Minutes of the MATURA Patient Advisory Group (MPAG) – Tenth meeting

Room: Room B02, The Heart Centre, Charterhouse Square, QMUL

Date and Time: Tuesday 25th February 2020 2pm-4pm

Attendees:
Zoe Ide, Lead, MPAG Chair
Gaye Hadfield, MATURA Project Manager, QMUL
Sonia Jeevanason, Lay member of MPAG
Eleanor Goddard, Lay member of MPAG (via Zoom).
Louise Boyce, Lay member of MPAG
Dr Felice Rivellese, Clinical Fellow, QMUL (Via Zoom)
Jo Peel, Trial Manager, QMUL. (Via Zoom)

Apologies: Caroline Wallis, Chris Wills, Simon Stones, Leslie Cook, Prof Pitzalis, Prof Barton

1. Welcome:

Member participation and opinions on group changes:

Zoe started the meeting with a closed discussion on members' views, including future participation and opinions on how changes could be made to the group.

All attending members agreed they wish to continue their participation and are open to change/review on the way the group works. The first phase of the MATURA programme has now come to an end, and the group will move towards a more overarching Stratified Medicine support group.

Zoe proposed that the group could be more informal, get together via technology, with meetings more project based e.g. if there is a new grant application that needs to be submitted, or looking at study documents for studies e.g. the new EU study. It was agreed that it would be refreshing for new members to join. Current members all have good contributions to make despite not always being able to attend the meetings.

2. Synovial biopsy video

- Felice clarified that the next video of a patient who has had a biopsy talking to a patient who is considering having a biopsy, would be a great piece of information for patients prior to undergoing synovial biopsy

We have produced two videos a technical one for clinical staff and a patient being interviewed by a researcher and there is also a EULAR video, which is a tool for clinicians who are carrying out the procedure, and is too technical for patients.

The questions for the next video have already been approved by Ethics:

1. How did you feel when you were asked to take part in a study that required a biopsy?
2. Did you have any concerns about the biopsy?
3. Please describe what the procedure was like.
4. Do you have any advice for patients who are asked to take part in a research trial involving a biopsy?

- A leaflet will be created in addition to the video which will include the answers provided to the questions above.
- Funding will be covered by Felice's NIHR fellowship.
- Sonia and Louise volunteered to take part in the patient video. Louise will play the role of an apprehensive patient asking the questions, and Sonia will answer them based on her experience of a biopsy.

Action: Time/Date to be confirmed when Louise and Sonia are available (Jo thinks it will take approximately 2 hours to film)

3. Results, Including R4RA trial preliminary results

- Felice's most recent publication looked at methods for counting B cells and how the number of B-cells was related to the progression of RA:

  B Cell Synovitis and Clinical Phenotypes in Rheumatoid Arthritis: Relationship to Disease Stages and Drug Exposure
  Rivellese F[1], Humby F[1], Bugatti S[2], Fossati-Jimack L[1], Rizvi H[3], Lucchesi D[1], Lliso-Ribera G[1], Nerviani A[1], Hands RE[1], Giorli G[1], Frias B[1], Thorborn G[1], Jaworska E[1], John C[1], Goldmann K[1], Lewis MJ[1], Manzo A[2], Bombardieri M[1], Pitzalis C[1]; PEAC-R4RA Investigators.
  Arthritis Rheumatol. 2019 Nov 29. doi: 10.1002/art.41184

- A thorough Explanation was given on semi-quantitative scoring of B cells, which uses a microscope to view and count stained B-cells and has been used in Stratified Medicine studies in EMR: Early Arthritis (PEAC) and Difficult to treat RA (R4RA)
- Digital image (scores obtained with the help of a computer) and molecular analysis (studying genes known to be present only in B cells) were used to verify that semi-quantitative scoring was a reliable measurement of B cells.
- The results show that it may be more difficult to find an effective treatment for patients who have lots of B-cells.
- A lay summary of the paper is being prepared for the MATURA website

R4RA overview

- 164 patients were randomised to either Rituximab or Tocilizumab after a synovial biopsy procedure had taken place and samples were classified as B cell rich or poor.
- The hypothesis was that because Rituximab works by reducing B-cells, patients with diseased tissue classified as B cell poor would be better treated with a different drug – Tociluzimab.

- The results of R4RA strongly suggest that in patients with low numbers of B-cells that Tocilizumab works better, but the results aren't 100% clear.
- Felice explained that in Early RA patients, 35% of patients were B cell rich, however patients who have tried treatments 47.7% were B cell rich. At the moment we cannot be sure of why the B cells increase.

The next project

- The most commonly used score is DAS28 (number of tender swollen/tender joint in 28 joints, ESR and CRP levels and Patient Global Health 0-100). DAS28 score must be above 5.1 in order to be treated with biologic.
- Research from the Edinburgh team (WS2) has shown that a 2 component DAS28 (Swollen joints and CRP) correlates better with levels of synovitis. In one of Felice's next projects the usual DAS28 will be compared with the 2 component DAS28 (Swollen joints and CRP)

B Cell levels in different Joints

- Louise raised the question "do B cell levels differ depending on the joint being biopsied?". Felice responded that it has been ethically approved in PEAC for different joints to be biopsied at one time however he has not yet felt comfortable asking patients for this.
- It was discussed whether, as patients, the attendees would be happy for two joints to be biopsied. The general response was that they would for research purposes, however they have had established RA for many years, and their response may be different from early RA patients who are apprehensive about their new diagnosis.

A new project idea was proposed by Felice requesting support from MPAG, looking at disease activity score and synovitis in RA, focusing on the following:

1) Assess the correlation of disease activity scores with synovitis
2) Validate 2c-DAS-28 (2 component DAS) as outcome measure, defining cut-off levels of response (ongoing discussion with external supervisors on the best methodology)
3) Evaluate disease activity scores and long term outcomes (e.g long term radiographic damage)

Clinical Records Management System for Imflammatory Arthritis database (CReMSIA) overview:

- CReMSIA is currently a database of follow-up data of patients who have taken part in a EMR study involving a synovial biopsy.
- CReMSIA gives the possibility to study long term outcomes (eg study radiographs to look at damage, and see if there is anything at the biopsy stage of the study that could identify patients who are likely to develop more damage.
- New amendment has been submitted to include a control arm of the study (NHS standard care patients) who have not had a synovial biopsy as part of an EMR research study.

Post meeting note: This amendment has now been approved and implemented at Mile End Hospital.

Areas Felice requires support from MPAG:

- NIHR advanced fellowship application (opens in April and deadline in June)
- Plans to apply for Foreum career research grant (Foundation for Research in Rheumatology).
- Felice previously applied with the Lay title "Mechanisms of joint damage in Rheumatoid Arthritis" and was shortlisted to 3 in final round but unsuccessful. He was encouraged to reapply with a moresimple study (not to include experiments involving mice etc and to include CReMSIA).

Places R4RA results will be available:

- R4RA public website http://www.r4ra-nihr.whri.qmul.ac.uk

- ISRCTN Registry (www.isrctn.com) – Public registry for clinical research
- EudraCT website https://www.clinicaltrialsregister.eu/ctr-search/search (EudraCT: 2012-002535-28)
- Participants are given a letter on completion of the trial which provides information on where the results will be published.

Ways of presenting results to patients:

The group proposed selecting 5 or 6 simplified headline messages which can be fully explained in ways patients will understand. Following this it will need to be discussed how to provide this information. For example, a leaflet. The group thought it best to wait for the final publication before deciding headlines. It is hoped the publication will go to the Lancet or New England Journal of Medicine

4. Description of a new funding call

There is an NIHR Funding opportunity "Mechanisms of Health Interventions" 5th March 2020. NIHR funded R4RA and they will fund additional studies looking into the mechanisms of how different medicines work

Funding is restricted to:

1. Use of samples collected using NIHR funding
2. Evaluation of known biomarkers for mechanisms of action – we are concentrating on the fact that Rituximab attacks B cells, and Tocilizumab works on the cytokines.

So we are not asking for funding for the discovery of new markers, but to use previously collected samples to find evidence/further insight of how treatment works.

When an application was submitted in November 2017, they raised a query regarding whether a synovial biopsy was going to be acceptable, which EMR challenged as there was no evidence that patients dislike having biopsies. Now the R4RA results are available, funding will be re-applied for.

The plan is to look at 3 different things:

1. Because Rituximab specifically attacks a molecule known as CD20 we will see whether treatment with rituximab is not working because of B- cells lacking CD20 surviving in the synovial tissue.
2. Analysis of blood samples to find out whether levels of known blood markers for B-cells (CXCL13, ICAM1 and blood type I Interferon) correlate with how well Rituximab works for patients.
3. Tocilizumab works by reducing the levels of a cytokine (proteins produced by cells involved in the immune response) known by Interlukin 6, IL6. We will evaluate whether the expression of genes associated with IL-6 in both the synovial tissue and blood are associated with response to TOCI.

MPAG members are happy to support this research as part of the stratified medicine programme.

Action: GH will email a draft lay summary for members to review

5. 3TR see https://www.3tr-imi.eu

- 3TR is a large scale public private initiative which will provide new insights into why medicines are effective or ineffective across 7 different immune-mediated diseases (Chronic obstructive pulmonary disease, Asthma, Crohn's Disease, Ulcerative Colitis, Multiple Sclerosis, Systemic Lupus Erythematosus, Rheumatoid Arthritis).

- The project will study over 50,000 patient samples across 50 clinical trials with the aim to improve disease management
- There are 69 academic and industry partners, covering 15 European countries.
- Zoe has accepted an invitation to be the RA patient representative for 3TR and she will be the link to MPAG
- Jo described a proposed study for RA in which patients for whom DMARDs have been ineffective will be randomized either to a **Control Group** when they will be randomly assigned to treatment with a biologic drug or to the **Intervention Group** when they will be given the biologic treatment considered most likely to work based on the molecules present in their synovial tissue .
- The point was raised that the DAS28 criteria for biologic treatment varies depending on the country.

6. Upcoming events:

- Lay summaries for website – ongoing
- EMR Twitter account is now active @EMR_QMUL
- Barts Science Festival 17th June 2020, Mile End
  Post meeting note: This event has been cancelled due to COVID-19
- Final MRC review 6th May 2020

7. Updates since last meeting (24th April 2019):

- The Tate Exchange took place 12-16th June 2019 'Arthritis & Art, creating without constraint' which was a great success.
- May & November 2019 MATURA reviews at MRC. They commended the links with other consortia/projects
- Scientific Symposium 24th September 2019. Gaye thanked Louise and Zoe for attending.

8. STRAP Timelines:

- End of recruitment was 31st May 2019 and the data will be available for analysis in August 2020
- Following the results from R4RA, the STRAP analysis plan is being amended to include molecular data

9. Management of ongoing WS1 research

- Research projects on the STRAP data will start in August and although this is past the formal end date for MATURA we will continue to work with other academic groups using data and sample transfer agreements in place
- A new consortium agreement will be developed for industry members allowing them to to work together which, unlike academics, would not be possible if there were individual agreements.