Clinical Review

Insights and Implications of the VA Rheumatoid Arthritis Registry

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The VA Rheumatoid Arthritis Registry addresses the underrepresentation of veterans in rheumatoid arthritis research, serving as a repository that links banked serum, plasma, and DNA samples with an array of patient-level information.

Rheumatoid arthritis (RA) is a systemic autoimmune disease that manifests primarily in the joints, leading to substantial morbidity, reduced survival, and enormous health care costs. As a result, RA exerts a major impact on patients and health care systems. U.S. military veterans and active-duty personnel have traditionally been underrepresented in RA research, likely due in part to the challenges posed by conducting investigations across federal facilities or the common refrain that such populations are not generalizable to the demographic groups (eg, younger women) most prone to develop RA.

Although RA is 3 to 4 times more common in women than in men (the latter comprising about 90% of the U.S. veteran population), its relevance to the VA health system has grown with the increase in women veterans. Well-defined risk factors for RA, such as cigarette smoking, are highly prevalent in these populations, as are comorbid conditions that frequently complicate its disease course, most notably cardiovascular disease.[1] Men with RA, a disease demographic common in the VA, seem to experience a more severe disease arthritis course than do women with RA and more commonly have extra-articular manifestations, which are known to contribute to worse outcomes.[2] Yet, data from predominantly male RA cohorts are sparse.

To address this gap in RA research, the VA Rheumatoid Arthritis Registry (VARA) was established in 2002 with its first patient enrolled in early 2003. Since its early inception, the registry has served as a research resource not only for VA investigators, but also for their collaborators, the VA health system, and U.S. veteran patients. This report reviews the resources available in VARA, the important insights gained in these efforts, and implications for both patients and health systems providing care. Future directions and opportunities for VARA and other disease registries are provided.

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REGISTRY BACKGROUND

The VARA is a prospective, observational, multicenter study that includes VAMCs in 12 cities (Birmingham, Alabama; Brooklyn, New York; Dallas, Texas; Denver, Colorado; Jackson, Mississippi; Iowa City, Iowa; Little Rock, Arkansas; Omaha, Nebraska; Portland, Oregon; Philadelphia, Pennsylvania; Salt Lake City, Utah; and Washington, DC). In addition to support from VA research, this multicenter effort has been supported by the VA Office of Research Development, the National Institutes of Health, industry, and nonprofit foundations. The VARA serves as a repository linking banked serum, plasma, and DNA samples with an array of patient-level information, including sociodemographics, medical history, medications, comorbid conditions, longitudinal disease activity measures, and other variables (eFigure, available at www.fedprac.com).

Clinical data are entered by investigators during routine rheuma-

tologic care, facilitated by the use of standardized patient note templates in the VA Computerized Patient Record System, semi-automated data abstraction, and a secure intranet-based platform. With regulatory approvals, including approval of the VARA Scientific and Ethics Advisory Committee (SEAC), registry data are accessed using the VA Informatics and Computer Infrastructure (VINCI), allowing for secure linkage with detailed administrative data, including medication dispensing, diagnostic and procedural codes, and vital status.

The VARA includes > 2,200 veteran patients, all having provided informed consent, aged ≥ 18 years at disease onset, and satisfying the American College of Rheumatology (ACR) classification criteria for RA (Table 1). Serum, plasma, and DNA samples are collected at enrollment and banked in a central biorepository housed at the Nebraska Western-Iowa VA Health Care System in Omaha. In addition to providing ethical and scientific review, the VARA SEAC also provides oversight for biospecimen access. Upon receipt of specimens, the central biobank performs standardized laboratory assays on serum, including C-reactive protein (CRP), rheumatoid factor (RF), and anticyclic citrullinated (anti-CCP) antibody. These data are made available for all future investigations.

VARA RESEARCH INSIGHTS

The VARA has served as a valuable resource for a wide scope of clinical and clinical-translational research, ranging from studies of disease outcomes and their determinants, genetic and environmental risk factors, the validation of biomarkers, and health care resource utilization, among others (Table 2).

Mortality and Morbidity

The VARA researchers observed a more than 2-fold increase in mortality risk among men with RA compared with age-matched men without RA in the general U.S. population (standardized mortality ratio [SMR] 2.1; 95% confidence interval, 1.8-2.5), a risk that seems to be higher than that observed in other RA cohorts.[3] Of the variables associated with mortality in this group, several potentially modifiable factors can be identified, including high erythrocyte sedimentation rate (ESR); elevated Disease Activity Score (DAS)-28 (a composite measure of disease activity including assessments of 28 joints); prednisone use; and low body weight. Patients with a body mass index < 20 kg/m^2 (considered underweight) had an SMR > 5.0. Based on more recent VARA evaluations, this association seems to be driven primarily by prior weight loss rather than absolute body weight.[4]

Table 1. VARA Participant Characteristics at Enrollment[a]

	Participants, %
Sociodemographics	
Age, y, mean (± SD)	63 (11)
Male	91
Race	
White	78
African American	16
Other	6
Smoking status and select comorbidities	
Smoking, ever	80
Hypertension	57
Cardiovascular disease	22
Diabetes mellitus	21
RA-related measures	
Disease duration, y, mean (± SD)	12 (12)
RF positive	80
Anti-CCP positive	78
Prednisone use	42
Methotrexate use	52
Anti-TNF use	22

Abbreviations: CCP, cyclic citrullinated peptide; RA, rheumatoid arthritis; RF, rheumatoid factor; TNF, tumor necrosis factor; VARA, VA Rheumatoid Arthritis Registry.
[a]Based on initial 1,720 participants.

In contrast to oral prednisone use, which is associated with increased mortality risk, the use of methotrexate (MTX), the most commonly prescribed disease-modifying drug in RA, was associated with about a 40% reduction in all-cause mortality.[3] This finding was consistent with data from other groups demonstrating that MTX use, alone or in combination with other treatments, is associated with substantial reductions in RA-related mortality, a benefit that seems to result from a robust cardioprotective effect in this population.[5] Indeed, prior examinations of a VARA subpopulation revealed high rates of major acute coronary events during observation, a risk that was higher with increased disease activity.[1] Studies are now underway in non-RA patients to examine the effectiveness of MTX in secondary cardiovascular disease prevention.

Although not associated with a reduced mortality risk in a previous study, hydroxychloroquine (HCQ) seems to be associated with favorable changes in lipid profiles.[3] The VARA participants using HCQ were far more likely to achieve target lipid goals than were participants not using HCQ, including total cholesterol to high-density lipoprotein cholesterol (HDL-C) ratio and HDL-C to low-density lipoprotein cholesterol ratio.[6] Importantly, these lipid changes appeared soon after HCQ initiation but were lost within 1 year of discontinuation. These results, coupled with data from separate

Table 2. Select Research Publications and Findings From VARA

Research Area	Lead Author, y	Findings
Morbidity and mortality in veterans with RA	Banerjee S, 2008[1]	Relatively high rate of cardiac events among male veterans with RA; higher disease activity predictor of cardiac events
	Mikuls TR, 2011[3]	Male veterans have 2-fold mortality risk vs age-matched men from the general population; correlates of mortality: prednisone use, disease activity, low BMI, white race, visit frequency, RF level, subcutaneous nodules, comorbidity, and absence of MTX
	Kerr G, 2014[6]	Hydroxychloroquine associated with improved lipid profiles in RA
Measuring disease burden in RA	Shaver TS, 2008[11]	DAS-28 often "not measurable" in real-life clinical practice; agreement between different remission criteria only fair (kappa statistic 0.2 to 0.4) with prevalence of remission varying widely based on criteria used
	Michaud K, 2009[9]	Poor to modest agreement between commonly used RA disease activity measures
	Curtis JR, 2011[28]	Development of administrative claims-based algorithm to assess RA treatment effectiveness
	Shahouri SH, 2011[10]	Sustained remission using ACR/EULAR criteria low in clinical practice; remission status and examination results vary substantially among physicians; issues of reliability and agreement between different remission criteria
	Masri KR, 2012[12]	Noninflammatory factors contribute to patient global self-assessments, impacting validity and reliability of measures incorporating global well-being scores
	Caplan L, 2013[29]	BMI does not impact joint count assessments in RA
RA risk factors	Gregersen PK, 2009[14]	REL, an encoding member of the NF-kappaB family of transcription factors, identified as a novel risk locus in RA
	Briggs FB, 2010[15]	Multiple polymorphisms shown to interact with PTPN22 (known risk variant in RA), affecting susceptibility to RA
	Mikuls TR, 2010[16]	ACPA positivity in RA influenced by interaction between HLA-DRB1 status and a deletion polymorphism in glutathione-S-transferase
	Davis L, 2014[30]	REL polymorphism associated with lipid profiles
Correlates of disease activity and severity in RA	Mikuls TR, 2007[31]	No major differences in disease expression between African Americans and whites with RA with exception of low frequency of subcutaneous nodules in African Americans
	Kerr GS, 2010[18]	Vitamin D deficiency common among veterans with RA and associated with ACPA status, higher tender joint counts, and increased CRP concentrations
	Miriovsky BJ, 2010[32]	ACPA and RF concentrations associated with lower rates of disease remission
	Mikuls TR, 2011[19]	Circulating levels of soluble CD14 increased in RA vs controls; associations with race, BMI, and RA disease activity
	Cannon GW, 2011[22]	MTX adherence associated with improved disease control
	Dwivedi N, 2012[20]	Antibody to deiminated histones and NETs associated with Felty's syndrome in RA
	Harlow L, 2013[21]	Antibody to hsp90 associated with RA-related interstitial lung disease
	Mikuls TR, 2013[23]	PTSD affects 12% of U.S. veterans with RA; associated with RA disease activity
	Sokolove J, 2014[17]	RF and ACPA synergistic in promoting inflammation in RA
Health care use	Oei HB, 2009[33]	High rates of stopping or switching agents in patients with RA treated with biologic agents
	Richards JS, 2009[34]	The Osteoporosis Self-Assessment Tool does not reliably identify men with RA who have osteoporosis
	Richards JS, 2012[35]	Nonadherence to bisphosphonate therapy high in patients with RA and more common with longer disease duration and minority race/ethnicity
	Cannon GW, 2014[27]	Treatment persistence similar among 3 available anti-TNF agents, although differences exist in frequency of dose escalation; annual anti-TNF costs defined

Abbreviations: ACPA, anticitrullinated protein antibody; ACR, American College of Rheumatology; BMI, body mass index; CRP, C-reactive protein; DAS, Disease Activity Score; EULAR, European League Against Rheumatism; MTX, methotrexate; NET, neutrophil extracellular traps; PTSD, posttraumatic stress disorder; RA, rheumatoid arthritis; RF, rheumatoid factor; TNF, tumor necrosis factor; VARA, VA Rheumatoid Arthritis Registry.

groups suggesting that HCQ may also improve insulin resistance and even prevent the onset of diabetes, suggest that HCQ could play an important adjuvant treatment role by reducing cardiovascular morbidity in RA.[7]

Measurement Pitfalls

Proposed best practices in RA management increasingly call for the adoption of a "treat-to-target" approach, with the goal of achieving and maintaining patients in a state of low disease activity or remission.[8] Although this strategy receives broad endorsement, its routine implementation is limited in the absence of a single universally accepted method for quantifying disease activity or assessing treatment response in the clinical setting. Indeed, several different measures of RA disease activity have been proposed, including at least 1 that was developed by VARA investigators.[9]

In a prior study, only poor to modest agreement was found among various proposed measures of treatment response and similar differences among the many proposed definitions of clinical remission.[9-11] Moreover, important limitations with the validity and reliability of the patient global health assessment in clinical practice was observed. This reflected, at least in part, the contributions of many non-RA factors to its value.[12] This is important, because the patient global health assessment is common to several composite disease activity measures, including remission criteria published by both the ACR and European League Against Rheumatism.[13]

RA Risk Factors

As part of a large collaborative consortium, VARA has been instrumental in studies examining risk factors for developing RA. These efforts have included reports of novel genetic risk factors in addition to others highlighting the importance of both gene-gene and gene-environment interactions in disease susceptibility.[14-16] Among existing literature, these reports inform future efforts to further the understanding of RA pathogenesis in addition to those working to identify methods of risk stratification and disease prevention.

Disease Activity and Severity

The VARA has served as an important resource for studies examining biomarkers and other predictive factors in RA. In addition to serving as important diagnostic tools in the clinic, a recent report highlighted the potential synergistic role of RF and anti-CCP antibody in promoting disease inflammation.[17] In this study, patients who were positive for both autoantibodies had much higher disease activity compared with seronegative patients or individuals with just 1 positive autoantibody. Likewise, patients who were positive for both RF and anti-CCP had higher serum concentrations of CRP and several proinflammatory cytokines than did patients who were seronegative or who had only 1 positive autoantibody.

In vitro studies done in parallel corroborated these observations, demonstrating for the first time that anticitrullinated protein antibody (ACPA)-containing immune complexes stimulated macrophage production of cytokines, which was further enhanced in the presence of RF. Other biomarkers investigated have included 25-hydroxy vitamin D, soluble forms of CD14 and autoantibodies to deiminated histones, neutrophil extracellular traps, and citrullinated heat shock protein.[18-21]

Of high relevance to the VA, VARA has demonstrated robust associations of treatment noncompliance, posttraumatic stress disorder (PTSD), and cigarette smoking with worse RA outcomes.[22-24] In a longitudinal study of about 1,500 VARA enrollees, PTSD was independently associated with higher pain levels, tender joint counts, and self-reported disability in addition to worse patient global well-being.[23] In contrast, PTSD demonstrated no associations with measures more commonly attributed to ongoing inflammation, including swollen joint counts, ESR, or DAS-28 scores. In addition to demonstrating associations of PTSD with a more severe RA course, these findings suggest that the higher disease burden observed in patients with comorbid PTSD may be attributable to noninflammatory factors that may call for management strategies beyond disease-modifying therapies.

Cigarette smoking is a well-known risk factor for RA, and emerging data, including preliminary results from VARA, suggest that smoking may render a detrimental impact on outcomes.[25] Current or former smoking (observed in about 4 of 5 VARA enrollees) is associated with higher ACPA and RF levels, relevant because these autoantibodies are predictive of worse long-term outcomes, including the accrual of joint damage.[24-26] Disease activity of VARA participants, measured with multiple clinical measures and an array of proinflammatory cytokines, was higher among current smokers and significantly lower in former smokers, with the former smoking group demonstrating disease activity levels approaching that of never smokers.[24] In addition to its benefit in other chronic health conditions, these results suggest that smoking cessation may be a viable approach in ameliorating the systemic inflammatory effects of RA.

Health Care Use

The economic and societal burden posed by RA is enormous and growing. A large proportion of this growth relates to the near exponential increase in direct treatment costs accompanying the emergence of highly effective biologic therapies. Capitalizing on direct links between the VARA and administrative databases maintained in VINCI (eFigure, available at www.fedprac.com), a recent investigation focused on the use of agents targeting tumor necrosis factor (TNF).[27] These efforts have shown that among the 3 most commonly prescribed TNF inhibitors, persistence on initial treatment is similar over time, although important differences exist across agents in the frequency with which patients with RA undergo dose escalation. Recognizing that several reports have demonstrated their cost-effectiveness in RA, annual VA costs for a course of anti-TNF therapy approximated $13,000 to $17,000 per patient treated, and higher costs did not seem to translate into improved patient outcomes.[27]

FUTURE DIRECTIONS

Several recent initiatives have been undertaken within the VARA with the goal of expanding the breadth and depth of research that it supports. Ongoing efforts will link VARA with data from the National Death Index, allowing for examinations of cause-specific mortality. Given the high frequency of VA beneficiaries receiving dual care outside the VA system, future links with datasets, such as those from Medicare, will be essential to assure a more optimal capture of relevant health outcomes. Indeed, in recent surveys, almost 1 in 2 VARA participants reported the receipt of dual care, which was most common in those aged > 65 years or receiving prior joint replacement surgery (Pascale Schwab, MD, written communication, April 1, 2015).

Efforts are underway to add other well-annotated specimens to the biorepository, such as synovial fluid and tissues obtained during routine care. The VARA investigators, under regulatory approvals, have begun to collect serum samples longitudinally to complement the prospective disease activity assessments already in place. Other efforts will include the full adoption of standardized patient note templates and transitioning data entry from a decentralized and semi-automated process to one that is centralized and fully automated. This change will reduce the resources required for site investigators and study personnel.

OTHER RHEUMATIC DISEASE REGISTRIES

The VA health care system is the largest integrated health system in the U.S. and as such, represents an ideal setting for the investigation of chronic health conditions and patient outcomes. The assets and potential of this system have been at least partially borne out in VARA over the past decade and now extend to other rheumatic disease registries in the VA, including those focused on spondyloarthritis (PULSAR) and gout (Crystal registry). Together, these registries are poised to provide valuable information about these rheumatic conditions and will continue to serve as models for patient registries from other medical disciplines in the VA and elsewhere. ●

Author disclosures

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