The patient with ANCA-associated vasculitis and pulmonary haemorrhage
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Disclosure of Interest
Rachel B. Jones

Formal association with a company:
GliaxSmithKline
Thank you. So, I’m going to talk about the patient with ANCA-associated vasculitis and pulmonary haemorrhage.

slide 3

Outline

- Overview of pulmonary disease diagnostic approach to alveolar haemorrhage
- Recent outcomes from alveolar haemorrhage
- Current treatment approaches for pulmonary renal AAV

What I’d like to do in the next 30 minutes is to run through an overview of pulmonary disease in ANCA-associated vasculitis and the diagnostic approach to alveolar haemorrhage, as well as some recent outcome data from studies of alveolar haemorrhage and ANCA-associated vasculitis and the current treatment approaches that we take for alveolar haemorrhage and pulmonary renal syndrome in ANCA-associated vasculitis.

slide 4
So, just a step back a bit so we know that ANCA-associated vasculitis comprises three different diseases: granulomatosis with polyangiitis, microscopic polyangiitis and eosinophilic granulomatosis with polyangiitis. All of these conditions have different histological features and different clinical manifestations, yet they’re brought together by similarities in terms of histology that they all have features of small vessel vasculitis and particularly in GPA and MPA there’s renal involvement as a frequent manifestation and all three conditions can manifest as pulmonary capillaritis with lung haemorrhage.

**Anti-neutrophil cytoplasm antibodies - ANCA**

So they’re brought together by this small vessel vasculitis, as well as the association with anti-neutrophil cytoplasm antibodies directed against proteinase 3 in the majority of patients with GPA and MPO for most patients with MPA and some patients with EGPA.
So, the spectrum of pulmonary involvement in ANCA-associated vasculitis is quite wide. As nephrologists, we are often brought to treat these patients because they frequently have kidney involvement alongside and most of the treatment trials have been performed on patients with kidney involvement. So, the spectrum is wide for the different diseases. For GPA nodules and cavities are a frequent finding and in microscopic polyangiitis, lung fibrosis and usual interstitial pneumonias is being increasingly recognised as a manifestation of the disease and of course, in EGPA asthma is a frequent finding.

But again, these three conditions are brought together by the similar manifestation of alveolar haemorrhage due to pulmonary capillaritis, manifest and diffuse bilateral infiltrates on chest x-ray and ground glass changes and consolidation on CT scanning.
Now recently, there have been a couple of studies published, which have looked at large series and their incidence and outcomes in patients with alveolar haemorrhage. These two studies have added significant additional data to the literature. I’ve summarised some of the key demographic findings from the two studies on this table. So, this study here was published by the French Vasculitis Study Group and they had fairly strict criteria for alveolar haemorrhage but they looked at all patients who met the criteria and didn’t just focus on severe patients. In this study here, published by a group in the Czech Republic and in Cambridge, they focused on severe alveolar haemorrhage defined as significant hypoxia with oxygen saturate less than 89% and requirement for blood transfusion. What you can see is that alveolar haemorrhage is more common in PR3-ANCA disease. It’s more common as a first manifestation, we know we frequently see it in patients who are initially presenting and less frequently as a relapse manifestation. However, in the French study, half of the patients who relapsed did actually have some degree of mild or moderate pulmonary haemorrhage, so it’s not uncommon but severe pulmonary haemorrhage as a manifestation of relapse is rarer. Both studies showed that there was a high association with renal involvement. The French study had strict criteria and the patients had to have a decline in kidney function and the association was 76% had renal involvement including a decline in renal function and in the Czech study 98% had renal involvement and half of those patients were on dialysis at presentation. Mechanical ventilation of course, you’d expect that to be high in a study, which focused on severe alveolar haemorrhage. Just under half the patients had mechanical ventilation and a further quarter had non-invasive ventilation in the Czech study and was much lower in the study which looked at all alveolar haemorrhage that actually quite high compared to other studies, which have reported rates of around 5%.

slide 9
Severe presenting manifestations in AAV

- 70% renal involvement
- ~30-40% alveolar haemorrhage
  - ~75-95% present as pulmonary renal syndrome
  - Randomised treatment trials for renal disease
  - Treatment by nephrologists
- Pulmonary renal syndrome
  - Rapidly progressive glomerular nephritis
  - Fibrinoid necrosis, cellular crescents, pauci immune
  - Diffuse alveolar haemorrhage
  - Pulmonary capillaritis

So, we know as nephrologists that renal involvement in ANCA-associated vasculitis is common, it’s the most common severe manifestation with 78% of patients having renal involvement at diagnosis. We know from studies that we’re seeing that approximately 30%, a maximum of 40% of patients have some degree of alveolar haemorrhage at presentation, so it’s not uncommon. As we’ve just seen, a high proportion of these patients have concomitant renal involvement with alveolar haemorrhage. So, they present as a pulmonary renal syndrome and we know that that means that they have rapidly progressive glomerulonephritis with the hallmark features on kidney biopsy and they also have an associated diffuse alveolar haemorrhage with pulmonary capillaritis. These patients come to nephrologists frequently treated by nephrologists and in the randomised treatment trials, the evidence base for treatment is derived from treatment trials involving patients with renal disease.

Alveolar haemorrhage in AAV

Mild
- Mild illness
- 25-30% AAV
- Good outcome

Spectrum

Severe
- Hypoxia
- Fall in Hb
- Respiratory failure
- 5-10% AAV
- Good outcome

- Key diagnostic features
  - Haemoptysis
  - Dyspnoea
  - Alveolar infiltrates
  - Anaemia

- Other causes excluded
  - Infections
  - Pulmonary oedema
  - Malignancy/pulmonary emboli

So, it is important to look out for alveolar haemorrhage and have a high index of suspicion because the spectrum is very broad with the majority of patients presenting non-ventilated dependent or requiring and presenting with a fairly mild illness and may not even be clinically detectable. Key diagnostic features such as haemoptysis, dyspnoea, alveolar infiltrates on chest x-ray and anaemia may but may not be present. However, having said that, those patients that fall into the mild-moderate category generally have a good outcome. At the severe end of the spectrum where patients have clear hypoxia, a falling haemoglobin, transfusion requirements and respiratory failure needing non-invasive or mechanical ventilation, which is a much smaller proportion of patients with ANCA-associated vasculitis, the mortality is high.
Of course, it’s important to exclude other causes and there’s wide differential diagnosis and particularly infection, pulmonary oedema can often coincide or manifest in very similar ways to pulmonary haemorrhage. We also have to remember other key factors that can overlap with the diagnosis of vasculitis such as malignancy and pulmonary emboli, which can coincide with pulmonary haemorrhage but can also present as haemoptysis. So, a wide level of concern for differential diagnosis is required. In order to assist the diagnostic approach of course, there are a number of diagnostic investigations that are performed and of course, chest x-rays are performed and generally, they are very sensitive but not specific in terms of telling you that the patient has pulmonary haemorrhage. Then, in the milder spectrum of pulmonary haemorrhage, they’re actually less sensitive and 13% of patients can have a complete normal chest x-ray with mild alveolar haemorrhage. So CT has greater sensitivity than chest x-ray but again, lacks a precise degree of specificity. So a more invasive procedure that we often turn to our respiratory colleagues for help with is a bronchoscopy and bronchoalveolar lavage and the detection of hemosiderin-laden macrophages is very sensitive but of course, it’s an invasive procedure and is difficult to perform in a patient who’s hypoxic but not yet on a ventilator. Of course, bronchoscopy is extremely helpful when considering other causes such as infection and malignancy and having a good working relationship with the respiratory physician is key in order to optimise treatment and diagnoses for these patients. Lung function testing is also used having the advantage of being non-invasive and is useful to help detect pulmonary haemorrhage in the previous 48-72 hours although there are difficulties with performing lung function testing in terms of accessibility to the tests and having them performed rapidly enough for diagnostic purposes. The onset of pulmonary haemorrhage, it’s fair to say it can vary between a fairly insidious onset and a fairly rapid onset. Of course, we all worry about the very rapidly acute presenting patients but actually looking at the two studies that have recently been published, you can see from the data available from the French study that actually a lot of the patients had haemoptysis ongoing for certainly days if not weeks or even months. Again, from Zdenka Hruskova’s study you can see that actually, again a significant proportion of patients had pulmonary haemorrhage ongoing for quite a long time. So having earlier diagnosis is important in these patients. Of course, these patients present a real treatment challenge in terms of the drugs that we use which are immunosuppressive versus the high risk of infection that pulmonary haemorrhage presents.
So of course, we usually step back and look at what the standard treatment approach in ANCA associated vasculitis is. As we know, the standard treatment paradigm involves firstly a time between the development of the symptoms, so the actual time of diagnosis and this is where we really could intervene in terms of earlier diagnosis, better referral patterns, detecting pulmonary haemorrhage at an earlier stage and treating it before it becomes severe. Then of course, when the patient is diagnosed, we move him to remission and induction therapies, which are typically for 3-6 months followed by remission maintenance therapy for a year to a year and a half. If patients are well and have had no relapses, at that time point therapy may be withdrawn and they enter a follow-up phase. Therapies are tailored according to the severity of the disease manifestations. But focusing in on the severe diseases, pulmonary haemorrhage

<table>
<thead>
<tr>
<th>Subtype Description</th>
<th>Constitutional symptoms</th>
<th>ANCA status</th>
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<tbody>
<tr>
<td>Localized</td>
<td>Yes</td>
<td>+/-</td>
</tr>
<tr>
<td>Early systemic</td>
<td>Yes</td>
<td>+/-</td>
</tr>
<tr>
<td>Generalized</td>
<td>Yes</td>
<td>+/-</td>
</tr>
<tr>
<td>Severe</td>
<td>Yes</td>
<td>+/-</td>
</tr>
<tr>
<td>Refractory</td>
<td>Yes</td>
<td>+/-</td>
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So there is still a question over plasma exchange and I’ll come on to that in a minute. But what was found in these studies looking at a subgroup is that

and renal involvement, this is a summary of these standard treatment approaches for severe disease. Initially we’ve learnt from treatment trials particularly the MEPEX, CYCAZAREM and CYCLOPS EUVAS studies that lower dose cyclophosphamide can be used for 3-6 months in intravenous or oral format in order to achieve high remission rates and lowering cyclophosphamide exposure and potentially lowering infectious risks. Now, we also learnt from the MEPEX study, which was a randomised trial comparing plasma exchange to intravenous methylprednisolone that early outcomes in terms of renal recovery were better with plasma exchange although this did not translate into a longer-term benefit in terms of mortality and long-term preservation of renal function. So there is still a question over plasma exchange and I’ll come on to that in a minute. But what was found in these studies looking at a subgroup is that
25% of patients in these early EUVAS trials actually did have some degree of pulmonary haemorrhage either mild or moderate. A ventilated dependent severe pulmonary haemorrhage was exclusion criteria, so we have no data from those trials on that important category of patients.

Mortality in alveolar haemorrhage

But nevertheless, we do know that those patients who did have mild-moderate pulmonary haemorrhage did do well. We know that the mortality in the early EUVAS trials overall was 25% at 5 years. Data from the French cohort study of 80 patients published recently had approximately a 15% mortality at 5 years, which compares reasonable favourably to outcomes from clinical trials, which actually suggest that again, in mild-moderate alveolar haemorrhage outcomes are reasonably good with the treatments that we currently use.

Standard treatment protocols for severe disease

What we have known recently is that rituximab has now become an accepted alternative to cyclophosphamide as an induction therapy for severe ANCA-associated vasculitis and now can be put into the treatment paradigm to replace cyclophosphamide based on data from the RAVE study where it was used just with glucocorticoids to treat severe disease. Although in the RAVE study, they excluded patients again, with ventilated dependent severe pulmonary haemorrhage and patients with severe advanced renal involvement. The RITUXVAS trial was a smaller trial, which also looked at rituximab as induction therapy. In the RITUXVAS study, 2 pulses of
cyclophosphamide were used and there was an option to use plasma exchange and about a third of patients in the trial did actually receive plasma exchange.

slide 16

**Rituximab for remission induction in ANCA-associated vasculitis**

- Chimeric IgG1/κ anti-CD20 Mab
- Depletes B cells
  - ADCC, CDC, apoptosis
- FDA/EMA licence 2011/2013
  - Single course for active disease
- US randomised induction trial, RAVE
  - New and relapsing major organ disease, n=197
- EU randomised induction trial, RITUXVAS
  - New renal disease, n=44

So based on the RAVE study, rituximab has been licensed for ANCA-associated vasculitis both in Europe and in the US.

slide 17

**B cell depletion: Rationale in AAV**

There’s good rationale for the use of a B cell therapy in vasculitic manifestations including pulmonary capillaritis because of course, it eliminates B cells which are the precursor cells that form the antibodies in the disease which activate neutrophils and we know that neutrophils cause damage across the vascular endothelium.

slide 18
We know that both the RITUXVAS and RAVE studies excluded severe pulmonary haemorrhage but a subgroup analysis has been performed on the RAVE study focusing in on patients with alveolar haemorrhage. Now both studies have remission as their primary endpoint. The remission definitions were different but what both studies found were similar remission rates between the rituximab and the control cyclophosphamide groups. In the subgroup analysis in the RAVE trial, which was the larger study recruiting just under 200 patients where 28% of them had some degree of alveolar haemorrhage, remission was observed in 41% of the cyclophosphamide and in 57% of the rituximab group suggesting that rituximab was of benefit for the treatment of pulmonary haemorrhage.

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Case 1: Rituximab in non-ventilated AH

- 44 yr old male
  - March 2006
- Presenting features
  - Dyspnoea
  - Haemoptysis
  - Epistaxis
  - Weight loss
  - Rash
- Examination
  - Respiratory rate 24/min
  - Sats 93% on air
  - Blood ++++, protein +++
- Blood results
  - Hb 8.6
  - Creatinine 318
  - CRP >250
  - PO2 9.1 (air)

I think that in clinical practice because there are no treatment trials that focus in on alveolar haemorrhage as the main endpoint, we use subgroup analysis and we use our own clinical experience and certainly in Cambridge, we’ve used rituximab to treat alveolar haemorrhage. I’ll just run through a very quick case as an example of this. So we treated a 44-year old patient, who presented in March 2006 who initially presented with classic features of vasculitis with lung haemorrhage, with haemoptysis and dyspnoea. Alongside his alveolar haemorrhage, he was also found to have renal involvement with significant blood and protein in his urine, a serum creatinine of 380 micromole/l and confirmatory histological findings on kidney biopsy. At the time of presentation, he was anaemic having previously had a haemoglobin of 13, so he was having lung haemorrhage.
At that time, he was not in significant respiratory distress, he did not require ventilation and was treated just with cyclophosphamide and steroids and had an early response so was not treated with any additional therapy at that time. But he did go on to have a very difficult treatment course and he had a relapse at 4 months, which was renal relapse, another relapse at 11 months, 16 months and 27 months. At each of his relapses, he had renal involvement. In addition, he had a number of significant adverse events: pulmonary embolism, which is not uncommon in patients with vasculitis and two episodes of hospitalisation with infective complications.

This patient had very nice biomarkers in terms of what happened at each relapse. Each relapse is indicated by arrows along the top. You can see the rise in creatinine with each relapse, and this is sort of similar rise in his PR3-ANCA at the same time of each relapse.
This is a summary of his first two years of treatment. You can see the green arrows a lot of cyclophosphamide used, a lot of intravenous steroids, plasma exchange not at the initial diagnosis but at his relapse at 11 months, he had other therapies in between. Then at the relapse at 27 months, his cyclophosphamide was stopped because he relapsed despite all this cyclophosphamide and he was given plasma exchange steroids,

his chest x-ray looked like that
and he went on at that point to receive rituximab. We gave an initial 2 grams and then gave 1 gram every 6 months and with that his steroid dose could be tapered and actually withdrawn

and his biomarkers from that time of relapse looked like this. So he’s stayed in nice stable remission ever since.
So that is an example of where rituximab is used. Clearly, it's one case but throughout clinical practice, rituximab is being used without large randomised study data. So what happens in the case of severe alveolar haemorrhage where patients are ventilated-dependent? How can we adapt and improve our treatments in this situation? Well, there is no randomised trial data and each patient presents as a major treatment challenge and we look to the standard treatments to start with and adapt the regimens as needed based on clinical manifestations and treatment progress. There are questions whether more plasma exchange should be used, other adjunctive therapies perhaps using IVIG, which is a nice therapy to use in a patient at high infectious risk. Should we be using rituximab instead of cyclophosphamide? Is it a safer drug or not? Should we be using lower dose steroids to reduce infection risk or perhaps more intravenous steroids to give it a more rapid onset of response?

Why do we worry? Well, of course, these patients are sick and there's a high mortality associated with severe alveolar haemorrhage. This is the Czech data, which shows that at 5 years approximately 40% of patients had died which is double that seen in the French study where at 5 years 20% of patients were dead with a less severe pulmonary haemorrhage presentation. The risk factors for death were age, as you would expect, 71% mortality versus 31% mortality, dialysis dependence, ventilated dependence. Now, this was not statistically significant but there was certainly a trend that patients who were on the ventilator did worse in terms of mortality. What was also interesting is that mortality was much higher in patients treated before 2003 versus after 2003 and that does suggest that perhaps our use of is improving and perhaps we our
diagnostic ability is improving and we are treating patients earlier.

slide 28

Mortality in AAV Trials

<table>
<thead>
<tr>
<th>All causes (% of patients in the respective group)</th>
<th>MEPEX</th>
<th>CYCAZAREM</th>
<th>CYCLOPS</th>
<th>NEPAM</th>
</tr>
</thead>
<tbody>
<tr>
<td>56 (10.7)</td>
<td>12 (25)</td>
<td>7 (4.5)</td>
<td>14 (9.3)</td>
<td>2 (0.2)</td>
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<tr>
<td>Infection (%)</td>
<td>20 (50)</td>
<td>17 (31.1)</td>
<td>1 (1.0)</td>
<td>6 (50)</td>
</tr>
<tr>
<td>Active vasculitis</td>
<td>8 (1.6)</td>
<td>5 (1.0)</td>
<td>0 (0.0)</td>
<td>2 (14)</td>
</tr>
<tr>
<td>Cardiac/ventricular dysfunction</td>
<td>1 (3.1)</td>
<td>4 (8.1)</td>
<td>0 (0.0)</td>
<td>2 (14)</td>
</tr>
<tr>
<td>GI bleed/dysphagia/ulcer</td>
<td>3 (0.5)</td>
<td>2 (0.5)</td>
<td>1 (1.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>PE or complication of anticoagulation</td>
<td>3 (0.5)</td>
<td>1 (0.5)</td>
<td>1 (1.0)</td>
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</tr>
<tr>
<td>Malformancy</td>
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<tr>
<td>Pulmonary fibrosis</td>
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<tr>
<td>Other</td>
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<td>1 (0.2)</td>
<td>0 (0.0)</td>
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</tbody>
</table>

*Active vasculitis at time of death also including one death due to gastrointestinal (GI) bleeding in the context of warfarin therapy.

<table>
<thead>
<tr>
<th>Rituximab not safer than CYC in RAVE &amp; RITUXVAS</th>
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<tbody>
<tr>
<td>RAVE 6 months</td>
</tr>
<tr>
<td>Mortality</td>
</tr>
<tr>
<td>RITUXVAS 12 months</td>
</tr>
<tr>
<td>Severe adverse events</td>
</tr>
<tr>
<td>RAVE</td>
</tr>
<tr>
<td>RITUXVAS</td>
</tr>
<tr>
<td>Stone, NEJM 2010</td>
</tr>
<tr>
<td>Mortality</td>
</tr>
<tr>
<td>RACE</td>
</tr>
<tr>
<td>RITUXVAS</td>
</tr>
<tr>
<td>Jones, NEJM 2010</td>
</tr>
</tbody>
</table>

- Severe Pulmonary haemorrhage treatment challenge
  - Infection vs alveolar disease, 15-20% thromboembolism
  - Rapid acting therapies increasing immunosuppressive burden

So of course, we worry because of the high mortality but as we’ve seen across EUVAS studies irrespective of lung or pulmonary haemorrhage about 50% of deaths are associated with infection. So there’s a real balance between treating too much and treating too little in pulmonary haemorrhage. We had great hopes that from the RAVE and the RITUXVAS study that we may find rituximab was associated with a trend towards more safer outcomes but neither study has shown us clear signs that rituximab is safer than cyclophosphamide. Now that may be because we’ve improved our use of cyclophosphamide. We’re now using much lower doses and perhaps cyclophosphamide is now a much safer drug with lower dose treatment regimens. Of course, RAVE and RITUXVAS were not powered for safety as a key endpoint but as yet, we have no clear data on improved safety with rituximab. But it is still a different therapeutic option that can be considered.

slide 29

Adjuvant Plasma Exchange for Remission
Induction in Severe Disease?

- Plasma Exchange ‘MEPEX’ Trial

Renal independence in survivors

Mortality

So just to go back to plasma exchange we know that all the plasma exchange trials have been performed in excluding severe alveolar haemorrhage. We know that the MEPEX study is the largest of the trials that have been published so far. The one-year data showed improved renal survival in the plasma exchange group but no improvement in terms of mortality.
There have been a couple of meta-analyses which have looked in more detail at plasma exchange outcomes across different trials again, focusing on patients with renal involvement. There’s a suggestion that plasma exchange may be associated with better outcomes in terms of end stage renal failure and death but it’s not clear cut.

Then what is the data like focusing on plasma exchange and severe alveolar haemorrhage? Well, this is all derived from non-randomised data. Of course, there’s a selection bias in all of the studies where plasma exchange is typically selected for the more severe patient. This data from Zdenka’s study from the Czech Republic showed no survival benefit with plasma exchange but again, it was fairly small numbers who didn’t receive plasma exchange because of the perceived benefit of plasma exchange in severe pulmonary haemorrhage. Also there was a clear selection bias. So it’s difficult to know.
So we still don’t know what the true benefit of plasma exchange is in severe pulmonary haemorrhage. But some of these questions are now being addressed in the PEXIVAS study, which is a global study, it’s the largest randomised controlled trial ever performed in ANCA-associated vasculitis.

PEXIVAS factorial design

This trial is going to primarily address the benefit of plasma exchange versus no plasma exchange in renal vasculitis and pulmonary haemorrhage including patients who may be ventilator-dependent. So this is going to provide some very important data. In addition, investigators are allowed to choose between cyclophosphamide or rituximab as their preferred induction agent and again we have data on rituximab as well as on cyclophosphamide in the severe ventilator-dependent patient. The other useful information we will get from this study is comparison of two different dosing regimens in terms of glucocorticoid dose because there’s still a really big question about what is the optimal glucocorticoid dose.
So we have a couple of years to wait until we see results from the PEXIVAS study, so in the meantime we have to struggle on and treat patients as best we can. I think again, the question is we have no randomised data of newer treatments such as rituximab or alternative treatments such as IVIG. We are using them in individuals that we feel would benefit. Another example case is a patient we treated recently in Cambridge, a 72-year old gentleman, who had significant co-morbidities with diabetes, hypertension who was originally diagnosed with his vasculitis in 2011 and had clear renal involvement with biopsy confirmation, who was initially treated with cyclophosphamide and steroids and his creatinine stabilised to 280 with a low eGFR. He was switched to azathioprine maintenance therapy and prednisolone at low dose.

Case 2 severe alveolar haemorrhage

- March 2014
  - NSTEMI
  - Volume overloaded
  - Haemoptysis
  - Oxygen saturation <90%
    - Non invasive ventilation
    - No bronchoscopy
  - PR3-ANCA positive 17, ESR 70, CRP 50, Hb 8.1
- Differential diagnosis
  - Pulmonary oedema, infection, vasculitis

He was well until March 2014 when he presented to hospital with a non-ST elevation myocardial infarction. He was transferred over to Addenbrooke’s and was volume overloaded and he was having significant haemoptysis and required a 4-unit blood transfusion. He had significant hypoxia, he was a very high risk patient for mechanical and full ventilation and he was commenced on non-invasive ventilation, he was too sick to have a bronchoscopy performed and at that time he was found to be ANCA positive having been ANCA negative and despite a 4-unit blood transfusion he was still significantly anaemic. So this patient really presented in a very common clinical conundrum of what was the main problem going on, was it his pulmonary oedema with his myocardial infarction,
his infection or was it his vasculitis? This was his chest x-ray

and his CT.

Jones slide 2014

slide 36

slide 37

slide 38
Case 2, treatment and progress

- **Initial treatment**
  - 4 Unit Blood transfusion
  - 3x1g IV methylprednisolone

- **Treatment for pulmonary oedema**
  - Diuresis, haemodialysis

- **Treatment for infection**
  - Antibiotics, anti-fungals

- **Further treatment for vasculitis**
  - 5x plasma exchange
  - 2g rituximab
  - 20mg prednisolone

- **Coronary angiography**
  - Critical left coronary artery disease
  - By-pass grafting recommended

As is often the case, we take a belt and braces approach, and transfused him. Initially he had some methylprednisolone to treat what appeared to be active vasculitis and he was diuresed and actually started on haemodialysis to remove fluid. He was treated for infection both with antibiotics and anti-fungals but he failed to improve over a course of a week. He continued to have a frank haemoptysis and so he was treated with plasma exchange followed by initially a 1 gram of rituximab. Over the first week or so after that, he started to improve significantly. Alongside this he was treated with lowish dose prednisolone to minimise further infective complications and he dramatically improved and had a second gram of rituximab two weeks after the first. He’s now considerably better although he does still have ongoing cardiac issues and is waiting for coronary artery bypass grafting.

slide 39

Summary

- Alveolar haemorrhage is a common severe feature of AAV
  - Strongly associated with renal disease
  - Likely under recognised

- Majority mild/moderate haemorrhage (25%)
  - Outcomes associated with standard treatments good

- Severe pulmonary haemorrhage rare (5%)
  - High mortality (50%), major treatment challenge
  - Treatment options increasing, but no RCT data......

- PEXIVAS is the largest vasculitis trial and first to include severe alveolar haemorrhage
  - Data on efficacy/safety of plasma exchange, rituximab, different steroid dosage

I think that case really highlights how although we don’t have randomised trial data we do have to modify our treatment strategies and take each patient on a case by case basis. These patients present as a major challenge to us and we do really look forward to having more randomised data from the PEXIVAS study. Now I would like to summarise and say that I think alveolar haemorrhage is a common feature of ANCA-associated vasculitis in mild to moderate forms and perhaps is under-recognised partly due to lack of suspicion and also lack of specificity and sensitivity of the diagnostic test. It is strongly associated with renal disease and as nephrologists, we are often the people treating these patients. Severe pulmonary haemorrhage, although it is a rare feature of ANCA-associated vasculitis, it is associated with a high mortality and presents as a major treatment challenge. Yes, there is no perfect randomised control trial data but we do hope
Chairman: Thank you very much for this nice overview of this very important topic which as you stressed one should expect should be treated by the lung specialist but they are usually not experienced in the field and rely completely on the nephrologist, so this is now open to discussion. Yes.

Question: So, is there any reason why not to give azathioprine maintenance after you’ve given rituximab?

Prof. Jones So this is slightly a different question. So neither the RAVE nor the RITUXVAS studies incorporated azathioprine into their remission maintenance therapy. So the data we have is without azathioprine. The RAVE study has now published its relapse data without azathioprine compared to cyclophosphamide with azathioprine and the relapse rates were about the same at an 18-month time point. So the suggestion from that data is that you don’t necessarily need azathioprine. I think the reality is that we know that rituximab is a drug with a long biological effect and B cell depletion can last for a year or so after treatment. Actually, what happens beyond those 12 months in terms of relapse, those 18 months in terms of relapse will be very useful. I think it’s also important to say that the relapse rates in the RAVE study are actually quite high in both groups and that does leave a question as to whether if you did use azathioprine or another remission maintenance strategy for example, repeat rituximab dosing, whether you would actually have a lower relapse rate. So yes, you could use azathioprine and I think if you’re not using azathioprine, you should have a high index of suspicion for relapse and be bringing your patients back for monitoring.

Chairman: Thank you. Doctor ---.

Question: Rachel thank you very much. Do you know if there are any data out investigating the timing between the rituximab infusion and the plasma exchange? Obviously, you don’t want to give it before the plasma exchange but is it 12 hours, 24 hours, 3 days, 5 days?

Prof. Jones: Yes, I don’t think there’s any data. I mean, our strategy is always to give rituximab after plasma exchange where possible and I think it’s very difficult but I think if you work, you’re really keen to give something before rather than waiting until the plasma exchange is finished I would say 24 hours at least as a minimum. You do get B cell depletion within 24 hours but clearly any residual rituximab is then going to be washed out when you start your plasma exchange.

Chairman: Thank you. Doctor ---.

Question: I also have two questions related to rituximab. The first one is that if with this current level of evidence and uncertainty, you should choose rituximab as first treatment of the patient with first presentation of vasculitis and alveolar haemorrhage and – if combined with cyclophosphamide or not with cyclophosphamide at all. The second, whether you believe that with rituximab and rituximab maintenance can have any impact on the long-term outcome of these patients with alveolar haemorrhage, which is still very poor as you demonstrated?

Prof. Jones: Yes, ok so, the first question I wouldn’t use rituximab first line. I would use cyclophosphamide first line a patient presenting with pulmonary renal syndrome. I think with both
the cases I showed the first was clearly a patient who was refractory and was having probably haemorrhage despite cyclophosphamide. So that’s a situation where turning to another therapeutic option is ideal and clearly, rituximab worked extremely well. In this other case I presented, we used rituximab honestly because I have a perceived bias that is has a lower infectious risk but that’s my own bias and that patient had already had significant cyclophosphamide exposure and it’s a burden, a risk in terms of how much cumulative cyclophosphamide a patient receives. But honestly I think cyclophosphamide is first line but I have a relatively low threshold switching to rituximab if we are not getting a good response with cyclophosphamide is the way I would say it. Sorry, your second question was about rituximab maintenance therapy. I mean, yes the data certainly from the – study or the initial data that we’ve seen so far that has suggested that rituximab is a very good maintenance agent and if it prevents relapses whether they’re renal pulmonary haemorrhage or any severe manifestation, then you know that does argue that it would be a very good treatment, yes.

Chairman: Thank you. Any other questions? If not we can introduce the other speaker.