ID: RE16-00001 Clinical Follow-up of Anti-Carbamylated Antibody Status in Rheumatoid Arthritis NCT02958319

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Clinical follow-up of Anti-Carbamylated Antibody Status in Rheumatoid Arthritis patients at 6, 12 and 18 months

Concept

Patients with rheumatoid arthritis with positive antibodies against carbamylated proteins (anti-CarP) have a more severe clinical course

Background

The immune based pathophysiology of rheumatoid arthritis is one of the most studied. We already know that the citrullinated peptide antigen inducing antibody formation and subsequent [LVG1] anti-cyclic citrullinated peptide (anti-CCP). In some patients this can explain the clinical manifestations. However it is also apparent in some groups of patients with rheumatoid arthritis who do not have anti-CCP antibodies. It is possible that there is the presence of a variety of antigens exposed during the disease, and perhaps different clinical presentations associated with each of them.

The use of anti-CCP has been included in the classification criteria of rheumatoid arthritis developed by the American College of Rheumatology in 2010 and generated the presence of two sub-groups of patients with rheumatoid arthritis, the positive and negative for anti-CCP. It is very important to study the presence of anti-CCP antibodies in rheumatoid arthritis patients because they influence the clinical behavior and response to treatment. In very early or undifferentiated arthritis, the presence of anti-CCP antibodies can predict the presence of erosions in the course of the disease. On the other hand, patients with anti-CCP tend to have better responses to treatment with methotrexate.

Initially it was thought that the obvious pathophysiological link between rheumatoid arthritis and citrullinated peptides leading to formation of antibodies was the apparent cause of the clinical manifestations, but soon it was demonstrated that there were groups of patients with clinical manifestations of rheumatoid arthritis that did not have anti-CCP antibodies so its genesis was not explained by citrullination. Then it is plausible to find a diversity of antigens exposed during the illness and perhaps different clinical presentations associated with each one or its combinations. So, some studies are attempting to show other possible antigens involved in rheumatoid arthritis and one of them uses homocitrulline as an antigenic basis to rheumatoid arthritis pathophysiology. The carbamylation or homocitrullination is a posttranslational

modification of proteins that occurs when the amino acid lysine reacts with cyanate in a non-enzyme-mediated process generating homocitrulline. Mydel, Bokarewa and cols. demonstrated that immunization of mice with homocitrulline- and citrulline-containing peptides leads to development of erosive arthritis following intra-articular injection of homocitrulline-containing peptides and proposed that homocitrulline induced activation of T cells is a key mechanism in the pathogenesis of autoimmune arthritis as it serves as an initial triggering event for neo-epitope recognition of citrulline containing peptides. Recently It has been shown that rheumatoid arthritis patients have homocitrullinated proteins in their joints which can trigger an inflammatory response with formation of antibodies against homocitrulline.

Shi et al. showed in a study of 571 rheumatoid arthritis patients and 350 healthy subjects the following statements:

- Anti-CarP antibodies are different from anti-cyclic citrullinated peptide and they do not cross-react.
- The Anti-CarP antibodies are present in sera of patients with rheumatoid arthritis.
- Anti-CarP antibodies are found in sera of patients without anti-CCP.
- The Anti-CarP antibodies are associated with increased progression to radiographic damage.

Thus, anti-CarP antibodies are a promising new serological marker for anti-CCP negative Rheumatoid Arthritis and are associated with a more severe clinical course.

Hypothesis

Patients with rheumatoid arthritis with positive antibodies against carbamylated proteins (anti-CarP) have a more severe clinical course and elevated cardiovascular risk.

Design

It is a parallel study for clinical follow-up, observational.

Description of Subject Population(s)

- Patients older than 18 years old, both genders, with rheumatoid arthritis diagnosis according to ACR EULAR 2010 classification that accepted and signed informed consent that were seen at the Rheumatology Clinic in Hospital Universitario “Dr. José Eleuterio González”, Monterrey, NL. México.
- Exclusion: Chronic kidney disease and pregnant patients

Assessment Tools and Procedures

- DAS-28 VSG
- Lipid profile

Length of Study in Months

- 18

Primary Endpoints

- Clinical activity measured by DAS28-VSG in patients with rheumatoid arthritis according to antibodies against carbamylated proteins (anti-CarP) status at 6, 12 and 18 months

Secondary Endpoints

- Number and accumulative dose of DMARDs according to antibodies against carbamylated proteins (anti-CarP) status at 6, 12 and 18 months
- Cardiovascular risk according to antibodies against carbamylated proteins (anti-CarP) status at 6, 12 and 18 months

Clinical Information

- Total number of subjects 262
- Number of subjects for each treatment arm 131
- Study Duration Per Patient (in Months) 18

Primary Objective

The primary objective of this study in adult subject with RA is as follows:

1. To explore the clinical differences in activity indexes (DAS28-VSG) at 6, 12 and 18 months of follow up according the anti-CarP status

Study Secondary Objective(s)

- To investigate the remission rate (DAS28-VSG) according the anti-CarP status
- To compare the percentage of subjects with DAS28-VSG LDA at 6, 12 and 18 months according the anti-CarP status
- To compare the accumulative dose of prednisone between groups according the anti-CarP status
- To compare the number and doses of DMARD´s used to treat RA between groups according the ant CarP status

Study Design

- Prospective, Non-Randomized, Open Label
- Inception Cohort Study

Study Primary Efficacy Endpoints

The primary efficacy endpoints is as follows:

- The percentage of subjects who meet DAS28-VSG < 2.6 at 6, 12 and 18 months in the Anti CarP+ve arm compared Anti CarP-ve arm

Study Secondary Efficacy Endpoints

The secondary efficacy endpoints are as follows:

- Percentage of subjects with DAS28-VSG LDA at 6, 12 and 18 months at 6, 12 and 18 months in the Anti CarP+ve arm compared Anti CarP-ve arm
- Median of the cumulative dose of prednisone at 18 months at 6, 12 and 18 months in the Anti CarP+ve arm compared Anti CarP-ve arm
- Mean of the number and doses of DMARD´s used to treat RA at enrollment at 6, 12 and 18 months in the Anti CarP+ve arm compared Anti CarP-ve arm
- Cardiovascular risk according to anti-CarP status

Study Sample Size Calculation

A total of 262 subjects will be followed in this study. According the pilot study were we found a 12 month remission rate in the Anti CarP+ve of 33% arm compared Anti CarP-ve arm of 50%, with a difference of 17% in remission rate at 12 month follow-up. We need 131 patients per group. A 2 group continuity corrected chi square test with a 2-sided significance level (alpha) of 0.05 was used to compare sample size and a 0.2 (beta) to power.

Study References

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