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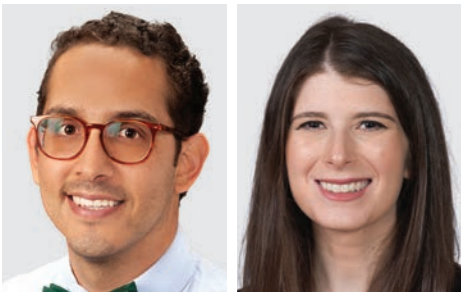
Editorial

Keep It in Mind: Assessing the Risk of Dementia in Patients With Rheumatoid Arthritis and Opportunities for Intervention



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Chronic systemic inflammation contributes directly to increased cardiovascular disease (CVD) burden in patients with rheumatoid arthritis (RA).[1] In addition, chronic systemic inflammation is believed to play an important role in the development of other aging-related conditions, including cognitive impairment and dementia.[2] Aging-related chronic systemic inflammation, also known as inflammaging, and neuroinflammation are increasingly recognized as central to the pathogenesis of neurodegenerative diseases such as Alzheimer dementia. Although results are not uniform across studies, an increased risk of dementia in adults with RA, when compared to age-matched comparators, has been reported in several epidemiological studies.[3] The magnitude of this risk varies across studies, and according to one recent study from the Rochester Epidemiological Project (REP), increased risk has declined over time, narrowing the gap between adults with and without RA.[4]

In this issue of *The Journal of Rheumatology*, Kodishala et al present the results of a retrospective population-based cohort study assessing risk factors for incident dementia in adults with RA from the REP.[5] The REP includes granular data on participants, including diagnosis, comorbid conditions, and treatments, as well as important disease features such as clinical characteristics (eg, erosive disease, extraarticular manifestations) and laboratory markers (eg, presence of rheumatoid factor and/or anticyclic citrullinated peptide antibody, inflammatory markers). Incident dementia, the outcome of interest, was ascertained through the use of International Classification of Disease, 9th and 10th revision codes; despite some limitations, including the inability to distinguish among dementia subtypes, diagnostic code-based algorithms have been shown to have moderate positive predictive value in the identification of all-cause dementia.[6] Multivariate Cox proportional hazard models were employed to describe risk factors associated with incident dementia in patients with RA, adjusting for relevant covariates, including CVD and CVD risk factors.[5]

During a median follow-up of 8.5 years, 11.6% (103/886 patients) of patients with RA received a diagnosis of dementia.[5] Similar to what has been reported in the general population, hypertension, heart failure, depression, and antihypertensive medication use at baseline were associated with an increased risk of dementia, including after adjusting for covariates.[7,8] In contrast with the effect of CVD on the risk of incident dementia, where increased risk seems to be concentrated at a younger age,[9] older age at RA incidence was associated with an increased risk of dementia.[5] Depression, anxiety, and any CVD at any point during follow-up also were associated with increased risk for dementia. Interestingly, the authors are the first to demonstrate that large joint swelling and the presence of rheumatoid nodules were associated with an increased risk of dementia during follow-up; however, other disease features often associated with more severe disease (eg, severe extraarticular manifestations, erosive disease) did not show this association. No association between risk of dementia and use of either conventional

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synthetic disease-modifying antirheumatic drugs (csDMARDs) or biologic DMARDs (bDMARDs) was observed.

Although the study by Kodishala et al has some inherent methodological limitations (eg, retrospective, homogenous population), the results highlight clinically meaningful risk factors for identifying adults with RA at higher risk for dementia.[5] CVD screening and preventive measures should be addressed in adults with RA, as in all individuals. Screening for depression and anxiety, and referral for further evaluation and treatment also could have a significant impact on clinical care. Although outside the scope of the current study, chronic pain and certain medications (eg, anticholinergics, antidepressants, benzodiazepines) remain important risk factors for and potential causes of reversible cognitive impairment.[10,11] Finally, lifestyle modifications, including regular physical activity, have been shown to mitigate the risk of cognitive impairment in dementia, and these benefits on self-reported cognitive difficulties also have been reported in patients with RA.[12,13]

The possible role of antiinflammatory therapies, including DMARDs, in the prevention and treatment of dementia remains of particular interest. In light of the mechanistic contribution of tumor necrosis factor (TNF) to the pathophysiology of Alzheimer dementia, TNF inhibition has been evaluated in 2 small randomized studies and has shown some benefit in adults with Alzheimer dementia.[14,15] However, prior observational studies examining this association in adults with RA have shown mixed results.[16,17] Two recent cohort studies using a national claims dataset have assessed the effect of DMARDs in the development of dementia in adults with RA. One study incorporating propensity score matching did not find a difference in dementia risk in adults with RA treated with TNF inhibitors, interleukin 6 inhibitors, or Janus kinase inhibitors compared to abatacept.[18] A second study using the same dataset found decreased risk associated with treatment with biologic/targeted synthetic DMARDs (b/tsDMARDs) compared to csDMARDs only, including after adjusting for covariates; however, no differences were observed among classes of b/tsDMARDs.[19] These observational studies should be interpreted with caution, and additional longitudinal studies are needed to assess the effect of DMARD treatment on incident dementia. Nevertheless, recent declines in excess risk of dementia in adults with RA may point to an overall benefit of adequate disease control related to b/tsDMARDs, rather than a class-specific benefit. Although Kodishala et al[5] did not observe an association between DMARD use and dementia, they report an increased risk of dementia in patients with a phenotype suggestive of late-onset RA (ie, older age at RA diagnosis, large joint involvement, no erosive disease), a subgroup of patients who have been reported to receive lower rates of DMARDs (including bDMARDs).[20] Although the risks and benefits of DMARD use should be considered in each patient through a shared decision-making process, these observations may support another potential benefit of DMARD use in this patient population and may suggest that chronological age should not preclude the use of these therapies in older adults.

The current study by Kodishala et al[5] adds substantially to the existing literature on incident dementia in adults with RA, underscoring the role of known CVD risk factors and providing new insights into RA-specific predisposing factors. Further longitudinal studies in diverse populations of adults with RA are needed to confirm the findings of this study and address outstanding questions, such as the degree of protection against dementia offered by DMARD therapy and the treat-to-target approach. Mitigation of dementia risk in adults with RA may represent an important opportunity for improving the health and well-being of aging adults with RA.

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