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Editorial

The impact of smoking on rheumatoid arthritis outcomes

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1. Introduction

The use of tobacco is a risk factor for the development of rheumatoid arthritis (RA). This is particularly so for the forms associated with the production of anti-citrullinated protein antibodies (ACPA), which is linked with its interaction with certain predisposing genetic factors, especially the HLA DRB1 alleles containing the shared epitope. This has been particularly well documented in Northern Europe [1]. Moreover, smoking is likely to have an impact on the outcome of the rheumatism, particularly in terms of the activity and the severity of the disease as well as the response to treatment.

2. Smoking and the activity of RA

While passive smoking (Swedish BARFOT study) and prior use of tobacco do not appear to have an influence on the activity of RA [2], this is not the case for active smoking. Indeed, both with established forms (American VARA registry) and early stages of RA, active smoking appears to be associated with more substantial joint inflammation, as indicated by a greater number of swollen joints and higher values of CRP [3,4]. This results in higher DAS28 values. These effects of active smoking on the activity of the disease do not appear to be linked to confounding factors such as anxiety, being overweight, etc. Compared to non-smokers, the levels of pro-inflammatory cytokines and rheumatoid factors (which are known to amplify the inflammatory reaction induced by ACPA) are higher. Indeed, this relationship between tobacco and activity is seen only with RA ACPA+. Furthermore, it is only found at a given time (cross-sectional approach) and in a limited number of studies. Indeed, in the American BRASS cohort comprising 1100 proven cases of RA followed for seven years, active smoking was not a parameter that could predict the level of activity measured during the years of follow-up [5]. This observation has been confirmed in other studies [6]. In this case, the effects of tobacco are probably eclipsed by the maintenance treatment, which is often stronger in smokers with rheumatoid arthritis who have a higher baseline activity.

3. Smoking and the severity of RA

The severity of the disease can be defined by the degree of structural damage, the occurrence of extra-articular manifestations and/or of complications, particularly those involving infections and tumors.

3.1. Smoking and progression of radiological lesions

A significant association between the use of tobacco and structural damage has, for the most part, been shown in cross-sectional studies, which are subject, however, to many biases. Longitudinal studies, on the other hand, paint a very different picture. Two studies regarding recent RA cases have suggested a link between active smoking and the degree of structural damage measured at two years [6] or the radiological progression at one year. Thus, in the SWEFOT therapeutic trial, active smoking was associated with a more substantial proportion of patients who had a faster radiological progression (FRP) (total Sharp score ≥ 5 at one year) with an OR of 2.78 (95% CI: 1.48–5.19) after adjustment for the therapeutic strategy (methotrexate [MTX] as monotherapy versus MTX + infliximab or tritherapy). This allowed the authors to construct a matrix for predicting a FRP according to three variables (i.e. the initial erosions, CRP and tobacco use) [7]. While a recent meta-analysis involving six confirmed cohorts indicates that smokers have a faster radiological progression, this link between tobacco and structural progression was lost after adjustment for the ACPA (not affected in at least one of the two preceding studies). This data was confirmed in a recent analysis of the ESPOIR cohort, in which the radiological progression at one or three years was not different between active smokers and former smokers/non-smokers [8]. The risk of developing structural damage appears to be lower, however, in smokers as has already been reported for the English cohort of Norfolk and the Swiss SCQM-RA registry, for which a dose dependant inverse relationship has been noted between the

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use of tobacco and radiological progression [1]. This phenomenon may be explained by the fact that recourse to biological maintenance treatments or to systemic glucocorticoids is more common in these patients. Even though there are several limiting factors in these studies, particularly in terms of heterogeneity of the collection of information regarding the use of tobacco, all of these elements clearly show that the link initially suggested between tobacco and the structural severity is in fact mediated by ACPA, for which production increase in response to smoking, amongst other factors.

3.2. Smoking and extra-articular manifestations

Tobacco use is a factor that appears to contribute to the occurrence of extra-articular manifestations (e.g. nodules, diffuse interstitial lung disease [ILD], and vasculitis). Indeed, in a case-controlled study carried out based on the BARFOT registry, aside from the degree of activity of the disease and the functional consequences during the first years of progression, active smoking at the early stage of the disease was also found to be an independent risk factor for the occurrence of extra-articular manifestations (EAM) [9].

3.3. Rheumatoid nodules

Several studies have revealed a link between active smoking and the occurrence of subcutaneous nodules in European, African-American and Asian populations [1].

3.4. Diffuse interstitial lung disease

At least three studies have revealed a role for tobacco use in the development of subclinical or clinical DILD [10]. Thus, in a British multicenter case-control study, tobacco use was a risk factor for the development of ILD; similar to age, being male, and being positive for auto-antibodies (RF and/or anti-CCP). In multivariate analysis, for patients without anti-CCP, tobacco use remains a risk factor. It appears to be associated with specific types of ILD (mostly common interstitial lung disease rather than non-specific disease), although not with the extension of lesions. In this study, male smokers (or who had a history of smoking) and seropositive individuals had a higher risk of developing ILD [11]. This relationship is not surprising in the sense that tobacco use promotes citrullination of proteins of the windpipe and the bronchial tree and hence, contributes to the in site production of ACPA in predisposed subjects, with the antibodies playing a role in the genesis of ILD. It also has a direct role in the occurrence of bronchopulmonary lesions [10].

3.5. Periodontal diseases

Porphyromona gingivalis periodontitis, like tobacco use, is a risk factor for the development of RA. It is also an EAM mediated by ACPA, susceptible of being sustained by the activity of the disease as well as by smoking, which is also a risk factor for periodontal disease.

3.6. Tobacco use and complications

3.6.1. Tobacco use and the risk of infections

The risk of infections with RA is due to several interlinked factors that include the activity/severity of the disease, immunosuppressive treatments (particularly glucocorticoids), advanced age of the patients, certain comorbidities (e.g. diabetes, chronic bronchopulmonary pathologies and chronic kidney failure) as well as smoking, which alters the innate self-defense mechanisms. These effects on the immune system can persist for years after exposure to tobacco [12]. Indeed, in the English Norfolk registry involving 2,318 patients followed for more than seven years, the risk of severe infections was enhanced by active smoking, with a relative risk of 1.6 (95% CI:1–2.5) [13]. Furthermore, while a study carried out with 259 patients afflicted with RA who received one or more arthroplasties of the hip and/or the knees showed that tobacco use was not associated with a postoperative risk of infection [14], a recently published meta-analysis of 66 studies that evaluated the risk factors for periprosthetic infection in case of installation of an arthroplasty revealed that RA and tobacco use are two risk factors, similar to diabetes, obesity, corticoids, intrajoint infection prior to a cortisone derivative and being male. Smoking nearly doubled the risk of infection (RR = 1.83 [1.24–2.70]) [15]. The risk was reduced considerably when the use of tobacco was interrupted three months prior to the surgical procedure.

To reduce the risk of infection with RA, anti-pneumococcal vaccination is recommended. Here again, tobacco use appears to have an impact on the vaccination response, since the level of IgG and the immune response toward the two serotypes of the conjugated heptavalent vaccine appear to be lower in active smokers who have RA treated with MTX [16].

3.6.2. Tobacco and the risk of death

The risk of death is enhanced with RA compared to the general population. Based on the data from the American Nurses Health Study (NHS; 1976–2012), Veterans Affairs Rheumatoid Arthritis (VARA) cohorts and the British Clinical Practice Research Databank (CPRD), data base, the risk of death is 1.5 to 3 times higher with RA [17–19]. This increase in mortality, regardless of the cause, is explained in part by active smoking. After adjustment for age and gender, the risk of death was twice as high for active smokers compared to non-smokers or former smokers. This risk of death is linked with the more frequent occurrence of cardiovascular issues and lung cancers.

4. Impact of smoking on treatments

Tobacco use is likely to have an influence at three levels: the response to therapy, drug survival and dose reduction.

4.1. Tobacco use and the response to conventional prophylactic treatments

The studies to date are exclusively in regard to MTX. These are based on the early cohorts of the Epidemiological Investigation of Rheumatoid Arthritis (EIRA), SWEFOT (initial phase on MTX as monotherapy) and BEST (subgroup on MTX as monotherapy with increasing doses) and they found a reduced response to treatment at three and/or six months in case of active smoking at the start of the treatment [1,20,21]. There does not appear to be an impact of having been a smoker, or of the degree of smoking. No difference was noted according to the ACPA status [20].

4.2. Tobacco and the response to antagonists of TNF-alpha

The data to date are mainly in regard to three entities (i.e. infliximab, etanercept and adalimumab). There is currently no data available for golimumab and for certolizumab. Data from a study in Hungary that was presented at the EULAR conference of 2015 (Szekanecz et al. Ann Rheum Dis 2015, 74:474) has yet to be published in full. As for MTX, based on the data derived from the EIRA cohort, as well as English (BSRBR), Portuguese, and Swedish registries, active smoking is associated with a lesser response to anti-TNF at three and/or six months and with lower rates of remission [1,20,22,23]. The results derived from the English registry are compelling for infliximab, while they are much more ambivalent

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