Table 1. Patient and Transplant Characteristics, Authorisations

| **PATIENTS** | **CASE 1** | **CASE 2** | **CASE 3** |
|---|---|---|---|
| Residency | Iceland | USA | Turkey |
| Gender | Male | Male | Female |
| Age at Primary Procedure | 36 | 30 | 22 |
| Etiology of Tracheal disorder | Malignancy? (not verified) Relapse of Tracheal Mucoepidermoid Carcinoma? | Malignancy, Tracheal Adenoid Cystic Carcinoma | 1st Transplantation Iatrogenic Injury 2nd (Re)-transplantation Material Fatigue/ Collapse of the previous Synthetic Tracheal Transplant |
| **PRIMARY PROCEDURE** | **SYNTHETIC TRACHEA** | **SYNTHETIC TRACHEA** | **PULMECTOMY + SYNTHETIC TRACHEA** |
| Date of Procedure | Jun 9, 2011 | Nov 17, 2011 | Aug 7, 2012 |
| Pre-operative Hospitalization | No | No | No |
| Type of Surgery (planned months in advance) | Elective | Elective | Elective |
| Scaffold Material (Synthetic) | Nanocomposite polymer (POSS-PCU; polyhedral oligomeric silsesquioxane [POSS] covalently bonded to poly-[carbonate-urea] urethane[PCU]) | Electrospun polyblend of PET/PU 70/30; polyethylene terephthalate (PET) and polyurethane (PU) | Electrospun polyblend of PET/PU 70/30 nanofibers; polyethylene terephthalate (PET) and polyurethane (PU) |
| CE Marking | No | No | No |
| Scaffold Manufacturer | Prof. Seifalian, University College London, UK | Nanofiber Solutions, Ohio, USA | Nanofiber Solutions, Ohio, USA |
| Import of Scaffold to Sweden | Private | n/a | n/a |
| “Off label ”Use of Growth Factors and Bone Marrow Stimulating Drugs in “Supra-therapeutic” Doses | Yes | Yes | Yes |
| Application for Vetting of the Ethics to the Regional Ethical Review Board | No | No | No |
| Application to the Swedish Medical Products Agency | n/a | n/a | n/a |
| Reporting of Transplant Related Side-Effects and Complications to Swedish Medical Products Agency | n/a | n/a | n/a |
| **SECONDARY PROCEDURE** | **-** | **-** | **RE-TRANSPLANTATION SYNTHETIC TRACHEA** |
| Date of Procedure | - | - | Jul 9, 2013 |
| Pre-operative Hospitalization | - | - | Yes |
| Type of Surgery (planned months in advance) | - | - | Elective |
| Scaffold Material (Synthetic) | - | - | Electrospun PET; polyethylene terephthalate (PET) |
| CE Marking | - | - | No |
| Scaffold Manufacturer | - | - | Harvard Apparatus Regenerative Technology, HART, Holliston, MA, USA |
| Import of Scaffold to Sweden | - | - | n/a |
| “Off label ”Use of Growth Factors and Bone Marrow Stimulating Drugs in “Supra-therapeutic” Doses | - | - | Yes |
| Application for Vetting of the Ethics to the Regional Ethical Review Board | - | - | No |
| Application to the Swedish Medical Products Agency | - | - | n/a |
| Reporting of Transplant Related Side-Effects and Complications to Swedish Medical Products Agency | | | n/a |

Table 2. Etiology of Tracheal Disorder and Transplantation-associated Drugs

| **PATIENTS** | **CASE 1** Transplantation Jun 9, 2011 | **CASE 2** Transplantation Nov 17, 2011 | **CASE 3** **1st Transplantation** Aug 7, 2012 | **CASE 3** **2nd Transplantation** Jul 9, 2013 |
|---|---|---|---|---|
| Etiology of Tracheal Disorder | Malignancy? (not verified) Relapse of Tracheal Mucoepidermoid Carcinoma? | Malignancy, Tracheal Adenoid Cystic Carcinoma | Iatrogenic Injury | Material Fatigue/ Collapse of the previous Synthetic Tracheal Transplant |
| Histological Verification of Malignancy before/after Transplantation registered in the Medical Records | No | Yes | | |
| Surgical RADICALITY of Tumour Resection at Native Tracheal Extirpation and Synthetic Tracheal Transplantation | n/a (NO registered postop histological analysis of native trachea in the Karolinska records) | No (surgical radicality was not achieved at extirpation of native trachea) | | |
| **TRANSPLANTATION ASSOCIATED DRUGS** | | | | |
| Application to Medical Products Agency | n/a | n/a | n/a | n/a |
| Application to Reg. Ethical Review Board | No | No | No | No |
| "OFF LABEL" – EXPERIMENTAL USE (Indication and Dosage) of Growth Factors and Bone Marrow Stimulating Drugs in "Supra-therapeutic" Doses | Yes (despite previous malignant tumor) | Yes (despite non-radical extirpation of malignant tumor) | Yes | Yes |
| **Recombinant Human Transforming Growth Factor-β3** Manufacturer: R&D Systems, Minneapolis, MN, USA. **RESEARCH USE ONLY, NOT FOR USE IN HUMANS OR ANIMALS ACCORDING TO MANUFACT** | Yes **Perioperative** Dose 10ug/kg cm2 (Scaffold) | n/a (presumably, but not r in the medical records) | n/a (presumably, but not found in the medical records) | n/a (presumably, but not found in the medical records) |
| **Filgrastim, Granulocyte Colony Stimulating Factor (G-CSF) Neupogen®** Manufacturer: Amgen Europe BV, Breda, Netherlands | Yes **Perioperative + Postoperative** 20.000.000 U every other day for 10 d. **WEEKLY DOSE 80.000.000 U** | Yes **Perioperative? Postoperative** 20.000.000 U every other day for 15 d. **WEEKLY DOSE 80.000.000 U** | Yes **Perioperative? Postoperative** 20.000.000 U every other day for 16 d. **WEEKLY DOSE 80.000.000 U** | Yes **Perioperative? Postoperative** 30.000.000 U every other day for 14 d. **WEEKLY DOSE 120.000.000 U** |
| **Epoetin beta (synthetic analogue of Erythropoietin) NeoRecormon®** Manufacturer: Roche, Grenzach-Wyhlen, Germany. **THE MAXIMUM DOSE FOR LABELED INDICATIONS SHOULD NOT EXCEED 60,000 IU PER WEEK ACCORDING TO MANUFACT** | Yes **Perioperative + Postoperative** 40.000 IU every other day for 12 d. **WEEKLY DOSE 160,000 IU** | Yes **Perioperative n/a Postoperative** 40.000 IU every other day for 15 d. **WEEKLY DOSE 160,000 IU** | Yes **Perioperative + Postoperative** 40.000 IU every other day for 16 d. **WEEKLY DOSE 160,000 IU** | Yes **Perioperative n/a Postoperative** 40.000 IU every other day for 14 d. **WEEKLY DOSE 160,000 IU** |
| Complications | Yes **RIGHT MAIN PULMONARY ARTERY THROMBUS** (occlusion of the right main pulmonary artery graft interponate that was inserted during the transplantation due to vascular | Yes **VENOUS THROMBOSIS** in the left jugular, subclavian and axillary vein systems + Pulmonary Embolus in left underlobe is diagnosed on the last day of treatment | No | Yes **PUMP-THROMBOSIS** on Extracorporeal Membrane Oxygenation (ECMO) support (extremely rare complication in modern ECMO circuits) > Massive Hemolysis, Acute |

| | | | | |
|---|---|---|---|---|
| | injury of the right pulmonary artery) is diagnosed 9 days after start of treatment | | | Tub. Necrosis, Acute Renal Failure > 7 weeks of Hemodialysis **+ ARTERIAL EMBOLUS RIGHT LEG** diagnosed 7d. after start of treatment |
| Long term Complications | Yes Chronic occlusion of RT pulm. Artery + multiple distal PE | No | No | Yes Chronic Renal Failure Cystatine GFR 45-55mL/min/1,73m$^2$ |

Table 3. Transplant-related and General Complications, Final outcome

| **TRANSPLANT RELATED COMPLICATIONS** | **CASE 1** | **CASE 2** | **CASE 3** |
|---|---|---|---|
| Transplant associated granulations | Yes (significant) | Yes (scantly) | Yes (significant) |
| Anastomotic (transplant) dehiscence | Yes (all anastomosis, disconnected transplant) | ? (see under tracheo-mediastinal fistula) | Yes (distal anastomosis) |
| Tracheo-esophageal fistula | Yes | No | Yes |
| Tracheo-mediastinal fistula | Yes | Yes (suspected in CT report 28 Nov, 2011 and Jan 10, 2012) | Yes (massive air leakage out of thoracotomy) |
| Near fatal airway (stent) occlusion | Yes (terminally) | No | Yes (multiple occasions) |
| Normal airway epithelium in transplant | No | No | No |
| Transplant material fatigue/collapse | No | No | Yes |
| Thrombo-embolic (TE) events | Yes (RIGHT PULM ART. OCCLUSION + THROMBOSIS of left brachioceph, jugular and subclavian veins + MULTIPLE DISTAL PULMONARY EMBOLIES) | Yes (VENOUS THROMBOSIS in left Jugular, subclavian and axillary vein systems + PULMONARY EMBOLUS in left lower lobe) | Yes (2 TE-events: ECMO PUMP THROMBOSIS + PERIPHERAL ARTERIAL EMBOLIZATION) |
| Re-transplantation | No | No | Yes (due to material fatigue in 1st transplant) |
| Chronic infection | Yes (mediastinitis, abscess) | - | Yes (thoracic rest cavity) |
| Laryngeal nerve paralysis (left sided) | Yes | No | No |
| **GENERAL COMPLICATIONS** | | | |
| Respiratory failure | Yes | Yes | Yes |
| Pneumonia (P), Wound infection (W) | Yes (Chronic P) | Yes (P, W) | Yes (P) |
| Sepsis | Yes | Yes | Yes |
| Hemoptysis | Yes | Yes | No |
| Acute (A) Chronic (C) Renal Failure | Yes (A) (terminally) | No | Yes (A, C) |
| Splenic Infarction | No | No | Yes |
| Multiple Organ Dysfunction Syndrome | Yes (terminally) | No | Yes |
| **POST-TRANSPLANT INTERVENTIONS/THERAPY** | | | |
| Airway/Transplant stenting (multiple interventions) | Yes | No | Yes |
| Bronchoscopy dependency | Yes (intermittent) | No | Yes (every 4th hour, 24-7) |
| Recurrent extirp of transplant assoc granuloma | Yes | n/a | Yes |
| Chronically Tracheotomized | No | No | Yes (> 2 years) |
| Esophageal stenting | Yes | No | Yes |
| Esophagectomy | Yes (stapled transection) | No | Yes |
| Esophageal Reconstruction | Yes (subcutaneous colon interponate) | No | Yes (planned for colon interponate) |
| Thoracoplasty incl. Pedicled m. Lat. Dorsi Flap | No | No | Yes |
| Chronic Thoracic Drainage | No | No | Yes (2 drainages > 2 years, daily aspiration) |
| Nutrition through PEG/Gastrostomy | Yes (partly) | No | Yes (2 years) |
| Laparotomy | Yes | No | Yes (3 times) |
| Chronic Antibiotic/Antifungal therapy | Yes (intermittent) | No | Yes (> 2 years) |
| Extracorporeal Membrane Oxygenation | No | No | Yes (3 times, in tot. 72 d.) |

| | | | |
|---|---|---|---|
| Hemodialysis | No | No | Yes (7 weeks) |
| Prolonged ventilator dependency | Yes | No | Yes (305 days) |
| **FINAL OUTCOME** | | | |
| Dead/Alive, Date | Died Jan 30, 2014 (after 8 months of hospitalization) | Died Mar 5, 2012 | Alive (hospitalized in the ICU after more than 26 months) |
| Cause of Death | Refractory respiratory insufficiency, total transplant disconnection | Airway bleeding Tracheo-arterial fistula? | - |
| Total numbers of Transplant Associated Surgical Interventions in the Karolinska Medical Records | 32 | 12 | 139 (until August 2014) |
| Total numbers of Bronchoscopies registered in the Karolinska Medical Records | n/a | n/a | 4.199 (until September 2014) |