Steroids as treatment for glomerulonephritis: time for a rethink

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Abstract

Glucocorticoids have been a cornerstone of treatment for inflammatory and autoimmune kidney diseases for almost 70 years, yet it is fair to say, we still don't know how *best* to use them. Significant adverse events are associated with their continued use, which contribute to premature patient mortality. Steroid avoidance or minimisation is possible and has been tested in various glomerular diseases, as a result of novel agents or innovative regimens using established therapeutics. It is now time to seriously address our use of steroids and educate physicians on better ways of managing inflammatory kidney diseases.

Background

Glucocorticoids have been a cornerstone of treatment for inflammatory and autoimmune renal disease since their discovery and introduction to treat nephrosis and nephritis in the early 1950's, when ACTH was first used, followed by cortisone, prednisone and prednisolone. Early usage for nephrotic syndrome was with a very short course of steroid therapy, 5-7 days, but then evolved into 3 months of therapy, either as a continuous tapering course or an intermittent alternate day strategy, which was sometimes continued for 12 months or more. The extended courses were associated with higher rates of prolonged remission (1). In patients with nephrotic syndrome due to minimal change disease results were good, but in those with membranous glomerulopathy or proliferative nephritis there was little improvement in renal parameters with steroids alone (2). Especially in nephrotic states, responses to steroids in children were generally better than in adults (3). Early experience was highly variable in terms of duration and doses delivered. Both short (up to two weeks) and long term (over 12 weeks) protocols were used. Daily doses ranged from 60 to 1300 mg of cortisone, 80-200 units of ACTH, or 20-100 mg of prednisolone(or prednisone), with protocols based on anecdotal experience prevailing, rather than being based on any systematic dose response comparisons (3). Early use, in small numbers of patients with autoimmune diseases, such as systemic lupus erythematosus (SLE) and vasculitis

(periarteritis and Wegener's granulomatosis), demonstrated some benefit in alleviating symptoms, but improvements were often short lived and relapses common following cessation of treatment (4). For those with kidney involvement, higher doses and more prolonged therapy was felt to be needed for durable remission of urinary abnormalities (5), while for some, despite significant cumulative doses, renal failure was not prevented, although improvements in histological appearances were sometimes found (4, 6). In the early 1960's, following the introduction of percutaneous renal biopsies, comparison of two historic cohorts, comprising 26 patients with similar degrees of lupus nephritis activity, suggested that higher steroid doses were required to better attenuate disease (7). This proved to be a turning point in establishing high dose steroid use in treatment of glomerulonephritis. In those lupus nephritis patients treated with lower doses (50 mg of cortisone daily, equivalent to 10 mg of prednisone) all died within 14 months, 80% with renal failure. In a subsequent cohort treated with almost 50 mg prednisone daily, for six months, 44% died, but only 31% in renal failure (7). This relative success was influential in suggesting that efficacy of steroid monotherapy was dependent on greater and more prolonged exposure. However, this retrospective comparison of cohorts treated at different times, ascribing changes in outcome to one variable alone, was at a time when many other factors will have changed in the management of such patients (anti-hypertensive therapy, antibiotics etc). While steroids alone were sufficient for most patients with certain forms of nephrotic syndrome (2), it was clear that addition of other immunosuppressive agents demonstrated a better overall outcome in patients with other forms of glomerulonephritis, such as anti-GBM disease, lupus nephritis and focal necrotising glomerulonephritis associated with small vessel vasculitis (8-12). However, it seems that despite the introduction of cytotoxic or other immunosuppressive strategies alongside steroid therapy, sometimes even when combining two immunosuppressive agents (such as azathioprine and cyclophosphamide), continued use of high doses of steroids was commonplace and had become an established and unquestioned cornerstone of the protocols (9, 11, 13).

Controlled trials addressing the dosing of steroids have been lacking especially in adult patients.

Adverse events

Significant complications from steroid use were noted early on and have been consistently reported (14). Development of Cushing's syndrome, weight gain, infections, diabetes, osteoporosis, myopathy, peptic ulcer disease as well as changes in mental health manifested by mood changes, anxiety, agitation and sometimes frank psychosis were all described in early cohorts (7, 9). In addition, the impact on cardiovascular disease was also highlighted. In one early trial of prednisolone in nephrotic patients with generally well preserved renal function (creatinine <150 μmol/l), treated for over six months using modest doses (by current standards) of prednisolone (20-30 mg a day), two year mortality from cardiovascular disease in prednisolone-treated patients was significantly greater than in the untreated patients (11% vs 2%) (2). Recent trial data in vasculitis has demonstrated cardiovascular adverse events in between 16-20% of patients exposed to any prolonged steroid dose (whether classified as high or standard dose)(15). In addition, epidemiological data suggests that even modest doses of daily prednisolone over prolonged periods of time, in patients with SLE or vasculitis, are associated with significant increases in cardiovascular mortality (16). Untangling the role of the disease activity, necessitating higher dose of steroid use, from the drug itself, is complex and may need an experimental approach to fully define the effect of disease and treatment. However, data from early (and late) steroid withdrawal studies in kidney transplantation have suggested that there is a benefit from steroid avoidance with regards reducing cardiovascular events and cardiovascular risk factors (17). Serious infections occur in 10-33% of patients with lupus nephritis treated with a steroid based regimen and additional immunosuppressants (18, 19), and in 27-33% of ANCA associated vasculitis patients, with significantly lower rates in patients exposed to lower steroid doses (15). Overall, treatment-related adverse events, rather than disease itself, account for the majority of the high one year mortality found in ANCA associated vasculitis, suggesting that while we have made huge inroads in preventing death, disease progression

and organ failure in these patients, there remains an urgent need to find less toxic treatment regimens (20), with steroids being a prime candidate for change.

The need for steroid minimisation in management of glomerulonephritis.

Since steroids are associated with many of the adverse events causing morbidity and premature death in our patients with glomerulonephritis is there a way to use less or none at all, while maintaining treatment efficacy? For the most part, high steroid doses are used during induction therapy with a gradual (and often ill-defined and highly individual) dose taper. In some trials, steroid cessation has been included with disease remission as a primary end point. There are two main strategies for steroid avoidance in induction therapy, substituting steroids for other agents (to provide sufficient rapid disease control), or using less (starting doses or more rapid tapering schedule). Attempts at using steroids with a more favourable side effect profile, such as those with altered gut-release mechanisms, have been tried in some conditions, such as IgA nephropathy (21). Alternatively, there are non-steroidal glucocorticoid receptor modulators (agonists, such as Fosdagrocorat), that act as anti-inflammatories but do not have the same diabetogenic or bone-resorbing effects, that have been tested in patients with rheumatoid arthritis, but not yet trialled in inflammatory kidney diseases (22). Better understanding of some of the pathophysiological mechanisms involved in inflammatory kidney diseases may provide a clear rationale for particular non-steroid based therapies, and the subsequent development of a number of novel agents that target particular pathways or cells such as neutrophil or monocyte activation (rather than B or T cells) or particular complement pathway components, shown recently to be critical in various forms of glomerulonephritis, (23-25). In fact failure of treatment strategies based on steroids for certain forms of glomerulonephritis, may be in part due to the failure of targeting those critical pathophysiological pathways by glucocorticoids. Glucocorticoids act not only on inhibiting leukocyte activation but also on intrinsic kidney cells such as glomerular parietal epithelial cells and podocytes (26), which may underlie some of their effect in proliferative GN and minimal change disease or FSGS respectively (27), but so do other agents such as

calcineurin inhibitors (28) and possibly rituximab (29). Finally, combination therapies that were not previously considered or tested, may provide the rationale for steroid minimisation. However, steroid avoidance is only worth considering as a particular strategy if efficacy is maintained (or improved) and adverse events are actually reduced, meaning that we need to test any such strategies in randomised trials compared to standard of care with currently accepted steroid dosing (Table 1). Some adverse events, such as cardiovascular disease, require more prolonged follow up to understand if the steroid avoiding strategy is of clear benefit

Lupus Nephritis

In lupus nephritis (class III, IV, V) steroid avoidance was tested in a single centre cohort study, where rituximab and mycophenolate were combined as induction agents, with two doses of methylprednisolone. Results were compared to historic controls (30), and demonstrated a high rate of remission, comparable to the ALMS trial, and a 10% serious infection rate. A randomised trial was initiated but not completed, due to recruitment delays, but is still required to demonstrate improvements in adverse events. Steroid dose reduction and a more rapid taper, compared to previous trials, has been attempted by addition of voclosporin, a calcineurin inhibitor, to mycophenolate, in patients with lupus nephritis and while it demonstrated better remission rates compared to the control group, the voclosporin arms were associated with higher rates of adverse events (31). Combining belimumab and rituximab has been/is being tested in various lupus and lupus nephritis trials (Beat Lupus, Calibrate, Bliss-Believe), but steroid reduction/avoidance with such combination therapy has yet to be formally tested. Newer agents that have shown promise in treating SLE/lupus nephritis may yet allow for a more extreme steroid avoidance, but these agents have so far been tested in addition to standard treatment with steroids and immunosuppressants.

ANCA associated vasculitis (and pauci-immune glomerulonephritis)

Steroid dosing was tested in the randomised Pexivas trial. High dose and standard dose steroids were tested, although the standard dose was lower than that used in previous

EUVAS trials, such as CYCLOPS, the mandated methylprednisolone pulses used, meant that the total steroid exposure was greater in both Pexivas arms than previous trials (Figure 1). Nonetheless, for the first time lower oral steroid doses demonstrated equal efficacy with regards the primary endpoint of end-stage renal disease and death, but with fewer serious infections. Long term outcomes with regards other adverse effects, in particular cardiovascular disease, were not different (15). Cohort studies have used more extreme steroid minimisation, and demonstrated feasibility of such an approach, using 1-2 weeks of steroids only, by combining rituximab and low dose cyclophosphamide. Comparison to previous historic trial cohorts appears favourable with fewer serious infections (32), but this needs validating in a prospective randomised trial. Of interest, long term follow up demonstrated that 80% of patients never needed steroid therapy, suggesting that steroid use can be realistically avoided in a majority of patients. Complete steroid avoidance is now possible following the discovery of a role for alternative pathway complement components in an animal model of MPO-ANCA vasculitis, and clinical trials of a C5a receptor antagonist (Avacopan). In a phase 2 trial in patients with well-preserved renal function, efficacy was maintained without steroids and quality of life improved (24). A Phase 3 trial, recently completed and only reported in abstract form, confirmed the efficacy (with non-inferiority to steroids at 26 weeks, and superiority at 52 weeks), but did not result in improved adverse event profile. However, specific steroid-related effects, as assessed by the glucocorticoid toxicity index, were improved.

Nephrotic syndrome

1. **Membranous glomerulonephritis**

Treatment of membranous glomerulonephritis has been tested in a number of recent trials, since the discovery of circulating antibodies to podocyte proteins has allowed stratification and monitoring of therapy. Supportive care for up to 6 months is recommended to allow for spontaneous remissions. Use of immunosuppression is reserved for those at risk of progressive renal decline or with significant adverse effects of the nephrotic syndrome. Steroid monotherapy is ineffective and successful treatment regimens have been limited to a

number of protocols, based on the Ponticelli regimen, or a modified version of it using cyclophosphamide and steroids, or with calcineurin inhibitors. Adverse events, and in particular steroid-related ones, are common in the steroid/cyclophosphamide regimens (33) and alternative strategies have been proposed, that could reduce these (34). Based on the rationale of targeting antibody-producing B cells, depletion therapy with rituximab or other anti-CD20 antibodies or B cell activation with BAFF antagonism has been tested and compared to supportive care alone, or to calcineurin inhibitor therapy. A direct comparison to the Ponticelli regimen has been carried out in the Starmen trial(35), in which sequential tacrolimus and rituximab was compared to a modified Ponticelli regimen and in the RI-cyclo trial, which are yet to report. Complete steroid avoidance using rituximab was compared to standard of care with anti-proteinuric therapy alone or to ciclosporin, in the Gemritux (36) and Mentor (37) studies, respectively. In Gemritux, addition of rituximab to supportive care increased the rates of complete and partial remission during prolonged follow up, but not at 6 months, while in Mentor, rituximab was shown to be non-inferior to ciclosporin at 12 months, but superior at 24 months, following withdrawal of ciclopsorin at 12 months (37). Clearly steroid avoidance is now possible in membranous GN but direct comparison of efficacy and adverse events with, what is still considered by many to be the standard of care, the modified Ponticelli regimen, will be required for this to be become accepted first-line therapy.

2. Minimal change

High dose steroids have remained as first line treatment for minimal change disease, but dosing and tapering regimens have really only been compared in paediatric populations and extrapolated to adults, despite there being a very different tempo to remission in the two populations (38). The optimal duration and dose adjustments beyond KDIGO guidelines on use of high doses until remission is achieved and a taper over a prolonged period of months, has not been established for adults (39). In addition, despite these steroid regimens, the majority of patients will experience at least one relapse. Steroid-sparing alternatives were generally reserved for those with frequently relapsing or steroid-dependent nephrotic syndromes. A recent randomised trial comparing steroid with tacrolimus induction

demonstrated equal efficacy with regards remission and relapse rates, (although not achieving the pre-defined, non-inferiority margin), while adverse events were not statistically different in the two cohorts. At four weeks, fewer tacrolimus treated patients were in complete remission compared to prednisolone treated patients, but proportions were similar by eight weeks (40). Steroid minimisation was also reported in a randomised study in which initial treatment with ten days of methylprednisolone (0.8mg/Kg) was followed by either tacrolimus monotherapy or prednisolone for a further 34-38 weeks (41). Again, remission and relapse rates were similar across the two trial limbs, even at four weeks, but adverse events were commoner in the prednisolone treated limb. Taken together these data provide a rationale for steroid minimisation or complete avoidance in patients with de novo minimal change disease, especially in those at a high risk of steroid toxicity. In those patients with minimal change disease or FSGS who are steroid dependent, or frequently relapsing, use of rituximab may allow steroid minimisation or withdrawal (42, 43), but this strategy has yet to be tested in de novo patients. However, current trials are beginning to address this issue, by testing rituximab in addition to a standard or curtailed steroid regimens (Turing study, Rifireins trial)(44, 45) in those presenting de novo or at time of a flare.

IgA nephropathy

Immunosuppression in IgA nephropathy has been a controversial area, and specifically the risk and benefit of prolonged use of high dose steroids for patients with significant proteinuria and high risk of progression to ESRD. Some studies suggest that prolonged steroid use may be of benefit in reducing proteinuria (46, 47), while others have shown no short (or long term) benefit in terms of declining renal function in patients treated with steroids alone or in combination with other immunosuppressants (48, 49). The balance between efficacy and harm from steroid based regimens is clearly the main issue, and the excess adverse events in patients treated with high dose methylprednisolone was the main reason for termination of the Testing trial (50), with a subsequent trial using half the steroid dose currently underway (51). Reducing steroid adverse effects by using a modified release steroid agent, with

potentially greater impact on the gut mucosal immune system and fewer systemic effects was the rationale behind the phase 2 Nefigan study (21). This recruited IgA patients with persistent proteinuria, despite optimal RAAS blockade, and tested nine months of treatment with modified release budesonide or placebo. Modified release Budesonide resulted in greater reduction in proteinuria, a marker of future renal decline, and this compound is now being trialled in a phase 3 study. In an attempt to find other non-steroid based strategies to treat proteinuric IgA nephropathy, other trials are being carried out, including testing of complement blockade (of either the lectin and alternative pathways)(52), Spleen tyrosine Kinase (SYK) inhibition(53), and B cell targeting strategies using antagonists of B cell stimulating cytokines such as BAFF or April. None of these studies involve co-administration of steroids.

Who are we treating?

If we were to start afresh with therapy for glomerulonephritis, how would we approach this? It seems unlikely that we would have the same protocols we use now, based on efficacy and side effects, morbidity and mortality. Steroids clearly have a rapid benefit in supressing a number of inflammatory symptoms and initiating renal recovery, and might be used for a short period of time (days perhaps) until other agents begin to exert their effect. We would potentially carry out a number of dose-response trials using steroids, testing duration, starting dose and taper, to better understand how to use them, in conjunction with other induction agents. We would think about combination therapies that involve agents working on different inflammatory pathways implicated in disease, as is done in cancer therapy, to minimise adverse effects from any one particular agent, so perhaps we might start to test protocols with low dose steroids rather than high. Alternatively, if we were lucky enough to find a single key pathway mediator that regulated disease, such as complement in haemolytic uraemic syndrome, we would develop agents that focussed on that pathway. However, no such pivotal molecule has been found to date. We would pay more attention to patients' quality of life feedback when they repeatedly tell us of their dislike for prolonged use

of steroids, but that they put up with them because of their fear of uncontrolled disease, when we now know that alternatives could be used. Steroid avoidance or minimisation is now possible, using alternatives (Table 1) for a limited number of glomerulonephritides, but requires physicians to reach for other agents or use other strategies than simply prescribing steroids and we are now at a point when we can challenge the continued use of steroids for various other glomerular diseases, through innovative clinical trials. We have options for some diseases already and we could have more, but we need to design trials in which steroids are avoided and learn how best to use novel alternatives, for the benefit of our patients.

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Table 1

Selected steroid sparing strategies in GN

Disease	Trial/Cohort	Steroid sparing strategy	Adverse events	references

			compared to conventional steroid treatment	
SLE/lupus nephritis	Rituxilup cohort ;	RTX and MMF;MP pulses 500 mg x2		(30)
ANCA Associated vasculitis	Pexivas;	More rapid steroid taper	Reduced infections with lower steroid dose	(15)
	Clear trial; Advocate trial*	Avacopan instead of prednisolone; MP with RTX induction	Similar infectious and serious adverse events	(24)
	Cyclovas cohort	RTX and 6 week low dose CYP; 1-2 weeks of oral steroid and MP pulses with RTX	Fewer infectious complications and diabetes in steroid minimisation arm	(32)
Membranous Glomerulonephritis	Mentor Gemritux Starmen*	Rituximab or ciclopsorin Tacrolimus followed by rituximab	No steroid comparator	(36, 37)

	RI-Cyclo*	Rituximab		
Minimal Change disease	Mintac trial; ChiCTR-TRC-11001454	Tacrolimus Tacrolimus following 10 day MP	No difference in adverse events or infections Fewer serious adverse events in tac treated group, including diabetes, and psychiatric disorders,	(40) (41)
IgA nephropathy	Nefigan trial	Oral Budesonide	No standard steroid comparator; but similar number serious adverse events	(21)

			compared with placebo	

*Not yet published, or only in abstract form