Outcomes in PRImary NEPHrotic syndrome in Scottish adults (OPRINEPH): protocol for a registry-based observational study.

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Abstract

Nephrotic syndrome is defined by heavy proteinuria, hypoalbuminaemia and oedema. Patients with nephrotic syndrome are at increased risk of adverse consequences such as infection, thrombosis and progressive renal failure. Anecdotal and small observational studies report poor outcomes in adults (and particularly older adults) with nephrotic syndrome. However, hard outcomes in adult nephrotic syndrome have not been defined in well-designed, large-scale studies.

Herein we describe the protocol for an observational study aimed at assessing outcomes in primary nephrotic syndrome in Scottish adults. We will perform a registry-based data-linkage study. Our primary data source will be the Scottish Renal Biopsy Registry. This will be linked to three other datasets: Scottish national mortality data, Scottish SMR01 data (coded diagnoses for acute hospital admissions) and Scottish community prescribing data. Our primary outcome will be patient survival. We will determine this – and a range of secondary morbidity outcomes – in pre-specified subgroups stratified by age, primary glomerular diagnosis, baseline renal function, treatment regime and response to treatment.

Our results will guide physicians, patients and their families in assessing the likely prognosis of patients with nephrotic syndrome and may also generate hypotheses that could be tested in randomised controlled trials of therapeutic interventions.

Introduction

Background

Nephrotic syndrome is defined by heavy proteinuria, hypoalbuminaemia and oedema (Glassock *et al.*, 2015). It can develop at any age and result from a range of different primary and secondary glomerular pathologies. Patients with nephrotic syndrome are at increased risk of adverse consequences such as infection, thrombosis and progressive renal failure.

Anecdotal and small observational studies report poor outcomes in adults (and particularly older adults) with nephrotic syndrome (Nolasco *et al.*, 1986). This may reflect differences in physiological reserve and in the underlying glomerular disease. For example, minimal change nephropathy in children typically responds to glucocorticoid treatment within days in children, whereas in adults it often take months to respond or is steroid-refractory (Hogan & Radhakrishnan, 2013). However, hard outcomes in adult nephrotic syndrome have not been defined in systematic, large-scale studies. We aim to address this.

Herein we describe the protocol for an observational study aimed at assessing outcomes in primary nephrotic syndrome in Scottish adults (OPRINEPH).

Aim

We aim to determine mortality and morbidity outcomes in Scottish adults with primary nephrotic syndrome. We will restrict our analysis to primary nephrotic syndrome because patients with secondary nephrotic syndrome constitute a heterogenous group, in which clinical outcomes may be driven by the underlying systemic disease.

Methods

Study design

We will perform a registry-based data-linkage study. Our primary data source will be the Scottish Renal Biopsy Registry (https://www.srr.scot.nhs.uk/Biopsy-Registry/Main.html). This national registry has collected data from all patients undergoing kidney biopsy in Scotland since 2014 (McQuarrie *et al.*, 2009). This will be used to identify patients for inclusion in the study and to collect laboratory data. This will be linked to three other datasets using a unique patient identifier (CHI): Scottish national mortality data, Scottish SMR01 data (coded diagnoses for acute hospital admissions) and Scottish community prescribing data (pending approval from data linkage oversight committee).

Study dates

Patients will be included if their kidney biopsy was obtained between 01/01/2014 and 31/12/2017. The study period for any individual patient will start on the day of biopsy (for mortality and renal outcomes). In an attempt to offset lead-time bias, the study period will

start 6 months before the date of biopsy for all other secondary outcomes. The study period for any individual patient will end on the day of death or on 31/12/2018 (whichever is the sooner).

Study subjects

The study cohort will include all adults with nephrotic syndrome due to biopsy-confirmed primary glomerulonephritis. Patients will be included if they satisfy all of the inclusion criteria:

i) underwent biopsy of a native kidney between 01/01/2014 and 31/12/2017 where "nephrotic syndrome" was recorded as the primary or secondary indication and where this was the first biopsy for that indication

ii) aged over 18 years on the day of biopsy

iii) diagnosis compatible with a primary glomerular disorder including – but not restricted to – the following:
- *minimal change disease*
- *membranous nephropathy*
- *focal segmental glomerulosclerosis*
- *mesangiocapillary glomerulonephritis and C3 glomerulopathy*
- *IgA nephropathy*

Patients will be excluded if they meet any of the exclusion criteria:

i) biopsy diagnosis not a recognised cause of nephrotic syndrome (e.g. tubulointerstital nephritis)

ii) nephrotic syndrome secondary to a systemic disease including – but not restricted to – the following:
- *diabetes mellitus*
- *systemic lupus erythematosus*
- *dysproteinaemia*
- *neoplasia*
- *drugs*
- *systemic vasculitis*

Primary outcome

The primary outcome will be patient survival (time from date of biopsy to date of death).

Secondary outcomes

We will record the following secondary outcomes:

1) cause of death

i) cause of death, classified as:
- infective
- cardiovascular (not including thromboembolic)
- thromboembolic
- haemorrhagic
- cancer
- end-stage renal failure
- other

2) morbidity

i) number of hospital attendances
ii) cumulative duration of time in hospital (as inpatient)
iii) primary diagnoses responsible for attendance at hospital, classified as:
- infective
- thromboembolic disease
- cardiovascular disease (not including thromboembolic disease)
- renal failure (AKI, worsening renal function, progressive CKD)
- bleeding disorders
- other

3) renal outcomes

i) requirement for permanent renal replacement therapy (including transplant)

laboratory indices (at 6, 12, 18 and 24 months after the date of biopsy will be collected according to the protocol listed in

ii) Table 1; the 24-month data will be used to compare outcomes between patient sub-groups):
- eGFR
- serum albumin
- uPCR or uACR

Subgroups

We will analyse the results according to pre-specified patient sub-groups. We will determine all outcomes in the following groups:

i) whole cohort
ii) age 18 – 59 years
iii) age over 60 years

Within each of these two age-bands (18 – 59 and over 60), we will also determine all outcomes in the following sub-groups:

a) sex
    i) male
    ii) female

b) primary glomerular disease
    i) minimal change disease
    ii) membranous nephropathy
    iii) focal segmental glomerulosclerosis
    iv) other including IgAN, mesangiocapillary glomerulonephritis and C3GN

c) baseline GFR
    i) eGFR > 30
    ii) eGFR < 30

d) treatment
    i) patients receiving immunosuppression (if receiving ANY of the medications listed in Table 2 for a consecutive period of 7 days or more during a window 6 months before and 12 months after the date of biopsy)
    ii) patients not receiving immunosuppression (if not satisfying the inclusion criterion in d) i)

e) response to treatment
    i) complete remission by 6 months (if uPCR < 30 mg/mmol AND serum albumin > 35 g/L at 6 months after biopsy)
    ii) partial remission by 6 months (if no complete remission AND uPCR < 350 mg/mmol at 6 months after biopsy)
    iii) no remission by 6 months (if no complete or partial remission by 6 months)

Statistical analysis

The primary outcome (patient survival) will be analysed using survival (Kaplan-Meier) analysis. Survival will be compared between our pre-specified subgroups using a Cox proportional hazards model.

The secondary outcomes will be presented as aggregated data for each of our subgroups. Time-dependent outcomes (e.g. number of hospital admissions during follow-up) will be expressed per unit time, with duration of follow-up as the denominator (e.g. number of hospital admissions per patient-year). For categorical outcomes, subgroups will be compared using Chi^2 or Fisher's exact tests. Progression to RRT will be analysed by survival analysis.

Ethics & dissemination

The study protocol was reviewed and approved by the Scottish Biopsy Registry steering group. Approval was granted by the information governance team at National Services Scotland Public Health and Intelligence.

We plan to present our results at the Scottish Renal Association annual meeting and to publish them in a peer-reviewed journal.

Conclusions & perspective

We will conduct a registry-based observational study, using data linkage to describe hard outcomes in adults with primary nephrotic syndrome. Our results will guide physicians, patients and their families in assessing the likely prognosis of patients with nephrotic syndrome. This may be valuable in guiding treatment decisions and anticipatory care planning, particularly in older adults. Our results may also be useful in generating hypotheses that could be tested in randomised controlled trials of therapeutic interventions in adult nephrotic syndrome.

References

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Tables

Time-point	Window
date of biopsy	30 days
6 months after date of biopsy	30 days
12 months after date of biopsy	60 days
18 months after date of biopsy	90 days
24 months after date of biopsy	90 days

Table 1 - protocol for collecting follow-up laboratory data. The result closest to evert one of five time-points will be recorded. Any result falling within the following window either side of the time-point will be accepted.

Medicine	Read code
Advagraf 0.5 mg	Z547.
Advagraf 1 mg	Z547.
Advagraf 3mg capsule	Z579.
Advagraf 5mg	Z546.
CHLORAMBUCIL 2mg tablets	h13y.
CICLOSPORIN	h82..
CICLOSPORIN 100mg capsules	h827.
CICLOSPORIN 100mg/mL sugar free oral solution	h82x.
CICLOSPORIN 10mg capsules	h82E.
CICLOSPORIN 25mg capsules	h826.
CICLOSPORIN 50mg capsules	h829.
CYCLOPHOSPHAMIDE	h14..
CYCLOPHOSPHAMIDE 1g injection (pdr for recon)	h145.
CYCLOPHOSPHAMIDE 200mg injection (pdr for recon)	h143.
CYCLOPHOSPHAMIDE 500mg injection (pdr for recon)	h144.
CYCLOPHOSPHAMIDE 50mg tablets	h141.
MYCOPHENOLATE	h84..
MYCOPHENOLATE MOFETIL 1g/5mL oral suspension	h846.
MYCOPHENOLATE MOFETIL 250mg capsules	h841.
MYCOPHENOLATE MOFETIL 500mg tablets	h843.
MYCOPHENOLIC ACID 360mg gastro-resistant tablets	h84y.
NEORAL 100mg capsules	h82C.
NEORAL 100mg/mL sugar free oral solution	h82D.
NEORAL 10mg capsules	h82F.
NEORAL 25mg capsules	h82A.
NEORAL 50mg capsules	h82B.
PREDNISOLONE 1mg tablets	fe61.
PREDNISOLONE 2.5mg e/c tablets	fe6h.
PREDNISOLONE 25mg tablets	fe6z.
PREDNISOLONE 5mg e/c tablets	fe6i.
PREDNISOLONE 5mg soluble tablets	fe6j.
PREDNISOLONE 5mg tablets	fe62.

PROGRAF 0.5mg capsules	h837.
PROGRAF 1mg capsules	h834.
PROGRAF 5mg capsules	h835.
RITUXIMAB 100mg/10mL infusion concentrate	hh11.
RITUXIMAB 500mg/50mL infusion concentrate	hh12.
SANDIMMUN 100mg capsules	h825.
SANDIMMUN 25mg capsules	h824.

Table 2 – Codes for immunosuppressive medications.