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(54) Title: DETERMINING ENCAPSULATING PERITONEAL SCLEROSIS

(57) Abstract: Patients on peritoneal dialysis are at risk for developing encapsulating peritoneal sclerosis (EPS) The present invention is directed to a method to diagnose or determine the risk for encapsulating peritoneal sclerosis (EPS) in a patient. An increase in soluble CD25 indicates EPS or a risk for developing EPS in said patient. The invention is also directed to a kit for carrying out measurement of soluble CD25.

Title: Determining encapsulating peritoneal sclerosis

The invention

The present invention is directed to a method to determine the risk or diagnose a patient with encapsulating peritoneal sclerosis (EPS) using soluble CD25 as a biomarker.

Background:

In patient with renal failure there are three treatment options: kidney transplant, hemodialysis (HD) and peritoneal dialysis (PD). When no donor suitable kidney is available, only hemodialysis and peritoneal dialysis remain. In hemodialysis waste products such as creatinine and urea are removed by the blood by a counter current flow of dialysate fluid and the blood in an extracorporeal circuit. Hemodialysis is most often performed in a specialised facility in a hospital or dedicated clinic. Peritoneal dialysis (PD) uses the patient's peritoneum in the abdomen as a membrane across which fluids and dissolved substances (electrolytes, urea, glucose, albumin and other small molecules) are exchanged from the blood. Fluid is introduced through a permanent tube in the abdomen and flushed out either every night while the patient sleeps (automatic peritoneal dialysis) or via regular exchanges throughout the day (continuous ambulatory peritoneal dialysis). PD is used as an alternative to hemodialysis though it is far less commonly used in many countries, such as the United States. It has comparable risks but is significantly less costly in most parts of the world, with the primary advantage being the ability to undertake treatment without visiting a medical facility. The primary complication of PD is infection due to the presence of a permanent tube in the abdomen.

Encapsulating peritoneal sclerosis (EPS) is a severe complication of peritoneal dialysis (PD) with a prevalence of 3-5%. EPS is characterized by progressive sclerosis of the peritoneal membrane leading to partial or total encapsulation of the gut by a fibrotic cocoon, resulting in obstruction of

the bowels. The mortality of EPS is high and ranges between 30-60%. At present, EPS cannot be detected with certainty during its early stages. Patients with EPS come in with abdominal pain and inflammation, but further no other specific symptoms. A CT scan may show EPS however cases have been reported that also CT scans did not show EPS (Habib et al BMC Nephrology 2013, 14; 203). Laparoscopy may also provide the diagnosis. EPS may also occur after kidney transplantation having a major negative impact on patient survival after kidney transplantation. Unfortunately there is no biomarker or other diagnostic tool available that can identify patients at risk for developing EPS. Such a tool would be highly valuable as timely discontinuation of peritoneal dialysis could halt the development of EPS before irreversible sclerosis has established, and may thus increase the survival rate after kidney transplantation.

An object of the present invention is therefore to provide a method to diagnose a patient with EPS preferably at an early stage before symptoms of EPS start such as abdominal pain, loss of ultrafiltration, ascites, bowel obstruction and elevated markers of inflammation such as C-reactive protein.

Another object of the invention is to determine the risk of a patient developing EPS.

Summary of the invention

In patient undergoing peritoneal dialysis (PD) encapsulating peritoneal sclerosis (EPS) is a severe complication. It is not uncommon that patients that first undergo PD later have a kidney transplant or move to hemodialysis. It has been seen that EPS develops after a patient is off PD. It is thus of the utmost importance to monitor patients on PD and that have been on PD for EPS development. The present invention is therefore in a first aspect directed to a method to determine the risk for encapsulating peritoneal sclerosis (EPS) in a patient, comprising the steps:

a. Providing a sample from said patient

b. Measuring an amount of soluble CD25 in said sample thereby providing a measured amount of soluble CD25,

wherein an increase in soluble CD25 indicates a risk for developing EPS in said patient.

In a second aspect the invention is directed to a method to diagnose encapsulating peritoneal sclerosis (EPS) in a patient, comprising the steps:

c. Providing a sample from said patient

d. Measuring an amount of soluble CD25 in said sample, thereby providing a measured amount of soluble CD25,

wherein an increase in soluble CD25 indicates EPS in said patient.

In a third aspect the invention is directed to a method of treatment of EPS in a patient undergoing peritoneal dialysis, comprising the steps

a) Providing a sample from said patient

b) Measuring a amount of soluble CD25 in said sample, providing a measured amount of soluble CD25,

c) Apply treatment of EPS when an increase in soluble CD25 is determined in said patient, wherein the treatment of EPS is selected from the group comprising cessation of PD, immunosuppressive treatment, treatment with corticosteroids, surgical treatment, nutritional treatment and/or combinations thereof.

In a preferred embodiment of the present invention and/or embodiments thereof the increase in soluble CD25 is at least 20% relative to a previous amount of soluble CD25 of said patient. The previous amount is an amount of soluble CD25 that has been measured before the measured amount of soluble CD25. Preferably, the increase in soluble CD25 is present for more than 3 months, preferably more than 4 month more preferably

more than 6 month. Preferably the increase is present from about 3 to 36 months.

In a preferred embodiment of the present invention and/or embodiments thereof the amount of soluble CD25 has been determined at least 2 times, preferably 2 to 30 times. In a preferred embodiment of the present invention and/or embodiments thereof the interval between determinations of soluble CD25 is at least 0.25 month, preferably from 0.5 to about 24 month.

In another preferred embodiment of the present invention and/or embodiments thereof the increase of soluble CD25 is at least 500 pg/ml relative to a previous amount of soluble CD25 of said patient, preferably the increase is between 500 and 20,000 pg/ml relative to a previous soluble CD25 amount of said patient. The previous amount of soluble CD25 has been measured before the measured amount of soluble CD25. In preferred embodiments, the previous soluble CD25 amount is from at least 1 month before the measured amount , preferably the time between the measured and previous amount of soluble CD25 is between 0.25 and 10 years.

In another preferred embodiment of the present invention and/or embodiments thereof said patient undergoes peritoneal dialysis.

In another preferred embodiment of the present invention and/or embodiments thereof the patient is off peritoneal dialysis.

In another preferred embodiment of the present invention and/or embodiments thereof the patient shows the following symptoms: abdominal pain, disordered bowel movement, ascites, vomiting, fever, weight loss, malnutrition.

In another preferred embodiment of the present invention and/or embodiments thereof the sample is chosen from the group consisting of blood, serum, and/or peritoneal dialysis fluid. Preferably, the sample is not peritoneal dialysis fluid.

In another preferred embodiment of the present invention and/or embodiments thereof the amount of soluble CD25 is determined by a method selected from the group consisting of ELISA, radio-immuno assay, mass spectrometry.

In another aspect the invention is directed to the use of soluble CD25 in a method to determine the risk of EPS in a patient.

In another aspect the invention is directed to the use of soluble CD25 in a method to diagnose EPS in a patient

A further aspect of the invention is directed to a kit of part for use in a method according to claims comprising

an agent and/or reading device to determine the amount of soluble CD25 in serum or blood of a patient

normal values for soluble CD25 in dialysis patients being peritoneal or hemodialysis patients

instructions for use.

Detailed description of the invention

Figure legend

Figure 1 shows that the level of soluble CD25 was increased for a patient that was diagnosed EPS already 2 years before the diagnosis of EPS.

Figure 2 shows that patients on PD, wherein a increase in soluble CD25 can be seen, developed EPS, whereas patients that do not show an increase in soluble CD25 remain stable and did not develop EPS.

Figure 3 shows that patients with EPS have a much higher soluble CD25 level than patients that undergo haemodialysis that do not have EPS. After treatment the values for EPS patients return to the values of haemodialysis patients.

Figure 4 shows that values of dialysis patients are higher than healthy values.

Definitions

CD25 is the alpha chain of the IL-2 receptor. It is a type I transmembrane protein present on activated T cells, activated B cells, some thymocytes, myeloid precursors, and oligodendrocytes that associates with CD122 to form a heterodimer that can act as a high-affinity receptor for IL-2. A large proportion of resting memory T cells constitutively express CD25 in humans. CD25 is expressed in most B-cell neoplasms, some acute nonlymphocytic leukemias, neuroblastomas, and tumor infiltrating lymphocytes. CD25 also exists in soluble form, *sIL-2R,* and may be elevated in these diseases and is occasionally used to track disease progression. For the purpose of the present invention soluble CD25 and CD25 are used both. Whenever CD25 is used it is to be understood that soluble CD25 is meant. Soluble CD25 is also referred to as serum CD25 or sCD25, or sIL-2R. These terms are used interchangeably in the present application.

Peritoneal dialysis (PD) is a dialysis method to remove waste product from the blood and uses a person's peritoneum in the abdomen as a membrane across which fluids and dissolved substances (electrolytes, urea, glucose, albumin and other small molecules) are exchanged from the blood. Fluid is introduced through a permanent tube in the abdomen and flushed out either every night while the patient sleeps (automatic peritoneal dialysis) or via regular exchanges throughout the day (continuous ambulatory peritoneal dialysis). The PD fluid used typically contains sodium, chloride, lactate or bicarbonate and a high percentage of glucose to ensure hyperosmolarity. A large volume of fluid is introduced to the abdomen over the next ten to fifteen minutes. The total volume is referred to as a *dwell* while the fluid itself is referred to as dialysate. The dwell can be as much as 2.5 litres, and medication can also be added to the fluid immediately before infusion.http://en.wikipedia.org/wiki/Peritoneal_dialysis#cite_note-Nursing-3 The dwell remains in the abdomen and waste products diffuse across the peritoneum from the underlying blood vessels. After a

variable period of time depending on the treatment (usually 4–6 hours), the fluid is removed and replaced with fresh fluid. The fluid removed is referred to as effluent. This can occur automatically while the patient is sleeping (automated peritoneal dialysis, APD), or during the day by keeping two litres of fluid in the abdomen at all times, exchanging the fluids four to six times per day (continuous ambulatory peritoneal dialysis, CAPD). The amount of dialysis that occurs depends on the volume of the dwell, the regularity of the exchange and the concentration of the fluid. APD cycles between 3 and 10 dwells per night, while CAPD involves four dwells per day of 2-2.5 litres per dwell, with each remaining in the abdomen for 4–8 hours. Encapsulating peritoneal sclerosis (EPS) is characterised by fibrosis of the peritoneal membrane, and may progressively encapsulate the intestines leading to a clinical spectrum of intestinal obstruction. The pathogenesis includes inflammation, angiogenesis and fibrosis. It is a severe complication of peritoneal dialysis (PD) with a prevalence of 3-5%. The mortality of EPS is high and ranges between 30-60%. Symptoms associated with EPS are any of abdominal pain, disordered bowel movement, ascites, vomiting, fever, weight loss, and/or malnutrition. EPS is not strictly related with PD and may also occur in intraperitoneal chemotherapy, due to peritonitis, especially due to Staphylococcus aureus, fungi, and Pseudomonas sp,. EPS has also been associated with the use of practolol (a betablocker withdrawn from the market) and exposure to chlorhexidine (an antiseptic that is now avoided in PD patients). It should be understood that the present invention is not only related to EPS in relation to PD, but also with other causes.

The present invention is therefore directed to a method to determine the risk for and/or diagnose encapsulating peritoneal sclerosis (EPS) in a patient. The inventors found that soluble CD25 is a marker for EPS. They found that an increase in the amount of CD25 indicates EPS or a risk for EPS. As patient may have to dialyze for a long time before he or she can have a kidney transplantation it important to monitor whether EPS

may develop as it is a severe complication with a high mortality rate. It is not uncommon that the EPS develops or is diagnosed after the patient is off PD, for example when moved to haemodialys or having received a donor kidney. EPS severely complicates the health of the patient. The method and other aspects of the invention and/or embodiments thereof may be used for patients on PD or having been on PD for example to monitor whether EPS may develop and thus may have a preventive measure. The method and other aspects of the invention and/or embodiments thereof may also be used to diagnose EPS in patient having symptoms associated with EPS, such as abdominal pain, disordered bowel movement, ascites, vomiting, fever, weight loss, malnutrition. Patients with symptoms associated with EPS may have PD, or may have had PD but may also be a patient that has never received PD.

The method and/or other aspects of the invention and/or embodiments thereof comprise measuring the amount of soluble CD25 in a sample from a patient. Any suitable method to measure the amount of soluble CD25 may be used. A skilled person is well aware of methods to determine the amount of CD25 from a sample of a patient. Suitable method may include ELISA, radio-immuno assay, and/or mass spectrometry. The factor indicating EPS or a risk for EPS is an increase in soluble CD25. Different methods may have different resolution and sensitivity, it is therefore preferred to compare measurement of soluble CD25 of the same methods, i.e. Elisa with Elisa, and mass spectrometry with mass spectrometry.

It is stressed that the amount of soluble CD25 is measured. CD25 is the alpha chain of the IL-2 receptor. It is a type I transmembrane protein present on activated T cells, however CD25 is also secreted in soluble form and is present in any kind of bodily fluid, such as Amniotic fluid, Aqueous humour, vitreous humour, Bile, Blood, Serum, Breast milk, Cerebrospinal fluid, Cerumen (earwax), Chyle, Chyme, Endolymph and perilymph,

Exudates, Feces , Female ejaculate, Gastric acid, Gastric juice, Lymph, Mucus, such as nasal drainage and phlegm, Pericardial fluid, Peritoneal fluid, Pleural fluid, Pus, Rheum, Saliva, Sebum (skin oil), Semen, Sputum, Synovial fluid, Tears, Sweat, Vaginal secretion, Vomit, Urine. Suitable bodily fluid for the purpose of the present invention comprise serum, blood, pleural fluid, cerbrospinal fluid, urine, saliva, peritoneal fluid. Most suitable bodily fluids are serum, blood, pleural fluid, and urine. Also peritoneal dialysis fluid, i.e. the fluid that has been used in PD may also contain CD25. Preferably, the soluble CD25 is measured in blood, serum, and/or peritoneal dialysis fluid. The normal values for soluble CD25 are different for different bodily fluids, however as the present invention is directed to the relative difference between measurements, any bodily fluid may be used. It should be understood that when comparing the amount of soluble CD25, the amount is preferably determined in the same bodily fluid. The amount of soluble CD25 in peritoneal dialysis fluid is for example lower than in serum or blood. The present invention however is directed to a the relative difference between measurements. Thus although the absolute soluble CD25 level may be lower in peritoneal dialysis fluid and increase in soluble CD25 does indicate EPS. As a patients on PD regularly dialyses, the peritoneal dialysis fluid may be a suitable sample for measurement of soluble CD25. There is then no need to draw blood. A patient can monitor the soluble CD25 levels easily at home in peritoneal dialysis fluid. In a preferred embodiment the soluble CD25 is measured in serum and/or blood but not in peritoneal dialysis fluid. The absolute value of soluble CD25 in blood in serum is higher than in peritoneal dialysis fluid, making it easier to measure. The amount of soluble CD25 in peritoneal dialysis fluid is however low. In a preferred embodiment the soluble CD25 is measured in serum and/or blood but not in peritoneal dialysis fluid.

The amount of soluble CD25 is often increased in patient at risk for EPS, however as the present invention is directed to the relative

increase in the amount of soluble CD25, it is still able to determine whether a patient is developing EPS or not. Healthy person have a soluble CD25 level in serum of about 4000 pg/ml, with a maximum of 8000 pg/ml. Hemodialysis patients, and predialysis patients vary between 4000 pg/ml and 12000 pg/ml soluble CD25 in serum. However even with a higher starting value, one may still use the present invention as it measures the difference between a previous amount and the current amount. If the latter amount is higher then there is an increase.

The increase in soluble CD25 indicates EPS or a risk for developing EPS. The increase in soluble CD25 may be relative to a previous measured amount of soluble CD25 of said patient or to a healthy value of soluble CD25. In a preferred embodiment of aspects of the present invention and/or embodiments thereof the increase is at least 20%. This means that the measured amount of soluble CD25 is at least 20% higher than a previous amount of soluble CD25, it means that the measured amount is at least 120% of the previous amount of soluble CD25. Preferably the method of determination of soluble CD25 of the two or more amounts of soluble CD25 is the same. Preferably the bodily fluid used for the measurement of soluble CD25 of the measured amount and previous amount is the same. In a preferred embodiment the increase in soluble CD25 is relative to a previous amount of CD25. Soluble CD25 has different values in different tissue, however the relative increase is an indication of a risk of EPS. The measured amount of soluble CD25 and the previous amount of soluble CD25 therefore should be carried out on the same bodily fluid sample. Thus if the previous amount of soluble CD25 was on blood, the measured amount of soluble CD25 should also be in blood. Between different measurements techniques there may be differences, therefore preferably the measured amount and the previous amount of soluble CD25 should be measured by the same technique, in preferably the same experimental conditions.

Preferably the time between the previous amount of soluble CD25 and the measured amount of CD25 is at least 1 months, more preferable at least 3 months, more preferably at least 5 months, more preferably at least 6 months. It is to be understood that between a previous amount of soluble CD25 and the measured amount of soluble CD25 more measurements of amounts of soluble CD25 may have been done. In a preferred embodiment, the soluble CD25 amount of a patient is regularly determined, such as once a week, once every two weeks, once every month, or yearly, or even irregular intervals. In a preferred embodiment of aspects of the present invention and/or embodiments thereof, the amount of soluble CD25 is determined at least 2 times, such as between 2 and 30 times, or even more times such at least 40, 50, 60, 75, or 100 times. Preferably the amount of soluble CD25 is determined between 5 and 25 times, preferably between 7 and 20 times, more preferably between 8 and 18 times, more preferably between 9 and 16 times, more preferably between 10 and 15 times, more preferably between 11 and 14, and most preferably between about 12 to 13 times. Preferably the interval between determinations or measurements is at least one weeks, preferably at least two weeks or 0.5 month, preferably at least 1 month, more preferably at least 1.5 month. In a preferred embodiment, the interval between measurements or determination is between 0.5 and 12 month, more preferably between 1 and 10 months, more preferably between 2 and 8 months, more preferably between 3 and 6 months, more preferably about 4 to 5 months. For example if a measurement indicates an increase in soluble CD25, more measurement may be planned with shorter intervals. For example the measurement is increased with respect to normal soluble CD25 levels, additional measurements may be performed. If for example the measurement does not show an increase of soluble CD25 as compared to normal healthy value, yearly measurements may be sufficient to monitor the risk for developing EPS. The increase is at least 20% compared to a previous second amount of soluble CD25. Preferably the increase is at least

22%, at least 25%, more preferably at least 27%, more preferably at least 30%, more preferably at least 35%, more preferably at least 40%, more preferably at least 45%, more preferably at least 50%, more preferably at least 55%, more preferably at least 60%, more preferably at least 65%, more preferably at least 70%, more preferably at least 75%, more preferably at least 80%, more preferably at least 90%, more preferably at least 100%, more preferably at least 110%, more preferably at least 120%, more preferably at least 130%, more preferably at least 150%, more preferably at least 175%, more preferably at least 200%, more preferably at least 225%, more preferably at least 250%, more preferably at least 275%, more preferably at least 300%, more preferably at least 400%, more preferably at least 500%, more preferably at least 600%, more preferably at least 700%, more preferably at least 800%, more preferably at least 900%, more preferably at least 1000%.

In a preferred embodiment of the invention and/or embodiments thereof the increase of measured soluble CD25 is at least 1,000 pg/ml relative to a previous amount soluble CD 25 amount of said patient. The increase is the difference between the measured amount of soluble CD25 and the previous amount of soluble CD25. The increase may be at least 100 pg/ml, preferably at least 200 pg/ml, preferably at least 300 pg/ml, preferably at least 400, pg/ml, preferably at least 500 pg/ml, preferably at least 750 pg/ml, preferably at least 1,000 pg/ml, more preferably at least 1250 pg/ml, preferably at least 1,500 pg/ml, more preferably at least 2,000 pg/ml, more preferably at least 2,500 pg.ml, more preferably at least 3,000 pg/ml, more preferably at least 4,000 pg/ml, more preferably at least 5,000 pg/ml, more preferably at least 6,000 pg/ml, more preferably at least 7,000 pg/ml, more preferably at least 8,000 pg/ml, more preferably at least 9,000 pg/ml, more preferably at least 10,000 pg/ml, more preferably at least 12,000 pg/ml, more preferably at least 15,000 pg/ml, more preferably at least 17,000 pg/ml, more preferably at least 20,000 pg/ml. Preferably the

increase of soluble CD25 is between 100 and 30,000 pg/ml, more preferably between 200 and 25,000 pg/ml. more preferably between 500 and 20,000 pg/ml, more preferably between 1,000 and 17,000 pg/ml, more preferably between1500 and 15,000 pg/ml, more preferably between 2,000 and 12,000 pg/ml, more preferably between 3,000 and 10,000 pg/ml, more preferably between 5,000 and 9,000 pg/ml, more preferably between 6,000 and 8,000 pg/ml.. For bodily fluids that have a higher absolute amount of soluble CD25 such as blood and serum the increase of soluble CD25 is preferably between 1,000 and 30,000 pg/ml, more preferably between 2,000 and 25,000 pg/ml. more preferably between 2,500 and 20,000 pg/ml, more preferably between 3,000 and 17,000 pg/ml, more preferably between4,000 and 15,000 pg/ml, more preferably between 5,000 and 12,000 pg/ml, more preferably between 6,000 and 10,000 pg/ml, more preferably between 7,000 and 9,000 pg/ml. For bodily fluids that have a lower absolute amount of soluble CD25, such as peritoneal dialysis fluid and urine, the increase of soluble CD25 is between 100 and 5,000 pg/ml, more preferably between 200 and 4,000 pg/ml. more preferably between 300 and 3,000 pg/ml, more preferably between 400 and 2,500 pg/ml, more preferably between 500 and 2,000 pg/ml, more preferably between 700 and 1,500 pg/ml, more preferably between 800 and 1,250 pg/ml, more preferably between 900 and 1,000 pg/ml. In preferred embodiments the measurements of soluble CD25 is performed with ELISA.In preferred embodiments of the aspects of the invention and/or embodiments thereof, the increase in soluble CD25 is present for at least 3 months. This means that first an increase in soluble CD25 is determined and that at least 3 month later the increase is still present or even increased. Preferably, the increase is present for at least 4 month, preferably at least 6 months, preferably at least 8 months, preferably at least 10 months, preferably at least 12 months, preferably at least 15 months, preferably at least 18 months, preferably at least 21 months, preferably at least 24 months, preferably at least 30 months, preferably at least 36 months.

Also the method and/or other aspects and/or embodiments of the present invention may comprise a single determination of soluble CD25. An increase in soluble CD25 then means an increase relative to a healthy amount of soluble CD25. In healthy individuals, the normal value of soluble CD25 in serum is from around 4,000 pg/ml, ranging from 2,000 pg/ml to 8,000 pg/ml. An amount of soluble CD25 of at least 8,000 pg/ml indicates EPS, or a risk for developing EPS. Preferably the determined amount of soluble CD25 is at least 9000 pg/ml, more preferably the determined amount is at least 10,000 pg/ml, more preferably the determined amount is at least 12,000 pg/ml, more preferably the determined amount is at least 14,000 pg/ml, more preferably the determined amount is at least 16,000 pg/ml, more preferably the determined amount is at least 18,000 pg/ml, more preferably the determined amount is at least 20,000 pg/ml of soluble CD25. In preferred embodiments, the amount of soluble CD25 is determined in blood or serum, preferably serum. Suitably, the method comprising the single determination is on patients that have been on PD but are at the time of the determination of the soluble CD25 off PD. In preferred embodiments the single determination of soluble CD25 is performed by ELISA.

Preferably, the increase in soluble CD25 is present for at least 3 months, preferably at least 4 month, more preferably at least 6 month, preferably at least 8 months, preferably at least 10 months, preferably at least 12 months, preferably at least 15 months, preferably at least 18 months, preferably at least 21 months, preferably at least 24 months, preferably at least 30 months, preferably at least 36 months. Preferably the increase is present from about 3 to 36 months. It was found that an increase in soluble CD25 may be seen already 1-3 years before the onset of EPS. If an increase in soluble CD25 has been determined, in preferred embodiments, a further measurement of soluble CD25 amount is performed. Preferably the further amount of soluble CD25 amount also shows an increase. The further amount of soluble CD25 is preferably determined at least 3 month later

than the measured amount of soluble CD25, more preferably at least 4 month later, more preferably at least 6 month later. Preferably the increase is present from about 3 to 36 months, meaning that an increase of soluble CD25 of further amounts of soluble CD25 are seen 3 to 36 months from the measured amount of soluble CD25. Patients with EPS and at risk for EPS show an sustained increase in soluble CD25. The increase may be relative to a previous amount, or relative to a normal healthy value.

Patients that undergo PD or have undergone PD generally have a higher soluble CD25 level than healthy persons. For patients on PD the increase relative to a previous amount is more indicative than an absolute increase compared to a healthy soluble CD25 amount. In a preferred embodiment, for the patients on PD a first amount of soluble CD25 is determined, and a second amount of soluble CD25 is determined, wherein the second amount of soluble CD25 is at least 20% higher than the first amount of soluble CD25.

Preferably for the patients on PD the second amount of soluble CD25 is at least 22% higher than the first amount of soluble CD25, more preferably at least 25% higher, more preferably at least 27% higher, more preferably at least 30% higher, more preferably at least 35% higher, more preferably at least 40% higher, more preferably at least 45% higher, more preferably at least 50% higher, more preferably at least 55% higher, more preferably at least 60% higher, more preferably at least 65% higher, more preferably at least 70% higher, more preferably at least 75% higher, more preferably at least 80% higher, more preferably at least 90% higher, more preferably at least 100% higher, more preferably at least 110% higher, more preferably at least 120% higher, more preferably at least 130% higher, more preferably at least 150% higher, more preferably at least 175% higher, more preferably at least 200% higher, more preferably at least 225% higher, more preferably at least 250% higher, more preferably at least 275% higher, more preferably at least 300% higher, more preferably at least 400% higher, more

preferably at least 500% higher, more preferably at least 600% higher, more preferably at least 700% higher, more preferably at least 800% higher, more preferably at least 900% higher, more preferably at least 1000% higher.

In a preferred embodiment of the present invention and/or embodiments thereof, for the patients on PD a first amount of soluble CD25 is determined, and a second amount of soluble CD25 is determined, wherein the second amount of soluble CD25 is at least 200 pg/ml higher in urine and peritoneal dialysis fluids and at least 500 pg/ml higher in serum or blood than the first amount of soluble CD25.

In a preferred embodiment of the present invention and/or embodiments thereof, for the patients on PD a first amount the increase between first and second amount of soluble CD25 may be at least 500 pg/ml, preferably at least 1,000 pg/ml, more preferably at least 1,500 pg/ml, more preferably at least 2,000 pg/ml, more preferably at least 2,500 pg.ml, more preferably at least 3,000 pg/ml, more preferably at least 4,000 pg/ml, more preferably at least 5,000 pg/ml, more preferably at least 6,000 pg/ml, more preferably at least 7,000 pg/ml, more preferably at least 8,000 pg/ml, more preferably at least 9,000 pg/ml, more preferably at least 10,000 pg/ml, more preferably at least 12,000 pg/ml, more preferably at least 15,000 pg/ml, more preferably at least 17,000 pg/ml, more preferably at least 20,000 pg/ml. Preferably the increase of soluble CD25 between the first and second amount is between 500 and 30,000 pg/ml, more preferably between 1,000 and 25,000 pg/ml. more preferably between 2,000 and 20,000 pg/ml, more preferably between 3,000 and 17,000 pg/ml, more preferably between 4,000 and 15,000 pg/ml, more preferably between 5,000 and 12,000 pg/ml, more preferably between 6,000 and 10,000 pg/ml, more preferably between 7,000 and 9,000 pg/ml.

For bodily fluids that have a higher absolute amount of soluble CD25 such as blood and serum the increase of soluble CD25 is preferably between 1,000 and 30,000 pg/ml, more preferably between 2,000 and 25,000

pg/ml. more preferably between 2,500 and 20,000 pg/ml, more preferably between 3,000 and 17,000 pg/ml, more preferably between4,000 and 15,000 pg/ml, more preferably between 5,000 and 12,000 pg/ml, more preferably between 6,000 and 10,000 pg/ml, more preferably between 7,000 and 9,000 pg/ml. For bodily fluids that have a lower absolute amount of soluble CD25, such as peritoneal dialysis fluid and urine, the increase of soluble CD25 is between 100 and 5,000 pg/ml, more preferably between 200 and 4,000 pg/ml. more preferably between 300 and 3,000 pg/ml, more preferably between 400 and 2,500 pg/ml, more preferably between 500 and 2,000 pg/ml, more preferably between 700 and 1,500 pg/ml, more preferably between 800 and 1,250 pg/ml, more preferably between 900 and 1,000 pg/ml.

Other preferred embodiments described above are preferred embodiments for the preferred embodiments of the present invention and/or embodiments thereof, for the patients on PD wherein a first and second amount of soluble CD25 is measured. It is to be understood that the first amount of soluble CD25 equals the previous amount of soluble CD25, and the second amount of soluble CD25 equals the amount of measured amount of soluble CD25.

In a preferred embodiment, for patients that are off PD but have been on PD an amount of soluble CD25 is determined. Preferably the amount of soluble CD25 is at least 8,000 pg/ml. Preferably the amount of soluble CD25 is measured in blood or serum. For patients that do not undergo PD, a single determination of soluble CD25 may be sufficient to determine a risk for EPS or diagnose EPS. An amount of soluble CD25 of at least 8,000 pg/ml indicates EPS, or a risk for developing EPS. In preferred embodiments of the present invention and/or embodiments thereof, In a preferred embodiment, for the patients that are off PD preferably the amount of soluble CD25 is at least 10,000 pg/ml, more preferably the amount is at least 12,000 pg/ml, more preferably the amount is at least 14,000 pg/ml, more preferably the amount is at least 16,000 pg/ml, more

preferably the amount is at least 18,000 pg/ml, more preferably the amount is at least 20,000 pg/ml. In a preferred embodiment for patients off PD, the method to determine the soluble CD25 in blood or serum is ELISA.

Other preferred embodiments described above are preferred embodiments for the preferred embodiments of the present invention and/or embodiments thereof, for the patients that are off PD and wherein a single measurement of soluble CD25 is sufficient to determine EPS or a risk for EPS. It is to be understood that more soluble CD25 amounts may be determined, e.g. over time, for example to verify the status of EPS. It is however sufficient for patients that are off PD, but have undergone PD previously, to determine the amount of soluble CD25 once, where an amount of soluble CD25 of at least 8,000 pg/ml is indicative of EPS or a risk for EPS.

Once a patient is diagnosed for EPS, one may start treatment.

Treatment may be one of several option. Suitably the peritoneal dialysis is stopped. Also immune suppressive drugs may be used to treat EPS. Immunosuppressants such as azathioprine, myocophenolate mofetil and/or sirolimus may be used in patients with EPS, optionally co-administered with corticosteroids. A suitable treatment involves the administration of corticosteroids and tamoxifen. Corticosteroids may also be used in treating EPS. Another suitable treatment is a surgical procedure to remove the adhesive lesion, such as enterolysis and (localised) peritonectomy. The procedure of enterolysis implies the ablation of fibrotic tissue and lysis of the adhesions. Peritonectomy is the removal of (part of) the peritoneal surface. In addition, nutritional management may be used, such as total parenteral nutrition, especially when the bowel is (partially) obstructed. Combinations of treatments may be used.

Once EPS has been treated, the patient may be monitored again. After treatment of EPS and/or removal of EPS the amount of soluble CD25 should decrease again. A decrease of at least 20% in soluble CD25 amount compared to a previous amount of soluble CD25, may indicate that the EPS

is gone and/or the treatment has been successful. Suitably the decrease is at least 22%, at least 25%, more preferably at least 27%, more preferably at least 30%, more preferably at least 35%, more preferably at least 40%, more preferably at least 45%, more preferably at least 50%, more preferably at least 55%, more preferably at least 60%, more preferably at least 65%, more preferably at least 70%, more preferably at least 75%, more preferably at least 80%, more preferably at least 90%, more preferably at least 100%, more preferably at least 110%, more preferably at least 120%, more preferably at least 130%, more preferably at least 150%, more preferably at least 175%, more preferably at least 200%, more preferably at least 225%, more preferably at least 250%, more preferably at least 275%, more preferably at least 300%. The decrease may be at least 500 pg/ml, preferably at least 1,000 pg/ml, more preferably at least 1,500 pg/ml, more preferably at least 2,000 pg/ml, more preferably at least 2,500 pg.ml, more preferably at least 3,000 pg/ml, more preferably at least 4,000 pg/ml, more preferably at least 5,000 pg/ml, more preferably at least 6,000 pg/ml, more preferably at least 7,000 pg/ml, more preferably at least 8,000 pg/ml, more preferably at least 9,000 pg/ml, more preferably at least 10,000 pg/ml, more preferably at least 12,000 pg/ml, more preferably at least 15,000 pg/ml, more preferably at least 17,000 pg/ml, more preferably at least 20,000 pg/ml,

Preferably the decrease of soluble CD25 is between 500 and 30,000 pg/ml, more preferably between 1,000 and 25,000 pg/ml. more preferably between 2,000 and 20,000 pg/ml, more preferably between 3,000 and 17,000 pg/ml, more preferably between 4,000 and 15,000 pg/ml, more preferably between 5,000 and 12,000 pg/ml, more preferably between 6,000 and 10,000 pg/ml, more preferably between 7,000 and 9,000 pg/ml.

For bodily fluids that have a higher absolute amount of soluble CD25 such as blood and serum the decrease of soluble CD25 is preferably between 1,000 and 30,000 pg/ml, more preferably between 2,000 and 25,000

pg/ml. more preferably between 2,500 and 20,000 pg/ml, more preferably between 3,000 and 17,000 pg/ml, more preferably between4,000 and 15,000 pg/ml, more preferably between 5,000 and 12,000 pg/ml, more preferably between 6,000 and 10,000 pg/ml, more preferably between 7,000 and 9,000 pg/ml. For bodily fluids that have a lower absolute amount of soluble CD25, such as peritoneal dialysis fluid and urine, the decrease of soluble CD25 is between 100 and 5,000 pg/ml, more preferably between 200 and 4,000 pg/ml. more preferably between 300 and 3,000 pg/ml, more preferably between 400 and 2,500 pg/ml, more preferably between 500 and 2,000 pg/ml, more preferably between 700 and 1,500 pg/ml, more preferably between 800 and 1,250 pg/ml, more preferably between 900 and 1,000 pg/ml.

Kit of part for use in a method according to claims comprising

an agent and/or reading device to determine the amount of soluble CD25 in serum or blood of a patient

normal values for soluble CD25 in dialysis patients being peritoneal or hemodialysis patients

instructions for use

reading device

Normal values of soluble CD25 for PD patients are less than 8,000 pg/ml for serum or blood and less than 500 pg/ml for urine and peritoneal dialysis fluid.

The reading devices may be a point of care measurements such as test strips for blood or urine that may indicate healthy level of soluble CD25 or an increased level of soluble CD25, electronic devices that may measure the soluble CD25 in blood or urine and that preferably indicate whether the measured amount of CD25 is increased or not.

Experimental section

Soluble CD25 was measured in serum obtained from patients with the Diaclone sCD25 ELISA kit. The Diaclone sCD25 ELISA kit is a

solid phase sandwich ELISA for the *in-vitro* qualitative and quantitative determination of soluble CD25 in supernatants, buffered solutions or serum and plasma samples. A capture Antibody highly specific for CD25 has been coated to the wells of the microtitre strip plate provided during manufacture. Binding of CD25 samples and known standards to the capture antibodies and subsequent binding of the biotinylated anti-CD25 secondary antibody to the analyte is completed during the same incubation period. Any excess unbound analyte and secondary antibody is removed. A horsh radis peroxidase (HRP) conjugate solution is then added to every well including the zero wells, following incubation excess conjugate is removed by careful washing. A chromogen substrate is added to the wells resulting in the progressive development of a blue coloured complex with the conjugate. The colour development is then stopped by the addition of acid turning the resultant final product yellow. The intensity of the produced coloured complex is directly proportional to the concentration of CD25 present in the samples and standards. The absorbance of the colour complex is then measured and the generated OD values for each standard are plotted against expected concentration forming a standard curve.

EPS was diagnosed using the criteria of the ISPD ad hoc committee on ultrafiltration management in peritoneal dialysis. Perit Dial Int 2000;20:S43-55.

Serum sCD25 was measured in serum samples that were collected at yearly intervals during routine evaluation of peritoneal membrane function. Of seven EPS patients the serum sCD25 concentrations in the years before the diagnosis are given and compared to seven control PD patients with a similar duration of PD treatment but that did not develop EPS. The difference between both groups was significant in the year before EPS diagnosis (-1 year). All serum samples were collected while patients were on PD.

Figure 1 shows soluble serum CD25 of PD patients. Difference in amount of soluble CD25 from patients that develop EPS and patients that do not develop EPS. One year before EPS was determined the increase in soluble CD25 was already significant. Figure 1 shows that the level of soluble CD25 was increased for a patient that was diagnosed EPS, already 2 years before the onset diagnosis of EPS.

Figure 2 shows change of serum concentration in the 2 years before diagnosis of EPS. The serum soluble CD25 measurements in the years before the diagnosis of EPS are given, while patients were still on PD. Stable PD patients with a similar duration of PD treatment served as controls. The change in serum concentrations sCD25 between year -3 and year -1 are given. The change between EPS patients and controls is significantly different. As can be seen in figure 2, the difference between the soluble CD25 of year -3 and year -1 is significantly higher for patients that develop EPS than for patients that do not develop EPS. Figure 2 shows that for patients on PD, wherein a increase in soluble CD25 can be seen, develop EPS, whereas patients that do not show an increase in soluble CD25 remain stable and did not develop EPS.

In figure 3 the soluble CD25 (sIL-2R) in serum was measured for hemodialysis controls, EPS patients and after EPS was cured. EPS patients were all on hemodialysis at time of diagnosis of EPS and after they were cured. Therefore the serum sCD25 concentrations of stable hemodialysis patients were taken as control values. The difference between EPS patients with active disease and hemodialysis patients is statistically significant. It is also seen that after curing EPS, the values go back to normal. Figure 3 shows that patients with EPS have a much higher soluble CD25 level in serum than patients that undergo haemodialysis that do not have EPS. After medical treatment with a combination of tamoxifen and/or steroids or a combination of medical treatment of tamoxifen and/or steroids and

surgery the values for EPS patients return to the values of haemodialysis patients. Thus the method may also be used to monitor treatment.

Figure 4 shows that the level soluble CD25 in serum of stabile PD patients may be high. The relative difference of two measurements thus gives with patients on PD a better indication for EPS then a single determination.

Claims

1. Method to determine the risk for encapsulating peritoneal sclerosis (EPS) in a patient, comprising the steps:

a) Providing a sample from said patient

b) Measuring the amount of soluble CD25 in said sample thereby providing a measured amount of soluble CD25

wherein an increase in soluble CD25 indicates EPS or a risk for developing EPS in said patient.

2. Method to diagnose encapsulating peritoneal sclerosis (EPS) in a patient, comprising the steps:

a) Providing a sample from said patient

b) Measuring the amount of soluble CD25 in said sample thereby providing a measured amount of soluble CD25

wherein an increase in soluble CD25 indicates EPS in said patient.

3. Method of treatment of EPS in a patient undergoing peritoneal dialysis, comprising the steps

a) Providing a sample from said patient

b) Measuring the amount of soluble CD25 in said sample, thereby providing a measured amount of soluble CD25

c) Apply treatment of EPS when an increase in soluble CD25 is determined in said patient, wherein the treatment of EPS is selected from the group comprising cessation of PD, immunosuppressive treatment, treatment with corticosteroid, surgical treatment, nutritional treatment and/or combinations thereof.

4. Method according to any of the previous claims, wherein the increase is at least 20% relative to a previous amount of soluble CD 25 of said patient, preferably the previous amount of soluble CD25 amount is from at least 3 month before the measured amount of soluble CD25.

5. Method according to any of the preceding claims wherein the amount of soluble CD25 has been determined at least 2 times, preferably the interval between determinations is at least 1 month.

6 Method according to any of the preceding claims wherein the increase of soluble CD25 is at least 100 pg/ml relative to a previous amount of soluble CD25 amount of said patient, preferably the previous amount of soluble CD25 amount is from at least 3 month before the measured amount of soluble CD25.

7. Method according to any of the previous claims wherein the patient undergoes peritoneal dialysis.

8. Method according to any of the previous claims wherein the patient is off peritoneal dialysis.

9. Method according to any of the preceding claims wherein the patient shows the one or more of the following symptoms: abdominal pain, disordered bowel movement, ascites, vomiting, fever, weight loss, and/or malnutrition.

10. Method according to any of the preceding claims wherein the sample is chosen from the group consisting of blood, serum, peritoneal dialysis fluid.

11 Method according to any of the preceding claims wherein the sample is not peritoneal dialysis fluid.

12. Method according to any of the preceding claims wherein the soluble CD25 is determined by a method selected from the group consisting of ELISA, radio-immuno assay, mass spectrometry.

13. Use of soluble CD25 in a method to determine the risk of and/or diagnose EPS in a patient.

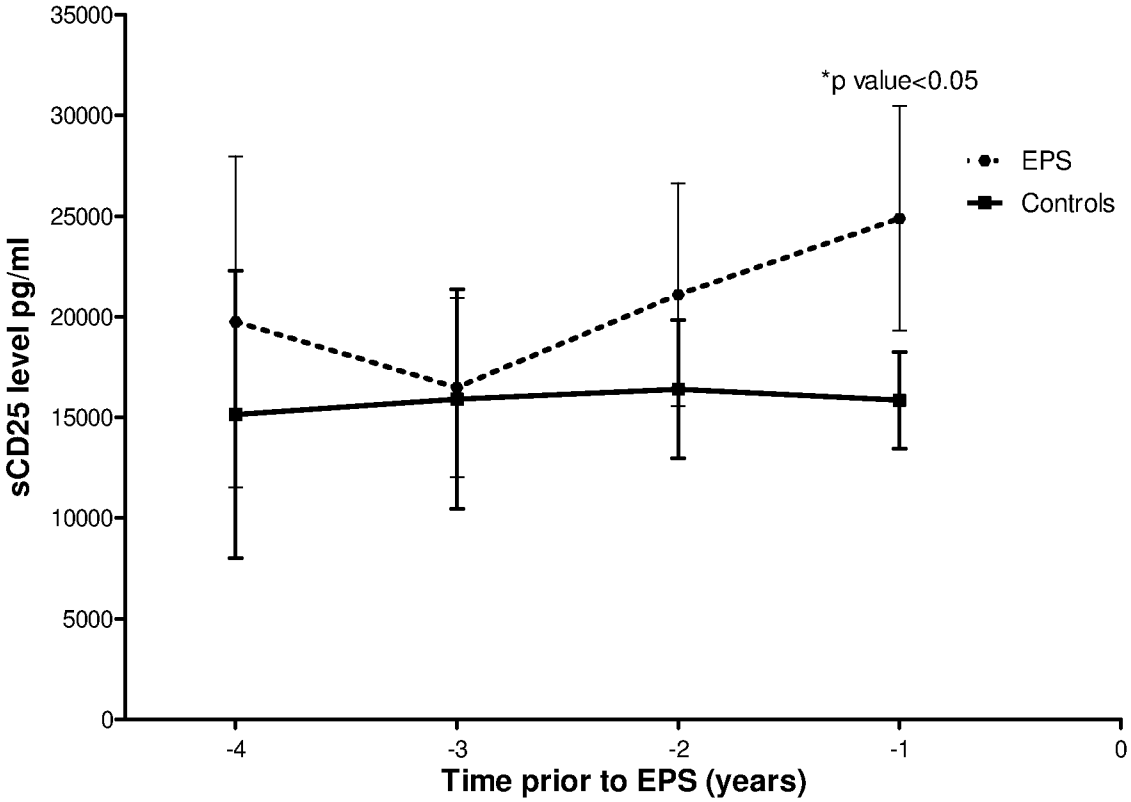
14.. Kit of part for use in a method according to claims comprising

a) an agent and/or reading device to determine the amount of soluble CD25 in serum or blood of a patient

b) normal values for soluble CD25 in dialysis patients being peritoneal or hemodialysis patients

c) instructions for use

Figure 1



*p=0.01, Mann-Whitney U test

Figure 2

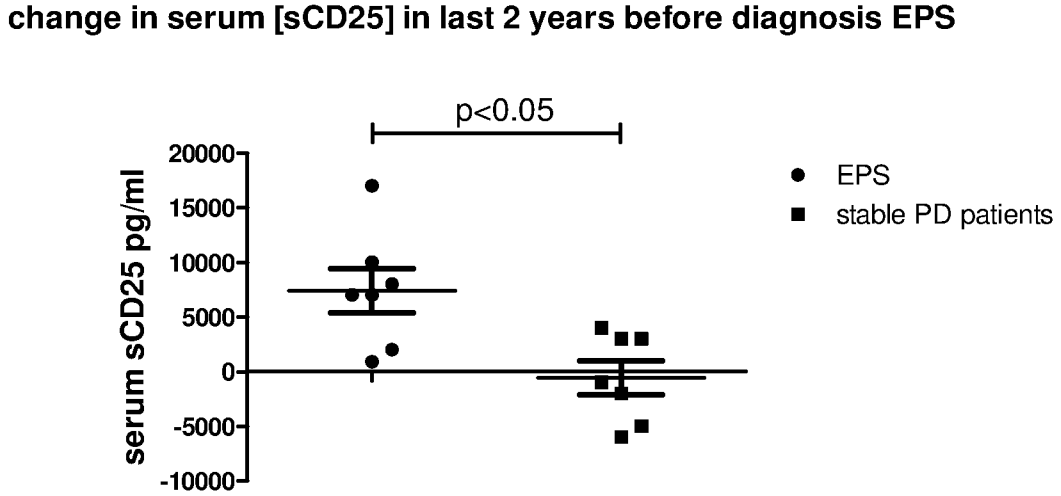
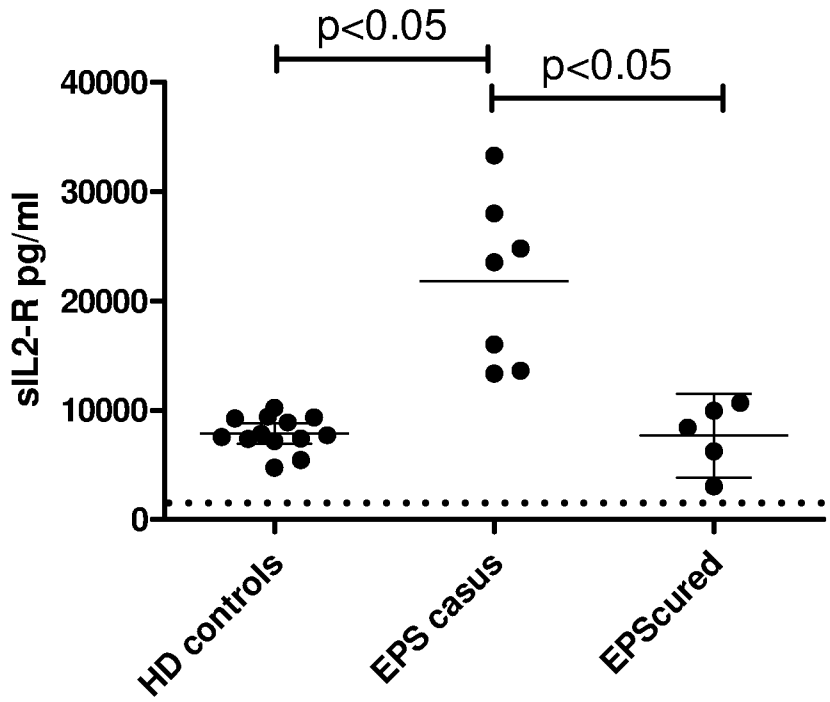
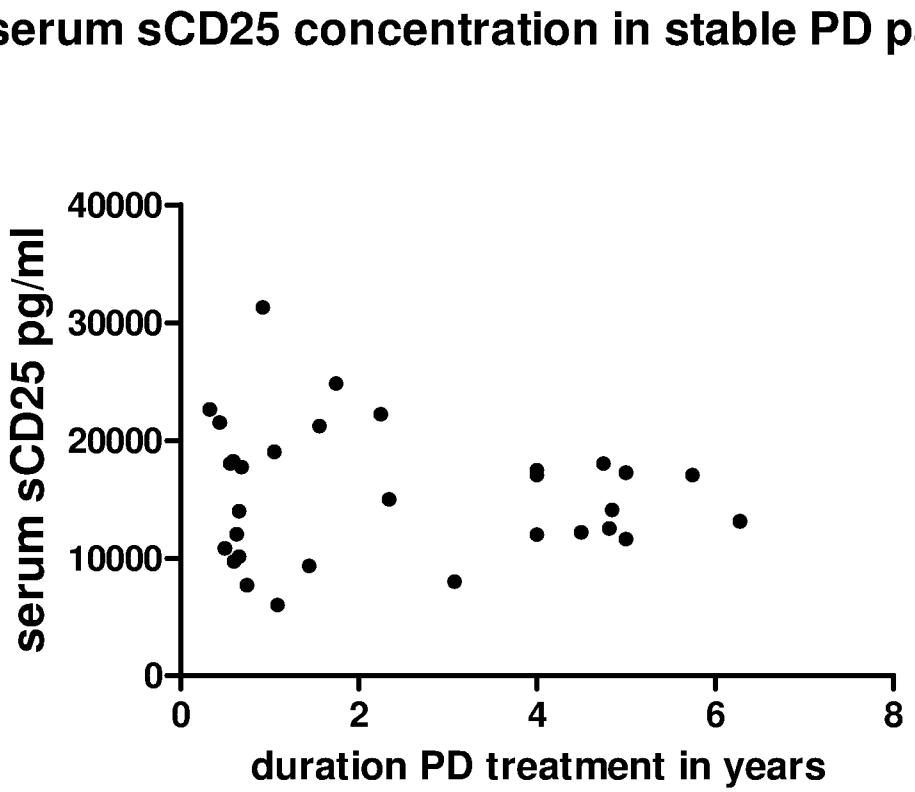

change in serum [sCD25] in last 2 years before diagnosis EPS
p<0.05
serum sCD25 pg/ml
20000
15000
10000
5000
0
-5000
-10000
EPS
stable PD patients

Figure 3



Upper 95% CI of mean:HD controls:8829, EPS cured:11500

Figure 4


serum sCD25 concentration in stable PD patients
serum sCD25 pg/ml
40000
30000
20000
10000
0
0
2
4
6
8
duration PD treatment in years

INTERNATIONAL SEARCH REPORT

International application No
PCT/NL2014/050423

A. CLASSIFICATION OF SUBJECT MATTER
INV. G01N33/68
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, BIOSIS, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 August 2014	14/08/2014

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Schindler-Bauer, P

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Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/NL2014/050423

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