Guidance for Clinicians with Patients Receiving Immunosuppression Treatment for Autoimmune Conditions of their Native Kidneys During Covid-19

Version 2, 1 April 2020

Aims

To provide therapeutic guidance on the management of patients receiving immunosuppression for autoimmune conditions.

Overview of Guidance

This advice was created by a panel of clinicians with expertise in the care of kidney patients who have autoimmune disease of their native kidneys. Acknowledging there is currently minimal evidence in this area, it is based on expert renal opinion together with national guidance applicable to the wider UK population. The advice will be updated regularly as the situation evolves.

THIS ADVICE RELATES TO KIDNEY PATIENTS RECEIVING IMMUNOSUPPRESSIVE TREATMENT FOR AUTOIMMUNE CONDITIONS OF THEIR NATIVE KIDNEYS. SEPARATE ADVICE IS AVAILABLE FOR KIDNEY TRANSPLANT PATIENTS.

Executive Summary

The Renal Association (RA) guidance directs which patients in this group should follow prolonged self isolation - link below.

Advice is that otherwise well patients on single agent immunosuppressive therapy should follow social distancing but do NOT need to start prolonged self isolation.

Whilst well, patients are recommended to continue normal immunosuppressive medication.

For induction regimens for acute disease:

- There is evidence, in general, that cyclophosphamide based regimens cause a greater degree of immunocompromise
- Prompt reduction of high dose steroid regimens such as in the PEXIVAS regimen should be followed.

If patients develop COVID-19 symptoms, they should not stop maintenance steroids abruptly

High dose steroids

- May be counterproductive in early COVID-19 infection
- May be considered in progressive pulmonary disease/ARDS

Decisions to reduce or pause immunosuppressive therapy will need to be made on an individualized basis and in keeping with the treatment of other infectious diseases.

Useful Links

The RA renal risk stratification for which renal patients in this group should be in prolonged self isolation (also called shielding)

National guidance on shielding these patients

Other useful links are at:

https://www.gov.uk/government/publications/wuhan-novel-coronavirus-initial-investigation-of-possible-cases

https://www.england.nhs.uk/coronavirus/

https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected

And more specifically for patients:

Kidney Care UK website

Clinical Guidance for Managing Well Patients

ADVICE ABOUT IMMUNOSUPPRESSIVE THERAPY

INDUCTION MEDICATION FOR CONDITIONS SUCH AS VASCULITIS AND SLE

Some kidney patients, particularly those on steroids, intravenous cyclophosphamide and biologics, will be significantly immunosuppressed and should therefore be considered 'high risk'. This is particularly true in the induction phase of their treatment.

There is currently no policy that asymptomatic patients should be swabbed for COVID-19 prior to each dose of intravenous induction therapy. As testing becomes more widely available this policy may change but current studies suggest patients with early disease may have negative nasal swabs in 30% of cases. All patients should be triaged on arrival before any infusion to exclude symptoms of active COVID-19 infection and to check for raised temperature. Those who are considered to have possible infection can then be seen in a separate area away from other at risk patients and appropriate treatment plans made.

On present evidence, patients should plan to complete standard induction medication unless directed otherwise by their renal team. When considering which induction regimens to use, whilst there may be theoretical risks in the longterm about vaccination responses after rituximab, there is evidence that cyclophosphamide is a more potent immunosuppressant and requires more hospital attendances for intravenous dosing, so is potentially more likely to be associated with increased risk of infections.

Patients should stay on their maintenance immunosuppression and steroids provided infection free.

Immunsupressive therapy needs to be reviewed on a case by case basis balancing the risk of inadequately treated disease, or acute relapse, against the risk of the effect of COVID-19 infection in the individual patient.

Where standard immunosuppression protocols are modified on a balance of risk, units are recommended to optimize surveillance for relapse; including but not limited to advice on relapse risk and symptoms to patients, increased clinical assessment (can be remote), use of urine sticks at home, inflammatory markers, renal function and autoantibody screening and lymphocyte subset analysis where possible.

Patients on long term glucocorticoids (steroids, prednisolone) SHOULD NOT stop these abruptly.

Patients receiving hydroxychloroquine SHOULD CONTINUE this as it may afford some protection against COVID-19 (as yet unproven in clinical trials)**.**

If units are unable to deliver intravenous induction medication due to staff shortages or patients being unable to attend hospital:

- **In vasculitis:** If at all possible to maintain hospital visits (and recognising the risks during COVID-19) and given the risks of uncontrolled disease, the ongoing use of IV cyclophosphamide based induction regimens maybe preferable to oral ones but rituximab affords fewer hospital visits and less monitoring..
- If intravenous infusions are not available, it may be necessary to use only oral induction – ideally these would be monitored by clinicians familiar with their use. Oral cyclophosphamide is an alternative to IV cyclophosphamide (but is associated with higher infective complications). Oral mycophenolate mofetil can be considered but the evidence supports use only in patients deemed low risk of relapse with GFR >15mls/min and without rapidly deteriorating renal function, and requires concomitant steroid dosing though high dose steroids should be avoided if possible in COVID-19 (PMID: 30612116 DOI: 10.1136/annrheumdis-2018-214245)
- **In lupus:** Oral mycophenolate mofetil can be used as a well-established alternative to iv cyclophosphamide in induction therapy. (PMID: 30564454 PMCID: PMC6269635 DOI: 10.1136/rmdopen-2018-000793). If possible to administer rituximab, it may be worth considering the Rituxilup protocol which is steroid sparing (PMID: 23740227 DOI: 10.1136/annrheumdis-2012-202844)

  In general, in order to reduce infection risk, clinicians are recommended to reduce steroids promptly in line with protocols found in the PEXIVAS trial (PMID: 32053298 DOI: 10.1056/NEJMoa1803537) and the Aura-LV Trial (PMID: 30420324 DOI: 10.1016/j.kint.2018.08.025)

- **MAINTENANCE PHASE OF IMMUNOSUPPRESSION TREATMENT**

  If well, all patients should continue to take their maintenance medication unless directed otherwise by their renal team. In individual cases where there has been prolonged disease quiescence and the risk of severe COVID-19 infection is felt to be high for a given patient, clinicians may consider modifying maintenance immunosuppression regimens on a case by case basis.

  In the case of long acting rituximab maintenance regimens, delaying intervals between rituximab infusions could be considered for patients where the risk of disease flare is deemed low and the risk of

adverse outcomes with COVID-19 infection is high. Lower doses of rituximab may be considered given evidence from the Mainritsan study suggesting equivalent efficacy. This link summarises the safety of lower doses and even omitting rituximab doses (https://ancavasculitisnews.com/2020/03/18/lower-number-rituxan-maintenance-therapy-infusions-by-omitting-dose-does-not-affect-remission-analysis-suggests/ . There is currently no evidence on the impact of rituximab on the severity of COVID-19 infection.
Where standard immunosuppression protocols are modified on a balance of risk, units are recommended to optimize surveillance for relapse with increased clinical assessment, autoantibody screening and lymphocyte subset analysis where possible.

Clinical Guidance for Managing Patients with or Suspected of having Covid-19

Patients should follow national guidance on COVID-19 https://www.nhs.uk/conditions/coronavirus-covid-19/
If after reading national guidance they need to phone the national 111 helpline, they should let them know they are a patient on immunosuppressive therapy and if possible have their medication list ready.
Patients should also inform their own renal unit by telephone or email that they have developed possible symptoms as soon as possible so they can get timely advice about medications.
Where patients present with possible symptoms, other causes of these should always be excluded such as CMV, pneumocystis, bacterial pneumonia and urinary sepsis, and in those at risk of pulmonary haemorrhage, consider the possibility of disease flare and most importantly, that acute infection can precipitate disease flares in most forms of renal autoimmunity.
There is emerging evidence in the transplant population that some patients on immunosuppressive therapy for solid organ transplants have a worse prognosis. It is not yet clear whether this relates to the use of high dose steroids and no clear evidence yet exists for autoimmune disease patients, but units may wish to take this into account.
Therefore, in some cases based on the risk of COVID-19 and the current state of their underlying autoimmune disease, the renal unit may recommend that immunosuppressive therapy be paused, or significantly reduced, for the duration of the infection (14 days after onset of symptoms if symptom free in the absence of anti-pyretics for a minimum of three days).
For those on maintenance glucocorticoids (steroids, prednisolone), treatment should not be stopped abruptly and advice should be sought from their treating team.
High dose steroids may be associated with prolonged viral shedding and possible poor outcome. There is no evidence to support their therapeutic use in COVID 19 and they should be not be initiated unless for other therapeutic indications.
There is currently no guidance that these patients should be specifically tested for COVID-19 unless they are sufficiently affected to warrant hospital admission. However, if testing becomes more widely available we would recommend that this group is tested as soon as symptoms develop so that immunosuppression can be paused promptly where thought necessary. If they have a kidney clinic appointment but have symptoms of COVID-19, they should NOT attend the kidney appointment unless specifically requested to do so after they have contacted their kidney team via telephone or e mail.
There is some evidence that patients who are immunosuppressed may shed the COVID-19 for longer than those without immunosuppression. This may need to be taken into account when advising on a patient's timescale of quarantine after infection.

Patients concerned about COVID-19 may choose to stop immunosuppressive therapy without consulting their renal unit. Presentations after a period without immunosuppression may therefore in some cases represent disease relapse - please be alert to this possibility.

ARE THERE ANY OTHER SPECIFIC DRUGS KIDNEY PATIENTS SHOULD BE CAREFUL ABOUT AT THIS TIME?

Patients should be advised to avoid non-steroidal anti-inflammatory drugs (NSAIDs e.g ibuprofen, indomethacin, nurofen, voltarol) at this time. Those with flu like symptoms should be advised to take paracetamol instead. Kidney patients should be asked to avoid NSAIDs at all times anyway, but in addition there is some evidence that

NSAIDs may be additionally harmful in the clinical course of COVID-19 so should be particularly avoided at this time. https://www.cebm.net/oxford-covid-19/nsaids-in-acute-respiratory-infection/
Advice has been placed separately on the Renal Association (RA) website for the use of ACE inhibitors and angiotensin receptor blockers https://renal.org/renal-association-uk-position-statement-patients-novel-corona-virus-infection-use-blood-pressure-medications/

WHAT PRECAUTIONS SHOULD PATIENTS BE ADVISED TO TAKE?

Patients concerned about the risk of infection should be advised to take precautions as outlined by https://www.nhs.uk/conditions/coronavirus-covid-19/
Kidney patients on immunosuppressive medication fall into a high risk group for the effects of the COVID-19. These patients should therefore be advised to follow the government self isolation policy
Risk stratification for self-isolation

SHOULD PATIENTS WHO ARE INTENDING TO TRAVEL ABROAD CHANGE THEIR PLANS?

Kidney patients on immunosuppressive therapy are advised against all travel abroad or within the UK at this time.

SHOULD PATIENTS WHO ARE IMMUNOSUPPRESSED STILL COME TO FACE TO FACE KIDNEY APPOINTMENTS?

As patients on immunosuppressive therapy rely on regular blood tests to safely guide therapy, it is likely they will need to have some clinic appointments during the COVID-19 pandemic.
Patient may require reassurance that attendance for vital bloods and medical review is NOT at odds with government advice to maintain prolonged social isolation.
However, clinicians should aim to provide remote consultations including local provision of blood tests where possible in order to reduce the need for patients to attend face-to-face appointments.
Some face to face appointments are likely to be needed. These should be minimized to reduce crowding in waiting rooms and delays to consultations. All outpatients should be triaged on arrival to exclude symptoms of active COVID-19 infection and to check for raised temperature. Those who are considered to have possible infection can then be seen in a separate area away from other at risk patients.

NEPHROTIC SYNDROME

Risk stratification for self-isolation is now available here.

Clinical Guidance For Managing Well Patients

Advice About Immunosuppressive Therapy

Induction Medication For Newly Presenting/Relapsing Nephrotic Syndrome

FSGS/MCD

Standard therapy should be with steroids or CNI, there is no current evidence to recommend one over the other. Steroids may work faster and less monitoring is required, patients can be sent away with dipsticks and managed remotely. However high dose steroids linked to prolonged COVID-19 viral shedding / severe disease. If rapid response, consider accelerated wean from high dose steroids but possible longer tail through the pandemic to prevent relapse. CNI can be considered depending on local arrangements for safe monitoring of levels. We do not recommend use of IVIG in patients with hypogammaglobulinaemia, it will not contain any anti COVID-IgG.

Membranous Nephropathy

Delay treatment if at all possible. If severe deteriorating nephrotic syndrome, with complications, consider CNI, or rituximab. CNI likely to give a swifter response. There is evidence that cyclophosphamide based regimens cause a greater degree of immunocompromised so should be avoided in the pandemic.

Maintenance Phase of Immunosuppression Treatment

FSGS/MCD and Membranous Nephropathy

Aim to continue the lowest dose immunosuppression to maintain remission, but avoid relapse. Avoid weaning of patients with a history frequent relapse who have been stable on low dose IS for some time, and without toxicity, during the pandemic. Consider delaying next infusion of rituximab (or any other biologic), depending on the risk/benefit in individual patients. It is possible that rituximab may prevent a response to a future vaccine should it become available.

Ace/Arb

Advice has been placed separately on the Renal Association (RA) website for the use of ACE inhibitors and angiotensin receptor blockers

Clinical Guidance for Managing Patients with or Suspected of having Covid-19

Patients should inform their own renal unit by telephone or email that they have developed possible symptoms as soon as possible so they can get timely advice about medications. If on immunosuppression and unwell, consider stopping oral maintenance agents except steroids on a case by case basis. Discuss timing of restarting with their nephrologist, with minimum 3 day period after resolution of symptoms.

Updates:

This advice will be updated as soon as new evidence becomes available.

Advice on patients who are acutely nephrotic or at risk of relapsing nephrotic syndrome will be added as soon as possible