The treatment of steroid-responsive, recurrent minimal change nephropathy with steroids alone vs. steroids and Cellcept

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A. Introduction

a.) Rationale

The nephrotic syndrome is characterized by HTN, hyperlipidemia, hypoalbuminemia and edema. In about 20-25% the nephrotic syndrome in adults is caused by minimal change nephropathy. Allmost all cases are idiopathic, infrequently patients have an identifiable cause like medication induced (NSAIDS, Rifampin, Interferon, Lithium), underlying malignancy or Lupus. The plasma creatinine frequently stays normal during flares, but can occasionally be slightly elevated, even acute renal failure can occur. The kidney biopsy by definition is either normal or reveals mild mesangial cell proliferation (as opposed to immune complex deposition on light microscopy/immunofluorescence). The pathogenesis is related to cytokine releasing steroid sensitive T-lymphocytes that injure the glomerular epithelium, which then causes a loss in *charge* selectivity, causing loss of negative charged albumin. A kidney biopsy is mandatory to establish the diagnosis.

Steroids (with a slow taper to reduce the likelihood of relapse) are the treatment of choice in minimal change disease, and cause a partial or complete remission in over 90% of cases. In more than 25% of cases the treatment duration exceeds 12 weeks until complete remission is achieved. Patients are considered to be steroid-resistant if proteinuria persists for > 16 weeks, or after 12 weeks if there was no decrease in proteinuria. 30-50% of adults recur (frequent relapsers) and 10-20% of patients who relapse during the steroid taper turn out to be steroid dependent. Additional treatment options includes addition of immunosuppressive drugs like alkylating agents (Cyclophosphamide or chlorambucil), CyA, Mycophenolate or Levamisole.

Since patient numbers with minimal change disease are fairly low there is no established "standard of care" established and only few comparing studies have been done with steroids alone vs. steroids/immunosuppressive agent in adults. Most of the studies were done with Cytoxan and had favourable results in terms of long term remission.

Cellcept has never been studied in patients with minimal change disease but with other primary glomerulopathies. There was no evidence of hematologic, hepatic or other toxic side effects. The studies showed promising results for the clinical outcomes. This study will compare the effect of Cellcept added during steroid taper in frequently relapsing patients. Positive results could potentially introduce a known and approved drug with good side effect profile as well as high tolerability to a new diagnosis.

b.) Review of the literature

The largest studies in patients with minimal change nephropathy so far have been done in the pediatric population where this disease is the most common cause for the nephrotic syndrome.

In the adult population there are more of clinical anecdotes with very small patient numbers in frequent relapsers. One prospective study was done by Koike et al looking at 10 frequent relapsers alone (and the interval between relapses) comparing steroids alone and steroids with low dose Cyclosporine: the study showed a decrease in relapses from 2.9/year to 0.7 per year if Cyclosporine was added. Two other studies were published during the last 10 years: 1.) favourable effects were shown in the combination treatment with steroids and Cyclophosphamide by Prabhakar (retrospective study with 177 patients with

mixed clinical courses were Cyclophosphamide was added after 3 relapses) with increase in the amount of remissions and 2.) in a retrospective study by Mak et al with 51 patients with mixed courses an increased number of sustained remissions could be obtained by the addition of Cyclophosphamide as well.

The therapeutic use of Mycophenolate has been advocated by Briggs et al and Choi et al for the use of primary Glomerulopathies with very promising results. The treatment also had been shown to be very well tolerated with no hepatic, hematologic or other toxic side effects. Additionally stabilization of the renal function could be obtained.

B. Hypothesis

Efficacy of treatment of minimal change nephropathy with Cellcept has not been established: with the addition of Cellcept the interval between relapses in frequently relapsing patients with minimal change nephropathy might be increased with a more favourable side effect profile.

C. Methods

a.) Conceptual and Operational Definitions

Study outcome measured = **the time to relapse**, if more than 3 episodes occur in a 12 months period, Cellcept will be started, urine protein will be measured on a regular basis and the patient needs to be monitored for progressive disease.

Conceptional operation = (Definition of outcomes)

- Nephrotic syndrome defined as the presence of edema, proteinuria in excess of 3g/24h,
- Remission is defined as complete when loss of edema and return of proteinuria to the normal range is obtained (<0.5 g/24h).
- relapse is defined as reappearance of the nephrotic syndrome with proteinuria with or without edema for > 1 week.
- **primary outcome = proteinuria (>500 mg/day)**

Operational definition= (measurement of outcome)

- Clinical evaluation (edema, hypertension)
- serial creatinine
- proteinuria

b.) Study design

The study should be done as a interventional, prospective, double blinded and randomized-placebo controlled study, with frequent relapsers only, divided in two arms. One arm should include patients receiving steroid treatment alone and the other arm should include patients with additional Cellcept-treatment during steroid taper.

c.) Statistical analysis (for 80% power)

Question: what effect will be seen with n amount of subjects?

- Continous outcome= time to relapse
  - → **t-test** $16(SD/delta)^2+1$
- mean time to relapse = 6 months +/- 1month
- 2 standard deviations=4-8 months → 95% of patients in this range

- **unpaired t-test with standard devialtion 1 and n=10 → difference of 1.3 can be shown**

d.) Sample size

The sample size will be defined by the limited amount of patients per year presenting with minimal change nephropathy. (estimated at 5/year per institution). Likely multiple centers necessary since about patients per year present.

D. Subject selection

Only patients with biopsy-proven minimal change nephropathy and who have shown to be frequent relapsers (two or more relapses within the first 6 months after a steroid-induced remission, or 4 or more within the first year) will be included. Steroid dependent patients (two consecutive relapses appearing when the steroid dose is decreased or stopped) or early relapsers (relapse within the first month after treatment) should be excluded.

Patients who have had > 4 flares within the past 12 months should be excluded since the likelihood of developing steroid resistant disease is high and the treatment might have to be adjusted. Also patients with active infections (Hepatitis B,C, HIV, TB), and possible underlying disease causing nephropathy like malignancies and Lupus should be excluded since these patients tend to have different courses.

E. Miscellanous

Possible ethical concerns: There has not been a standard of care treatment for minimal change nephropathy established. Steroids represent the first line treatment, but there are several options in terms immunosuppressive therapy. Since positive results in studies with Cellcept in other glomerular diseases have been obtained, and the drug in our study would be ADDED in order to increase the time to relapse, no one can make the argument of the patients being withheld. Therefor it would NOT be unethical to randomise the patients to two different arms.

Risks and benefits:

- risks=drug side effects,
- benefits= increased time to relapse

F. Literature

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