Specific management of IgA nephropathy: role of triple therapy and cytotoxic therapy

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GUIDELINES

a. **Triple therapy with cyclophosphamide, dipyridamole, and warfarin has not been shown to be superior to conventional treatment as sole therapy in patients with IgA nephropathy. (Level II evidence)**

b. **Treatment with cyclophosphamide and prednisolone is superior to supportive treatment alone in patients with IgA nephropathy. (Level II evidence)**

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on Level III and IV evidence)

- **There is currently no evidence to demonstrate that the addition of azathioprine, cyclophosphamide, dipyridamole, or warfarin, alone or in combination, with corticosteroids has any additive benefit. At the same time, these therapies expose patients to significant toxicity. Gonadal toxicity makes this treatment a concern in young patients. (Level IV evidence)**

- **The specific utility of these agents in patients with steroid-resistant nephrotic syndrome due to IgA nephropathy remains to be tested in clinical studies. However, a number of case series have shown that remission can be induced by pulse cyclophosphamide in some steroid-resistant patients. (Level IV evidence)**

Background

IgA nephropathy is the most common glomerular disease in Australia and New Zealand. Although the natural history of IgA nephropathy is variable, many patients develop progressive loss of renal function over many years. End-stage kidney disease (ESKD) is said to develop in 20% of cases after 10 years and in 30% after 20 years, whereas another 30% show some decline in renal function (Rekola et al 1991). In addition to non-specific renal interventions (control of hypertension, ACE inhibition, etc) there is evidence that interventions to specifically treat IgA nephropathy may also slow the progression to ESKD.

The objective of this guideline is to evaluate the available clinical evidence pertaining to the impact of triple therapy with cyclophosphamide, dipyridamole, and warfarin on

renal functional decline in chronic IgA nephropathy. While proliferative or crescentic IgA also causes renal impairment and ESKD, these guidelines only refer to chronic progressive IgA nephropathy.

Search strategy

Databases searched: MeSH terms and text words for IgA nephropathy were combined with MeSH terms and text words for triple therapy. This search was carried out in Medline (1966 to September Week 2, 2004). The Cochrane Renal Group Trials Register was also searched for trials of IgA nephropathy not indexed in Medline.

Date of searches: 17 September 2004.

What is the evidence?

There have been two RCTs comparing triple therapy and no treatment in patients with IgA nephropathy and proteinuria:

- Walker et al (1990) in a randomised prospective study of 52 patients with mesangial IgA nephropathy, allocated 25 patients to treatment with cyclophosphamide (for 6 months), and dipyridamole and warfarin (2 years). Tweny-seven patients served as controls and received no treatment. Despite reductions in urinary protein excretions with triple therapy, no significant effect on preservation of renal function could be confirmed over the 2 years of the study, either with triple therapy or when patients received warfarin and dipyridamole alone.

- Woo et al (1991, 1991a) demonstrated reduction of proteinuria and stabilization of renal function in a group of 52 patients treated with cyclophosphamide, dipyridamole and warfarin. However, a 5-year post-trial assessment (Woo et al 1991, 1991a) found no difference in renal function between the treatment and control groups. Only half of the patients in the treatment group remained on treatment with dipyridamole and low-dose warfarin at 5 years, which may have accounted for the failure to show significant difference in renal function compared to the control group. Patients who stopped treatment had significantly worse renal function and were more likely (6 of 14) to progress to ESKD compared to those who continued treatment (0 of 13).

- Murakami et al (1994), retrospectively evaluated renal outcome in a total of 38 children and adolescents with IgA nephropathy who were selected for 6-month therapy for clinical (proteinuria > 1 g/m^2/24 hour) and pathological features (mesangial proliferation, crescent formation, and tubulo-interstitial changes) suggestive of progressive renal failure. Seventeen patients were treated with a combination of prednisolone, cyclophosphamide and dipyridamole, and the remaining 21 patients were treated with the same drugs plus warfarin. There were no untreated controls. All of the patients were followed-up for more than 2 years (range: 2–10 years, mean 4.8). In both groups, the mean urinary protein excretion value was significantly reduced after the therapy, compared

with that at entry into the study. The significant reduction continued for up to 6 years in group A and up to 5 years in group B. Creatinine clearance was stable until 5-6 years after the trial in both groups, but 4 patients progressed to ESKD after that period. Post-therapy biopsy was performed in 14 patients, and was compared with the pre-therapy biopsy. The activity score improved in both groups, but the chronicity score did not. These results suggest that there was a temporary effect and limited benefit with this treatment of combined drugs for children and adolescents with IgA nephropathy. The additive effect of warfarin was not substantiated.

There has been one RCT of dipyridamole and warfarin alone.

- Lee et al (1997) looked at the effect of double therapy with warfarin and dipyridamole in a study of 21 patients with IgA nephropathy and mild renal impairment, where 10 patients were assigned to treatment with dipyridamole and low-dose warfarin and 11 patients to the control group on no treatment. At the end of the trial, renal function remained stable in patients on treatment while a significant deterioration was seen in the control group. This study used a longer duration of treatment (3 years vs 2 years) and warfarin at lower 'anticoagulant doses' than the Walker et al (1990) study, which had previously shown no benefit from triple therapy.

There has been one RCT comparing triple therapy with added prednisolone to anticoagulation and dipyridamole alone:

- Yoshikawa et al (1999) randomised 78 children with Ig A nephropathy to receive prednisone (2 mg/kg/day tapered over 2 yrs) and azathioprine (2 mg/kg/day) and heparin/coumadin and dipyridamole (5 mg/kg/day) or to receive heparin/coumadin and dipyridamole (5 mg/kg/day) alone. After 2 years of treatment, urinary protein excretion and serum IgA concentration fell significantly in patients receiving steroid/azathioprine, but remained unchanged in patients receiving anticoagulation alone. When comparing renal biopsies taken at the study endpoint to those at baseline, the percentage of glomeruli showing sclerosis was unchanged in children receiving prednisolone, azathioprine, heparin-warfarin, and dipyridamole for 2 years but increased significantly in those receiving heparin-warfarin and dipyridamole. Although this data is promising, given the known response to steroids in this condition (see guideline titled "Specific management of IgA nephropathy: role of steroid therapy") the role of azathioprine or anticoagulation in influencing renal outcomes in this study is difficult to interpret.

There have been two randomised studies of dipyridamole alone:

- Katafuchi et al (2003) randomised 189 patients to receive prednisolone 20 mg/day x 1 month followed by tapering over 18 months, plus dipyridamole 150 mg/day or dipyridamole 300 mg/day.

- Shoji et al (2000) studied 21 patients, randomised to receive prednisolone 0.8 mg/kg/day tapered to 10 mg for 1 year or dipyridamole 300 mg/day. After 1 year of therapy, proteinuria was reduced in patients treated with steroids, associated with improvement in renal histology. By comparison, anti-platelet therapy had no significant effect on proteinuria or renal histology.

The addition of cyclophosphamide to steroid has also slowed the progression in patients with histologically severe disease pathology (mesangial proliferation, crescent formation, and tubulo-interstitial changes) in some case series (Walker et al 1990). There have been a few small studies in which the use of cytotoxic therapy (in the absence of anticoagulant therapy – as triple therapy) has been studied.

- Tsuruya et al (2000), retrospectively reviewed 45 patients with moderate to severe histological changes (including crescents) treated with combination therapy using prednisolone and cyclophosphamide (n = 26) or conventional therapy (n = 19). In the combination therapy group, urinary protein excretion significantly decreased and the progression rate was significantly lower than in the control group.

- Ballardie et al (2002) studied 38 patients with progressive IgA nephropathy and renal impairment (serum creatinine > 130 µmol/L) who were randomised to treatment with prednisolone 40 mg/d (reduced to 10 mg/d by 2 yrs) and cyclophosphamide 1.5 mg/kg per day (adjusted down to the nearest 50 mg) for the initial 3 months, then azathioprine at the same dose continued for a minimum of 2 years, or no treatment. While cumulative renal survival after 5 years was significantly improved by intervention, it remains to be established if this represents the effect of steroids, cytotoxic therapy or their combination.

- Chen et al (2003) retrospectively analysed the medical data of 60 patients with IgA nephropathy treated with corticosteroid alone or in combination with cyclophosphamide. They found that corticosteroid and combination therapy with corticosteroid and cyclophosphamide were equally effective.

- Rasche et al (2003) conducted a prospective, uncontrolled trial to evaluate the effect of intravenous cyclophosphamide pulse and low-dose oral prednisolone therapy in 21 patients with biopsy-proven IgA nephropathy. Overall, the loss of renal function per year was significantly slowed compared to historical data before therapy was initiated, and proteinuria decreased.

A meta-analysis performed in 2002 concluded that there was no additional benefit from using cytotoxics (Samuels et al 2003).

Summary of the evidence

Despite initial enthusiasm for the combination of dipyridamole, warfarin and cyclophosphamide, recent studies have shown variable benefit in patients with chronic IgA nephropathy (Level II evidence). Many of the positive studies also used corticosteroids in treatment arms, making interpretation of the specific role of triple therapy and cytotoxic therapy in improved outcomes difficult.

What do the other guidelines say?

Kidney Disease Outcomes Quality Initiative: No recommendation.

UK Renal Association: No recommendation.

Canadian Society of Nephrology: Treatment with cyclophosphamide, dipyridamole, and warfarin should not be used (Shoji et al 2000).

European Best Practice Guidelines: No recommendation.

International Guidelines: No recommendation.

Implementation and audit

No recommendation.

Suggestions for future research

No recommendation.

References

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Appendices

Table 1 Characteristics of included studies

Study ID (author, year)	N	Study Design	Setting	Participants	Intervention (experimental group)	Intervention (control group)	Follow up (months)	Comments
Katafuchi et al, 2003	103	Randomised controlled clinical trial	Single hospital, Japan	103 patients diagnosed with IgA nephropathy	Low-dose prednisolone	No treatment	60	
Lee et al, 1997	21	Randomised controlled trial	Hospital, Singapore	21 patients with IgA nephropathy	Dipyridamole and low- dose warfarin	No treatment	36	
Shoji et al, 2000	21	Randomised controlled clinical trial	Hospital, Japan	21 patients with biopsy-proven IgA nephropathy	Corticosteroid	Antiplatelet therapy	12	
Walker et al, 1990	52	Randomised controlled clinical trial	Renal clinic, Australia	52 patients with mesangial IgA nephropathy	Cyclophosphamide for 6 mo, dipyridamole and warfarin 24 mo	No treatment	24	
Yoshikawa et al, 1999	78	Randomised controlled clinical trial	20 Japanese paediatric renal centres	78 children with newly diagnosed IgA nephropathy showing diffuse mesangial proliferation	Prednisolone, azathioprine, heparin-warfarin, dipyridamole for 2 yrs	Heparin-warfarin and dipyridamole	24	

Table 2 Quality of randomised trials

Study ID (author, year)	Method of allocation concealment	Blinding			Intention-to-treat analysis	Loss to follow up (%)
		(participants)	(investigators)	(outcome assessors)		
Katafuchi et al, 2003	Not specified	No	No	No	No	12.6
Lee et al, 1997	Not specified	No	Unclear	Unclear	No	Unclear
Shoji et al, 2000	Computer generated	No	No	No	No	9.5
Walker et al, 1990	Not specified	No	No	No	Yes	1.9
Yoshikawa et al, 1999	Sealed envelopes	No	Yes	Yes	No	5.1

Table 3 Results for continuous outcomes

Study ID (author, year)	Outcomes	Intervention group (mean [SD])	Control group (mean [SD])	Difference in means [95% CI]
Katafuchi et al, 2003	SBP (mmHg) at 60 mo	127(18)	124(13)	3.00 (95%CI: -5.98, 11.99)
	DBP (mmHg) at 60 mo	78(12)	76(11)	2.00 (95%CI: -4.59, 8.59)
	Serum Cr (mg/dL) at 60 mo	0.99(0.66)	1.01(0.40)	-0.02 (95%CI: -0.33, 0.29)
	Urinary protein (mg/dL) at 60 mo	118(143)	100(98)	18.00 (95%CI: -52.92, 88.92)
	Change in UP-UCR* from baseline	-0.84(1.78)	0.26(1.65)	-1.10 (95%CI: -2.10, -0.10)
Lee et al, 1997	Serum Cr (mg/dL) end of treatment	2.5(1.2)	3.3 (1.1)	-0.80 (95%CI: -1.97, 0.19)
	CrCl (mL/min) end of treatment	52 (27)	31 (22)	21.00 (95%CI: -0.19, 42.19)
	Urinary protein (g/day) end of treatment	1.3 (1.1)	1.5 (1.1)	-0.20 (95%CI: -1.14, 0.74)
Shoji et al, 2000	Proteinuria (mg/d) at 1 yr	289.6(234.8)	712.2(391.7)	-422.60 (95%CI: -727.01,-118.19)
	Serum Cr (mg/dL) at 1 yr	0.77 (0.17)	0.77 (0.25)	0.00 (95%CI: -0.20, 0.20)
	GFR (mL/ min/1.73m^2) at 1 yr	110.1(26.4)	107.6 (22.3)	2.50 (95%CI: -19.46, 24.46)

	Serum IgA (mg/dL) at 1 yr	254.6 (98.8)	313.4 (86.2)	-58.80 (95%CI: -142.33, 24.73)
	SBP (mmHg) at 1 yr	109.1 (12.5)	116.1 (4.6)	-7.00 (95%CI: -15.05, 1.05)
Walker et al, 1990	Change in serum Cr (mmol/L)	0.02 (0.24)	0.01 (0.05)	0.01 (95%CI: -0.09, 0.11)
	Change in urine protein (g/24 h)	-0.53 (1.20)	0.13 (1.77)	-0.66 (95%CI :-1.48, 0.16)
	Change in urine erythrocytes (log rbc/mL)	0.05 (0.95)	-0.26 (0.78)	0.31 (95%CI: -0.16, 0.78)
	Change SBP (mmHg)	0.6 (17)	-3.8 (16.63)	4.40 (95%CI: -4.75, 13.55)
	Change SDP (mmHg)	1.0(10.5)	-0.2 (19.75)	1.20 (95%CI: -7.31, 9.71)
Yoshikawa et al, 1999	Urinary protein excretion at end of treatment (g/d)	0.22 (0.31)	0.88 (1.34)	-0.66 (95%CI: -1.12, -0.20)
	Creatinine clearance (ml/min/1.73m^2)	147 (33)	145 (44)	2.00 (95%CI: -15.98, 19.98)
	Serum IgA	229 (87)	281 (92)	-52.00 (95%CI: -91.78, -12.22)

*UP-UCR = urine protein-creatinine ratio

Table 4 Results for dichotomous outcomes

Study ID (author, year)	Outcomes	Intervention group (number of patients with events/number of patients exposed)	Control group (number of patients with events/number of patients not exposed)	Relative risk (RR) [95% CI]	Risk difference (RD) [95% CI]
Katafuchi et al, 2003	Improved kidney function	28/43	27/47	1.13 (95%CI: 0.82, 1.58)	0.08 (95%CI: -0.12, 0.28)
	Unimproved kidney function	15/43	20/47	0.82 (95%CI: 0.48, 1.39)	-0.08 (95%CI: -0.28, 0.12)
Lee et al, 1997	ESRD	1/10	4/11	0.28 (95%CI: 0.04, 2.07)	-0.26 (95%CI: -0.60, 0.08)
Walker et al, 1990	Amenorrhea	1/7	0/11	4.50 (95%CI: 0.21, 97.23)	0.14 (95%CI: -0.15,0.44)
	Oligospermia	1/18	0/16	2.68 (95%CI: 0.12, 61.58)	0.06 (95%CI: -0.09, 0.20)
Yoshikawa et al, 1999	Developed chronic renal insufficiency	0/40	1/38	0.32 (95%CI: 0.01, 7.55)	-0.03 (95%CI: -0.10, 0.04)
	Treatment stopped due to adverse event	2/40	1/38	1.90 (95%CI: 0.18, 20.10)	0.02 (95%CI: -0.06, 0.11)