Rapamycin and inulin for third-dose vaccine response stimulation (RIVASTIM): Inulin – study protocol for a pilot, multicentre, randomised, double-blinded, controlled trial of dietary inulin to improve SARS-CoV-2 vaccine response in kidney transplant recipients

Julian Singer, Matthew Tunbridge, Griffith B Perkins, Tania Salehi, Tracey Ying, Huiling Wu, P Toby Coates, Steven J Chadban

ABSTRACT

Introduction Kidney transplant recipients (KTRs) are at an increased risk of hospitalisation and death from COVID-19. Vaccination against SARS-CoV-2 is our primary risk mitigation strategy, yet vaccine effectiveness in KTRs is suboptimal. Strategies to enhance vaccine efficacy are therefore required. Current evidence supports the role of the gut microbiota in shaping the immune response to vaccination. Gut dysbiosis is common in KTRs and is a potential contributor to impaired COVID-19 vaccine responses. We hypothesise that dietary fibre supplementation will attenuate gut dysbiosis and promote vaccine responsiveness in KTRs.

Methods and analysis Rapamycin and inulin for third-dose vaccine response stimulation-inulin is a multicentre, randomised, prospective, double-blinded, placebo-controlled pilot trial examining the effect of dietary inulin supplementation prior to a third dose of COVID-19 vaccine in KTRs who have failed to develop protective immunity following a 2-dose COVID-19 vaccine schedule. Participants will be randomised 1:1 to inulin (active) or maltodextrin (placebo control), administered as 20 g/day of powdered supplement dissolved in water, for 4 weeks prior to and following vaccination. The primary outcome is the proportion of participants in each trial arm that achieve in vitro neutralisation of live SARS-CoV-2 virus at 4 weeks following a third dose of COVID-19 vaccine. Secondary outcomes include the safety and tolerability of dietary inulin, the diversity and differential abundance of gut microbiota, and vaccine-specific immune cell populations and responses.

Ethics and dissemination Ethics approval was obtained from the Central Adelaide Local Health Network (CALHN) Human Research Ethics Committee (HREC) (approval number: 2021/HREC00354) and the Sydney Local Health District (SHLD) HREC (approval numbers: X21–0411 and X20–0411). Results of this trial will be published following peer-review and presented at scientific meetings and congresses.

Trial registration number ACTRN12621001465842.

INTRODUCTION

At the beginning of 2022, the number of deaths worldwide caused by the COVID-19 pandemic exceeded 5.5 million. Immunosuppressed populations such as kidney transplant recipients (KTRs) are at high-risk for COVID-19-related adverse events (AEs).
Reducing or altering immunosuppression in KTRs is an attractive strategy to augment vaccine responses, yet must be balanced against the risk of enhanced allo-immunity and subsequent organ rejection. While this approach may be suitable for some KTRs, it may be declined by others who are not prepared to accept an increased risk of acute rejection, or would prefer to remain stable on their long-term immunosuppression regimen.

Improving the gut microbiome may be another way to improve the vaccine response. The commensal microorganisms that reside in the gastrointestinal tract have wide-reaching effects on systemic immunity and are critical in the development and licensing of immune cells, and in maintaining adequate immune responses to encountered antigens, including those encountered through vaccination.11–14 In KTRs, disruption of the gut microbial landscape, termed dysbiosis, is a common occurrence and contributes to the observed immune dysfunction in this group.15,16 Normalisation of the gut microbiome may be achieved by prebiotic dietary interventions, which promote the growth of beneficial microbiota.17 Inulin, a naturally occurring, non-digestible fibre promotes the selective growth of beneficial short chain fatty acid (SCFA) producing species, such as Bifidobacteria, occurring at the expense of microbiota which lack the metabolic machinery necessary for fibre fermentation.17–19 Importantly, Bifidobacteria spp and SCFAs have been independently associated with improved virus-specific antibody responses and increased reactivity to parental vaccines,20,21 including those directed against COVID-19.22 Whether the microbiota of prevalent KTRs are amenable to dietary interventions, and whether correction of dysbiosis can promote the immunogenicity of COVID-19 vaccines are therefore important research questions.

Rapamycin and inulin for third-dose vaccine response stimulation (RIVASTIM-inulin) will assess the efficacy and tolerability of dietary inulin supplementation to enhance vaccine response in KTRs who have failed to develop vaccine-induced protective immunity to COVID-19, prior to a third vaccination. We hypothesise that dietary fibre supplementation will enhance the abundance of key microbiota species and improve the immune response to a third vaccine dose with an mRNA COVID-19 vaccine. The data generated from this pilot trial will inform the design and viability of larger clinical trials to assess the efficacy of dietary prebiotics to improve vaccine responses.

**METHODS AND ANALYSIS**

The RIVASTIM clinical trials represent protocols for parallel studies designed to investigate the effect of either rapamycin (RIVASTIM-rapamycin)23 or inulin supplementation (RIVASTIM-inulin) on the immune response to a third SARS-CoV2 vaccination in KTRs. The trials were conceived, designed and authored, and will be conducted concurrently by the RIVASTIM authors. To improve research quality and efficiency, the trial protocols share...
common methodologies in participant screening and enrolment, data collection and management, and outcome assessments.

RIVASTIM-inulin is a pilot multicentre, parallel-arm, randomised, placebo-controlled, double-blinded, exploratory trial, examining the effect of dietary inulin on the immune response to a third dose of mRNA COVID-19 vaccine in KTRs who have failed to demonstrate protective immunity following a two-dose vaccine schedule. KTRs who have received two doses of a COVID-19 vaccine will be enrolled and their immune response to vaccination assessed by measurement of the anti-RBD IgG titre. Those with a satisfactory immune response (anti-RBD IgG ≥100 U/mL) will exit the study and be advised to receive a third mRNA COVID-19 vaccination as per recommended guidelines. KTRs who fail to demonstrate protective immunity (anti-RBD IgG<100 U/mL) will proceed to randomisation.

Randomisation will occur at a participant level with an allocation ratio of 1:1, stratified by study site and the magnitude of immune response following two doses of vaccine (anti-RBD IgG titre; non-responder: <0.4 U/mL; low responder: 0.4–99 U/mL). An outline of the trial is shown in figure 1. Following randomisation, participants will receive a dietary supplement in the form of a white, soluble and largely flavourless powder consisting of inulin (active arm) or maltodextrin (control arm). Participants will consume 10 g of supplement dissolved in 200 mL water daily, escalating to 10 g twice daily after 1 week. Following a 4-week lead in period, participants will receive a third dose of mRNA COVID-19 vaccine, with the subsequent antibody response measured at 4–6 weeks postvaccination. Participants will continue the dietary supplement up until the time of antibody assessment.

The first study participant was enrolled on the 8 November 2021 and recruitment is anticipated to continue until March 2022, with the final study visit of the last recruited patient expected to occur in May 2022.

Study setting
The trial will be conducted at the renal transplant units of two tertiary referral hospitals in Australia: (1) The Royal Adelaide Hospital, Adelaide, South Australia and (2) The Royal Prince Alfred Hospital (RPA), Sydney, New South Wales.

Eligibility criteria
The inclusion and exclusion criteria are in table 1.

Recruitment
Prospective participants will be identified through the following means:
1. Review of local transplant recipient databases at each trial site. (Only local site clinical staff will have access to identifying information for the purpose of recruitment.)
2. During routine clinical review with their treating nephrologist or transplant centre.
3. Potential participants may also indicate their interest in trial participation by responding to a QR code displayed during the Transplant Australia COVID-19 Vaccination Update Webinar, broadcast in November 2021.

Prior to enrolling, patients will be provided with written information regarding the rationale behind the trial, the potential risk and benefits of participation, and the personal commitment involved. Patient’s will be enrolled by trained research staff and consented for trial participation, the collection of data and the storage of biological samples (see online supplemental file 1). Recruitment will continue until target recruitment is fulfilled, or until recruitment of dual-vaccinated transplant recipients is no longer feasible, or if delaying a third vaccination becomes no longer ethically permissible due to clinical urgency. Participants will not receive payment for participation.

Randomisation
Participants are randomised 1:1 to either inulin or maltodextrin (control). Randomisation will occur via computer-generated stratified block randomisation with randomly
permitted block sizes of 2, 4 and 6. Stratification will occur by site and the response to a two dose COVID-19 vaccine schedule (low responder anti-RBD IgG 0.4–99 U/mL; or non-responder, anti-RBD IgG<0.4 U/mL).

**Allocation concealment**

The allocation sequence is generated by an independent and blinded statistician, and administered centrally through an external web-based randomisation module contained within a purpose built Research Electronic Data Capture (REDCap) data management platform. The randomisation algorithm and treatment allocation are not accessible to study investigators or research staff. Trained study investigators will enrol participants, while at each study site, an un-blinded administrative assistant who is not a member of the study team will perform randomisation via the web-based platform and assign the concealed intervention to each participant.

**Blinding**

The study participant and their treating nephrologist, in addition to investigators, research staff and outcome assessors will be blinded to treatment allocation. Unblinding is not permitted during the trial except in the occurrence of a serious AE (SAE). In such an event, the principal investigator (PI) will decide whether unblinding is required, and if deemed necessary, will direct the unblinded administrative assistant to contact the participant’s treating healthcare professional to discuss their treatment allocation. Wherever possible, trial staff will remain blinded and the participant will continue with trial follow-up and their study treatment.

**Trial interventions**

Inulin is a naturally occurring non-digestible dietary fibre that may be extracted from natural sources, such as chicory root, or produced synthetically in commercial quantities by enzymatic processes. Accessible in powdered form, inulin is readily soluble in water with a neutral unflavoured taste, and is widely used as a food additive and dietary supplement. On ingestion, inulin functions as a prebiotic by trafficking undigested to the colon where it is metabolised by fibre-fermenting bacteria to release SCFAs, and promote the growth of SCFA producing genera. Inulin exerts a dose-dependent response on the gut microbiota, with a dose of 20 g/day sufficient to significantly alter the composition of the microbiome whist limiting untoward gastrointestinal adverse effects. Adverse gastrointestinal symptoms are dose-related and commonly occur with initial ingestion. A dose escalation strategy (10 g/daily for 1 week, increasing to 10 g twice daily for the remainder of the study), is employed to minimise the risk of adverse gastrointestinal symptoms. Participants who experience mild adverse effects (bowel discomfort, bloating, flatulence) will be instructed to reduce the dose to 10 g/day. Study subjects who develop persistent gastrointestinal or other symptoms will be asked to discontinue the study intervention and continue with trial follow-up.

Maltodextrin is a polysaccharide which is easily soluble in water and rapidly absorbed in the upper gastrointestinal tract, leading to negligible interaction with colonic microbiota. In addition to its inert effect on the gut microbiota, maltodextrin was selected as a placebo due to its similar physical appearance and taste to inulin.

**Intervention description**

Participants will be randomly allocated and blinded to their study treatment in one of two groups:

1. Inulin—fibruline Instant, a soluble dietary fibre extracted from chicory roots. (Cosucra group, Warcoing, Belgium).
2. Maltodextrin (Bulpowders, Braeside, Victoria, Australia).

The study products are prepared and packaged by Bulk Powders Pty Ltd (Braeside, VIC, Australia) specifically for the trial in identical sealed, opaque and numbered 1 kg bags with an accompanying 10 g measuring scoop. Participants will be instructed to consume 10 g (1 level scoop) dissolved in approximately 200 mL of water each morning for 7 days, increasing to 10 g each morning and night (20 g/daily) as tolerated, for the remainder of the trial period. Participants will be provided with the study supplement in a sealed bag, which will be weighed prior to allocation. At the final trial visit, participants will return any unused supplement, with the bag again weighed to determine the total weight of supplement consumed during the study.

All trial participants will receive a third dose of a COVID-19 mRNA vaccine, either Pfizer-BioNTech BNT162b2 (30 µg, IM) or Moderna mRNA-1273 (50 µg, IM) determined by local practice and vaccine availability. Study participants will receive written pre-vaccination information on the benefits and potential risks and harms of the COVID-19 vaccine and be screened for contraindications to immunisation such as SAEs attributable to a previous dose of a mRNA COVID-19 vaccine. All patients will be advised of the need to continue with additional public health measures (eg, physical distancing, hand washing, wearing a face mask and COVID-19 testing and isolation as required).

**Concomitant care and interventions**

All participants will continue with usual transplant management as per local standard of care and at the discretion of their treating nephrologist. Any changes to medications will be recorded. Participants will be asked to continue with their usual diet and medications but abstain from dietary supplements (including non-study prebiotics and probiotics) for the duration of the study. The trial Sponsor has indemnity to compensate those who suffer from potential harm resulting from their participation in the trial.

**Management of COVID-19 positive participants during the trial**

Study participants who return a positive COVID-19 result during the trial will be managed in consultation with
The secondary outcome measures include the following:

1. Change in the median magnitude of the SARS-CoV-2 spike-specific, antiviral T cell response 4–6 weeks following vaccination, determined as the frequency of cells that secrete IFNγ in response to stimulation with spike-protein (Wuhan)-derived peptides by ELISpot.

2. AEIs following immunisation (AEFI) including AEs of special interest (AESI) will be assessed via phone consultation at 1 week, and again at 4–6 weeks postvaccination during the final follow-up visit, and include:
   a. Changes in kidney allograft function, determined by serum creatinine, eGFR (CKD-EPI equation) and proteinuria.
   b. The occurrence of biopsy proven acute allograft rejection.
   c. The recurrence of primary kidney disease.
   d. Patient reported quality of life as recorded by the EuroQol 5 Dimensions (EQ-5D) questionnaire.

3. Tolerance of dietary inulin determined by the change in gastrointestinal symptom rating scale (GSRS) at baseline, week 4 and the final trial visit. Adherence to the intervention will be assessed by the weight of unconsumed supplement returned at the final study visit.

4. The proportion of participants who generate a serological response 4–6 weeks following a third COVID-19 vaccination. A serological response is defined as reaching a threshold of anti-receptor-binding domain antibody (anti-RBD IgG) ≥100 units/mL (measured with an Elecsys Anti-SARS-CoV-2 immunoassay (Roche)). This RBD antibody threshold was chosen on the basis of pre-clinical and clinical studies,31 32 and is consistent with the reported outcomes in published COVID-19 clinical vaccine trials.6 33

5. Changes in the community structure, relative abundance and functional characteristics of the gut microbiome following 4 weeks of dietary intervention, determined by 16S-rRNA metagenomic sequencing of participant stool samples.

6. The development of COVID-19 following randomisation, determined by:
   a. Positive SARS-CoV-2 PCR test, or rapid antigen test in the setting of symptomatic disease.
   b. Detection of SARS-CoV-2 anti-nucleocapsid antibodies at the time of primary outcome assessment.

Following trial registration, additional secondary outcome numbers 4–6 were approved by the HREC, and added to the trial protocol. These outcomes are exploratory in nature and will seek to inform the design and scope of larger clinical trials.

**Participant timeline**

Participants are followed from the time of enrolment to 1 week following their final assessment visit. The schedule of enrolment, randomisation, interventions and assessments is shown in figure 2.

**Sample size**

The aim of this pilot study is to investigate whether prebiotic supplementation with dietary fibre sufficiently improves COVID-19 vaccine responses to warrant further investigation in a larger trial. Current evidence supports the role of gut microbial communities in modulating the...
immune response to vaccination, including COVID-19 vaccines. However, evidence supporting interventions which target the microbiota in this setting are lacking and estimates of effect size cannot be accurately generated.

In defining a target sample size, we considered the following: (1) the number of eligible KTRs across the two sites; (2) their current vaccination status; (3) the feasibility of conducting a trial within the contemporary resource setting; (4) local prevalence of COVID-19 and (5) the recommended sample size requirements for a pilot study. A recruitment target of approximately 60–120 participants was considered feasible, and sufficient to generate a meaningful estimate of effect size with adequate confidence. With full recruitment of 120 participants, and assuming a 25% virus neutralisation endpoint in the control group, we would require 54% virus neutralisation in the intervention group to demonstrate superiority using a one-sided hypothesis with 2.5% α-risk and 90% power.

**Patient and public involvement**

This trial was presented at the Transplantation Australia Webinar. Of 513 national attendees, 42 registered their interest to learn more and potentially enrol in the study. Interested patients were geographically diverse. To provide an opportunity for regional patients to participate, recruitment for the study occurred during outreach clinics in South Australia and New South Wales.

**Data collection and management**

Clinical and safety laboratory tests (haematology, chemistry, urinalysis) for enrolment and end-point criteria (anti-RBD IgG) are performed at the hospital laboratory of each study site. All study data are collected by trained research staff and entered directly onto study-specific electronic data capture forms (eDCF) created and housed within a secure, web-based data management tool (REDCap). The DCFs contain inbuilt protections to promote data quality, including range checks for numerical data values, restrictions on alphanumeric entries and prevention of duplicate records. The RIVASTIM REDCap database is stored on secure servers in an on-site limited access data centre at the RPA Hospital and operated behind the Sydney Local Health District (SLHD) firewall. All electronic information and transmissions are protected via Secure Sockets Layer encryption. Access to the RIVASTIM REDCap database is limited to approved research staff, with individual user authentication and logging of all data entry and modification, and access to restricted modules (randomisation, scheduling and data export) privileged. The database is maintained by the SHLD Information and Communication Technology Services with regular back-up processes in place.

**Collection and evaluation of biological samples**

Blood samples will be taken from participants for immunological assessment at randomisation and at 4–6 weeks following vaccination. Blood will be drawn from participants by clinical research staff and collected in 7×9 mL EDTA and 1×5 mL CAT serum separator vacutainer tubes. Peripheral blood mononuclear cells will be isolated from whole blood by density gradient centrifugation in Ficoll-Paque and aliquoted and cryopreserved in liquid nitrogen for batch testing, with sera aliquoted and stored at −80°C. Phenotypic and functional assessments of vaccine-specific T cell responses will be initially assessed by IFNγ release assay (ELISpot) following stimulation with overlapping peptides spanning the length of SARS-CoV-2 spike protein, with any notable change triggering a more in-depth investigation. For example, the assessment of spike-specific circulating T follicular helper cells based on the frequency and phenotype of CD4+ T cells expressing CD40L following stimulation with spike protein-derived peptides may be analysed via FACS. Using participant serum, the titres of SARS-CoV-2 spike-protein-specific IgG and the capacity of participant serum to neutralise SARS-CoV-2 viral entry into ACE2 cells will be assessed. The capacity of preimmunisation and postimmunisation serum to induce spike-protein-specific antibody-dependent innate immune responses will be measured.

Isolation and sequencing of the faecal metagenome will occur on self-collected stool samples placed in a DNA stabilising solution (OMNigene GUT OM-200, DNA Genotek, Canada). Stool samples will be aliquoted and stored at −80°C until batch testing. Analysis of the faecal metagenome will be performed by comparative sequencing of 16S-rRNA amplicons (V4 region). Estimation of participants habitual diet will be captured using a 4-day food diary, completed at the time stool samples are collected.

Validated questionnaires are completed by participants to capture adverse gastrointestinal symptoms (GSRS) and health-related quality of life (EQ-5D) information.

All biological specimens will be deidentified and labelled with the participants unique study identifier. Stool and blood samples will be stored and maintained in access-restricted laboratory freezers at their corresponding trial site (Adelaide Health and Medical Sciences building, University of Adelaide, or the Transplant Institute, RPA, Sydney).

**Confidentiality**

Prior to study enrolment, participants will consent to research staff accessing their electronic medical record to obtain baseline and demographic information, and the results of laboratory assessments. The privacy and confidentiality of screened and enrolled participants will be preserved with all study data stored in the RIVASTIM REDCap database under a unique numerical study identifier. No identifying information or individually identifiable participant data will be reported in publications, presentations, or in any report arising from this study.
Statistical methods

The primary analysis will be by intention-to-treat (ITT), with participants assessed according to their treatment allocation. Participants who develop a positive SARS-CoV-2 PCR result during the study will be excluded from the primary analysis to avoid confounding. A per-protocol analysis will also be reported, with participants who failed to adhere or tolerate the dietary intervention and consumed <80% of the prescribed supplement, and participants who withdrew or were lost to follow-up excluded from the analysis. A sensitivity analyses adjusting for potential confounding may be performed should significant imbalances in baseline characteristics between the treatment groups occur. Multiple imputation will be used to handle data missing at random from baseline characteristics. Data missing at random for the primary and secondary outcome will not be imputed, with these cases excluded from ITT analysis. If >10% of the primary outcome data is determined to be missing not at random, a best-worst and worst-best case sensitivity analyses will be performed.

Subgroup analyses will be performed to examine for statistical interaction between treatment arm and: (1) the initial response to two-dose vaccine schedule (non-responder or low responder), (2) the duration between previous vaccine dose (less than, or greater than 6 weeks) and randomisation. Patients who develop primary COVID-19 infection during the study period will have both primary and secondary outcomes analysed as a prespecified subgroup analysis.

The primary endpoint is the proportion of participants in each trial arm that achieve in-vitro neutralisation of live SARS-CoV-2 virus using the $\chi^2$ test. An unadjusted and adjusted relative risk (RR) will be calculated. For the adjusted RR estimate, the primary outcome of a threshold SARS-CoV-2 anti-RBD IgG titre will be analysed using a log-binomial regression model. The initial immune response to a two-dose vaccine schedule (anti-RBD IgG titre; low responder: 0.4–99 U/mL or non-responder: <0.4 U/mL) will be included in the model as a fixed effect, with study site as a random effect.

Secondary outcomes will be analysed using univariate and multivariate methods dependant on the outcome type. Baseline characteristics and demographic data will be reported as mean±SD for normally distributed data and median±IQR for non-normally distributed data, with categorical variables reported as frequencies.

Changes in the differential abundance of key bacterial species will be approached using analytical methods such as DESeq2, 40 ANCOM, 41 MaAsLin2 42 or linear discriminant analysis effect size, 43 depending on the data characteristics. We anticipate a 2–4 fold increase in Bifidobacterium species in response to inulin supplementation. 44 45

All statistical analyses will be described in detail with arising publications. A two-sided significance level of 5% will be used for all analyses.

Oversight and monitoring

The coordinating trial centre is located at the Royal Adelaide Hospital. The trial steering committee (TSC) is cochaired by the PI at each study site and includes the trial associate investigators. The TSC is responsible for the study conception, drafting and completion of the study protocol and associated documents, recruitment plan, data monitoring and integrity, end point adjudication and approving publications arising from the study.

Following publication of all study results, deidentified participant level data may be made available on reasonable request to the PI, or in the case of published works, through the corresponding author.

AE reporting and harms

All protocol deviations and AEs will be documented, regardless of their potential relationship to the study intervention. AEs will be recorded using an adaptation of the National Institute of Health’s Common Terminology Criteria for Adverse Events by a study team member on an eDCF. Screening for AEs will occur during each study visit and during scheduled clinical follow-up with their treating nephrologist, and will be captured up to 7 days following the final study visit. AEFIIs with the exception of mild and/or short-lived symptoms, will be reported to the Therapeutic Goods Administration. SAEs will be reported to the trial sponsor with 24 hours of the study team being made aware of the event.

Ethics and dissemination

The study is conducted in accordance with the National Statement on Ethical Conduct in Human Research (2018), the CPMP/ICH Note for Guidance on Good Clinical Practice and consistent with the principles that have their origin in the Declaration of Helsinki. Compliance with these standards provides assurance that the rights, safety and well-being of trial participants are respected.

Ethics approval for the RIVASTIM trials was obtained from the Central Adelaide Local Health Network (CALHN) Human Research Ethics Committee (HREC) (approval number: 2021/HRE00354) and the SHLD HREC (approval numbers: X21-0411 and 2021/STE04280). Written informed consent to participate will be obtained from all participants. The results of the RIVASTIM-inulin trial will be published in peer-reviewed academic journals and presented at national and international scientific meetings. In addition, a lay summary containing the study aim, salient findings, conclusions and a take home message will be prepared and distributed to trial participants, research staff and interested members of the transplant community. Datasets and results generated as part of this study will be jointly owned by Central Adelaide Local Health Network, the University of Adelaide and the RPA Hospital (SLHD). Deidentified participant data may be made available from the corresponding author of published works on reasonable request and submission of a research plan of appropriate scientific merit and ethical standing.

DISCUSSION

Interventions that improve the efficacy of COVID-19 vaccinations are urgently required to reduce the burden of disease in at risk groups such as KTRs. Additional vaccine doses are recommended for this purpose, yet many KTRs fail to achieve protective immunity after a third, or even fourth vaccination. Vaccine hyporesponsiveness in this cohort is driven by deficiencies in the underlying immune response, and although immunosuppressive medications are likely the greatest contributor, dysregulation of the gut microbiota adds to the observed immune dysfunction. Strategies that address the underlying immune deficits in KTRs therefore offer an attractive pathway to restore vaccine responsiveness, but are not without risk. Maintaining graft function remains a priority for both patients and clinicians, and strategies that enhance vaccine responses must be demonstrated not to significantly enhance alloimmunity, lest organ rejection occur. The RIVASTIM trials, consisting of sister studies RIVASTIM-sirolimus and RIVASTIM-inulin, directly investigate two strategies to enhance the cellular and humoral response to a third vaccine dose in differing groups of KTRs. While RIVASTIM-sirolimus will examine the efficacy and safety of immunosuppression modification in KTRs, RIVASTIM-inulin assesses the response to and efficacy of a dietary prebiotic to improve vaccine immunogenicity.

As the primary outcome, RIVASTIM-inulin will assess in vitro neutralisation titres following a third vaccine dose, which are highly predictive of immune protection from symptomatic COVID-19. In addition, SARS-CoV-2 RBD IgG, which offers a close correlate of the efficacy of serum to neutralise SARS-CoV-2 and widely available in clinical practice, will be measured as a secondary outcome. However, antibody titres, while clinically significant, do not offer a compete explanation for the divergent vaccine responses observed across the cohort of KTRs. Despite recognition that COVID-19 vaccine efficacy in immunosuppressed individuals remains suboptimal, robust examination of the cellular and humoral immune responses in those with sufficient, partial, or negligible vaccine responses are lacking. Through sophisticated immunophenotyping, RIVASTIM-inulin will examine the adaptive immune responses prior to and following a third COVID-19 vaccination, to quantify which immune deficits contribute to vaccine hyporesponsiveness in KTRs, and whether these are impacted by an improvement in gut health. Detailed examination of the gut metagenome will comprehensively evaluate the relationship between the gut microbiota and vaccine response, and examine whether a response to targeted prebiotics can shift vaccine immunogenicity.

At the time of trial registration, Australia had low community transmission in a largely SARS-CoV-2 naïve population and was uniquely placed to assess interventions to improve vaccine efficacy. However, the subsequent emergence of variants of clinical significance such as Delta and Omicron have led to COVID-19 surges in Australia. Such surges may impact trial conduct, but also serve to highlight the need for emergent strategies to boost vaccine responsiveness for at-risk groups such as KTRs.

Dietary interventions designed to modulate the gut microbiota may offer an adjuvant approach to improve vaccine efficacy, however robust clinical trials in this field are thus far lacking. Results of the RIVASTIM-inulin trial will seek to inform vaccine policy, and may provide evidence for a meaningful, inexpensive, scalable and accessible intervention by which vaccine responses may be enhanced. Such discoveries would address our current unmet need to protect at risk populations from COVID-19-related morbidity and mortality and would hence be of global interest.

Trial status


Administrative information

RIVASTIM-inulin: study protocol for a pilot, multicentre, randomised, double-blinded, controlled trial of dietary inulin to improve SARS-CoV-2 vaccine response in KTRs. The trial was registered on the 26 October 2021 with the Australia New Zealand Clinical Trials Registry: ACTRN12621001465842. RIVASTIM is an investigator-initiated research trial with the coordinating trial centre, the Central Adelaide Local Health Network, as the study sponsor. No funding is provided externally. The principal and associate investigators are solely responsible for the conception, execution, analysis and dissemination of the research work.

Author affiliations

1 Kidney Node, Charles Perkins Centre, The University of Sydney, Sydney, New South Wales, Australia
2 Department of Renal Medicine, Royal Prince Alfred Hospital, Sydney, New South Wales, Australia
3 Central and Northern Adelaide Renal and Transplantation Service (CNARTS), Royal Adelaide Hospital, Adelaide, South Australia, Australia
4 School of Biological Sciences, The University of Adelaide, Adelaide, South Australia, Australia
5 Immunology, SA Pathology, Central Adelaide Local Health Network, Adelaide, South Australia, Australia
6 Discipline of Medicine, Adelaide Medical School, The University of Adelaide, Adelaide, South Australia, Australia
7 Discipline of Medicine, Adelaide Medical School, The University of Adelaide, Adelaide, South Australia, Australia
8 Discipline of Medicine, Adelaide Medical School, The University of Adelaide, Adelaide, South Australia, Australia
9 Discipline of Medicine, Adelaide Medical School, The University of Adelaide, Adelaide, South Australia, Australia
10 Discipline of Medicine, Adelaide Medical School, The University of Adelaide, Adelaide, South Australia, Australia
11 Discipline of Medicine, Adelaide Medical School, The University of Adelaide, Adelaide, South Australia, Australia
12 Discipline of Medicine, Adelaide Medical School, The University of Adelaide, Adelaide, South Australia, Australia

Contributors

PTC and SC conceived the study. PTC, SC, JS, GBR, MT, TS, HW and TY designed the study methodology. MT and JS wrote the first draft of the protocol, and JS prepared the study manuscript and constructed the figures and tables. All authors contributed to the protocol development and read and approved the final manuscript.

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Competing interests

None declared.

Patient and public involvement

Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication

Not applicable.


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ORCID iD Julian Singer http://orcid.org/0000-0002-1855-3581

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