controlled trials is unnecessary to evaluate the merits of either. This comparison is spurious. It is erroneous to suggest (as Olgard and Lewin do) that ‘substitution of a missing hormone’ will always be beneficial. Although the practice of medicine would certainly be simpler if this were true, reality is more complex.

This truth is exemplified by the case of hormone replacement therapy for post-menopausal women, which was supported by a vast body of theoretical, experimental and epidemiological data, but which was subsequently shown to be harmful in well-designed randomized trials. Unfortunately, thousands of women were injured and millions of dollars wasted due to this well-meaning error. Will vitamin D prove to be similarly harmful? Or remarkably helpful? We do not know. And until we do more trials, both possibilities remain.

Olgard and Lewin characterize my Editorial as ‘potentially dangerous’. I believe that the real danger lies not in calling for randomized trials to inform clinical practice, but rather in failing to learn from the lessons of the past.

History teaches that we do not understand physiology well enough to determine from first principles which treatments will be beneficial. To suggest that only ‘hospital administrators’ should insist on evidence rather than anecdote to guide treatment is a serious misconception. If physicians choose which therapies to prescribe based on theoretical considerations alone, we will be wrong more often than not. Funds that are squandered in this way will be unavailable for use on novel, indisputably beneficial therapies, which grow more expensive every year. Worse (like our historical colleagues who used their understanding of physiology to justify the prescription of arsenic for syphilis), we run the risk of causing harm despite our best intentions.

Well-designed randomized studies are costly, challenging to complete and have their own limitations. However, they are the best option available. Rather than pretending that we know the answers before the evidence is in, the nephrology community should get on with designing and executing more randomized trials.

Conflict of interest statement. Dr. Tonelli holds peer-reviewed research funding from the Centre for D-Receptor Activation Research to examine vitamin D status in remote-dwelling patients on dialysis.

Non-steroidal and non-cytotoxic therapies for nephrotic syndrome

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Keywords: cyclosporine; mycophenolate mofetil; nephrotic syndrome; rituximab; tacrolimus

Introduction

The treatment of difficult cases of idiopathic nephrotic syndrome (NS), mostly due to focal segmental glomerulosclerosis (FSGS) or membranous nephropathy (MN), is still a challenge. The complete or partial remission of proteinuria is required to decrease morbidity consequent to dyslipidaemia, dyslipidaemia and hypercoagulation, to diminish exposure to potentially toxic drugs and to slow progression to renal failure [1]. As the incidence of FSGS is increasing, at least in children [2], steroids remain the first choice treatment, even though steroid dependence or resistance is frequent. The association of cytotoxic drugs improves the remission in 50–80% of all the cases of NS due to FSGS [3,4] and MN [5,6]. However, a relevant proportion of patients do not attain satisfactory results; for instance, steroid-resistant FSGS, both in children [7] and adults [8], does not benefit from alkylating agents, with failures up to 70% of the cases. Moreover, the potential toxicity of these drugs—infections, gonadotoxicity and tumours—is a matter of concern that has triggered the search for other treatments.

Non-steroidal and non-cytotoxic treatment of difficult cases of nephrotic syndrome

ACTH This old drug has been used since the 1950s, when it was substituted by prednisone. ACTH reduced proteinuria in nephrotic MN during treatment focused on lipid-lowering effects. In MN, Ponticelli et al. reported that ACTH,
2 mg/week for 1 year, was as effective as methylprednisolone pulses and cytotoxic drugs [9]. ACTH reduced proteinuria in six children with FSGS non-responding to traditional therapy (Meyrier, ASN 2005), however, without protection on functional decline.

**Cyclosporine (CYA).** In children with steroid-resistant NS, CYA reduced the relative risk of persistent NS by 0.64 [7] and produced significant benefits in adults [10]. CYA reduced proteinuria in 70–80% of patients with steroid-resistant MN, lasting after drug withdrawal in 40% [10,11]. There is concern for the long-term use of CYA; however, the renal tolerability is reasonably good when CYA dosage is kept low [3–4 mg/kg/day, trough plasma level (TL) of 50–100 µg/l] [4,12]. A suitable option may be using low doses of CYA in association with other drugs, as recently proposed in MN with NS, treated with methylprednisolone pulses in association with either low CYA doses (2–3 mg/dL, TL 100 µg/l) for 18 months or cytotoxic drugs [13]. The frequency of either complete or partial remission was significantly higher in the group receiving CYA (85% versus 55%), albeit without difference in renal deterioration rate.

However, the fear of CYA toxicity, which may worsen renal function, still exists and has stimulated the search for alternative treatments.

**Tacrolimus (TAC).** A retrospective study in 16 children with NS, dependent on or resistant to traditional therapies, reported a high remission rate with TAC (81% complete and 13% partial, within 5 months) [14]. These benefits were reproduced in small groups of cortico-dependent or -resistant children, with complete remission in 50% of the cases and partial remission in 40% [15]. TAC in association with steroids in CYA-resistant nephrotic FSGS induced remission in 12/25 adults, with reversible nephrotoxicity in 40% [16]. No advantages in the switch from CYA to TAC were observed [17]. In all these reports, was given in a dose of TAC was given in a dose of 0.1 mg/kg/day.

In the present issue of NDT, Yu et al. report a study using low doses TAC in Chinese adult patients with steroid-dependent minimal change NS. TAC in a dose of 0.05 mg/kg/day (trough level 4–8 µg/l) or intravenous cyclophosphamide (750 mg/m²) was administered every 4 weeks for 24 weeks, together with low-dose prednisone, which was then tapered over 12 weeks [18]. The rates of complete remission were similar in the two cohorts (90% with TAC versus 77%), but the mean time to achieve remission was shorter with TAC. During the follow-up period of 23 months, the rate of sustained remission was similar (60% and 40%). This study is of interest, since TAC, even in small doses, was found to have a steroid-sparing effect similar to cytotoxic drugs.

In MN with NS persistent for >2 months, and in spite of maximal treatment with angiotensin antagonists, low doses of TAC (0.05 mg/kg/day; TL 3–5 µg/l) as monotherapy induced a remission rate higher than angiotensin antagonists. However, 6 months later, 43% of patients relapsed [19].

Notably, no direct comparison of effectiveness or renal toxicity between TAC and CYA in NS has been reported in the literature.

**Mycophenolate mofetil (MMF).** MMF, 30 mg/kg/day for 2 years, with low tapering doses of prednisone, induced remission in 19 children resistant to conventional therapy and reduction of relapses (from 6 to 2/year) with a 50% steroid-sparing effect. However, 60% of the children relapsed after withdrawal [20]. Similarly, in 9/18 adults with steroid- and CYA-resistant FSGS, MMF induced a decrease in proteinuria, but 50% relapsed at withdrawal [21].

In this issue of NDT, Jha et al. report a pilot study in Indian patients with NS due to FSGS and MN, comparing MMF and standard therapy (FSGS: prednisolone 1 mg/kg/day for 3–6 months; MN: alternating monthly courses of steroids and cyclophosphamide for 6 months) [22]. MMF was given at 2 g/day for 6 months along with prednisolone 0.5 mg/kg/day for 2–3 months. No difference in remission rates was observed (64 and 80% in MN and 70 and 69% in FSGS). This study reports that MMF was as effective as the conventional treatment for MN and FSGS in the short term and induced a faster remission and a decrease in steroid exposure in FSGS patients.

In MN, a combination of low doses of TAC (0.05 mg/kg/day), MMF (1 g/day) and prednisone (0.5 mg/kg/day) for 12 months induced complete remission in 53% and partial remission in 46% of patients. However, 1 year after ending the treatment, 73% of the cases relapsed [23].

Relapse at withdrawal remains an unsolved issue common to CYA, TAC and MMF and should be addressed in future trials, a problem that is as relevant as the induction of remission.

**Plasmapheresis and column A immunoabsorption.** Removing the hypothetical permeability factor is the rationale for plasmapheresis or protein A immunoabsorption, as reported in recurrent NS after transplantation. However, costs, relapses at withdrawal and little benefits on decline of renal function [24] limit this approach in native kidneys.

**Rituximab.** This anti-CD20 monoclonal antibody with B cell-depleting effects has suddenly become ‘a la mode’, after the serendipitous finding of antiproteinuric effect when given in B cell diseases [25]. Francois et al. reported its efficacy in 4 weekly doses of 375 mg/m² in an adult with multi-relapsing minimal change NS [26]. The number of case reports of difficult cases of idiopathic NS who were successfully treated with this drug is increasing day by day, but it is likely that there is a report bias [27–29].

The benefit of rituximab in a dose of four weekly injections of 375 mg/m² in 6/8 cases with severe MN was reported by Ruggenenti et al. [30] and confirmed by Fervenza et al. [31] in 15 MN with proteinuria >5 g/day despite maximal angiotensin antagonism. Rituximab was given at 1 g i.v. at Days 0 and 15, and repeated in the case of no anti-proteinuric effect at Month 6. Mean proteinuria decreased from 13 to 6 g/day; 60% of the patients attained partial or complete remission. The response was unpredictable, with no association with B cell depletion or CD 20 deposits at renal biopsy, nor with tubulo-interstitial damage.

Cravedi et al. [32] investigated the possibility of titrating rituximab in circulating B cells to optimize lympho cytolytic therapy in nephrotic MN resistant to angiotensin antagonists. Rituximab, 375 mg/m², was given and repeated only
Steroids and cytotoxic drugs are considered classic therapy of NS. Alternative treatments include cyclosporine, tacrolimus, mycophenolate, ACTH, plasma exchange and rituximab.

in the case of inadequate B lymphocyte depletion (needed in only 1/12 of the cases). The decrease in proteinuria was rapid over the first 6 months and continued over 1 year, without any difference between patients previously treated with the traditional four doses. The final cost was 4000 Euro instead of 14 000 Euro for the four doses.

Rituximab is thus a new option; however, cost and acute adverse events are to be considered, and its long-term efficacy and safety still need to be evaluated.

Conclusion

The search for a non-steroid and non-cytotoxic rescue therapy in difficult cases of NS needs clinical experience and careful analysis to avoid unnecessary exposure to toxic drugs (Table 1). However, the results recently reported in cases previously considered as multi-drug resistant are raising new hope. Most of these reports suffer from the limitations of low number of patients, and they should be considered as preliminary suggestions for the further planning sufficiently powered, randomized controlled trials.

Conflict of interest statement. None declared.


(See related article by X. Li et al. Tacrolimus as a steroid-sparing agent for adults with steroid-dependent minimal change nephrotic syndrome. Nephrol Dial Transplant 2008; 23: 1919–1925.)

References

ACCORD and ADVANCE: a tale of two studies on the merits of glycaemic control in type 2 diabetic patients

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Keywords: glycaemic control; type 2 diabetes

Insight from the present: ACCORD and ADVANCE

Amid much media interest, preliminary data of the ACCORD (Action to Control Cardiovascular Risk in Diabetics) study were released in view of the unexpected finding that type 2 diabetic (T2DM) patients in the intensive blood glucose-lowering treatment arm [target glycated haemoglobin (HbA1c) <6%] had an increased risk of cardiovascular death compared to those in the conventional treatment arm (target HbA1c 7–7.9%) (http://www.nhlbi.nih.gov/health/prof/heart/other/accord/index.htm).

The ACCORD study, sponsored by the National Institute of Health, was a large clinical trial of 10 251 T2DM patients designed to determine the best clinical approach to reduce the high rate of cardiovascular morbidity and mortality seen in T2DM patients at a high vascular risk. The main question asked being if an intensive glycaemic target as compared to the conventional one would result in favourable cardiovascular outcomes [1].

In the intensive arm, 257 patients died, compared with 203 within the conventional (standard) treatment arm. This was a difference of 54 deaths, or 3 per 1000 participants each year, over an average treatment duration of ~4 years. Importantly, it should be noted that these death rates in both arms were lower than those seen in similar populations in other studies. Interestingly, the press release also appeared to suggest that in the intensive arm non-fatal cardiovascular disease (CVD) events were less frequent; however, if an event did occur it was also more likely to be fatal.

In view of these unexpected results, the blood glucose-lowering sub-study of ACCORD was terminated 18 months prior to completion and all patients were switched to the pressure-lowering conventional treatment arm. However the lipid and blood pressure-lowering sub-studies are continuing, albeit now in the setting of conventional treatment targets for glycaemic control.

Patients who were eligible for the study were T2DM patients aged between 40 and 79 years with previous history of CVD, or those between 60 and 79 years with no history of CVD events; additionally those at high risk of CVD events (e.g. the presence of microalbuminuria, left ventricular hypertrophy) were also included. An HbA1c >7.5% on stable diabetes therapy and preserved renal function


Received for publication: 29.2.08
Accepted in revised form: 21.3.08

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