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

3TR Precis-The-RA
Zoom
10.00 – 12.00, 12th August 2020

Attendees:
Zoe Ide, Lead, MPAG Chair
Louise Boyce, Lay member of MPAG
Caroline Wallis, Lay member of MPAG
Gaye Hadfield, MATURA Project Manager, QMUL
Dr Felice Rivellese, Clinical Fellow, QMUL
Jo Peel, Trial Manager, QMUL
Emily Harvey, Study Coordinator, QMUL
Sheela Medahunsi, TRC Programme Manager, NIHR/QMUL

1) Welcome

Gaye welcomed all attendees and made a brief introduction for those who were new to the meeting. Gaye explained the meeting would focus on the 3TR Precis-The-Ra study, for which a Protocol Synopsis and Inclusion/Exclusion criteria has previously been distributed for review.

2) Introduction to the 3TR (The Taxonomy, Treatments, Targets and Remission) project

Jo presented slides, which provided background information to the 3TR project. The main points were:

- The project is a large scale public private initiative across seven different immune-mediated diseases (Chronic Obstructive Pulmonary Disease, Asthma, Crohn's disease, Ulcerative Colitis, Multiple Sclerosis, Systemic Lupus Erythematosus and Rheumatoid Arthritis)
- The RA patient recruitment centres are Manchester, QMUL, Lisbon, Córdoba, Amsterdam, Brussels, Novara, Barcelona and Cagliari.
- The study 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) or a targeted synthetic therapy (JAK inhibitor, tofacitanib).'*

A study diagram was displayed to showing the pathway for 1:1 randomisation, to either control (n=90) or treatment allocation according to biomarker (n=90).

Participants who are randomised to the treatment arm will be allocated treatment depending on biomarkers present in their samples. It is estimated that 70% will have a biomarker which can indicate which treatment will work best (Etanercept, Tofacitinib or Sarilumab). The participants who have insufficient RNA for Nanostring Analysis, following the biopsy procedure, will receive standard of care treatment (we estimate this will be approximately 20 patients). The total recruitment target is 200.

3) Questions on the Protocol Synopsis

Will participants continue with their allocated treatment when the participant has completed all study visits?
Felice confirmed that all participants who respond to the allocated treatment can continue on this through the NHS.

Post meeting note: This was discussed amongst the clinical team. Unfortunately the drugs included in the study are not easily approved for use by the Commissioners, as biosimilars are currently much cheaper. There is a plan to include a caveat in the PIS that we can't guarantee continuity of treatment, however the clinical team in parallel, will work on a plan to try to resolve this.

Will patients have to stop their DMARD treatment when enrolling into the study or will they remain on this treatment?
Felice explained that previous research shows that Methotrexate enhances the response to other treatments, therefore all participants will start/continue on Methrotrexate unless they have had previous side effects or there is any other contraindication to treatment

Louise raised that she was unable to participate in studies in the past as she had already tried various treatments. Louise would have liked to have been considered for studies, however there is often only a small window from disease diagnosis where you may be suitable for studies because of trying treatments.

Why is the biomarker split 70:30 rather than 50:50?
Jo explained that based on previous studies, it is expected that 70% of participants will have a biomarker that matches one of the allocated treatments. The other 30% will not have a biomarker and therefore will be randomly allocated 1:1:1 to Etanercept, Tofacitinib or Sarilumab

Why is the change in ACR50 20-65%?
A 50% improvement in ACR, ACR50, is considered to be a clinically significant improvement for patients. Previous studies have shown that the ACR50 rate is increased from 40% in standard care to 65% when a biomarker matched to treatment is present. In the patients with no matching biomarker we expect only 20% to achieve ACR50. Felice explained that we need to include sufficient patients to show a statistically significant difference between the two groups. If a smaller change e.g ACR20 (a 20%improvement in ACR) was used we would need a much larger number of participants to show statistical significance.

In the hypothesis, why are there two statements which are the mirror of each?
Jo shared the protocol synopsis and it was agreed the hypothesis had been repeated and this should be corrected.

Action: Combine the hypothesis into one statement

Although there are a large range of questionnaires, are any work-related questions included?
Jo went through the questionnaires and they did not include questions on work. Jo explained that the team were concerned about the questionnaire burden for patients. The SF-36 questionnaire, and the Work Limitations questionnaire, have been used in previous EMR studies however SF36 has been replaced by PROMIS -29 for 3TR, and there are no work related questions in PROMIS-29. This is issue will be raised with the 3TR team.

Action: Jo to discuss the questionnaires at the next 3TR meeting, and feedback that they do not include work related questions

Is there anything difficult to understand in the protocol synopsis?
There was confusion with the use of Biomarker +ve and Biomarker –ve in the hypothesis. This will be partly resolved by combining the hypothesis as mentioned above. It was suggested to include explanations and examples on what the different treatments are (Biologics and DMARDS).
It was agreed that the use of 'molecular pattern' and 'biomarkers' is difficult to explain to family and friends in lay terms. Louise gave an example "70% of participants will have things in their body which indicates what treatment will suit best, whereas 30% do not"

Action: Change the wording for 'biomarker' and 'molecular pattern' as patients do not feel they could explain this to their friends and family

Why is the cardiovascular risk assessment completed at baseline and not at screening?
Jo explained the cardiovascular risk assessment includes data collection on smoking, and CDV family history, therefore it is completed at visit 3 to help with analysis from baseline. An ECG is done at screening to ensure the patient is safe to enter the study

Is it expected that treatment will be allocated 2 weeks after the biopsy, would the MPAG be happy with this wait?
Felice reported that the wait for treatment on the NHS is normally longer than 2 weeks. Caroline shared her experience that it took a long time to receive treatment in the past (even DMARDS) and then for Biologics, you have to wait to be trained by a nurse on how to inject the treatment (healthcare at home), or if having an infusion you have to wait until a bed has been booked. The consensus was that 2 weeks is not a long time to wait.

4) Questions on the Inclusion/Exclusion criteria

Why does the exclusion criteria say 'known allergy to latex, etanercept, salirumab or tofacitinib' if patients have not tried these treatments before?
Jo agreed that this was incorrect and will be changed to refer to allergies of the solutions of which the treatment is incorporated

Action: JP to reword point 16 of the exclusion criteria

If you have high disease activity but a low amount of swollen joints, can you be included into the study?
Jo explained that the ACR50 response includes the swollen/tender joint count. If there are less than 3 swollen joints at baseline, it is more difficult to demonstrate a response. Felice added that the UK

NICE guidelines requires 3 swollen joints, and if there is a low SJ/TJ count initially, then it is likely there will not be an overall response.

Action: Felice to discuss with other clinicians the possibility of having < 3 swollen joints if there are signs of inflammation elsewhere

Post meeting note: This was discussed with the Chief Investigator and it was agreed that this inclusion criterion will remain in the study, due to ACR-50 being used as the measure of treatment response for this study. If participants with low swollen joint counts are recruited, this will significantly affect the analysis of the trial.

Louise raised that she had a really bad experience 6 years ago, where she would have participated in any study if there was a chance she would find suitable treatment. As she did not have swollen joints, she did not fit the criteria. Felice raised that he will be looking at making changes to the treatment criteria as part of his fellowship. Patients are currently unable to receive treatment if they do not show the signs/biomarkers to fit the criteria. Eg DAS28. Zoe added that people with big joint RA are less likely to receive treatment compared to those with hand and feet RA.

Action: Zoe to find out any updates on changing the guidelines on disease activity.

5) Additional questions

Would patients be happy to provide a stool sample, and what would be the best method of return?
Jo explained that they would like the process to be as easy as possible for the participants. Caroline advised that cancer screening stool samples are simple and returned via post. Zoe and Louise agree that they would be happy to provide the sample and return via post, or bring to their next appointment with the research team. It was agreed that the stool sample would not put them off participating in the study. Zoe suggested giving participants the option of return via post or research visit. Gaye raised that pre-paid envelopes may not provided, however this will be looked into. Jo confirmed that the stool sample will be optional to avoid participants declining participation.

Action: Jo to find out how the stool samples are carried out for cancer screening

Action: Jo to find out if pre-paid envelopes will be provided for patients to return sample via post

Would the MPAG be happy to review the PIS and patient facing documents?
It was agreed by all members that they would be happy to review the documents

Action: JP to send patient facing documents to the MPAG for review, once available.

What are the timelines for starting the study?
Ideally, the study documents will be submitted to REC in Autumn with the intention to start in 2021. This will depend on C-19.

Would patients be happy to attend Face-to-Face appointments (at the hospital) for a research visit within the next few months?

Zoe would commit to a certain amount visits but it would depend on local lockdowns or spikes in C-19 cases. Zoe would be happy to travel in London currently the but this could change. The situation at the time would take priority and the appointments may have to be cancelled. Zoe would not be concerned about the study visits itself, but the travelling to and from. She would take an individual risk assessment and would not want to feel pressure to attend.

Louise would be happy to attend a face-to-face appointment if she was driving, but would not feel comfortable using public transport as she has been shielding for 22 weeks. She was surprised with how well virtual appointments worked.

If Caroline was at the beginning of the disease journey and was desperate to find a treatment, she would balance the risk:benefit ratio of perhaps finding a treatment that was going to help against the risks of travelling and attending a hospital. She would only feel comfortable attending the visit via car.

Felice reported that virtual appointments are more beneficial to patients who have been followed up long term. New patients would require a face-to-face appointment before starting treatment, which could be potential research patients. Newly diagnosed patients might be more inclined to attend for face-to-face appointments for research purposes. Felice suggested that in 3TR planning, C-19 should be taken into account for travel and local lock-downs. The participants should not feel pressure to attend.

MPAG members agreed that new patients, who have not been shielding, may be more open to travel and seeing people.

Action: COVID should be taking into account when planning the study schedule (visits, travel etc)

<u>Is there an option of the nurse going to the patients home instead of hospital appointment?</u>
As it stands this is not carried out within the department, however it is a possibility for the future.

6) Dr Rivelesse's fellowship

Felice will request a 6 month fellowship extension with NIHR (due to end in September). He would like to organise the patient interview and discussion about the synovial biopsy procedure (Sonia and Louise). It was agreed that this could be recorded through Zoom for now, and replaced with a face-to-face film in the future.

Action: Felice to organise a Zoom patient video (discussion between Sonia and Louise about the synovial biopsy procedure)

Gaye closed the meeting thanking all MPAG members for attending and providing their very valuable feedback.