Clinical Paper

Systemic Therapy In Acquired Haemophilia – A Single Institute Experience

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ABSTRACT

A cornerstone of the management of Acquired Haemophilia A (AHA) involves inhibitor eradication. First line immunosuppressive agents are usually steroids, either alone or in combination with cyclophosphamide. We present the use of Rituximab, cyclophosphamide, vincristine and prednisolone (RCVP) combination as immunosuppressant in AHA in a small cohort of patients in order to control their symptoms and eradicate inhibitors.

This was a retrospective analysis of all AHA patients treated at the Northern Ireland Haemophilia centre over a six year period. During this time, a total of six patients were newly diagnosed with AHA. Four of these patients failed to respond conventional therapy of steroids and cyclophosphamide, they were however successfully treated with RCVP/RCV.

All patients achieved complete remission with this regimen after 1 to 2 cycles of treatment. Remission has been maintained for an extended time period (range 33-69 months).

As AHA is related to immune modulation and, in some cases, underlying malignancy we decided to use this regime as it is effective in either condition.

From our experience, we demonstrate that RCVP combination is a promising treatment in patients with AHA who fail to respond to steroids alone or who have been on pre-existing immunosuppression.

Key words: acquired haemophilia, inhibitor eradication, RCVP

Acquired haemophilia is a rare but serious bleeding disorder which occurs due to the development of autoantibodies (inhibitors) directed against coagulation factors, most commonly factor VIII. The overall incidence of acquired haemophilia is 1.4 per million per year\textsuperscript{1}. Given the population of Northern Ireland, we expect 2 new cases per year.

The majority of patients are elderly and in 50\% of cases, the aetiology of autoantibodies is idiopathic. In the remainder of patients, autoantibodies may be associated with underlying haematological or solid cancers, pregnancy and autoimmune diseases\textsuperscript{2}. Eradicating the autoantibody requires immunosuppression.

Between 2008 and 2012 6 patients were newly diagnosed with Acquired Haemophilia A (AHA) and were referred to the Regional Centre for Thrombosis and Haemostasis in Northern Ireland. Four of these patients received a combination of immunosuppressive agents with RCVP to successfully eradicate their inhibitors. Treatments were administered at 3 weekly intervals (Rituximab 375 mg/m\textsuperscript{2}, cyclophosphamide 750 mg/m\textsuperscript{2}, vincristine 1.4mg/m\textsuperscript{2} with maximum dose 2mg and prednisolone 1mg/kg body weight). A maximum of 2 cycles were administered (median of 1).

To our knowledge there are no published reports of this specific combination to date.

CASE DISCUSSION

Case 1

A 76 year old female presented with a three month history of spontaneous bruising. She had a past medical history of polymyalgia rheumatica, for which she was taking prednisolone 5mg.

Her Factor VIII level was <1\% and Factor VIII inhibitor level was 28 Bethesda units (BU) consistent with AHA.

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Her prednisolone was escalated to 1mg/kg (60mg daily). A CT chest, abdomen and pelvis was performed, there was no evidence of malignancy.

Despite high dose steroids, this patient’s treatment course was complicated by severe retroperitoneal bleeding, atrial fibrillation and anginal pain. By day 10 her FVIII level was 5%, but her inhibitor titre had risen to 37 BU.

She required activated recombinant activated factor VII to manage her retroperitoneal bleed.

A decision was made to commence Rituximab. This was given at a dose of 375mg/m² on day 10. The initial plan was to administer this weekly for 4 weeks.

Despite the addition of Rituximab the patient developed a significant right thigh haematoma on day 21. This was associated with a 20g/l drop in her haemoglobin. She required further bypassing agents to achieve haemostasis. Oral cyclophosphamide was commenced at a dose of 100mg daily on day 22 to add additional immunosuppression.

She developed a urinary tract infection, which required antibiotics and had an episode of acute psychosis presumably secondary to high dose steroids. The episode of acute psychosis was extremely distressing to both patient and family. She had ongoing haemorrhagic symptoms. We recognised the need to reduce her steroids back to maintenance dose as soon as possible. Following a multidisciplinary meeting, a decision was made to use a combination of cyclophosphamide, vincristine and prednisolone.

The regimen was the same as the RCVP regimen used in the treatment of Non-Hodgkin Lymphoma (NHL). Vincristine was given at 1.4mg/m² and cyclophosphamide 750mg/m², both drugs were given intravenously. Prednisolone was given at a dose of 40mg/m² orally, which equated to 100mg prednisolone, for 5 days the gradually weaned. This combination was given for the first time on day 48. Rituximab had already been given at 375mg/m² weekly and therefore was not given on day 48.

The rationale behind this treatment was that it would provide a boost in immunosuppression and only required 5 days of high dose steroids. It is a commonly used regimen in the treatment of NHL and therefore haematology staff were familiar with its administration and side effect profile.

CVP was well tolerated. By day 66 her FVIII level was 5% and her inhibitor had reduced to 3.83 BU.

CVP was administered again after 21 days, on this occasion Rituximab was also given. She received this second course on day 69.

By day 76, her FVIII level had risen to 23% and her inhibitor had become undetectable, this was 10 days post cycle 2 RCVP. She was on 5mg of prednisolone daily on discharge, which was her maintenance dose for her polymyalgia rheumatica.
She remains in remission from her acquired haemophilia 69 months after discharge.

It is impossible to determine if this patient experienced a delayed response to Rituximab or benefited from the high dose cyclophosphamide.

Case 2

A 75 year old male presented with haematemesis. A CT scan revealed a dilated oesophagus (filled with fluid and debris) and pancreatitis. On day 4 of his admission, an OGD was repeated. This revealed a large oesophageal clot measuring 21cm x 34cm. He aspirated during the procedure and was intubated and transferred to intensive care. He was referred to haematology when his coagulation screen revealed an isolated prolonged APTT of 44.30 seconds. This initially corrected to 35.20 seconds with an APTT 50:50 mix. His factor VIII level was found to be 2% and he had a detectable Factor VIII inhibitor at 17.49 BU.

He required a laparotomy to remove the oesophageal haematoma. Given the need for major surgery he underwent plasma exchange with FFP to remove the inhibitor and replace FVIII. He required extensive treatment with factor VIII bypassing agents (FEIBA) and activated recombinant FVII.

On day 8 post laparotomy, wound healing was complete and his pancreatitis had resolved, at this point he was commenced on combination immunosuppression with Rituximab, cyclophosphamide and vincristine. He received 375mg/m² Rituximab, 1.4mg/m² vincristine and 325mg/m² cyclophosphamide intravenously. Given his pancreatitis steroid use was avoided.

By day 4 post RCV his FVIII level had risen to 41% and his inhibitor was now 0 BU. His FVIII level continued to make a steady recovery and was 110% on discharge. This patient has had a sustained remission of 52 months to date.

Case 3

A 66 year old female presented with a one week history of widespread bruising. She had a background history of bullous pemphigoid managed with prednisolone 5mg and azathioprine 25mg. She also had a history of laryngeal carcinoma treated with chemotherapy and radiotherapy. She remained on PEG feeding. Other comorbidities included type II diabetes and hypothyroidism.

Her APTT was prolonged at 62.70. She was found to have a Factor VIII level of 2% and AHA was confirmed by the presence of a FVIII inhibitor at 16 BU.

The dose of prednisolone was increased from 5mg to 1mg/kg (70mg) daily. A CT scan was performed and there was no evidence of malignancy.

As she was already taking two immunosuppressant medications a decision was made to offer this patient combination Rituximab, cyclophosphamide, vincristine and prednisolone. Given her multiple comorbidities, a 50% dose reduction in cyclophosphamide was made. She received 375mg/m² Rituximab, 1.4mg/m² vincristine and 325mg/m² cyclophosphamide intravenously.

Following the first treatment her factor VIII level was recorded at 10% on day 7 post cycle 1 RCVP. She developed aspiration pneumonia and required intravenous antibiotics. She was not neutropenic. She also required an insulin sliding scale to control her blood glucose while taking steroids. Prior to commencing cycle 2 RCVP her FVIII level was 22%. Following her second cycle her FVIII level continued to rise to 33% on day 7 post cycle 2 RCVP and to 89% by day 23 post cycle 2. No further treatment was required.

Case 4

A 77 year old male presented with continuous bleeding from his tongue after accidentally biting it. He had a background of myasthenia gravis treated with 15 mg of prednisolone daily.

His coagulation screen revealed a PT of 14.3 APTT 73.9 and fibrinogen 4.11. His FVIII level was <1% and his inhibitor was recorded at 1200 BU.

His prednisolone dose was increased to 1mg/kg. There was no evidence of malignancy on CT scan.

His FVIII level failed to improve with steroids alone and given the extremely high level of inhibitor, he underwent plasma exchange. Following this, he was commenced on Rituximab 375mg/m² intravenously weekly for 4 weeks. This was initially successful in inducing a remission and he was discharged after 2 months with a factor VIII level of 29%. This continued to rise to 120% post 4 cycles of single agent Rituximab. His prednisolone was gradually reduced back to his maintenance dose of 15mg daily.

At routine clinic appointment 5 months later, his FVIII level...
was found to be 16% with an inhibitor of 1.91 BU. Given our success with other patients, a decision was made to treat this patient with RCVP. He received one course with each drug given at the usual dose. This has been successful in inducing a sustained remission for more than 46 months. The patient is back on maintenance dose steroids.

**TOXICITIES**

One patient was pyrexic while neutropenic. One patient developed aspiration pneumonia (non neutropenic) and was treated with intravenous antibiotics. No one required GCSF. Transfusion of packed red cells was given in one patient due to bleeding which was not related to a complication of systemic therapy. One patient with a background of type 2 diabetes required an insulin sliding scale due to fluctuating blood sugar related to high dose steroids. No patient developed neuropathy symptoms.

**DISCUSSION**

All patients with acquired haemophilia should be managed in a comprehensive care haemophilia unit. The principles of treatment consist of;

- arrest bleeding
- protect the patient against trauma and non-essential invasive procedures
- inhibitor eradication
- treatment of precipitating cause if present

Our discussion will focus on inhibitor eradication only.

**INHIBITORS ERADICATION:**

Inhibitor eradication should be started immediately after confirmation of the diagnosis, as untreated, the mortality of AHA is high. Severe bleeds may be seen in up to 90% of patients with mortality rates ranging between 8-42%.

A meta-analysis by Delgado et al claimed that achieving inhibitor eradication had a significantly better clinical outcome.

As AHA is such a rare disorder, randomised trials have not been possible, therefore there is no convincing data that one immunosuppressive regimen is better than another. To date much of the evidence regarding immune suppression comes from case series. The choice of regimen is not determined by the inhibitor titre or FVIII level but should be individualised to the patient.

**Prednisolone**

First line therapy typically involves steroids, usually prednisolone 1mg/kg daily which can eradicate the inhibitor in approximately 30% of patients. Steroids can be used alone or in combination with cyclophosphamide which has been shown to improve response rate significantly.

**Cyclophosphamide**

Data from the European Acquired Haemophilia Registry (EACH2) indicated combined therapy of steroids and cyclophosphamide achieved higher stable remission rates. Furthermore a meta-analysis by Delgado et al demonstrated higher complete remission rates in those treated with combined steroid and cyclophosphamide therapy rather than steroids alone (89% vs 70%). Higher response rates did not translate into better survival. Another observational study of 172 patients also failed to reveal any significant difference in mortality between patients treated with steroids alone.

| Age | Presentation | Associated disease | Immuno- suppression prior diagnosis | Factor VIII concentrate units | Inhibitor Level | Haemostatic treatment | Systemic therapy | Complete Remission (CR)duration (months) |
|-----|--------------|-------------------|-----------------------------------|----------------------------|----------------|----------------------|----------------|--------------------------------------|
| 76 F | Bruising     | Polymyalgia Rheumatica | P Tradesolone 5 mg | <0.01 | 28 | Recombinant human coagulation Factor VIIa | RCVP x2 | 69 months                           |
| 75 M | Haemoptysis  | none              | none                             | 0.02 | 17.49 | FEIBA, recombinant human coagulation Factor VIIa | RCV x1 | 52 months                           |
| 66 F | Haematoma    | Bullous Pemphigoid | Prednisolone 5mg, Azathioprine 25 mg | 0.02 | 16 | RCVP x2 | 33 months                           |
| 77 M | Bruising     | Myasthenia Gravis  | Prednisolone 15 mg               | 0.01 | 1200 | RCV x1 | 46 months                           |
and a combination of steroids and cytotoxic agents mainly cyclophosphamide. Cyclophosphamide is normally used in oral form in most of the published data. EACH2 data included only a very small proportion of patients (9) who had received intravenous cyclophosphamide. We used cyclophosphamide intravenously. We could postulate that an intravenous dose of 750mg/m² enhances the effectiveness of the RCPV regimen compared to the standard 2g/kg dose of cyclophosphamide.

As an alkylating agent, cyclophosphamide can result in myelosuppression, infertility, alopecia and increased risk of secondary malignancies. It is therefore not suitable in a pregnant or post-partum patient and should be used with care in the elderly. EACH registry data demonstrated a higher incidence of adverse effects in the group receiving combined treatment (41%) than in those receiving steroids alone (27%). Meta-analysis by Delgado et al also revealed substantial proportion of patients die as a result of complications associated with this agent, mainly neutropenia-related infections. Indeed, 15% of all deaths in the overall population resulted from infectious complications.

**Rituximab**

Rituximab is a monoclonal antibody directed against the surface molecule CD20 expressed by pre-B cells and memory B lymphocytes. It is administered as an intravenous infusion at a dose of 375mg/m² at weekly intervals for four weeks. EACH2 reported 59% of patients had complete remission with a rituximab based regime. A review by Franchini et al on 65 patients treated with rituximab and systemic agents showed a CR rate of 90%. However rituximab monotherapy is normally effective in patients with low inhibitor titers. Field et al suggested that in patients with high titres, single agent Rituximab alone may be effective but unable to achieve a sustained response and combination with other therapies may provide a better result. The Rituximab-based regimens take longer time to achieve complete inhibitor eradication and normalise FVIII than other agents. The current consensus is that Rituximab should be considered in patients who are resistant to first-line therapy.

Rituximab is not licensed for the treatment of acquired haemophilia, therefore applications for use and funding may delay administration.

**Vincristine**

Vincristine in combination with cyclophosphamide and prednisolone (CVP) was found to be effective in a small retrospective series of 6 patients. The authors described 5 patients achieving a complete response with no significant adverse effects.

**Our Experience**

We report encouraging results with combination therapy of rituximab, cyclophosphamide, vincristine and prednisolone in patients with AHA. This combination is more commonly used in the treatment of NHL. RCVP has also been used in steroid refractory chronic immune thrombocytopenic purpura. As AHA is related to immune modulation and underlying malignancy, we decided to use a regime which is effective in either condition.

Interestingly, 75% of our patients were already taking immunosuppression with either steroids or azathioprine. This leads to the question that if a patient is already on immunosuppressive therapy, is more potent immunosuppression required to induce a remission?

All patients achieved complete remission in this case series. There were no unacceptable toxicities despite patients being in their 6th and 7th decades. Patients in our cohort achieved remission after 1 to 2 cycles (median 1) of treatment. None of the patients relapsed and follow up ranged from 33 -69 months.

This shorter duration of treatment is beneficial to minimise treatment related cumulative toxicities and may prove to be cost effective by reducing hospital visits.

**CONCLUSION**

While we are unable to conclude that RCVP or RCV is superior to other regimens we suggest that it is a safe alternative treatment option in patients with acquired haemophilia A who are not responding to standard treatment with no additional toxicities observed.

Ideally, this regimen should be investigated further in prospective multicentre trials. However as the disease occurs so infrequently, such studies are very difficult to perform.

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