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Is Subclinical Vasculitis in Rheumathoid Arthritis a Predictor for the Outcome?

A META-ANALYSIS

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Abstract

The subclinical vasculitis draws the attention of the researchers after an imagistic study that showed on a positron emission tomography (PET) scan aortic inflammation and such a link with cardiovascular manifestations of rheumatoid arthritis (RA). This is the breaking point for linking the evolution of RA patients with subclinical vasculitis.

The main objective of the study was to outline the importance of the presence of vasculitis (subclinical) in the outcome of rheumatoid arthritis, an autoimmune, inflammatory disease. To attain our objective, a meta-analysis was performed. The data were gathered from the studies published on the major medical databases such as PubMed, PlosOne, EMBASE, clinicaltrials.gov. The keywords in our research were: subclinical vasculitis, outcome, rheumatoid arthritis. A number of 110 studies were found. After applying the inclusion criteria, four studies were included in our meta-analysis. Our main question to be asked was if the subclinical vasculitis favors or not the outcome of rheumatoid arthritis. The outcome was defined as the presence of extra joint manifestations and serious adverse effects such as death. The meta-analysis was performed using the REvMan5.4 software provided by Cochrane.

Results: A random-effects model for dichotomous data was used due to the high heterogeneity among the studies (I^2: 89%). Ninety - two subjects from the included studies were diagnosed with vasculitis and 706 patients didn't fulfill the criteria for vasculitis. As for the subclinical vasculitis, 92 patients from group one presented with it and 14 out of 706 non-vasculitis patients. They developed a worse outcome. The overall effect was that the subclinical vasculitis is a negative predictor for vasculitis.

Conclusions: Subclinical vasculitis can be a predictor for worse outcomes in rheumatoid arthritis.

Keywords: vasculitis, outcome, rheumatoid arthritis, meta-analysis

I. INTRODUCTION

Rheumatoid arthritis is an autoimmune, inflammatory disease untreated being a disabling condition. It was known that the male gender, the presence of nodules, the use of different disease-modifying antirheumatic drugs (DMARDs) ore corticosteroids, the presence of erosions are factors that modify the outcome of the disease [1].

The latest studies showed that the subclinical inflammation (e.g. presence of Doppler signal inside the joints as seen by ultrasound) can be a marker for the outcome of the patients with RA. But, another mini-invasive study provided data about the fact that different types of synovitis can be linked with the outcome of RA. Unfortunately, there are just a few studies with heterogeneous designs published in the literature and to perform an intra-joint biopsy even if you are skilled in ultrasound (US) can be time and resources consuming and physician and patient dependent [1].

So, the fact that the cutaneous vasculitis is one of the first extra-joint clinical manifestations in RA and that the cutaneous biopsy is more easily to be performed and accepted by the patient, one of our hypotheses was to outline the importance of subclinical cutaneous vasculitis in the systemic outcome of the patients with RA [1].

II. MATERIAL AND METHODS

A study based on a meta-analysis was performed. Meta-analysis was chosen because is a statistical tool that is capable of gathering a large amount of data irrespective to the type and the heterogeneity of the study, even thou we preferred the randomized, controlled, clinical trials with similar designs. In order to estimate the risk factor as a cutaneous subclinical

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vasculitis, the meta-analysis is capable of integrate all the data of the individuals studies and offer us a pooled effect. [2-6]

The data were gathered from the studies published on the major medical databases such as: PubMed, PlosOne, EMBASE, clinicaltrials.gov. The keywords in our research were: subclinical vasculitis, outcome, rheumatoid arthritis. A number of 110 studies were found. After applying the inclusion criteria, four studies were included in our meta-analysis. The inclusion criteria were the following: patients to be diagnosed with subclinical vasculitis, patients to be diagnosed with rheumatoid arthritis, open-access studies, complete data presented by the researchers to perform the meta-analysis. The different studies designs and the reduced numbers of those who aimed for subclinical vasculitis explains that only four studies were included in our meta-analysis.

Our main question to be asqued was if the subclinical vasculitis favours or not the outcome of rheumatoid arthritis. The outcome was defined as the presence of extra-joint manifestations and serious adverse effects such as death. The meta-analysis was performed using the REvMan5.4 software provided by Cochrane.

The hypothesis to be tested was if subclinical vasculitis can be a marker for the outcome of RA patients? Starting from this question, another prospective, mini-invasive studies can be performed.

III. RESULTS AND DISCUSSION

RESULTS

A random-effects model for dichotomous data was used due to the high heterogeneity among the studies (I^2: 89%). The heterogeneity is given by the I^2, which represents the number of total variations observed in the studies. Its value is situated between 0 and 100%. Zero means a lack of heterogeneity and if the value is closed to 100%, the heterogeneity is high with risks of bias data.

Ninety-two subjects from the studies included in the current meta-analysis were diagnosed with vasculitis and 706 patients didn't fulfill the criteria for vasculitis. As for the subclinical vasculitis, 92 patients from group one presented with it and 14 out of 706 non-vasculitis patients. They developed a worse outcome. The overall effect was that the subclinical vasculitis is a negative predictor for vasculitis (z: 1.86, p:0.06) (Fig.1.).

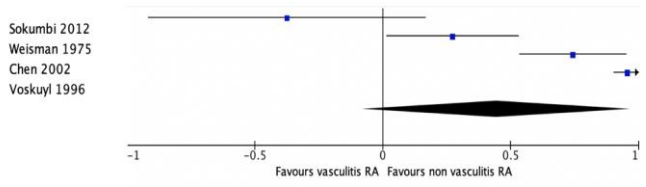

Figure 1. The forest plot of the meta-analysis

DISCUSSION

The vasculitis associated with RA was first recognized in the early 20th century, being associated with different DMARDs used at that time. It is well known that vasculitis means the inflammation of the blood vessel wall followed by necrosis (ischemia and infarction) [1, 7].

Even so, in many cases the biopsy is considered as the golden standard, due to the complications associated with the underlying disease it can be sometimes difficult to be achieved. That is why there are so little data about histopathological proven biopsies (subcutaneous) and the outcome of RA patients [8-15].

The risk factors known to be associated with vasculitis in RA are associated co-morbidities such as peripheral vascular disease, cerebrovascular disease, biological DMARDs, and severe RA.

In our meta-analysis, a non-vasculitis RA profile favors the outcome, even though the statistical data are biased by the heterogeneity of the studies selected and so the results should be interpreted carefully.

The male gender can be more exposed to vasculitis according to the data published. The most recent study included in our meta-analysis, published by Sokumbi et al., showed that the majority of histopathological confirmed vasculitis was seen in women. The same data were reported by Chen. But, the initial studies such as Voskuyl one reported that the male gender was more prone to develop vasculitis. So, maybe something changed concerning the environmental factors that improved the evolution of male patients versus female patients from the 20th century to the 21st century [7-10].

The vasculitis is associated with different DMARDs used in the treatment of RA. The DMARDs involved are methotrexate, TNF inhibitors, and abatacept. In the included meta-analysis studies, there were no or scarce data regarding the use or previous use of DMARDs.

In the Sokumbi study, the majority of the patients with proved vasculitis were on corticosteroids as well as on biological DMARDs. The biological DMARDs – the TNF inhibitors are to be blamed to induce vasculitis. The association between the biological DMARDs and vasculitis can be biased by the degree of the underlying disease – RA, a more developed and aggressive one [10-15].

The data of the genetic profile of our patients weren't disclosed to make some comments about the genetic predisposition for developing vasculitis.

IV. CONCLUSION

Subclinical vasculitis can be a predictor for worse outcome in rheumatoid arthritis.

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