Minutes of the MATURA Precision Medicine Patient Advisory Group (PM-PAG) – 16th Meeting
Zoom
10 – 11:30am, 6th December 2021

Attendees:
Zoe Ide, Lead, MPAG Chair
Sonia Jeevanason, Lay member of PM-PAG
Caroline Wallis, Lay member of PM-PAG
Jo Peel, EMR Trial Manager
Dr Myles Lewis, Clinical Reader in Rheumatology
Dr Felice Rivellese, Clinical Research Fellow
Louise Warren, EMR Trial Manager

Apologies:
Chris Wills, Lay member of PM-PAG
Louise Boyce, Lay member of PM-PAG

JP welcomed all attendees to the meeting.

JP explained that a new member would be joining the group and she will hopefully join the next meeting.

Myles gave an overview of the R4RA trial. In the trial, a biopsy was performed and the biopsy sample was analysed under the microscope and additionally the RNA was sequenced to look at the genes. Patients were treated with Rituximab and Tocilizumab. We believe that the RNA sequencing method is more accurate than looking down the microscope. The patients were grouped into B cell poor (B cell numbers are low) and B cell rich (B cell numbers are high) groups. Myles explained that in the trial, if a patient is B cell poor classified by RNA sequencing, they are half as likely to respond to rituximab. In addition to the primary endpoint (CDAI≥50% improvement at week 16), other methods were also used to measure how patients responded: DAS28 and CDAI≤10.

Myles explained that his new paper is currently undergoing a review process by the journal. Caroline asked if the patients could switch treatment. Myles explained that patients can crossover onto another drug (called a crossover trial). Patients may switch drug sometimes due to a side effect or if the treatment is not effective.

Myles explained that Tocilizumab targets IL-6 (a cytokine), Tocilizumab binds IL-6 and stops it from acting, also works on B-cells as well as inflammation. The cost of Rituximab and Tocilizumab is

comparable. Myles reported that he is hopeful that we can make progress with STRAP as we have with R4RA.

Myles explained that in this new paper they took gene expression information and looked at responders and non-responders, and used volcano plots (statistical method). Myles presented volcano plots and explained that it is harder to predict who will respond to Tocilizumab. In the R4-RA trial, patients switched treatment: there were 38 patients that did not respond to Rituximab and were switched to Tocilizumab, and also 26 patients that did not respond to Tocilizumab that switched to rituximab. Patients that did not respond to both drugs were classed as having refractory RA. There are some genes that signal response to both treatments, some that signal Rituximab and Tocilizumab alone. It was found that cells in connective tissue (fibroblasts) are linked to the refractory RA group, there are several types of fibroblasts implicated. A GeoMx technique was used which uses a microscope with a gene sequencing technique. The machine used is a Nanostring machine which is also used in the 3TR Precis-The-RA study. The future plan would be to use machine learning panels to develop a test. Zoe asked how do you know when is someone is refractory. Myles replied that the primary endpoint is defined at the very beginning of the study and you decide what you are going to measure to assess response to a treatment, this is to avoid bias in the trial.

Sonia asked if patients continue on the drugs for life. Myles replied that sometimes some patients find that the drugs become less effective over time and some patients produce antibodies to the drug. Prof Anne Barton is studying this and part of her research is to look at blood samples and see if patients develop antibodies. Sonia asked if the refractory patients have joint deformities and what treatments they will be given. Myles replied that the refractory group do show signs of joint deformities and that this patient group are often given steroid treatment. Zoe asked if machine learning is expensive. Myles replied that this will get cheaper and if this method is effective, there is a strong economic argument as the biologic treatments cost £1000s per year + cost of nurse administering the drug (in case of RTX) when a patient might not respond. Zoe asked how close we are to this being implemented and Myles explained that we are making progress and one drug company is interested in investing money to develop an assay. Sonia asked if everyone is susceptible to getting arthritis and if there are genetic/lifestyle factors. Myles explained that Prof Anne Barton is also studying this, RA is polygenic there are at least 150 genes involved, but can also have identical twins, where one has RA and the other does not. There are other risk factors, e.g. smoking.

<u>3TR</u>

Jo gave an overview of the 3TR project which is a large scale public private initiative which will provide new insights into the mechanisms of response and non-response to treatment within and across seven different immune-mediated diseases, one of which is RA. There will be 2 trials in RA undertaken by the 3TR consortium which will be led by Prof Pitzalis at QMUL. One of the studies which will recruit patients with established RA (>12 months) was discussed at a previous meeting (3TR-Precis-The-RA study). The second study will recruit patients with early RA (<12 months). Both studies will recruit patients across sites in the UK and Europe (Belgium, Netherlands, Spain, Italy, and Portugal).

<u>3TR-Precis-The-RA Study</u>

Jo reminded the group about the 3TR-Precis-The-RA study design. Patients will be randomised to the control arm (where their treatment with either sarilumab or etanercept will be assigned randomly) or the biomarker arm (where their treatment will be allocated according to their biomarker). The main objective is to test the use of a specific biomarkers in synovial tissue to guide treatment decisions in RA patients for whom csDMARD therapy is ineffective when starting on a biologic (anti-

TNF, etanercept or IL6 inhibitor, sarilumab). The ACR-50 will be used to measure disease activity at baseline and at the end of the study in order to compare groups response to treatment.

The 3TR-Precis-The-RA study was presented to the ethics committee, which was also attended by Zoe, and approval has been received. The aim is to start recruitment at Barts Health in early 2022.

3TR-Early RA Study

Louise presented the plan for the study involving patients with early RA (<12 months). Patients will undergo a biopsy however will be treated as per routine care. Participants will be followed up monthly for 12 weeks and if their disease activity is still high after 12 weeks, they may be eligible to participate in the 3TR-Precis-The-RA study. The objective is to explore the ability of synovial tissue biomarkers to stratify for treatment response in newly diagnosed RA patients starting on conventional DMARD therapy. The CDAI score (clinical disease activity index score) will be used to assess disease activity at the start prior to treatment and the end of the study following 12 weeks of treatment.

STRAP

Jo gave a quick update regarding the STRAP trial. The data is currently still undergoing analyses and a meeting will be held next year to discuss the results with the group.

Jo thanked all the members of the PM-PAG for their time.