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Commentary

The effect of anti-rheumatic drugs in reducing the risk of Parkinson's disease in patients with rheumatoid arthritis

Running title: risk of PD and anti-rheumatic drugs

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Abstract

This commentary highlights the major points raised by a recent study investigating the effect of anti-rheumatic drugs used for the treatment of rheumatoid arthritis (RA) in reducing the risk for Parkinson's disease (PD). Several studies in the past have assessed the effect of anti-rheumatic drugs used for the treatment of RA in lowering the risk of incident PD, but the results have been inconsistent. Those studies left unanswered the question as to whether the reported risk reduction is independent of treatment with disease modifying anti-rheumatic drugs (DMARDs) or not. Several of the reported data indicate that DMARDs appear to further reduce this risk. We raise several points that we think must be taken into account in future studies and emphasize the need for continuous research to explore the underlying mechanism, which could be responsible for the presumed reduced risk for PD development in RA patients treated with specific biologics.

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I. INTRODUCTION

A wealth of data explored in the recent past the effect of anti-rheumatic drugs used for the treatment of rheumatoid arthritis (RA) in reducing the risk of Parkinson's disease (PD) and Alzheimer's disease (AD)(1-4). Other studies have yielded conflicting results and RA *per se* (irrespectively of its treatment) has been associated with either lower of higher risk for those diseases (5). Nevertheless, a recent study has found that patients with rheumatoid arthritis have a lower risk of PD (6). To reach this conclusion the investigators of this nationwide case-control study analyzed data from the Finnish Parkinson's Disease (FINPARK) cohort, which includes 22,189 Finnish patients with clinically overt PD diagnosed in a 20-year period (1996 to 2015)(6). More precisely, the investigators analyzed cases with PD diagnosed during 1999 to 2015 and rheumatoid arthritis diagnosed >3 years before the diagnosis of PD. Each case was matched with up to 7 controls by age, sex, duration of rheumatoid arthritis, and geographical region. Overall, 315 cases with PD and 1,571 matched controls were included in the final analysis. As it was expected, the majority of the patients were female (>60%) (6); RA is more common in

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women than in men. The major finding of this large, well-executed study was that the use of DMARDs is not significantly associated with risk of PD, the only exception being chloroquine/hydroxychloroquine. Hence, no effect on the risk of other DMARDs, such as methotrexate, sulfasalazine, immunosuppressants and gold preparations, were noted. It must be noted though that a 3-year lag period exercised between exposure and outcomes (6). Chloroquine/hydroxychloroquine was indeed associated with decreased risk (adjusted odds ratio [OR] 0.74, 95% confidence interval [CI] 0.56-0.97) i.e a 26% lower risk of PD. The Authors' conclusion was that "this study provides Class II evidence that in individuals with rheumatoid arthritis using DMARDs, only chloroquine/hydroxychloroquine was associated with a potentially decreased risk of developing PD" and that the lower risk of PD in RA patients treated with chloroquine/hydroxychloroquine must be assessed further in terms of the potential underlying mechanisms (6).

This study had several limitations. For example, during the study period the number of patients on biological DMARDs (bDMARDs) was small and therefore it is not clear whether the sensitivity analysis of the effect of bDMARDs failed to find any association due to the small number of users. We must point here that the investigators included an endless list of anti-rheumatic drugs categorized separately ranging from sulfasalazine, chloroquine or hydroxychloroquine, gold preparations, including auranofin and sodium aurothiomalate, leflunomide and immunosuppressants. In the latter list several drug regimens were included consisting of azathioprine, certolizumab pegol, ciclosporin, mycophenolic acid, as well as biological DMARDs (bDMARDs)(6). In the list of bDMARDs the following biologics were included: abatacept, adalimumab, anakinra, etanercept, golimumab. As the authors pointed out, methotrexate was studied separately because of its common use but it is not clear whether RA patients treated with combination of methotrexate and bDMARDs were sub-analyzed. The same also applies for corticosteroids covering prednisolone, prednisone, and methylprednisolone. What is surprising us that the investigators did not assess dose-response or duration of treatment analyses. They argue that that was due to limitations caused by the sample size (6).

Another limitation of the study was the inability to analyze data related to smoking use. This would be of particular interest as smoking is a known modulator of an increased risk of RA in animal and clinical studies, while is associated with a reduced risk of PD. The authors speculated that if there was an effect this would be evident in the analysis of smoking-associated comorbid conditions, including cancer but this was not the case.

Genome wide association studies have suggested common immunogenetic pathways are shared by RA and PD (7). Also, several recent studies assumed that immune-mediated inflammatory processes noted in RA are also involved in the development of PD (8). That implies the potential of immunoregulatory drugs (used in the treatment of RA) in reducing the risk for future development of PD in successfully treated RA patients (9). However, if that was true and the dysregulation of the immunomodulatory inflammation had a significant impact in the development of PD, it would be expected that those anti-rheumatic drugs with the strongest anti-inflammatory potential would had the most significant effect in the reduced risk of PD, and that was not noted.

In our opinion these findings may not be merely explained by chance and may indeed bear a pathophysiological meaning given that data in animal studies have found that some of those immunomodulatory drugs have also an anti-PD potential effect. The reduced risk associated with chloroquine/hydroxychloroquine must be explored further. Hydroxychloroquine appears to be able to improve motor functions in an experimental model of PD (10). Also, chloroquine, in general, protects dopaminergic neurons against neurotoxins (11). Those experimental data must be treated with caution, as clinical data are not supporting an effect of hydroxychloroquine in reversing the progression of dementia in patients with AD(12). The authors have also speculated that the association between chloroquine/hydroxychloroquine and reduced risk of PD could be explained by a survival bias since both chloroquine and hydroxychloroquine are old drugs, and RA patients treated with those drugs have are arguably less severe disease and better overall health status than those treated with other DMARDs (6).

II. CONCLUSION

There is an increasing body of evidence indicating a reduced risk for PD in patients with RA but is not clear whether the effect of the reported risk reduction is independent of treatment with disease modifying anti-rheumatic drugs (DMARDs) or not. Several of the reported data indicate that DMARDs appear to further reduce this

risk. In a recent study such an effect appears to be exerted by chloroquine/hydroxychloroquine, a finding, which requires further investigation, in view of the reported anti-PD effect of those regimens.

AUTHORS CONTRIBUTION

ED and DPB scripted the draft. The Authors approved the final version of the manuscript.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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