Supporting Evidence Document:
CNI Protocol for MCD and FSGS

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Objective

The purpose of this protocol is to facilitate prescribing of calcineurin inhibitors (CNI) for the treatment of corticosteroid-dependent, or corticosteroid-resistant minimal change disease (MCD), or focal segmental glomerulosclerosis (FSGS); the following document summarizes the scientific evidence supporting the recommendations.

1. Corticosteroids are first-line therapy, followed by calcineurin inhibitors

First-line therapy for treating MCD and FSGS is corticosteroids (refer to the BCR corticosteroid protocol), unless the patient is at high risk for corticosteroid-associated toxicity. In patients who have uncontrolled diabetes, a psychiatric condition, severe osteoporosis, or another reason to not prescribe a corticosteroid, alternative first-line therapy would be CNIs for treating both FSGS and MCD.

2. Frequently relapsing or corticosteroid-dependent MCD and FSGS

In about 30% of patients, proteinuria will increase while predniSONE is being tapered despite previously achieving complete or partial remission.[1] For these corticosteroid-dependent patients, we recommend stopping the taper, temporarily maintaining the current predniSONE dose and adding a CNI, or cyclophosphamide.[2]

In patients with steroid-dependent MCD, both cyclophosphamide and CNIs induce remission in about 75% of patients.[1,3–7] However, patients treated with cyclophosphamide have a higher likelihood of achieving sustained remission;[8,9] at the expense of being exposed to a more unfavorable side effect profile.

In patients with frequently relapsing or corticosteroid-dependent FSGS, data for cyclophosphamide is limited to a few retrospective observational studies.[10–20] However, it is fairly established that patients with steroid-resistant FSGS don't respond well to cyclophosphamide (see the supporting evidence document for the cyclophosphamide protocol).[13] Therefore, treatment with a CNI in patients with frequently relapsing or corticosteroid-dependent FSGS is preferred.

3. Definition of corticosteroid resistance in a patient with MCD or FSGS

There are conflicting opinions regarding the duration of predniSONE therapy that defines corticosteroid-resistance. Some literature suggests the use of alternative immunosuppressive therapy after only 4 to 8 weeks of predniSONE, whereas others define resistance as persistent nephrotic syndrome after 4 months of predniSONE at a dose of 1 mg/kg/day.[21–24]

The 2012 KDIGO guidelines defines corticosteroid-resistance as persistent nephrotic syndrome after 4 months of predniSONE.[2]

4. Treating corticosteroid-resistant nephrotic syndrome in patients with FSGS and MCD

Only 10% of adult patients with MCD are believed

to be corticosteroid-resistant, thus patients who are not responding to corticosteroids should be re-evaluated for other causes of nephrotic syndrome. Resistance may be due to undetected FSGS, which may not have been seen in a biopsy specimen. Due to limited data, treatment of patients with corticosteroid-resistant MCD is extrapolated from two RCTs that have shown that cycloSPORINE is more effective than no treatment in inducing remission of proteinuria in patients with corticosteroid-resistant nephrotic syndrome due to FSGS.[25,26] Of note, there are other lower quality studies that confirm cycloSPORINE reduces proteinuria in patients with FSGS. Remission rates vary from 10 to 75% and depend on the definition of remission used, the prior use of alkylating agents and the concomitant use of low-dose predniSONE.[13,27–29]

5. Choosing between cycloSPORINE and TACrolimus

The overwhelming majority of clinical trials evaluating CNI therapy in FSGS and MCD patients used cycloSPORINE; however, most authorities believe that cycloSPORINE and TACrolimus are interchangeable, and preferably use TACrolimus in women because this drug is associated with fewer cosmetic side effects.

6. Dose and duration of CNI therapy

CNIs are effective at inducing remission, but this may take 3 to 6 months after the start of therapy (if remission isn't achieved after 6 months, an alternative strategy should be tried).[2] Relapses are frequent after withdrawal, especially if the CNI is given for only 6 months or less. A longer duration of therapy - we recommend at least 12 months after finishing corticosteroids - with a slow taper may result in more persistent remissions.[8,21]

Patients can be maintained on a CNI for years without untoward effects on kidney function, but deterioration may eventually occur even if proteinuria is remitted. Deterioration of kidney function is more likely in patients who use high-dose cycloSPORINE (> 5.5 mg/kg/day), in patients with pre-existing reduced GFR (< 60 mL/min/1.73 m^2), and in patients with pre-existent tubulointerstitial fibrosis.

7. Therapeutic CNI levels

There is insufficient data to suggest a therapeutic CNI level in adult patients with MCD or FSGS. The target levels we recommend (125 to 175 ng/mL for cycloSPORINE and 4 to 8 ng/mL for TACrolimus) are extrapolated from data in kidney transplantation,[30] or other glomerular diseases. Alternatively, the prescriber may chose to reduce the CNI dose progressively to the lowest level that will maintain remission.[2]

8. Drug interactions

Prescribers are reminded to be vigilant of the numerous drug interactions that exist with calcineurin inhibitors, particularly with drugs that inhibit or induce CYP 450 3A4 and/or P-gp. Refer to the BCR table on "Major Drug Interactions with cycloSPORINE and TACrolimus," at BCRenalAgency.ca.

References

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