Good afternoon ladies and gentlemen. First of all, I would like to thank the organisers for inviting me to participate in this CME course.
I will draw your attention back to the vasculitis topic now, which Rachel nicely introduced a few minutes ago. But while Rachel mainly focused on the lung involvement, I will now try to focus on the renal involvement, particularly the severe one.

Outline of the talk

- Vasculitis, ESRD and renal replacement therapy
- Vasculitis relapse - who, when, and how often?
- Immunosuppressive treatment in RRT patients
- Summary

So let me start
with a brief introduction on vasculitis and ESRD.

This is the revised nomenclature of vasculitides you may be aware of, which has been published recently. There are more vasculitides now divided into immune complex small vessel vasculitis and ANCA-associated vasculitis. You know that we may meet patients with different types of glomerulonephritis in different vasculitides.
but in anti-GBM disease while the ESRD is quite common in this patient, it is generally a rare
disease and relapses are even rarer. So I’m not going to go into detail about anti-GBM,
anti-glomerular basement membrane disease.

In the case of cryoglobulinemia and also IgA vasculitis formerly called Henoch-Schönlein purpura,
these conditions may both lead to ESRD in some cases but those are generally infrequent. Even
though we know there are some recurrences in the kidney grafts in IgA vasculitis and also that the
patients with cryoglobulinemia may relapse on renal replacement therapy there is little data in
the literature on this
and so the main focus of both the literature data and my talk will be on ANCA-associated vasculitis.

Rachel has already introduced these diseases,
so I don’t want to spend much time on them but I would like to emphasise that the typical renal involvement is associated with pauci-immune necrotising and crescentic glomerulonephritis.

What is the prevalence of ESRD in ANCA-associated vasculitis? We know that renal involvement is quite frequent even at presentation of the disease by – being different patient subsets not surprising haematology and nephrology units. About up to one third of the patients, who present with renal involvement are dialysis dependent and we know that with current treatment strategies about 60% of them will recover renal function. But eventually during the 5-year follow up, ESRD develops in up to 30% of ANCA-associated vasculitis patients.
What I would like to also emphasize is the fact that severe renal involvement is associated with poor prognosis or worse prognosis of patients with ANCA-associated vasculitides and this has been demonstrated in a number of studies.
I would like to present a case of a young female patient who was born in 1991 and at the age of 9, she was diagnosed with type 1 diabetes. At the age of 12 she presented with some skin lesions that were associated with systemic lupus or potential systemic lupus at that time and she was also positive for some compatible antibodies at that time and corticosteroid treatment was started. Later on, she developed haematuria proteinuria. While it was expected that the outcome of renal biopsies would be lupus nephritis, it was surprisingly pauci-immune necrotising glomerulonephritis and she was very strongly positive for anti- -- and antibodies. So the routine treatment with high-dose corticosteroids and cyclophosphamide was introduced and then she was switched to cyclosporine. She was followed by paediatricians at that time but she did not do well and was later switched to mycophenolate mofetil and even received some pulses of rituximab because her skin disease was complicated by recurrent disease activities.

At the age of 19 she was then referred to our department and the first months were complicated by a number of infectious complications particularly of viral origin. Then in August 2011, she suddenly deteriorated renal function, presented with renal relapse and during biopsy, we found that almost half of her glomeruli were already globally sclerotic.
Because it is a bright young woman, she asked us what her chances of renal recovery were.

So looking at the literature data, you may know this histopathological classification of ANCA-associated glomerulonephritis developed of few years ago. Our patient met the criteria for sclerotic class unfortunately because then
we know that these sclerotic class is associated with adverse prognosis of the patients.

So, there have been a number of studies trying to define risk factors associated with the risk of ESRD. This is one of the recently published ones and our patient unfortunately, fulfilled many of the risk factors and she did not recover renal function.
What we can conclude from the table of the risk factors is that early diagnosis and appropriate treatment management as well are extremely important for the good prognosis of the patient and it is the same as in the case of lung haemorrhage shown by Rachel as already mentioned earlier today.

Now, when we look at patients who are already on renal replacement therapy, what is the prevalence of ANCA vasculitis among them? There have been data from three registries published recently or mentioned recently at least in the abstract form and they found that the prevalence of ANCA-associated vasculitis among them is about 1%. It may be a different representation of GPA and MPA cases.
In the early 1990s Weidemann with colleagues examined ANCA antibodies in haemodialysis patients in German centres and they found that the ANCA positivity was quite high among haemodialysis patients but in 30 patients they identified clinical signs of vasculitis and out of these 30 patients only 7 had been diagnosed before these tests were done. It was before ANCA testing or it was just at the time of ANCA testing was started.

But the question was whether some patients may remain undiagnosed even today, which is maybe a point of discussion.
What we also know from the registry-based data from recent studies but also from reports on vasculitis patients, is that the patient with vasculitis on dialysis actually is very similar to other patients with non-diabetic causes of ESRD.

Our patient was at the time of the renal relapse had just been admitted to university and her question was whether she might be treated with peritoneal dialysis.
So again, we went back to the literature data and we found out that peritoneal dialysis is actually less used than haemodialysis in patients with ESRD but recent reports suggest that the outcome of patients treated with both haemodialysis and peritoneal dialysis is similar. While the risk of infection is undoubtedly increased in vasculitis patients on renal replacement therapy, both are compared to the patients who don’t need renal replacement therapy and also this increase in patients who need immunosuppression compared to those who are without immunosuppression there is no clear difference between peritoneal dialysis and haemodialysis reported.

So we introduced peritoneal dialysis in this patient and her father’s thoughts were about the possibility of transplantation.
We know that all patients who undergo renal transplantation do better than patients with dialysis.

The probability of the positive outcome is higher. We also know that patients with ANCA-associated vasculitis display a similar or the same, if not better patient and graft survival than compared to other patients with ESRD or – transplant. This is particularly true for granulomatosis or polyangiitis because in the case of microscopic polyangiitis, data from the Australian registry suggested that actually in patients with MPA might be doing worse after transplantation but it was not confirmed by other data recently.
An important issue of transplantation is the timing of the transplantation. Data from this British survey suggest that the patients who undergo kidney transplantation less than one year, today achieve remission are actually at higher risk of death than those in whom the transplant is postponed.

So, we definitely decided that we needed some time in our patients with active vasculitis before transplantation.
but what we needed to decide about was how to lead to maintenance in suppression, which is always an issue in patients on dialysis.

We need to consider the risk benefit ratio in all patients and the prevalence of relapses in ANCA-associated vasculitis in general is actually high, about 50% of patients within 5 years develop relapse.
There have been a number of studies trying to identify the risk factors for relapse for example, anti-PR3 positivity is repeatedly recognised as one of the risk factors. Renal involvement or renal insufficiency is actually usually associated with lower risk of relapse and this has been confirmed by other studies as well.
Looking at some studies that measured the relapses per patient year on pre-dialysis and on dialysis, we usually are able to notice some decrease in the number of relapses per patients year.

What is important is that this risk of relapses is further reduced in patients who undergo kidney transplantation. What is an issue about relapses in ESRD, so in patients with ANCA-associated vasculitis is that relapse may very easily mimic infectious complications as Rachel has already demonstrated in her case report as well. What is stressed is that patients after transplantation should be followed by a vasculitis doctor as well and monitoring of ANCA levels may probably help in measuring disease activity even though the relationship of ANCA levels with disease activity is not 100% clear in ANCA-associated vasculitis.
So in our patient taking into account that she did not actually go into stable remission and then her anti-MPO ANCA levels were still positive despite previous treatment, we decided to go for maintenance therapy and switch her to mycophenolate mofetil.
Immunosuppression is always a question of finding the right balance and it’s even more valid for patients on dialysis where the overdose can be very easy and we know that the patients are at an increased risk of infection. However, there is also the risk of extra renal manifestation and this can be severe, even life-threatening in a number of patients. Finally, the patients who under dosed can develop disease-related chronic damage.
The general approach is that maybe we now tend to over treat the patient but we have to take into account that the disease itself untreated is associated with a poor prognosis with only a 10% of survival at 1 year and patients with generalised -- for example, but Rachel has already shown this picture as well. Our patients tend to die of infection rather than of active vasculitis.

**Causes of death in AAV patients**

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>&lt;1 Year</th>
<th>&gt;1 Year</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active vasculitis</td>
<td>11 (11.1)</td>
<td>12 (20.0)</td>
<td>23 (17.6)</td>
</tr>
<tr>
<td>Renal failure secondary to vasculitis</td>
<td>2 (2.0)</td>
<td>6 (10.0)</td>
<td>8 (6.4)</td>
</tr>
<tr>
<td>Infection</td>
<td>20 (19.5)</td>
<td>31 (52.1)</td>
<td>51 (39.6)</td>
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<tr>
<td>Pneumonia</td>
<td>15</td>
<td>0</td>
<td>15</td>
</tr>
<tr>
<td>Septicemia</td>
<td>9</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>OMS</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>PCP</td>
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<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>9 (9.3)</td>
<td>1 (1.7)</td>
<td>10 (7.8)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
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<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Endomyocardial biopsy</td>
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</tr>
<tr>
<td>Pulmonary embolus</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Sudden death</td>
<td>1</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Malignancy</td>
<td>5 (5.1)</td>
<td>2 (3.4)</td>
<td>7 (5.3)</td>
</tr>
<tr>
<td>Solid organ</td>
<td>12</td>
<td>2</td>
<td>14</td>
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<tr>
<td>Heterologous</td>
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<td>1</td>
<td>13</td>
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<tr>
<td>Miscellaneous</td>
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<td>11 (18.3)</td>
<td>16 (12.6)</td>
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<tr>
<td>Pulmonary fibrosis</td>
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<td>1 (1.7)</td>
<td>10 (7.8)</td>
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<tr>
<td>Unknown</td>
<td>5 (5.1)</td>
<td>0</td>
<td>5 (3.8)</td>
</tr>
<tr>
<td>Total</td>
<td>50</td>
<td>74</td>
<td>124</td>
</tr>
</tbody>
</table>

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Immunosuppression in AAV on dialysis - when (not) to treat?

- Analysis of patients included in the MEPEX trial

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Tubular Atrophy (%)</th>
<th>Normal GAN/GL (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VHF</td>
<td>No</td>
<td>&lt; 3</td>
</tr>
<tr>
<td>IS</td>
<td>No</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>IS</td>
<td>Moderate</td>
<td>1-10</td>
</tr>
<tr>
<td>HLA</td>
<td>Severe</td>
<td>&gt; 10</td>
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<tr>
<td>PE</td>
<td>Moderate</td>
<td>1-10</td>
</tr>
<tr>
<td>PE</td>
<td>Severe</td>
<td>&gt; 10</td>
</tr>
</tbody>
</table>

Almost all patients may benefit from Immunosuppression

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and this is also true for patients on dialysis. So one of the important questions is when not to treat vasculitis patients on dialysis. There is quite an agreement in the literature that patients presenting with renal failure and diagnosed with ANCA-associated vasculitis should actually almost always be treated even with immunohistologic findings, the benefit of the immunosuppression exceeds the risk of infections or death in the first months.
But what is also suggested by some authors is that after 4 months if the patient remains dialysis-dependent and does not have any other extra renal involvement, maybe the maintenance immunosuppression should be stopped. This is really a very crucial point, which is not well understood, and there is conflicting data on that because some centres recommend low-dose immunosuppression in dialysis patients with vasculitis to prevent extra renal involvement. This probably has to be really individualised and assessed in each the patient, as there are clearly different points that have to be taken into account.

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Our patient developed further infectious complications after the relapse in the summer of 2011, which required temporarily withheld mycophenolate.
Just one month after that she developed further lung relapse with alveolar haemorrhage, which was also complicated by overhydration in the patient on peritoneal dialysis.

So we had to introduce haemodialysis in combination with her peritoneal dialysis. What are our treatment options in patients on dialysis? Basically, I think what Rachel said about lung haemorrhage is also valid for patients with vasculitis. It was mentioned earlier today that methotrexate should not be used in patients on dialysis. The other drugs that are routinely used in the treatment of vasculitides that include cyclophosphamide, azathioprine and mycophenolate mofetil require dose reduction,
which is best defined in the case of cyclophosphamide treatment where this is a table is showing the recommended dose reduction for renal insufficiency also taking into account the age of the patient. But Rachel has already mentioned a lot of data about rituximab as well. The safety of rituximab in dialysis patients has not been studied in detail because the patients were actually excluded from the RAVE and there were 9 patients on haemodialysis in the RITUXVAS trial but we know that patients on dialysis generally develop more adverse events and this may be the case of rituximab treatment as well. There are some suggestions that patients on dialysis receiving rituximab might develop hypogammaglobulinemia more often but it is really just a few patients described so we need to actually wait for more experience with this drug on dialysis. Plasma exchange is used for severe extra renal manifestations and an approach that might be considered instead of combined immunosuppression is to use corticosteroids only. We have to be aware of the fact that high dose corticosteroids actually show common side effects and the safety of high-dose corticosteroids is also an issue that is discussed and approached now in the PEXIVAS trial.

In the end, we decided in our young patient that she would receive one pulse of cyclophosphamide, this was mainly due to it being before we were able to get other treatments, then we started rituximab, and we continued with maintenance immunosuppression with 1 g every 6 months. In the end, the patient made it to successful kidney transplantation from a living donor.
Outline of the talk

- Vasculitis, ESRD and renal replacement therapy
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She’s doing very well right now.
The risk of infections and infectious related mortality is really high in patients with ESRD, which is valid also for patients with vasculitis. On the other hand, risk of relapse seems to be lower on dialysis and even decreases after transplantations. On the other hand, risk of even life-threatening extra renal relapses is still present, which suggests that maybe we need better biomarkers to assess the state of each patients and individualisation of the approach is clearly required.

I would like to remind you of the fact that May is actually Vasculitis Awareness Month and I would like to thank you for your attention and my colleagues for help.
Chairman: Thank you Zdenka. The lecture is now open to discussion. I feel that there are several important points. One is that even the patient who is treated for ESRD on dialysis should be checked regularly by somebody who is experienced in the treatment of vasculitis. Then the second point that the approach should be very much individual from giving almost nothing if the patient has very low risk of relapses to almost permanent and sometimes very aggressive immunosuppressive treatment if he is relapsing and if the activity of the disease is high. Is it ok?

Dr. Hruskova: Yes, I absolutely agree.

Chairman: Any other questions from the auditorium? No thank you.

Question: Yes, maybe one more question. There should be data available from myeloma treatment with rituximab because these patients often are also on dialysis. Are you aware of any data from that cohort of patients and the use of rituximab?

Dr. Hruskova: Excuse me, I didn't hear the question, could you repeat?

Question: Rituximab was first developed for the treatment of myeloma and these patients are often on dialysis. So is there any data available from that cohort?

Dr. Hruskova: Yes, there is some data on the use of rituximab in lymphoma patients as well but the authors mainly concentrated on the timing of rituximab treatment and dialysis and further chemotherapy. But in general, there are no real safety concerns about rituximab in dialysis patients.

Chairman: So, there are no more questions thank you again.