia Pacific

Quantifying Lifestyle Behaviors Holds the Key to Wider Adoption of Insurance-Linked Wellness Programs

Julianne Callaway, Vice President and Actuary, Strategic Research, RGA

Leigh Allen Assistant Vice President, Strategic Survey Research, RGA

Carmela Tedesco, Vice President, Business Initiatives Lead, RGAX

Jason McKinley, FSA, Actuary, Global Data and Analytics, RGA

Sophie Laposha (Intern), RGA

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