Long-term prognosis in chronic primary glomerulonephritides

Doctoral thesis

by

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TABLE OF CONTENTS

Table of contents……...2

List of original papers…….3

Acknowledgments……..4

Abbreviations……...7

Introduction……8

Glomerular disease studied in the thesis……...10

Membranous nephropathy……10

Cancer and membranous nephropathy…….12

IgA nephropathy…….....15

Aims of investigation……18

Registries used……..19

Identification of patient cohorts and their characteristics…….21

Definition of observation periods, sources and characteristics of outcome data and definitions of primary endpoints…….23

Statistical methods and analyses……...24

Summary of main results……..26

General discussion……28

Conclusions……...33

References…….34

LIST OF ORIGINAL PAPERS

I. Rune Bjørneklett, Bjørn Egil Vikse, Einar Svarstad, Knut Aasarød, Leif Bostad, Frøydis Langmark and Bjarne Iversen: Long-Term Risk of Cancer in Membranous Nephropathy Patients. American Journal of Kidney Disease 2007; 50: 396-403 PMID 17720518

II. Rune Bjørneklett, Bjørn Egil Vikse, Leif Bostad, Torbjørn Leivestad and Bjarne Iversen: Long term risk of ESRD in IgAN; validation of Japanese prognostic model in a Norwegian cohort. Nephrology Dialysis and Transplantation 2011 August 5 (Epub ahead of print) PMID 21821835

III. Rune Bjørneklett, Bjørn Egil Vikse, Hilde Kloster Smerud, Leif Bostad, Torbjørn Leivestad, Anders Hartmann and Bjarne Iversen: Pretransplant course and risk of kidney transplant failure in IgA nephropathy patients. Clinical Transplantation 2011; 25(3):E356-65 PMID 21651619

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ABBREVIATIONS

ACE Angiotensin converting enzyme

ARB Angiotensin receptor blocker

CPGN Chronic primary glomerulonephritides

CI Confidence interval

CKD Chronic kidney disease

eGFR estimated Glomerular filtration rate

ESRD End stage renal disease

FSGS Focal and segmental glomerulosclerosis

GFR Glomerular filtration rate

HLA Human leukocyte antigens

HR Hazard ratio

IgAN Immunoglobulin A nephropathy

KM Kaplan Meier

LRD Living related donor

MDRD Modification of diet in renal disease

MN Membranous nephropathy

PLA2R Phospholipase A2 receptor

PRA Panel reactive antibodies

RP Rapid progressive

SIR Standardized incidence ratio

SP Slow progressive

UD Unrelated donor

INTRODUCTION

Chronic primary glomerulonephritides (CPGN) is a group of diseases characterised by leakage of proteins and/or erythrocytes into the urine with or without decreased glomerular filtration rate (GFR), hypertension, oedema, hyperlipidemia and low serum albumin. Although CPGN often are benign conditions, there is an increased risk for development of end-stage renal disease (ESRD), a complication that sometimes can be avoided by using potent, but toxic, immunosuppressive drugs [1]. Patients who develop ESRD need dialysis or kidney transplantation for further survival. However, these treatments are expensive and associated with decreased quality of life and increased mortality risk. Even after having caused destruction of the native kidneys, CPGN may recur in a transplanted kidney and thus cause failure also of this kidney [2]. As the outcomes of patients with CPGN are varied and the treatment options often are toxic and dangerous, selection of patients for appropriate treatment and follow-up regimens is of major importance. A correct histopathological diagnosis is mandatory, but in itself not sufficient, to decide the optimal treatment in individual patients. Within the various diagnoses of CPGN patients, the outcome with regard to risk of ESRD is varied and prognostic parameters are important for optimal treatment decisions. Thus, the study of prognostic factors and the combination of such factors as useful prognostic tools in the various types of CPGN is very important [3-6]. The number of patients with various types of CPGN are relatively low within each group of diseases. In addition, time from diagnosis of renal disease to ESRD may vary from weeks to decades, facts that complicate the study of prognostic factors in patients with such conditions.

Although risk of ESRD is their major and most investigated hazard, CPGN patients are also at increased risk of other major clinical complications. One of which is an increased risk of

malignant tumors [7]. A complex and multicausal association between malignant diseases and CPGN is described. Malignant tumors may cause CPGN through immunological mechanisms [8], and immunosuppressive drugs used against CPGN increases long term risk of malignancies [9-11] and other unknown mechanisms may also contribute.

The Norwegian Kidney Biopsy Registry was established in 1988 and its major goal was to study the epidemiology, aetiology, prognosis and treatment of patients with glomerular and other renal diseases. This registry has now become the largest active kidney biopsy registry in the world, containing information regarding more than 11000 kidney biopsies. The scientific value of the Norwegian Kidney Biopsy Registry is greatly enhanced by the linkage possibilities with other Norwegian medical and population registries such as the Norwegian Nephrology Registry (ESRD), the Norwegian Cancer Registry (cancer), the Norwegian Medical Birth Registry (births and pregnancy complications), the Norwegian Population Registry (survival), the Norwegian Cause of Death Registry, and others. Outcome data regarding patients in the Kidney Biopsy Registry can easily and reliably by collected through record linkage with the other registries using the unique 11 digit Norwegian person number. In the present doctoral thesis, the kidney biopsy registry has been linked to other registries and we were thus able to investigate long-term risk of cancer in membranous nephropathy as well as risk factors for ESRD and risk factors for graft failure after kidney transplantation in IgA nephropathy patients.

In our studies we have focused on two different CPGN, membranous nephropathy (MN) and IgA nephropathy (IgAN). The characteristics of these conditions and the basis for our studies are described in the following section.

GLOMERULAR DISEASES STUDIED IN THE THESIS

Membranous nephropathy

MN is probably the most common cause of primary nephrotic syndrome in adult Caucasians and has a well-defined histological pattern characterised by deposition of subepithelial immune complexes in the glomerular basement membrane [12]. While the histological picture is similar, patients can clinically be divided into idiopathic or secondary MN.

Idiopathic disease typically accounts for 70-90 % of MN cases. A few years ago, auto-antibodies against phospholipase A2 receptor (PLA2R) was found in the majority, but not all, idiopathic MN patients [13]. Several recent findings indicate that PLA2R auto-antibodies might represent a causal mechanism in the development of MN, this is however not yet fully proven [14-18]. It is likely that we in the future will distinguish between PLA2R positive/negative idiopathic MN. Recently, two new types of auto-antibodies against podocyt membrane proteins in MN has been discovered, anti-aldose reductase and anti-manganese superoxide dismutase, the importance of these are still uncertain [19].

Secondary MN has multiple aetiologies that cannot be identified by the routinely used morphological methods; infections (hepatitis B/C, malaria and others), autoimmune diseases (systemic lupus erythematosus, rheumatoid arthritis, Sjøgrens syndrome, dermatomyositis, sarcoidosis and others), medication (gold, penicillamine, captopril, non-steroidal antiinflamatory drugs and others), genetic and other rare causes. Malignancies

are usually also counted as a cause of secondary MN, this issue will be more thoroughly presented after this general introduction to MN.

The most frequent presenting symptom in MN patients is nephrotic syndrome, most other patients present with less severe and often asymptomatic proteinuria. The natural course of MN is varied and depends on the aetiology and the clinical presentation. Spontaneous complete or partial remission is relatively common, also in untreated patients [20]. However, in cases with severe and long lasting proteinuria, development of ESRD is common, a complication that often can be prevented through use of various immunosuppressive drugs [21-24].

MN patients are also at increased risk of thromboembolic complications, probably partly due to an altered balance between pro- and anticoagulant factors caused by urine protein losses [25]. An increased risk of infections is also observed and probably mediated through loss of protective antibodies in the urine and side-effects of immunosuppressive drugs.

The initial therapeutic approach to MN patients is, if possible, to identify and remove the aetiological factor. This factor can however often not be identified. The majority of MN patients are treated with angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB) and other antihypertensive agents [26]. Statins are often instituted against hyperlipidemia that often accompanies the nephrotic syndrome, their efficacy in protecting MN patients from cardiovascular complications is however not proven in clinical studies [27]. Some authors advocate the use of prophylactic anticoagulation in nephrotic MN patients, especially those with very low serum albumin

values, but this approach is controversial and not tested in randomized clinical studies [28]. In MN patients with very heavy proteinuria, especially if no sign of improvement during the first 6-12 months, and/or a tendency of decreasing eGFR, treatment with immunosuppressive drugs is indicated [5]. In the future, titres of antibodies towards PLA2R may also guide treatment [16], these analyses are not yet commercially available (August 2011). A number of immune modulating substances have proven effective in MN; steroids (but not in monotherapy), cyclophosphamide, chlorambucil, cycklosporin, tacrolimus and anti CD20 antibodies [21-24, 29-32]. The optimal drug regimen, both efficacy and toxicity taken into account, is not yet defined [1]. When MN patients develop ESRD, kidney transplantation is the preferred treatment modality [33-35]. MN may recur in the transplanted kidney but rarely causes graft loss [2].

Cancer and membranous nephropathy

An increased risk of cancer in MN patients was first demonstrated by Lee and co-workers in 1966 [36], subsequently this association has been confirmed in a number of studies [37-45]. There have also been studies that question the quantitative importance of the association between MN and cancer [37, 41]. It has been claimed that the co-occurrence of MN and cancer could be coincidental and caused by increased screening for cancer in MN patients.

There are several theoretical immunological mechanisms that may explain how tumors might cause MN [8]. First, antibodies against tumor antigens could cross-react with podocyt antigens. Second, circulating tumor antigens could form circulating antigen/antibody complexes that are later trapped into the glomerular filtration barrier. Third, tumor antigens might get trapped in the glomerulus and later react with circulating

antibodies. Fourth, an extrinsic factor such as an oncogenic virus could cause both MN and cancer. The evidence in support of any of the above suggestive mechanisms has until recently been scarce. In a few, rather old, studies tumor antigens in glomerulus or antibodies directed against tumor antigens were demonstrated [46-50]. Some histological findings also indicate differences in pathophysiology between idiopathic and cancer associated MN. First, the dominant IgG class of the glomerular immunodeposits in idiopathic MN is IgG subclass 4 [51, 52] and in cancer associated MN are subclasses 1 and 2 [53]. Second, an increased number of immune cells in the glomerulus have been observed in cancer associated as compared to idiopathic MN [42].

Recently, it was demonstrated that in most cases of cancer associated MN, auto antibodies against PLA2R were not present [17]. This finding strongly suggests that idiopathic and cancer associated MN are different clinical conditions. That both PLA2R antibodies and cancer were present in a few cases indicate that the co-existence of both diseases was co-incidental in such patients.

In summary, the present bulk of evidence, particularly the new findings regarding PLA2R auto antibodies, strongly suggest that malignancy caused MN represents a true clinical entity. However, there may also be other mechanisms causing an increased risk of cancer among MN patients. Screening for cancer among MN patients could represent such a mechanism, but this effect should fade away during prolonged follow up after MN since most malignant tumors tend to become symptomatic over time. One should also not forget the possibility that the frequency of cancer associated MN in fact might be underestimated in biopsy series since many nephrologists will be reluctant to perform kidney biopsies in patients with advanced cancer and in cured cancer patients with MN, biopsies might be

considered unnecessary due to spontaneous remission of proteinuria after removal of the tumor.

The frequent use of immunosuppressive drugs among MN patients might obviously cause an increased risk of cancer as in other patient groups treated with such drugs [10, 11]. However, this mechanism can of course only explain an increased risk of malignant tumors occurring long time after the diagnosis of MN.

The timing between diagnosis of MN and cancer is an issue of its own that naturally is of substantial clinical interest. Theoretically, rapidly growing tumors will be discovered early while small and slow growing tumors might persist undetected for a longer time while still causing immunological effects like MN. In the textbook literature, it is often claimed that the great majority of tumors associated with MN are detected prior to or simultaneously with the renal diagnosis and subsequently it is not necessary to look for causally related malignant tumors in the follow up period after MN. The bulk of evidence in support of this view is however far from impressive [8, 39, 40] and thus an investigation of this particular issue has been the aim of paper I in the present thesis.

IgA nephropathy

IgA nephropathy (IgAN) is the most common glomerulonephritis in the world [54-56] and the characteristic morphological pattern is mesangial deposition of IgA and varying degrees of mesangial cell proliferation and expansion of mesangial matrix. The pathophysiological mechanism in IgAN is not fully understood but characterised by altered production and/or structure, reduced hepatic clearance and abnormal glycosylation of the IgA molecule [57]. As a result, IgA tend to deposit in the glomerular mesangium. Such depositions are indeed quite common in the general population and described in up to 16 % of assumed normal donor kidneys [58]. It seems as if only a subgroup of patients with mesangial IgA depositions develop glomerular inflammation, as characterized by cell proliferation and increased matrix production, and only a subgroup of these patients develop progressive fibrosis and loss of glomerular filtration rate (GFR).

The classical presentations of IgAN are persistent asymptomatic hematuria and proteinuria or episodic macroscopic hematuria, often following an upper respiratory tract or gastrointestinal tract infection. Some IgAN patients also present with nephrotic or chronic nephritic syndrome.

The long term prognosis of IgAN patiens is highly varied. Many IgAN patients can live several decades without signs of deteriorating kidney function, whereas others gradually experiences a decrease in GFR and develop ESRD [59]. Several prognostic factors at time of diagnosis in IgAN have been described, the most important ones are probably decline of GFR, level of proteinuria, hypertension and morphological pattern [59-67].

Subsequently, a number of prognostic models integrating the different risk factors have been developed [4, 6, 60, 68-72]. They all aim to predict risk of ESRD but differ substantially in what risk factors are included. The Oxford classification of IgAN [4] is a prognostic system that is primarily based on the morphological picture, and this system is validated and found applicable also in other patient cohorts [73-77]. A recently published French prognostic system is based on the presence or absence of hypertension and proteinuria above 1 gram/24 hours together with the morphological picture, this system has not yet been validated in other IgAN groups [68]. Finally, a Japanese system is based primarily on clinical risk factors with the morphological picture playing only a minor role, [6], validation of this system is a part of the present thesis and is specifically addressed in paper II.

Most IgAN patients are treated with blood pressure lowering agents including ACE inhibitors or ARB´s [78-80]. Some, but not all studies, have demonstrated a beneficial effect of omega 3 fatty chains [81-83]. In a number of relatively small studies, a beneficial effect of steroids on progressive cases of IgAN is demonstrated. However, large randomized controlled studies confirming these findings have so far unfortunately not been performed [3, 84-95]. Generally, long lasting and high dose steroid courses are causing serious side effects and such treatment should be restricted to IgAN patients with high risk of progressive disease [1, 3]. Prognostic tools to identify patients suitable for aggressive treatment are therefore very useful.

Despite active treatment, many IgAN patients develop ESRD, and for such patients kidney transplantation is the preferred treatment modality [33-35]. As IgAN can be considered as a systemic disease which affects the kidneys, it is not surprising that it often

recurs in the transplanted kidney [2]. On the other side, when kidneys with IgA depositions [58] are used for donation to non IgAN recipients, these depositions tend to disappear spontaneously [96]. IgAN is usually a slowly evolving condition and the post-transplant immunosuppressive treatment may further slow development of recurrent disease. Thus, recurrent IgAN rarely causes graft loss before long time after transplantation [97-103]. A rapid course of IgAN with crescents that has re-occurred in the transplanted kidney and caused graft loss has been described in a few casuistic reports [104-106]. Except for these few reports, little is known about the relationship between the initial disease presentation and course of IgAN before ESRD and the outcome after subsequent kidney transplantation. This issue is the topic addressed in paper III of the present thesis.

AIMS OF INVESTIGATION

I. To study whether patients with established membranous nephropathy has an increased long-term risk of cancer compared to the age and gender adjusted general population.

II. To study whether a new Japanese scoring system to quantitatively predict risk of ESRD after 10 years of disease duration in IgA nephropathy is valid also in Norwegian patients.

III. To study whether the initial clinical and histopathological presentation and course of disease prior to ESRD are risk factors for graft loss after kidney transplantation in IgA nephropathy patients.

REGISTRIES USED IN THE THESIS

The Norwegian Kidney Biopsy Registry

The Norwegian Kidney Biopsy Registry is located at Haukeland University Hospital, was established in 1988 and has registered clinical, biochemical, immunological and morphological data from most patients who have had a kidney biopsy performed in Norway since 1988. All kidney biopsies are evaluated by an experienced nephropathologist at the Gade Institute at Haukeland University Hospital in Bergen.

The Norwegian Renal Registry

The Norwegian Renal Registry is located at Oslo University Hospital Rikshospitalet, was established in 1980 and has registered cause of ESRD, date of commencement of renal replacement therapy (RRT), switch of RRT modality, follow up data on RRT patients including major co morbidities and causes of death on all patients established in RRT in Norway.

The Norwegian Cancer Registry

The Norwegian Cancer Registry is located in Oslo and was established in 1953. Registration of cancers in Norway has been based on compulsory reporting of cancer cases by hospital departments, histopathological laboratories and death certificates from Statistics Norway. The completeness of data is documented to be 98-99 % for solid tumors [107, 108]. The complete cancer epidemiologic information in the registry allows calculation of a reliable and accurate estimate of the expected number of cancers and identification of all observed cancer cases in any given cohort.

The Population Registry of Norway

The Population Registry is a part of the tax office in Norway and deaths among Norwegian citizens are registered on a weekly basis. Data from this registry includes whether a person is alive or not, and if the person is dead, date of death is available.

IDENTIFICATION OF PATIENT COHORTS AND THEIR CHARACTERISTICS

Paper I

Patients were included based on a search in the Kidney Biopsy Registry for MN and registered proteinuria. Patients registered between start of the registry in 1988 and the end of 2003 was included. Secondary causes of MN in the cohort were identified through registry information and clinical information on the pathology form. Clinical and morphological data were obtained from the Kidney Biopsy Registry and included; age in years, gender, eGFR (ml/min/1.73m2), s-albumin (g/dl), proteinuria (g/24 hours), systolic and diastolic blood pressure (mmHg), degree of nephron loss (0-3), glomerular sclerosis (0-3), interstitial inflammation (none, acute or chronic), chronic interstitial fibrosis (0-3) and glomerular immunodeposits (none, focal, diffuse) of immunoglobulin (Ig) IgA, IgG, IgM, complement factor 3 (C3) and C1q.

Paper II

The study cohort in paper II was identified by a search in the Kidney Biopsy Registry for patients with IgAN registered between start of the registry in 1988 and the end of 2004. Data necessary for calculation of ESRD risk, as defined in the Japanese scoring system for IgAN, were obtained from the Kidney Biopsy Registry and included eGFR (ml/min/1.73m2), proteinuria (dipstick or quantitative measure methods), systolic blood pressure (mmHg), serum albumin (g/l), hematuria (dipstick), morphology (presence or absence of; glomerulosclerosis, crescents or adhesions to Bowmanns capsule in more than 10 % of glomeruli and/or prominent changes in interstitium and/or blood vessels), gender and age.

Paper III

A search in the Kidney Biopsy Registry for patients with IgAN registered between start of the registry in 1988 and the end of 2004 were made and those identified were linked to the Renal Registry. The study cohort consists of those who had received a kidney transplant by the end of 2006.

Clinical and morphological data were obtained from the Kidney Biopsy Registry and included; age (years), gender, estimated GFR (MDRD formula) (ml/min/1.73m2), proteinuria (more or less than 1 g/l), systolic and diastolic blood pressure (mmHg), morphologically grade 1-2 or 3-4 according to the Japanese histology grading system for IgAN.

By combining data from the Kidney Biopsy Registry and the Renal Registry time from diagnosis of IgAN to ESRD (years) and mean annual loss of GFR (ΔGFR) (ml/min/1.73m2/year) were calculated. ΔGFR = (initial GFR minus residual GFR at initiation of ESRD) divided by time between diagnosis of IgAN and commencement of RRT. As we did not have data on residual GFR at initiation of RRT, this was set to 5 ml/min/1.73m2.

Data that could be of significance for graft outcomes were obtained from the Renal Registry and included donor source, donor age, donor gender, recipient age below 30 years, pre-emptive transplantations, the presence of panel reactive antibodies (PRA), number of HLA A/B/DR mismatches, the presence of tissue type HLA B8DR3 in recipients and the post-transplant immunosuppressive regimen.

Definition of observation periods, sources and characteristics of outcome data and definitions of primary endpoints

Paper I

The observation period of patients was defined as the time between the kidney biopsy and diagnosed cancer, end of 2003 or death whichever came first. Outcome data were obtained through record linkage of the study cohort with the Cancer Registry. All diagnosed cases of cancer, including information regarding subtype of cancer, in the study cohort were registered. The primary endpoint of this study was the standardized incidence rate (SIR) of cancer after MN diagnosis.

Paper II

The observation period of patients was defined as the time between diagnoses of IgAN and ESRD, end of 2008 or death whichever came first. Data regarding development of ESRD, which also was the primary endpoint of the study, was obtained from the Renal Registry.

Paper III

The observation period of patients was defined as the time between kidney transplantation and end of 2008, death or graft loss whichever came first. Outcome data was obtained from the Nephrology Registry and included steroid-sensitive acute rejection, steroid-resistant acute rejection and non-immunologic complications (ureter, vascular, wound/lymphocele, delayed graft function and infections) the first three months after transplantation. GFR one year post transplant and at the last follow up registration, graft loss, histologically verified recurrence of IgAN, retransplantations, deaths, deaths with functioning graft and cause of death were also obtained from the Nephrology Registry.

The primary endpoint was graft loss. Death with functioning graft was treated as a censoring event.

STATISTICAL METHODS AND ANALYSES

In simple comparisons (all papers), independent samples t-test was used for test of statistical significance in normally distributed continuous variables, Mann-Whitney test for not normally distributed continuous variables and Chi-square test for categorical variables.

In all papers, Kaplan Meier statistics and survival curves were used and log rank test was used for test of statistically significance of differences between the compared groups. In paper I the cumulative risk of cancer in the complete cohort, and in patients older versus younger than 60 years was illustrated. In paper II, the cumulative risk of ESRD in 9 risk groups were calculated and compared and the data was also used to create a simplified prognostic system with 5 risk groups. This was done by merging of risk groups that were not statistically different from each other when compared with log rank test. We also used the KM method to compare risk of pre-ESRD deaths between these 5 risk groups. In paper III, the KM method was used to compare graft survival between patients with rapid versus slow progression of IgAN as well as between patients with transplanted kidneys from living related versus (LRD) unrelated donors (UD).

In paper I, standardized incidence ratio (SIR) of cancer was calculated in a two-step manner. First, the expected number of cancer in the study group was calculated based on national cancer rate data adjusted for gender, age in 5 year intervals and time period in 5 year intervals. Second, SIR was calculated as the observed divided with the expected number of cancers in the study cohort.

In paper II, Cox regression statistics was used to analyse unadjusted and adjusted hazard ratios (HR) of the 8 prognostic elements in the Japanese prognostic system for IgAN.

In paper III, we converted the continuous variable ΔGFR into a dichotomous categorical variable named slow progression (SP) or rapid progression (RP) of IgAN. To identify the optimal definition of RP and SP of IgAN, we tested different cutoffs for ΔGFR (10, 20, 30, 40, and 50 ml/min/1.73m2/year) in an adjusted Cox regression model and chose the definition that best separated RP and SP patients. We also used Cox regression statistics to compare risk of graft loss between RP versus SP patients with IgAN in a model with adjustment for possible confounders.

SUMMARY OF MAIN RESULTS

Paper I

One hundred sixty-one patients with MN were identified. Fifteen patients had MN secondary a non-malignant cause. Cancer was diagnosed in 33 patients, 9 before and 24 after diagnosis of MN.

The mean annual incidence rate of cancer after MN was 2.4/100 person-years, 2.1/100 person-years 0-5 years after MN and 2.8/100 person years 5-15 years after MN diagnosis. SIR of cancer in the cohort after MN diagnosis was 2.3 (95 % CI, 1.4 - 3.4) after exclusion of secondary cases including those with cancer prior to MN, SIR of cancer was 2.3 (95 % CI, 1.5 – 3.5). SIR of cancer in male patients with MN was 2.1 (95 % CI, 1.3 – 3.4) and in female MN patients 2.5 (95 % CI, 1.0 – 5.2). SIR of cancer 0 – 5 years after MN was 2.2 (95 % CI, 1.1 – 3.9) and 2.3 (95 % CI, 1.2 – 4.0) 5 – 15 years after diagnosis of MN. The only single site cancer with a significantly increased SIR was prostate cancer (SIR 2.9, 95 % CI 1.1 – 6.4). After exclusion of the 3 cases with cancer diagnosed less than 6 months after MN, SIR of cancer was 2.1 (95 % CI, 1.3 – 3.2). After 15 years of follow up the cumulative risk of cancer was 34 %, 57 % in patients older than 60 years and 19 % in patients younger than 60 years.

Paper II

A total of 633 patients were identified and 146 of these developed ESRD, 121 after less than 10 years of follow up. Forty-five patients died before they reached ESRD.

The observed 10 year cumulative risk of ESRD was within or close to the expected range in 8 of 9 risk groups covering 94% of the cohort. The much lower than expected 10 year risk of ESRD in risk group 8 is partly explained by many pre-ESRD deaths among these patients.

The observed ESRD risk 15-17.5 years after diagnosis of IgAN substantially exceeded the predicted and observed 10 year risk in risk groups 3-5 (predicted 5-30 % risk). The cumulative risk of pre-ESRD deaths increased with increasing risk of ESRD. After merging of risk groups that did not have significantly different prognosis, 5 risk groups appeared with 0-5 %, 5-10 %, 10-50 %, 50-90 % and > 90% 10 year risk of ESRD. All components of the scoring system, except male gender, were associated with an increased risk of ESRD, also in an adjusted model. The HR of pre-ESRD deaths was 3.0 in patients with an initial eGFR < 60 ml/min/1.73m2 after adjustment for age and gender.

Paper III

One hundred six transplanted IgAN patients were identified. There were 14 patients with graft loss. Patients with versus without graft loss had higher ΔGFR (38 ± 40 versus 12 ± 17 ml/min/1.73m2/year, p=0.02) and shorter time from diagnosis of IgAN to ESRD (2.9 ± 2.8 versus 5.1 ± 4.3 years, p=0.048). The highest adjusted HR (6.0, 95 % CI 1.6 – 22) associated with being a rapid progressive IgAN patient was observed with a definition of RP as ΔGFR > 30 ml/min/1.73m2/year. At time of transplantation, RP patients were younger (30 ± 10 versus 46 ± 14 years, p<0.001) and a higher proportion received a LRD graft (82 % versus 42 %, p=0.01) than SP patients with IgAN. After transplantation, RP patients tended to have more morphologically verified recurrence of IgAN (18 % versus 5 %) than SP patients but this difference was not statistical significant. The only major difference in outcome was graft loss, 55 % in RP versus 8 % in SP patients (p>0.001). The unadjusted HR for graft loss in RP versus SP patients was 4.5 (95 % CI, 1.5 - 14). After adjustment for donor age, donor gender, HLA mismatches, PRA status, HLAB8DR3 status, pre-emptive transplantation, type of immunosuppressive regimen, LRD and recipient age < 30 years the HR of raft loss with RP versus SP increased to 12.8 (95 % CI, 2.2 – 74).

GENERAL DISCUSSION

Valid knowledge regarding prognostic factors and outcomes in patients with primary glomerulonephritides is of importance in clinical practise and has thus been the principal aim of the studies in the present PhD thesis. In paper I, we described a substantial increased risk of cancer in MN patients that was not, as suggested by previous reports [39, 40], limited to a short time period around the debut of the renal disease. As discussed in the paper, we do believe that tumors that at the time of diagnosis are clinically undetectable but immunologically active and the use of immunosuppressive drugs are the two most probable explanations of our findings. The fact that immunosuppressive drugs are associated with an increased risk of cancer underscores the importance of restricting the use of such drugs to patients with progressive disease only. Thus, the study of prognostic factors and the combination of such factors into prognostic systems is of clinical importance in the guidance of appropriate therapy. In paper II, we evaluated a recently published Japanese prognostic system for IgAN [6] and found it applicable also in Norwegian patients. With this prognostic tool, a large fraction of IgAN patients with a benign prognosis could be identified and these patients should not receive toxic drugs. Although the principal aim of treating CPGN patients is to avoid progression to ESRD, this goal cannot always be achieved with the treatment options currently available. For such patients, the optimal treatment option is kidney transplantation. Although the results of kidney transplantation generally are excellent, recurrence of CPGN sometimes leading to graft failure is a clinically significant concern [2]. In paper III, we investigated to what extent the presentation and course of IgAN in the native kidneys was associated with graft survival after kidney transplantation. An important finding was that those patients with a particularly rapid course of IgAN, defined as mean annual loss of GFR exceeding 30 ml/min/1.73m2 had a much higher risk of graft loss after kidney

transplantation. As we to date have no effective therapy against aggressive IgAN, neither before nor after transplantation, the current clinical impact of this finding is limited. On the other hand, it is noteworthy that among slow progressive IgAN patients, the risk of graft loss as well as risk of death with functioning graft is low, demonstrating that kidney transplantation is an excellent treatment option in such patients.

Cancer as an underlying cause of glomerulonephritides is fairly well documented among MN patients [37-42, 44, 45] but also, although less frequently, in patients with other glomerular diseases; most known of which is probably minimal change disease secondary to Hodgkin lymphoma [43, 109]. Long-term risk of cancer in primary glomerulonephritides patients is however much less well studied. To our knowledge, only one well-performed and population based study except ours has been published [7]. In this Danish study, using linkage of a kidney biopsy registry with a national cancer registry, generally the same observations regarding MN and cancer as we found, was reported. Of interest, in this study, an increased long-term risk of cancer was also reported in most other types of primary glomerulonephritides. This finding indicates a common risk factor for cancer in CPGN patients, the use of immunosuppressive drugs being the most likely one. The fact that the most commonly used types of immunosuppressive drugs in CPGN patients, cyclophosphamid and cyclosporin, are associated with an increased risk of cancer also in other patient groups [10, 11], supporting a similar explanation of the observations in the Danish study. When considering the clinical importance of the observed increased long term risk of cancer in MN, it is useful both to consider the relative and absolute risk increase. In our study, the cumulative risk of cancer among MN patients older than 60 years after 10 years of follow up was close to 60 %, much higher than the expected number of less than 30 %. When also taken

into account that most MN patients who were diagnosed with cancer died during follow up, our finding is undoubtedly of major clinical significance.

Many patients with primary glomerulonehritides, particularly IgAN and MN patients, have a benign prognosis regarding risk of ESRD also without treatment with immunosuppressive drugs [59]. Thus, prognostic tools to identify such patients are of importance to avoid potentially dangerous over-treatment with toxic drugs. In MN, a Canadian prognostic system was published many years ago [110]. This system has later been validated and found applicable also in MN populations from Finland and Italy [5]. However, it can be anticipated that new prognostic systems in MN will be suggested that includes serial titres of PLA2R auto antibodies when these becomes generally available. In IgAN, a well-accepted and validated prognostic system has been lacking and a number of different models have been suggested during the last few years [4, 6, 68]. They differ substantially in what prognostic factors are included, particularly regarding the importance of the histological picture. In paper II we conclude that a Japanese prognostic system [6] is applicable to predict 10 year risk of ESRD also in Norwegian IgAN patients. Despite this conclusion, we are not convinced that the Japanese system will become generally accepted as the optimal prognostic tool in IgAN. An ideal prognostic tool in IgAN should probably include a longer observation period than 10 years, deaths occurring in patients with progressive disease should be included as an end-point and expected time from diagnosis of IgAN to ESRD should also be included in the prediction. Our data indicate that eGFR, proteinuria, blood pressure and the histological picture are the most important independent risk factors for ESRD in IgAN patients and that a future prognostic scoring system therefore probably should be based primarily on these.

Recurrence of the initial disease in transplanted kidneys is observed with all subtypes of primary glomerulonephritides [2]. Graft loss due to recurrent disease is most often observed in patients with focal and segmental glomerulosclerosis (FSGS), in such patients it may occur shortly after transplantation [111]. In IgAN, graft loss due to recurrence is also commonly observed but usually occurs long time after transplantation [97-103]. In MN, recurrence is common after transplantation but it rarely causes graft loss [24]. In paper III we showed that a rapidly progressive course of IgAN, mostly seen in young patients, is associated with a substantially increased risk of graft loss. Young age and aggressive initial disease presentation are also associated with increased risk of recurrence and graft loss in FSGS patients [24].

There are some important strengths of the studies in the present thesis; first, they are all population based and thus, selection bias is avoided. Second, the cohorts are fairly large and with a long follow up time. Third, the major end-points (cancer, ESRD and graft loss) are all well-defined and clinically relevant. Fourth, end-points occurring in the study cohort have been identified from high quality national registries, a method that secures a valid and complete registration of the outcome parameters.

Some methodological weaknesses of our study must also be admitted. First and most importantly, we did not have information regarding disease evolvement and treatment between diagnosis of MN / IgAN and occurrence of cancer or ESRD. Such data would have been of interest regarding the understanding of causes and mechanisms of our findings. Information regarding the association between PLA2R auto-antibodies and idiopathic MN became known after paper I had been published. If the use of immunosuppressive drugs and PLA2R antibody status among patients in the study cohort of paper I had been known the following two subgroup analyses would have been very interesting to perform;

1. Long-term risk of cancer in PLA2R negative idiopathic MN patients.
2. Long-term risk of cancer in PLA2R positive MN patients who have received immunosuppressive drugs.

In paper III, we did have some information regarding treatment and course between kidney transplantation and graft loss of our patients but available information regarding recurrence of IgAN was scarce, due too few post-transplant biopsies.

In summary, the major clinical and prognostic implications of the findings in the present PhD thesis are; in particularly older MN patients, the possibility of an underlying cancer should be carefully investigated. If a tumor is not detected initially, it should be looked for also during the follow up period. Due to increased risk of cancer in MN, immunosuppressive drugs should only be used in patients with a high risk for ESRD. The Japanese prognostic scoring system for IgAN is applicable to predict 10 year risk of ESRD also in Norwegian patients. Patients with a predicted risk between 5 and 30 % are most likely to develop ESRD after more than 10 years of follow up. Progressive IgAN is associated with an increased all-cause mortality rate. Patients with a rapidly progressive course of IgAN (ΔGFR > 30 ml/min/1.73m2) have a much higher risk of graft loss after transplantation than other IgAN patients.

CONCLUSIONS

First, we have demonstrated that the risk of cancer is substantially elevated for many years of the follow up period after MN diagnosis, as opposed to previous reports that had indicated that the increased risk of cancer was limited to one year before and after MN diagnosis.

Second, we have documented that a recently published Japanese scoring system aimed at predicting 10 year risk of ESRD in IgAN patients also is applicable in Norwegian patients. Furthermore, this scoring system could be used to identify those patients at highest risk of pre-ESRD deaths and also those at highest risk of developing ESRD after more than 10 years of disease duration.

Third, we have shown that IgAN patients experiencing a rapid loss of renal function in their native kidneys have a greatly increased risk of graft loss after transplantation compared to other IgAN patients.

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