Ph.D. THESES

COMPARATIVE LABORATORY OBSERVATIONS IN PATIENTS WITH END STAGE RENAL FAILURE AND TREATED WITH CAPD AND HEMODIALYSIS

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INTRODUCTION AND AIM OF STUDY

Chronic renal failure (CRF) and its treatment mean a growing problem for both the patients and the society all over the world. Today's different lifestyle, the well known eating habits and other manners of life jeopardize especially the inhabitants of the developed countries in the respect of renal failure. Based on the trend, observed in the world, the number of patients suffering from chronic renal failure in our country is also growing dynamically.

Dialysis is the only chance to survive- beside renal transplantation- for patients suffering from chronic renal failure. The development of the techniques of dialysis in the last 40-50 years truly reflects the „technical revolution" in medical science. It is fortunate that nowadays many forms of treatment are routinely available and applicable, which provides the opportunity to treat patients individually. It is also true for Hungary. In our country, today, in spite of the dynamic and sudden increase in the number of patients, nobody dies of renal failure because of the lack of capacity of renal replacement therapy.

The primary goal of dialysis is the possible replacement of the lacking excretory renal function due to renal failure. The result of that, is the elimination of excess extracellular water, soluble materials and uremic toxins.

It has long been a known fact, that an abnormal immune response can be observed in patients with CRF. It is manifested in their inadequate response to hepatitis C and B virus vaccination. In addition, these patients are also more susceptible to bacterial infection that indicates the disturbance of the aspecific protective system. However it is a surprising fact that the signs of suppression and activation of certain components of the immune system appear together in CRF patients. These changes may be significantly increased by the technologies of dialysis. Nowadays it has not yet been made clear to how the different dialysis modalities influence the disturbance of function of the immune system.

An important question is to know the level of β2-microglobulin of chronically uremic patients, since this molecule plays a role in the development of dialysis-related amiloidosis (DRA), which is a limitating complication of life-expectancy (arthropathy, bone disease, fracture of the vertebra etc.) of the patients treated with long-term dialysis (8-10 years). The exact cause of increased serum level of β2-microglobulin is not known. Some authors consider the impaired renal elimination responsible for that, while others think that cell activation caused by foreign surface may play a role. The connection between the grade of the activation of the immune system and the increase of serum level of β2-microglobulin is not yet known.

However the question still has to be answered, whether the CRF itself or the cell activation effect of the different dialysis modality are in the background of *the* increased β2-microglobulin values observed in patients with CRF. We have a little comparative data about the activation effect of different dialysis modality. The study of cytokine levels can be well applied for answering the question.

More authors observed an increased production of TNF alpha, IL-1, IL-1R, sCD 25, sCD 23, neopterin, gamma-IFN in uremic patients. However there are a little data regarding the different process of cell activations, which are behind the observed cytokine overproduction. The study of the immune competent cells may be simply investigated by the CD analysis of the cells.

Furthermore, we have little about peritoneal processing during peritoneal dialysis. The CAPD patients lose many biologically active proteins with their dialysis solution. Such a protein loss makes the patients' immune functions significantly worse. The intraperitoneal protein loss, further increases in the course of PD peritonitis, just as the local production of

certain protein also increases. We think, that after peritonitis is cured, intraperitoneal changes, which happened during peritonitis, are important factors in the continuation of CAPD. For that the beginning of our study we considered absolutely essential to work out a standard, readily reproducible monitor system for examining dialysis solution.

While peritonitis is a serious complication of CAPD, so far the chronic hemodialyis treatment means increased risk for patients regarding to virus infection which may be transferred by blood and blood-products. While in the past, mainly hepatitis B and C virus were held responsible for the majority of hepatitis transmitted by transfusion, in the 1990-s the family of hepatotropic viruses enlarged by newly discovered viruses. Hepatitis G virus (HGV) is standing in the center of such investigations today.

In 1997, in Japan a new DNA virus was detected from a patient's serum suffering from hepatitis of unknown origin, which was then called TT virus. Many authors studied its prevalence in the healthy population, which was found about 1,5 %. The frequency of TTV approaches 40 % - or more according to data of some authors- in patients with polytransfusion. Although we have more information about the molecular structure, about the way of spreading and the epidemiological characteristics of TTV, up to the present time, its pathogenetic significance, (whether it does really mean a real danger for patients with polytransfusion), has not been clarified yet. For that we thought it necessary to examine the prevalence and the effect of TTV for the immune system in our patients.

According to the above-mentioned, I aimed to examine the effects of CRF and different dialysis modality and theirs possible complications on the immunoregulation. The summary of my goals are briefly described below:

1. Comparison of the effect of hemodialysis and peritoneal dialysis on the components of humoral and cellular immune response. Study of serum level of β2-microglobulin and neopterin in patients treated with hemodialysis, CAPD and predialysed group.
2. Analysis of protein level in peritoneal dialysis solution and its changes during PD peritonitis.
3. Comparative analysis of the effects of hepatotroic viruses (HCV, HGV) on the components of the humoral and cellular immune response in hemodialysed patients.
4. Study of the effect of TTV on T cell subgroups in hemodialysed patients.

PATIENTS AND METHODS

We have investigated three groups of patients In the first group there were patients with chronic renal failure who were just before starting the renal replacement treatment (predialysed: PRE). The serum creatinin level of these patients was above 500 μmol/l.

The second group was made up of patients treated with CAPD. The treatments were performed by Fresenius Stay Safe system, through a catheter inserted into the abdominal cavity. For the test, we used blood, drawn from patients by the routine method and dialysate solution, drained out after appropriate equilibration time and dialysate solution, collected during 24 hours for the peritoneal equilibration test. We stored the samples at –20 °C till preparation. Signs of acute infection were not noticed at the patients during study-time. Patients with tumor and systemic immune disease *did not take part in the survey*. In case of peritonitis we used the „first cloudy" dialysate and after than, we performed our measurements from the solution dwelled in abdominal cavity „through night" (overnight). We established the diagnosis of peritonitis based on clinical signs (fever, abdominal pain) and laboratory parameters (leucocytosis, raised sedimentation rate, protein contain above 200 mg% in dialysate, white blood cell>100 /mm3 and positive microbiologic culture).

The third group was the patients with conventional hemodialysis. These patients were treated in FMC nephrology center of Miskolc, three times per week, with an average four hours dialysis session. The hemodialysis treatment was performed through arteriovenous fistula, by polysulfone low flux dialysator with 1,3 m2 surface and which provides 180 ml/min urea clearance and 164 ml/min creatinine clearance at blood flow Qb 300 ml/min. The residual creatinine clearance of HD patients was below 5 ml/min. In every case we collected blood from punction of AV fistula before starting HD. Patients treated with central venous catheter did not take part in my survey. The control group was always healthy blood donors.

We have measured the level of serum creatinine, blood urea nitrogen, ASAT and ALAT Ilab 300 chemistry analyzer. We analyzed level of immune globulin (IgA, IgG, IgM), complement C3, C4, fibrinogen, CRP by Turbox nephelometer.

Level of β2-microglobulin and neopterin was measured by standard ELISA method. Neopterin was determined by sandwich ELISA method with HENNING ELITEST (Berlin) reagent. Analysis of β2-microglobulin was performed by ABBOTT IMX β2- microglobulin kit (USA, Illinois) on ABBOTT IMX instrument.

The detection of cell surface markers and intracytoplasmic cytokines was done by Coulter EPICS XL-4 flow cytometer.

For determination of lymphoid population we collected blood in BD Vacutainer tubes with Na-heparin. From that we separated mononuclear cells by Ficoll gradient centrifugation, which were labeled with monoclonal antibodies conjugated FITC and phycoerythrin. (CD3, CD4, CD8, CD19, CD56, CD3/HLA-DR, CD45RO, CD3/CD69).

The determination of the level of soluble cytokine and CA125 was done by sandwich ELISA method. IL2, IL-6, gamma-IFN, IL-4, IL-10, IL-13, TNF-alpha, TGF-beta.

The tests for virus-serology were made in our laboratory by ELISA method. We applied DiaSorin tests for detection HbsAg and DiaSorin third generation tests for detection anti-HCV. The detection of replicated hepatitis C virus was done by RT-PCR methods with Roche Amplicor system.

The detection of hepatitis G virus and TT virus were performed by two-step nested and seminested PCR reaction. (We used nested PCR reaction for detection of HGV RNA and seminested PCR reaction for TTV detection.)

We applied regression analysis and Student's impaired t test for statistical evaluation of the our tests results. Normality analysis of data distribution was examined by Kolmogorov-Smirnov' test. In the case of normal Gaussian distribution we applied Student's paired t test, while in the case of abnormal distribution, Mann-Whitney test was used for statistical analysis of data. Any difference was considered significant if p was<0,05. IBM computer, with Excel software, made the archivation and evaluation of the results.

RESULTS

1. Comparison of the effect of hemodialysis and peritoneal dialysis on the components of humoral and cellular immune response. Study of serum level of neopterin and β2-microglobulin in patients treated with CAPD, hemodialysis and predialysed group

The values of immunglobulin (IgG, IgA, IgM) and the complement C3, C4 were within the normal range and significant difference could not been observed between each group.

In the two dialysed populations we did not find significant difference in the counts of T and B cell, compared to the predialysed group. Although in HD population we identified a significant raised proportion of active T cells (CD3/HLA-DR). These values were

significantly different from measured in CAPD patients too. The proportion of naive T cells (CD45RA) was significantly lower, while the memory T cells were (CD45 RO) significantly raised in HD group, compared to CAPD.
Concerning the significant activation, we compared the cytokine level of HD patients to the values of healthy population. We measured significantly raised proinflammatory (IL-6) and Th1 (IL-2, gamma-IFN) cytokine level in HD patients, compared to healthy controls. The pattern of soluble cytokine of HD patients shows Th1 predominance. Significant difference was not found between the level of TNF-alpha and TGF.

The level of neopterin was showed raising tendency in the following order: PRE<CAPD<HD. We measured the highest level in the HD group. This was significantly elevated compared to both PRE and CAPD group. β2- microglobulin level also was significantly raised in HD group, compared to PRE and CAPD populations.

2. Analysis of protein level in dialysis solution and its changes during PD peritonitis

In order to determine the patients' peritoneal protein loss, we measured the concentration of a few proteins of the dialysis solution were collected during 24 hours. These proteins were important to immune response. During the course of peritonitis, the level of all protein fractions was showed significant elevation.

The β2-microglobulin levels of serum and overnight solution were shown to be in very close correlation to each other. It was also true for the connection of concentrations of 4 hours dwell time and overnight solution. The D/P of β2-microglobulin kinetics and creatinine D/P were somewhat correlated with each other.

3. Comparative study of the effects of hepatotropic viruses (HCV, HGV) on the components of humoral and cellular response in hemodialysed patients.

12 out of 607 patients were chronic hepatitis-B carrier (HbsAg+, aHBc-IgM-). We have investigated 437 patients for anti-HCV antibody. The 8% (35) of the patients were previously anti-HCV. We performed a verification test with Roche Amplicore system at seropositive patients. Altogether 25 (71%) of seropositvie patients were confirmed to be positive.

In the cases of 16 patients who were previously negative, we had a slightly negative and positive, contradictory results, which were around the cut off values. It was not be possible to say a correct, definitive serodiagnosis in the official laboratory either, so the result was: ambiguous. (Later these were proved to be negative by PCR verification test.)

We examined the presents of hepatitis C (HCV) and hepatitis G (HGV) virus genome at 35 patients. We divided our patients into different groups based on viraemia. (healthy, negative for HCV and HGV, HCV+, HGV+ and HCV HGV co infection) We did not find differences between each group at values of serum creatinine, blood urea nitrogen, all proteins, alkaline phosphatase, bilirubin and gamma-glutamil transpeptidase. Significantly raised alanine aminotransferase (ALAT) values were measured in HCV positive patients. Polyclonal gammopathy were seen more often in this population. According to the ELFO picture, we also measured the highest level of IgG in these patients. There was not found difference between the levels of serum IgA and IgM. As regards of autoantibodies, ANF and RF positivity were occurred at higher proportion in HCV positive patients.

The proportion of CD4 positive cells showed significant reduction in the HCV group. Correlation of this, a significant elevation of CD8 positive cells-count could be observed. We

did not found differences between each population in the proportion of CD3 and CD13 positive cells. The proportion of CD3/HLA-DR and CD3/CD69 positive cells were raised significantly in each hemodialysed groups, compared to healthy controls. The further elevation of CD3/HLA-DR cells-count could be observed in the HCV positive group.

The soluble IL-2 and IL-6 were higher in each HD group, compared to healthy controls. None of the viraemic type had effect on this elevation. The level of IL-13 was reduced in each population, compared to healthy controls. The level of intracellular gamma-IFN of CD4 positive lymphocytes was raised in all HD groups- although no significantly compared to healthy controls. According to that, the intracellular IL-4 levels were showed significant reduction compared to healthy ones. Similarly to the soluble cytokine, neither did the level of intracellular cytokine show connection to each type of viraemia.

4.Study of the effect of TTV on T cell subgroups in HD patients

The proportion of helper T (CD4+) and B-lymphocytes were slightly reduced, while the value of the cytotoxic (CD8) and killer (CD56) population were elevated in all hemodialysed patients (TTV negative and TTV positive). The results did not show correlation to neither persistency nor absence of TTV.

The proportion of active T cells was significantly higher in the two HD populations, compared to healthy controls. Elevation of IL-2 level and reduction of IL-13 level (Th1/Th2 shift) could be observed in HD patients, which also did not show connection with neither TTV presence nor absence.

DISCUSSION

1. Comparison of the effect of hemodialysis and peritoneal dialysis on the components of humoral and cellular immune response. Study of β2-microglobulin and neopterin serum level in each patient's group.

The homeostasis of human organism is dramatically changed in chronic renal failure. Retention materials and toxins accumulate, moreover, different cell activating cytokines and regulatory cytokines of immune function release. Overproduction of TNF alpha, IL-1, IL-1R, sCD 25, sCD 23, neopterin, gamma-IFN has been described in uremic patients. This activation may be significantly increased by each dialysis method. Beside the elevated serum level of soluble mediators, which refers to the activation of immune system, the patients' increased susceptibility of patients to infection may be observed at the same time.

We did not find significant difference between levels of immunglobulins and complement C3, C4. The proportion of CD19+ B lymphocytes was also within the normal range. Based on that, we presume, that the function of antibody producing B cells system is not basically influenced by chronic renal failure and dialysis.

At the same time, hemodialysis also means a „stress" for immune competent cells by extracorporeal circulation. The contact-activation may result in an increased cytokine release and T cell activation, during the course of dialysis. For this reason, we measured the distribution of peripherial lymphoid cells and the expression of activating markers in our patients.

We found that the CD3/HLA-DR and CD3/CD45RO+ T lymphocyte population were significantly elevated in patients treated with HD, compared to healthy people and patients, predialysed and treated with continuous peritoneal dialysis. We found a significant shift in the proportion of Th1/Th2 and Th1 predominance in HD patients, compared to the value of

healthy population, according to other authors. Moreover, in our patients we measured the gamma-IFN dependent neopterin levels, as an important activating marker of immune system. We observed an elevated neopterin levels in predialysed chronic uremic patients, compared to normal. A further increase in neopterin level was seen in CAPD and HD groups, however significant difference was not found between the values of predialysed and CAPD group, in contrast with HD group, where neopterin level was significantly higher.

We conclude from this, that the cell activation, originally caused by chronic renal failure, is not significantly increased by CAPD, as a medical intervention, contrary to hemodialysis, where, presumable the foreign surface contact, caused by extracorporeal circulation, means a further activating signal.

Today it is not clear yet, that the only reason of elevated β2-microglobulin, observed in patients with CRF, is the reduced renal elimination and the lack of it or cell activation also takes part of the process. In our work, we found the highest β2-microglobulin level in the HD group. The elevation of β2-microglobulin levels showed connection to the elevation of neopterin serum level and the presence of cell activating markers.

2. Analysis of protein level in peritoneal dialysis solution and its changes during PD peritonitis

A high quantity of protein loss has to be considered with the dialysis solution during the course of PD. We measured significant level of IgG, IgA, IgM and fibrinogen in the dialysis solution of symptomless CAPD patients. The daily total loss of these protein was considerable high, about 2,3 g/day. In addition to these, C3 and C4 complement component also appeared at measurable quantity in dialysis solution during peritonitis, moreover, we experienced a significant elevation of all protein fractions.

The protein loss may contribute to the reduction or the exhaustion of the equilibration capacity of peritoneum, over a long period of time. The result of that, the elimination of big molecular proteins (for example β2-microglobulin) is reduced. The PET test, introduced to the examination of peritoneal equilibration capacity, is basically suitable for the examination of the clearance of small molecule (glucose, creatinine). However, little data is available in the literature about effectivity of its application for the transport of big molecular-weight materials. So, in our further examinations we were looking for the answer, how β2-microglobulin elimination looks like in patients, divided into different transport groups („low", „normo", „high") by peritoneal equilibration test.

The routinely applied D/P values (based on measurement of glucose and creatinine concentration) do not correlate to values of D/P of β2-microglobulin. The elimination rate of β2-microglobulin is almost the same in all the three transport groups and does not depend on either its serum level. According to that, the transport groups, formed by D/P values, are not applicable for the case of β2-microblobulin, because its transport mechanism is basically different from the transport of small molecular weight materials.

3. Comparative analysis of the effects of hepatotropic viruses (HCV, HGV) on humoral and cellular components of immune system in hemodialysed patients

The routine examination of hepatitis B virus is a generally accepted practice for decades. The examination and verification protocols, in cleared form, provide reliable results. The picture is less favorable in the diagnosis of hepatitis C virus. At present there is no test for direct virus detection. The question is made more complicated, since different types of dysproteinaemia, aspecific antibody production due to polytransfusion can be observed in many HD patients, which made all serodiagnostic methods and virus serology more difficult.

For these reasons, we established a central laboratory in our institute, where we make hepatitis serodiagnosis of patients who are treated at different dialysis units of our country. In this way, we can eliminate diversity of results due to interference of different tests, as well as giving a possibility for continuous testing.

Moreover, we examined values of biochemistry and protein-chemistry, the antibody production and the degree of cell activation of our HCV, HGV positive patients. We also supported by our work, that HCV (and its associated infection) causes the elevation of hepatospecific biochemical parameter (ASAT, ALAT). We proved among the firsts in the literature, that on the other hand, hepatitis G virus for itself does not result detectable enzyme elevation in patients who are symptomless chronic virus carrier. HCV infection also causes polyclonal gammopathy, in its background there is the enhanced IgG production. Moreover, it also increases the possibility of antibody production, which means mainly RF and ANF production, according to our research. In addition to this, the disturbance of cellular immune system can be also proved in HCV infection. Besides the reduction of *percentile* proportion of helper T lymphocytes, this infection causes elevation in the proportion of CD8 positive cytotoxic cells. In case of HGV infection these changes cannot be observed.

4. Study of the effect of TTV on T cell subgroups in hemodialysed patients

Many investigators also examined the prevalence of the TTV infection in healthy population, which is about 1,5%. Studying this question is still significant, since the frequency of TTV approaches near 40% –or more, according to some authors' data -in polytransfused patients, such as HD. We searched for the answer, whether TTV does cause changes in HD patients, which can be detectable by laboratory methods.

Although the first investigators, who identified the virus, found elevated transaminase values, it is not obvious, whether it is really caused by TTV. In our researches the hepatospecific parameters of TTV positive patients were at normal range and did not show difference compared to healthy controls. We found significantly reduced proportion of CD3+, CD4+ and CD19+ cells in peripheral blood of HD patients, compared to healthy controls. This reduction did not show connection to either absence or presence of TTV. The elevation of CD8+ cytotoxic T lymphocytes and significant elevation of CD56 NK cells and the active lymphoid populations (CD3/HLA-DR, CD3/CD69 doubled positive cells) could be shown in all hemodialysed patients. However this elevation did still not show correlation to TTV persistency. The soluble and intracellular cytokine pattern showed significant shift in the proportion of Th1/Th2, so we measured raised Th1 level and reduced Th2 cytokine level. Either the presence or the absence of TTV did also not influence the shift in Th1/Th2, which was observed in both virus negative and positive HD population.

In conclusion we can say that life expectancy of HD patients is significantly shortened by infective complication. Beside the series of transfusion, the disturbed immune-regulation of HD patients means a further danger, which is a good breeding ground for development of infections. It is well known, that in HD patients the increased susceptibility to infection can be paradoxically observed besides the activation of immune competent cells. Some infection –for example HCV- increases further derailment of immune regulation, which can cause strong systemic immunpathological processes. According to our research we assume, that TTV has not got such an effect, and during hemodialysis, TTV positivity is not an important pathogenetical component.

SUMMARY

We found a significant T cells activation and predominance of Th1 lymphocyte in hemodialysed patients. The possible cause of that can be searched in the techniques of the treatment and the materilas used during the treatment, since the observed activation cannot be explained by the chronic renal failure itself.

The degree of cell activation is much lower in continuous peritoneal dialysis (CAPD) compared to HD, and the level of β2-microglobulin causing DRA is also lower. So CAPD assures a greater immunological reserve for the patients. This kind of treatment also means a better quality of life for the patients, so if it is possible, CAPD should be the first chosen dialysis modality for treatments of chronic renal failure. Our works also contributed to, that in the last years the application of this kind of treatment modality has came more and more to the front in the Hungarian dialysis network of Fresenius Medical Care, which treats more than 40 percent of native patients suffering from kidney failure.

Although CAPD is a more favorable treatment method, we have to take into account peritonitis, which is a rare but serious complication. During the course of peritonitis patients can lose additional significant quantity of protein with their dialysis solution, which may limit the continuation of the treatment. At the beginning of our research there was not adequate national reference value, so we considered that the continuous screening of the biologically active protein is important.

We proved by our work, that the well-proved transport groups of PET in CAPD, is not applicable for kinetics of for example β2-microglobulin. The routinely used D/P values (based on the measurement of concentrations of glucose and creatinine) do not correlate to D/P values of β2-microglobulin. The elimination rate of β2-microglobulin is nearly the same in all three transport groups, which does not depend on the serum levels. According to that in the case of β2-microglobulin the D/P transport group scheme is not applicable, since its transport mechanism is basically different from the transport of small molecular weight materials.

As we examined the infective complication of hemodialysis, our observation confirmed that the diagnosis of hepatitis B virus carried out with different test and in different laboratory, gives the very same results. However the diagnosis of HCV is more complicated than this, the results show a much bigger diversity. It is especially important (to emphasize), that in hemodialysed patients, we do not get an exact, unambigous serological diagnosis in about 3 percent of the cases. We presume, that behind of this, there are the transformed protein- patterns of the patients. According to our results, we consider it reasonable, to centralize the performation of virus sero-diagnostic tests of HD patients. For that, we established a central diagnostic laboratory for virus serology in the network of Fresenius Medical Care.

In connection with the examination of newly discovered hepatotropic viruses, we proved among the first in the literature, that hepatitis G virus does not mean significant danger for HD patients, contrary to hepatitis C virus. In the case of TTV, the real pathogenetic role is also questionable/ can be also questioned.

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