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ERA Long-Term Research Fellowship Project

IWG

Project's key info

Title of the project	Immunocompetence across autoimmune diseases
Working Group and ERA Committee involved in the project	Immunonephrology Working Group (IWG)
Principal Investigator(s) of the project	Andreas Kronbichler
Duration	12 months
Fellowship Grant	37.100,00 €
Start of the fellowship	Within 6 months after notification of the grant award to the fellow.

Receiving Institute

Name of receiving institute	University of Cambridge (UK)
Supervisor's name	Andreas Kronbichler
Supervisor's e-mail address	ak2283@cam.ac.uk

Project's detailed description

Project description

Immunocompetence plays a crucial role in autoimmune kidney diseases, and is defined as a state which allows control over a specific disease but also protects from serious infectious complications. After immunosuppression is initiated, most patients are rather prone to develop infectious complications as a consequence of immune system compromise, but upon completion of immunosuppression (withdrawal of immunosuppression) the risk of disease relapses increases. To date, there are no reliable measures of immunocompetence in autoimmune disorders. In ANCA-associated vasculitis, rituximab' use is associated with an excellent disease control during maintenance of remission, however, around 25% of patients develop severe infections after rituximab is initiated (Kronbichler A, *et al*. Ann Rheum Dis 2018; 77:1440-1447).

After rituximab therapy, the median time to repopulation of B-cells is approximately 3 years. During long-term follow-up, the same authors observed 18 flares among 71 patients with a median time to flare of around 115 months after rituximab initiation. All flares were preceded by either B-cell repopulation and/or a rise in the ANCA test. Importantly, patients with no repopulation at 48 months (sub-analysis of 38 patients) were protected against disease relapse ($p=0.024$), but importantly these patients had a worse infection-free survival in comparison to patients who had a B-cell repopulation at 48 months ($p=0.035$). Univariate predictors of B-cell repopulation in this small cohort were female sex (HR 2.01, 95% CI 1.03-3.94, $p=0.042$) and eGFR at the time of rituximab therapy (HR 1.20, 95% CI 1.09-1.31, $p<0.001$) (Mescia F, *et al*. FC061, ERA 2022, Paris). A recent analysis of samples from the RAVE trial (comparison of rituximab versus cyclophosphamide as induction and azathioprine as maintenance of remission therapy) revealed that some markers of immune system activation/inhibition correlate with long-

term outcome and this was particularly the case in rituximab-treated patients (Gamerith G, *et al*. Ann Rheum Dis 2022, doi: 10.1136/ard-2022-222479). These soluble immune checkpoints (sBTLA, sCD27 and sTim-3) might reflect a state of exhaustion, as high levels were associated with a lower relapse risk, but a higher risk to develop infections. Similarly, CD8+ T cell exhaustion was associated with a protection from disease recurrence across different autoimmune conditions, such as ANCA-associated vasculitis and systemic lupus erythematosus (McKinney EF, *et al*. Nature 2015; 523:612-6).

Cytomegalovirus (CMV) infections are considered as a consequence of reduced immunocompetence. The frequency of CMV antigenemia in patients with systemic lupus erythematosus was 58.6% in patients with systemic lupus erythematosus (SLE) in comparison to 14.8% in patients after transplantation (Cui J, PLoS One 2019; 14:e0221793). These opportunistic infections occur earlier in life (also given the demographics of SLE patients) than in other glomerular diseases. In general, most studies identified age (> 50-55 years), the use of immunosuppression/especially induction therapy), low lymphocyte count and of course the overall state of health (such as reduced Karnofsky performance score) as predictors of infections (Sakuma Y, et al. Clin Nephrol 2005; 63:68-73). Accurate risk prediction models of serious infections at baseline or during initial follow-up are missing at the moment.

In other conditions where a fine balance between state of immunosuppression and infections is needed, research made a significant progress over the past decade. In (kidney) transplantation, a specific marker of immunocompetence (torque teno virus (TTV)) is undergoing testing in a European randomized controlled phase 2 trial. Lower viral load is associated with acute rejection episodes, while higher load predicts a state of "overimmunosuppression" and thus reflects a state with a high risk of infection (Doberer K, *et al*. Am J Transplant 2020; 20:2081-2090). A first study in autoimmunity (rheumatoid arthritis) measured TTV load in patients at baseline and during follow-up after initiation of different immunosuppressive agents, namely infliximab, tocilizumab, abatacept, and rituximab. A particular increase in TTV load was observed in patients receiving rituximab (Studenic P, *et al*. Rheumatology 2022; 61:2815-2825). We are currently setting up a study to measure TTV in samples from patients included in several clinical trials (AAV and eventually Lupus Nephritis).

Goals of the project

The successful candidate will work with several clinical datasets derived from randomized controlled trials, including the RAVE trial (rituximab versus cyclophosphamide), PEXIVAS (plasma exchange versus no plasma exchange, standard steroid dose versus reduced dose) and RITAZAREM (rituximab versus azathioprine as maintenance therapy, information about induction therapy available).

1st goal: Clinical data obtained by the candidate will be analyzed with a focus on relapses and serious infections during follow-up. Most of these data are already available and analysis focusing on endpoints are ongoing. Development of a risk score to predict these outcomes of interest should be created and machine learning algorithms should be employed to do so.

2nd goal: In a second step, the research should be expanded and available datasets of recently completed lupus nephritis trials should be used. To do so, a close collaboration with the LNTN is envisaged. An official application will be submitted and we would hope that an agreement on collaboration will be possible.

Milestones:

1. Identification of baseline clinical risk factors which are associated with future disease relapse and serious infections in patients with AAV using a percentage of patients recruited into the PEXIVAS, RAVE and RITAZAREM trials. As baseline characteristics among these trials were not balanced, a total of around 500 patients (randomly selected) will be used in the derivation cohort. A sample of another 500 patients will be used to replicate these findings in an independent sample of the same trials. Machine learning algorithms will be employed. This should ideally be completed within the first 3-4 months of the research stay.
2. Manuscript preparation and discussion during one of the IWG meetings.
3. Expansion of the same approach to patients with lupus nephritis. Patients differ in terms of their baseline kidney function, proteinuria, age, antibodies, etc. Thus, a completely different set of variables will likely predict the outcomes of interest. Depending on the availability of datasets for data analysis, a similar approach as described above will be chosen to establish a risk score predicting relapses and serious infections at baseline.

This work might not be completed within the 12 months of the research stay and should be completed (with a manuscript, involving LNTN) upon return to the home institution.

Qualifications and/or expertise required to the fellow

- The fellow should have an interest in glomerular diseases and ideally a scientific track record in the field of autoimmune kidney diseases.
- Potential candidates should be able to ask scientific questions and develop the project as we are making progress. Basic knowledge and understanding of statistics (SPSS, R) are desirable.

Further details:

- Understanding of the pathogenesis, management, and follow-up of patients with ANCA-associated vasculitis.
- Understanding of the pathogenesis, management, and follow-up of patients with lupus nephritis.
- Interaction with a team of academic physicians working in the Department of Medicine and within the Vasculitis and Lupus group.
- Interaction and collaboration with international fellows working on several research projects.