Bratisl Lek Listy 2011; 112 (1)
29 – 33

CLINICAL STUDY

Pulmonary administration of activated recombinant factor VII

Grochova M[1], Kalnasova B[1], Firment J[1], Olejarova I[2], Roland R[3], Lazurova I[4]

Ist Department of Anesthesiology and Intensive Medicine, Faculty of Medicine, University Hospital of Louis Pasteur, Safarikiensis University, Kosice, Slovakia. **monika.grochova@fnlp.sk**

Abstract: Diffuse alveolar haemorrhage (DAH) is a serious pulmonary complication seen in patients with autoimmune disorders and patients treated with chemotherapy or after hematopoietic stem cell transplantation. The clinical management of DAH is complex and the condition has a high mortality rate. During inflammation, tissue factor is expressed in the lung alveoli and therefore pulmonary administration of human recombinant activated factor VIIa (rFVIIa) could be a rational treatment option (4.1).
A case report of the patient with an acute, bronchoscopically confirmed DAH from intensive care unit university hospital is described. The patient was treated by the intrapulmonary administration of 50 μg/kg rFVIIa in 50 ml of 0.9 % sodium chloride; 25 ml into each of the main bronchi.
An excellent response, defined as complete and sustained haemostasis after a single dose of rFVIIa was achieved. The oxygenation capacity, as reflected by the paO_2/FiO_2 (arterial oxygen pressure/inspiratory fractional oxygen content) ratio, decreased immediately after the bronchoscopy and the local rFVIIa instillation, but the following course of the patient's illness was favourable.
Symptomatic therapy - intrapulmonary administration of one dose of rFVIIa was found to have an excellent haemostatic effect in the patient with DAH. The intrapulmonary administration of rFVIIa seemed to have a high benefit-to-risk ratio. These findings warrant further exploration *(Ref. 12).* Full Text in free PDF *www.bmj.sk.*
Key words: diffuse alveolar haemorrhage, glomerulonephritis associated with endocarditis, intrapulmonary administration, activated recombinant factor VII.

Abbreviations: anti-BMG – antibodies against basal membrane of glomerules (present by Goodpasture's sy), anti-dsDNA – antibodies against double-files DNA (SLE), APTT – activated partial thromboplastin time, ARDS – acute respiratory distress syndrome, ASLO – anti streptolysin O, BAL – bronchoalveolar lavage, c-ANCA – antibodies against cytoplasma of neutrofils (present by Wegeners granulomatosis), CRP – C-reactive protein, CT scan – computer tomography scan, DAH – diffuse alveolar haemorrhage, EMEA – European medical association, FDA – Food and drugs association –USA, FFP – fresh frozen plasma, FiO_2 – inspiratory fractional oxygen content, i.v. – intravenous, ICU – intensive care unit, L 2–4 area – lumbar area 2–4, NUSCH – National Centre for Heart and Vessel Disease, OTI – orotracheal intubation, paO_2 – arterial oxygen pressure, paO_2/FiO_2 – arterial oxygen pressure/inspiratory fractional oxygen content ratio-oxygenation capacity, PC – platelet concentrate, PEEP – positive end expiratory pressure, PS – pressure support, rFVIIa – human activated recombinant factor VII, SLE – systemic lupus erythematodes, TF – tissue factor, TFPI – tissue factor pathway inhibitor.

Diffuse alveolar haemorrhage (DAH) is a serious pulmonary complication of mostly unknown aetiology and pathogenesis, although injury to alveolar capillary endothelium and alveolar inflammation, resulting in the release of inflammatory cytokines, has been implicated (4). The disease is usually seen after the haematopoietic stem cell transplantation (HSCT), after chemotherapy, as well as in patients with autoimmune disorders (1, 4). The extensive pulmonary inflammation leads to an abundant intra-alveolar expression of tissue factor (TF) resulting in a several-fold increase in molecular markers of thrombin generation in bronchoalveolar lavage (BAL) fluid (4). Effective local haemostatic strategies are lacking and mortality rate exceeds 50% in those who require mechanical ventilatory support (4). We hypothesized that the local administration of human recombinant activated factor VIIa (rFVIIa) might be an effective terapeutic option.

A new symptomatic therapy, involving intrapulmonary administration of FVIIa to stop the life-threatening critical bleeding in DAH is documented in six patients published by Heslet

[1]Ist Department of Anesthesiology and Intensive Medicine, Faculty of Medicine, University Hospital of Louis Pasteur, Safarikiensis University, Kosice, [2]National Institute of Cardiovascular Diseases, Bratislava, [3]Nephrologic and Dialysis Center Fresenius, Kosice, and [4]Ist Department of Internal Medicine, University Hospital of Louis Pasteur, and Faculty of Medicine, Safarikiensis University, Kosice, Slovakia

Address for correspondence: M. Grochová, MD, PhD, Uzhorodska 1, SK-040 11 Kosice, Slovakia.
Phone: +421.55.6402623

Acknowledgement: We would like to thank Štefan Trenkler MD PhD for the revision of English version, to Natália Štecová MD for the agreement with the application of rFVIIa and Laura Gombošová MD for the part of manuscript concerning medical care at medical department of university hospital.

(4) and two by Estella (1). It seems that pulmonary haemostasis occurs in DAH most probably from the alveolar side and to a much lesser extent from the lung vascular endothelial side, a viewpoint that is supported by the clinical observation of the patients with DAH and by the well-described pathophysiology of the lung as a haemostatic organ, with TF-dependent and TF-independent modes of action. But irrespective of the mode of action, rFVIIa has a potentially high benefit-to-risk ratio when administered via local intrapulmonary route. These findings warrant further exploration of the local pulmonary effect of rFVIIa and the safety of this novel treatment strategy in patients with DAH (4).

The activated recombinant factor VII (Novo-Seven™) is a haemostatic drug used in "on-label" and "off-label" indications for the management of massive and life- threatening bleeding non responding to the standard haemostatic treatment (7).

"On-label" use of rFVIIa (approved in USA by the FDA and in Europe by EMEA) is recommended for the control of bleeding in patients with haemophilia A and B with inhibitors against the factors VIII and IX, in patients with factor VII deficit, Glanzman's thrombasthenia refractory against transfusions of thrombocytes. The activated recombinant factor VII is used also in the "off-label" indications e.g. clinical situations related to the life threatening bleeding (e.g. trauma, intracranial bleeding, obstetrical bleeding, dilution coagulopathy, thrombocytopenia and thrombocytopathy, oral anticoagulation drugs overdose) in the dose 90–140 μg/kg. In trauma patient, the initial dose 200 μg/kg is preferred, with further doses 100 μg/kg in 1–3 hours intervals when needed (4).

Glomerulonephritis associated with endocarditis was described 90 years ago by Lohlein. The supposed embolic component of aetiology was later questioned and is observed in some modifications only in about 30 % of patients (e.g. localized infarcts, from which one half is septic one) (9, 10).

Case report

A 60 years old male patient, suspected of having systemic disease with multiorgan failure, was admitted to the ICU due to haemoptysis and hypoxemic respiratory failure.

Medical history: Allergy to trimetoxim/cotrimoxazol, hepatitis in the age of 13 years. Three months before the admission, the patient was treated with clindamycin and Coxtral as an outpatient and inpatient because of low back pain. MRI detected perivertebral inflammatory collection in L 2–4 area. Patient developed haemoptysis after the tooth extraction.

Two weeks before the admission, anaemia, low platelet count with petechias, increased values of serum urea, creatinine, ureic acid, liver function tests and increased temperature had been found.

Clinical course

The patient was admitted to the regional hospital, where gastroscopy for suspected haematemesis was performed. The source of bleeding was not revealed. During the bronchoscopic examination, bleeding from the right bronchus B 1–3 was detected. Although vasculitis was not confirmed by histological and histochemical examination of the skin, corticoid therapy was administered and plasmapheresis was performed due to supposed systemic illness (thrombotic microangiopathy or Goodpasteur´s syndrome).

Patient was transferred to the medical department of the University hospital in Košice on July 31, 2008. Weakness, low back pain, petechias and nodular haematomas were still present.

He was suspected of having systemic illness or sepsis with multiorgan failure (although repeated blood cultures were negative at this time), respiratory failure by ARDS, mycotic pneumonia, nephritis in relation to bacterial endocarditis. The kidney biopsy was not performed due to the severe state of the patient and low platelet count.

During the transoesophageal echocardiography, vegetations on aortic valve, aortal stenosis and aortal regurgitation stage II were detected.

Ultrasound evaluation of abdominal organs detected hepatosplenomegaly, cholecystolithiasis, acute nephropathy and dilation of vena cava inferior.

On August 7, 2008, because of worsening of clinical status and hypoxemic respiratory failure, the patient was transferred to the ICU for mechanical ventilation and intensive care. During tracheal tube suction, haemorrhagic content was present.

CT scan of lungs detected an area enhancement of opacity of lungs parenchyma with the picture of "milk glass". Maximum of changes were seen in dorsal segments of the right lung. Bilateral fluidothorax and enlarged paratracheal lymphonodes were present.

There was a transitory improvement of the state of the patient. After five days the patient was extubated, inhaling oxygen via face mask. However, the next day after haemodialysis, because of massive haemoptoe, decreasing of SpO_2 and tachypnoe the patient was reintubated and mechanical ventilator support was instituted. During hospitalisation, consultation with cardiologist and cardiac surgeon about the management of aortic valve damage and vegetations was performed. The surgical intervention was delayed due to the severe status of the patient and lung bleeding. On August 15, 2008 at 6:00 a.m., hypotension requiring catecholamine treatment developed, lung bleeding continued, that's why consultation with NUSCH about transfer to this centre was performed. Needed air transport was impossible because of hypoxaemia and lung bleeding. For this reason, the activated recombinant factor VII was given intrapulmonary after the consultation with haematologist, because the systemic administration could impair thrombotic vegetations on the aortal valve. The pneumologist administered rFVIIa (Novo Seven™) in dose 50 μg/kg diluted to 50 ml of 0.9% sodium chloride;
25 ml into each of the main bronchi at 11:00 a.m. via bronchoscope.

A cessation of pulmonary bleeding from the left main bronchus was seen during the administration into right bronchus. That was confirmed bronchoscopically.

The value of paO_2 before the administration of rFVIIa was 14.71 kPa, 1 hour after administration 9.60 kPa. The oxygen-

ation index before the administration rFVIIa was 265, 1 hour after administration 180. SpO_2 before and after administration was 98 % vs 95 %. A decreased oxygenation index could be caused by bronchoscopy per se, the examination of blood was performed immediately after bronchoscopy and was not repeated because of transport of the patient.

On august 15, 2008 before the administration of rFVIIa: Hb 6.5 g/l, HTK 0.19, Le 3 000, thrombocytes 93 000, segments 77 %, Ly 18 %, Mo 5 %. Quick 86 %, APTT 35 s (N=32 s), fibrinogen 1.76 g/l. Repeated transfusions of erythrocytes and platelets were given. On the day of transfer to NUSCCH, 2 TU of erythrocytes and 1 TU of platelets also were administered.

Other source of bleeding and anaemisation except lungs was not found.

On August 15, 2008 at 15:00 p.m., the patient with multiorgan failure was transported to NUSCH. During the transport, mechanical ventilation through tracheal tube was performed. By a repeated echocardiography, bacterial endocarditis of aortic valve with massive vegetations, high embolism potential and severe aortal regurgitation was confirmed. An urgent operation was performed on the same day. The aortal valve replacement with mechanical prosthesis was done. Patient was weaned from extracorporeal circulation using a combined therapy with dobutamine and noradrenaline. During first hours after the operation, enhanced blood loss that reacted on the standard haemostatic therapy was managed. The bleeding from airways did not recur. A mild addition of blood was seen during suction from airways to the next postoperative day. The patient was extubated on the fifth postoperative day. Because of an acute renal failure, dialysis until the 12th postoperative day was performed, first continuously, later by intermittent dialysis. All organ functions improved progressively except of kidneys, which improved to the level not needed elimination therapy. The patient was dismissed on the 39th postoperative day being circulatory stable, without fever, rehabilitated, with anticoagulant therapy.

On October 2008 the patient was readmitted to the medical department in Košice because of uroinfection due to Pseudomonas aeruginosa.

Laboratory evaluation during hospitalisation in Košice:

Immunology: normal count of eosinophils, increased CRP, increased level of gamma globulins 31.3 %, decrease C3 component of complement 0.24 g/l, circulated immunocomplexes 427 j., ASLO 400 IU/ml, positive antibodies antids-DNA and anti-BMG, c-ANCA first negative, later positive and anti-DNP negative were present.

Procalcitonin < 0.5 at admission and > 10 on August 15.

Decreased creatinine clearance 0.17 ml/s/1.73 m^2, proteinuria 0.94 g/d, microscopic haematuria were detected. Hb 87 g/l, thrombocytes 79 x 10^9/l, FW 70/110, urea 18, mmol/l, creatinine 242 µmol/l, AST 1.09 µkat/l, ALT 0.6 µkat/l, GMT 4.3 µkat/l, ALP 9.7 µkat/l.

Microbiological analysis: serology – viruses negat, Chlamydia trachomatis IgA pozit, blood cultures: Bactec negat, throat: Klebsiella sp., Candida tropicalis, BAL: Citrobacter sp., ET tube-Klabsiella species, Klebsiella pneumoniae ESBL+, Pseudomonas species, Acinetobacter calcoaceticus, Entrobacter species Ampc+, Enterococcus foecium and faecalis.

Urine – sterile cultivation.

Manan, galaktomanan antigen were negative.

Bronchoscopy

On August 8, 2008 a diffuse bleeding into the alveoli was detected.

On August 14, bleeding from the right and left low lobar bronchi – terlipressin (Remestyp) 0.5 mg into each bronchus was given, repeated dose 0.8 mg into left low lobar bronchus. August 15, 2008 – bleeding from both main bronchi – rfVIIa – Novo Seven was administered.

Treatment: ATB – piperacilin/tazobactam, vancomycin, metronidazol, fluconazol, voriconazol, amikacin, teicoplanin, H_2 receptors antagonist, terlipressin, dicynone, fresh frozen plasma, K-vitamin, transfusions of red blood cells and thrombocytes, sedation, mechanical ventilation, plasmapheresis, haemodialysis, corticosteroids.

Mechanical ventilation – Pressure support + PEEP, FiO_2 0.4–0.6.

From October 1, 2008, the patient is monitored by nephrologists. The results of the laboratory evaluation on February 26, 2009 were following: CRP 36.6 mg/l, Hb 124 g/l, creatinine in serum 202 µmol/l, clearance of creatinine 0.6 ml/s/1.73 m^2, proteinuria 0.13 g/d, microscopic haematuria was not present. C3 component of complement normal 1.4 g/l, circulated immunocomplexes mild increased – 50 j. The results of examination were improved. The positivity of anti-BMG continues, positivity of cANCA is now present. USG evaluation detected some signs of chronic kidneys damage.

Discussion

A patient suspected of having systemic illness (Wegener's granulomatosis, SLE or Goodpasteur's syndrome) with pulmonary bleeding, not responding to conventional therapy was successfully treated. At our institution, the treatment of pulmonary bleeding includes transfusion of fresh frozen plasma (FFP) and platelet concentrate (PC) to normalize systemic coagulation ability, administration of terlipressin via endotracheal and intravenous, K vitamin, dicynone. The diagnosis of DAH was confirmed bronchoscopically by detecting an ongoing bleeding at the bronchial segmental level before treatment with rFVIIa. The dose was approximately 50 µg/kg dissolved in 50 ml of saline distributed evenly in the right and left main bronchi. The terapeutical efficacy of rFVIIa was graded by Heslett et al. as an excellent, good, or poor response. The ‚excellent' response was defined as a complete and sustained haemostasis after a single treatment with rFVIIa. The response was graded as ‚good' when repeated intrapulmonary administration of rFVIIa was required to obtain haemostasis. A ‚poor' response was characterized by the lack of any effect by rFVIIa on bleeding. In our patient, the terapeutical efficacy was excellent. For the administration of rFVIIa, we were encouraged by publications of Heslett and Estella, who reported a successful intrapulmonary administration of rFVIIa in six and two patients with DAH (4, 1).

DAH is a clinical syndrome with an acute onset of alveolar infiltrates and hypoxemia, yielding a progressive diffuse alveolar bleeding with a high mortality rate. Clinical features include dyspnea, cough, haemoptysis, abnormal chest x-ray with bilateral alveolar infiltrates, and hypoxia usually accompanied with fever (4). On the base of those symptoms, the diagnosis of DAH was established in our patient. The treatment of DAH is empiric as much as the condition is a life-threatening medical emergency with no specific or proven effective therapy. The treatment with high-dose steroids given early to our patient could be beneficial; plasmapheresis was advocated, but there is no evidence that this intervention was successful in the treatment of ongoing low-volume critical bleeding. High and repeated i.v. doses of rFVIIa have been reported to have some haemostatic effect in patients with DAH. As was reviewed in report of Heslett, however, i.v. administration of a very high dose of rFVIIa did not induce hemostasis in his patient with DAH (4). This led him to explore the effect of local pulmonary administration of rFVIIa, and the efficacy of this treatment was demonstrated in six consecutive patients with DAH of different aetiology. The rFVIIa was administered at dose of approximately 50 μg/kg via BAL in six patients and as a nebulised aerosol in one case. The intervention with local intrapulmonary rFVIIa had a significant haemostatic effect ($p = 0.031$). This was the first reviewed an effective treatment of DAH using symptomatic treatment with local intrapulmonary rFVIIa. Later, Estella published a successful local intrapulmonary rFVIIa treatment in two patients. The clinical observation supports the hypothesis that pulmonary haemostasis can be induced more effectively from the alveolar side in DAH than from the endothelial side (4). The mode of action of the observed alveolar haemostasis is most likely explained by the TF-dependent pathway, where the alveolar TF is expressed during the inflammatory phase of DAH. On the other hand, TF pathway inhibitor (TFPI) is a strong inhibitor of the local activation of factor X to Xa by the FVIIa-TF complex. The observations of Heslett indicate that the intrapulmonary administration of FVIIa overrides the anticoagulant effect of TFPI (4). A safety issue of the local rFVIIa treatment, however, is the possible risk of inducing widespread alveolar fibrin deposition (that is, hyaline membrane formation), which is a hallmark of ARDS. There were, however, no signs of developing ARDS in the six treated patients because the oxygenation capacity, as reflected by the PaO_2/FiO_2 ratio, increased significantly in the six patients after the pulmonary rFVIIa administration. The benefit-to-risk ratio of local rFVIIa treatment in DAH therefore seems to be high (4). The intravenous administration of rFVIIa was also considered in our patient, but this could cause an enlargement of vegetations on aortal valve and the embolism during the transport (5). For the emerging situation, we had no possibility to use rFVIIa of the pharmaceutical company Pharmaorigin, Copenhagen, Denmark, which is holding a patent related to the local pulmonary treatment with rFVIIa. For this reason we administered intrapulmonary rFVIIa estimate for i.v. use.

Glomerulonephritis associated with endocarditis was described 90 years ago by Lohlein. The supposed embolic component of aetiology was later questioned and is observed in some modifications only in about 30 % of patients (e.g. localized infarcts, from which one half is septic one). Nowadays, immunocomplex aetiology is emphasised. Some bacterial strains (e.g. methicillin-resistent Staphylococcus aureus) can directly activate T-cells and induce generation of polyclonal gamapathy and immunocomplex glomerulonephritis. This fact was also considered in our patient. Cytoplasmatic ANCA can be rarely detected, as it was later in our patient. Pulse methylprednisolon therapy and plasmapheresis are reasonable treatment options. At the beginning, the relation between renal and lungs damage was problematic in our patient. Actually, a chronic renal insufficiency is present and for further evaluation, a renal biopsy is needed.

Although there were positive levels of antibodies, considering the development of the clinical status of the patient after the operation, it is clear, that all problems were related to bacterial endocarditis and its complications rather than a systemic illness. An open question remains the kidneys damage. The aim of this case report was to show the possibility of using rFVII a as rescue therapy in DAH not responding to the conventional treatment.

Conclusion

A new symptomatic therapy, involving the intrapulmonary administration of rFVIIa, to stop the life-threatening critical bleeding in DAH, is documented in patient with DAH. These findings warrant further exploration of the local pulmonary effect of rFVIIa and the safety of this novel treatment strategy in patients with DAH.

The intrabronchial administration of the activated recombinant factor VII to our patient helped to stop alveolar haemorrhage, permitted transport of the patient to NUSCH, where he was able to undergo the operation (aortal valve replacement) and so increased his chances to survive. From the evolution of his status after the operation it is clear, that all problems of the patient had been related to the endocarditis. The rate of septic embolism and secondary organs damage remains an open question.

References

1. Estella A, Jareńo A, Perez-Bello Fontaińa L. Intrapulmonary administration of recombinant activated factor VII in diffuse alveolar haemorrhage: a report of two case stories. Cases J 2008; 1: 150. doi: 10.1186/1757-1626-1-150.

2. Franchini M, Manzato F, Salvagno LG, Lippi G. Potential role of recombinant activated factor VII for the treatment of severe bleeding associated with disseminated intravascular coagulation: a systemic review. Lippincott Williams@Wilkins, 2007. Review article 589.

3. Hardy JF, Bélisle S, Van dar Linden P. Efficacy and safety of recombinant activated factor VII to control bleeding in nonhemophiliac patients: a review of 17 randomized controlled trials. Ann Thorac Surg 2008; 86: 1038–1048.

4. Heslett L, Nielsen JD, Levi M, Sengelov H, Johansson PI. Succesful pulmonary administration of activated recombinant factor VII in difuse alveolar hemorrhage. Crit Care 2006,10/ R 177.

5. Mallarkey G, Brighton T, Thomson A, Kaye K, Seale P, Gazarian M. An Evaluation of Eptakog Alfa in nonhaemophiliac Conditions. Drugs 2008; 68 (12): 1665–1689.

6. Roberts HR, Monroe DM, Escobar MA: Current concepts in hemostasis. Anesthesiology 2004; 100: 722–730.

7. Terapeutické postupy pri život ohrozujúcom krvácaní. http://www.ssaim.sk/Terapeuticke_postupy_pri_ZOK.doc

8. Badour LM, Wilson WR, Bayer AS, et al. Infective endocarditis. Diagnosis, antimicrobial therapy and management of complications. Circulation 2005; 111: 3167–3184.

9. Conlon PJ, Jefferies F, Krigman HR, et al. Predictors of prognosis and risk of acute renal failure in bacterial endocarditis. Clin Nephrol 1988; 49: 96–101.

10. Majumdar A, Chowdhary S, Ferreira MA, et al. Renal pathological findings in infective endocarditis. Nephrol Dial Transplant 2000; 15: 1782–1787.

11. Tlevjeh IM, Steckelberg JM, Murad HS, et al. Temporal trends in infective endocarditis. J Amer Med Ass 2005; 293: 3022–3028.

12. Yoh K, Kobayashi M, Yamaguchi N, et al. Cytokines and T cell responses in superantigen-related glomerulonephritis following methicillin-resistant Staphylococcus aureus infection. Nephrol Dial Transplant 2000; 15: 1170–1174.

Received November 18, 2009.
Accepted October 8, 2010.