Guideline topic: Pharmacological management of asthma
Evidence table 4.13a: Immunosuppresive agents

Author	Year	Study type	Quality rating	Population	Outomes measured	Effect size	Confidence intervals / p values	Comments
Adults								
Alexander[1]	1992	Double-blind, placebo-controlled Cross-over 12 weeks treatment Oral CsA	+	33 adult patients aged 18-65 yrs. Oral steroids 5-20 mg (mean 8.5mg/day) and high dose inhaled corticosteroids. Mean FEV1 1.7L (60% pred.) 20% reversibility to b 2-agonist	1] am and pm PEFR 2] frequency of exacerbations 3] FEV1/FCV 4] Adverse effects	10-12% increase 48% reduction 17% increase FEC1 5.7% reduction GFR	p< 0.005 p < = 0.023 p< 0.001 p< 0.02	CsA caused a progressive increase in PEFR/ FEV1 over 12 weeks which had not plateaued and persisted for at least 11 weeks following drug withdrawal. Placebo group received more oral steroids for treatment of more frequent exacerbations of asthma. Slight increase in BP, urea and creatinine with a reversible decrease in GFR seen in

								CsA group.
Bernstein[2]	1996	Double-blind placebo-controlled, parallel group 28 weeks treatment 12 week steroid reduction phase Oral gold	+	279 adult patients age 50 yrs 133 females and 146 males. Oral steroids >=10mg after 3 months pre-trial dose reduction. Mean FEV1 63.5% pred. 15% reversibility to b 2-agonist	1] % of patients achieving 50% reduction in steroid dose 2] FEV1/PEFR/ symptom scores/b2-agonist use 4] Adverse events	56% of patients on gold vs 32% of patients on placebo nil nil Twice as many GI and dermatological adverse event on gold	p< 0.001 ns p< 0.001 p=0.015	Large study show that 50% reduction in steroid dose was achieved in higher proportion of patients on gold than placebo, without a deterioration in lung function or asthma control. But gold was associated with a higher incidence of gastrointestinal and dermatological side effects. The primary end-point(50% reduction in oral steroid dose) was poorly chosen and no measure of the actual total steroid reduction achieved was provided. 32^ % of patients in the placebo arm asspcoated with as deterioration in asthma

								control.
Kishiyama[3]	1999	Double-blind, placebo-controlled 7 months of monthly high or low doxe IVIG vs albumin	+	40 patients aged 7-66 yrs (mean age 40 yrs). Oral steroids 2.5 to 80 mg/day (mean 16.7 mg/day). Mean FEV1 2.21, ATS defined asthma.	1] reduction in oral steroid dose 2] FEV1/PEFR/ Symptom scores/days off school/work 3] Headaches	Nil Nil 3 patients had asceptic meningitis on IVIG and other patients had severe headach	Ns Ns P-0.02	IVIG treatment provided no benefit in steroid requirement, lung function or exacerbation rate. However, IVIG was associated with an increase frequency of severe headache requiring opiate analgesia and a high rate of aseptic meningitis.
Lock[4]	1996	Double-blind, placebo-controlled, parallel group 36 233ks treatment Oral CsA	++	39 adult patients aged 26-67 yrs with asthma duration 2-56 yrs Oral steroids > 5mg/day (mean 12 mg/day] for > 1 yr Mean FEV1 < 65% pred. 20% reversibility to b 2-agonist	1] reduction in oral steroid dose on CsA 2] Mean PEFR am 3] FEV1 4] Symptom scores 5] Adverse effects	25% greater in CsA than placebo 10% increase PEFR Nil Nil More mild adverse effects 10% reduction GFR compared to baseline	P=0.043 P=0.026 Ns Ns P=0.0013 P=0.04	For patients on long-term oral steroids CsA provided a steroid sparing effect during treatment, without deterioration in lung function or increase in exacerbation frequency, that did not persist once CsA withdrawn. Minor infections, hypertrichosis, parasthesia

								and increase in BP all more common on CsA but well tolerated. Deterioration in GFR seen on CsA treatment persistent at 4 weeks post treatment withdrawal.
Nierop[5]	1992	Double-blind placebo-controlled cross-over 26 weeks treatment Oral gold	+	32 adult patients aged 28-72 yrs Oral steroids > 2.5 mg (mean 7.9 mg/day) and 800 mg inhaled corticosteroids Mean FEV1 60% pred. 15% reversibility to b 2-agonist	1] reduction in daily oral steroid dose 2] reduction in high dose steroid courses 3] FEV1/PEFR 4] Adverse effects	4mg/day vs 0.3 mg/day on placebo 0.9 exac. On gold vs 2.1 axac on placebo 6% increase FEV1 2 severe & 2 mild eczema, 3 nausea	P= 0.056 P=0.02 p< 0.001	Treatment with gold reduced daily oral steroid requirement by almost half (2l 5mg/day), associated with an increase in FEV1 of 6% and a reduction in asthma exacerbations. However, study flawed by the persistent reduction in steroid dose despite frequent exacerbations requiring high dose steroid courses. Small patient number.

Nizankowska[6]	1995	Double-blind, placebo-controlled, parallel group 34 weeks treatment (2 phases: 12 weeks efficacy and 22 weeks steroid reduction) Oral CsA	++	32 adult patients aged 25-57 yrs 27 females and 7 males Oral steroids 5-345mg (mean 16 mg/day) after attempt at reduction Mean FEV1 2.1L (64% pred.) 15% reversibility to b 2-agonist	1] PERF/FEV1/ FVC 2] b 2-agonist use 3] reduction in oral steroid dose 4]Symptom score 5] Adverse events	Nil -0.7 puffs/day -0.6 puffs/night Nil Nil Approx 25% of patients had nausea, diarrhoea, paraesthesiae and hypertrichosis.	Ns -1.2 to –0.1 -0.8 to –0.5 ns ns	During efficacy phase there was no benefit in lung function on CsA although there was an improvement in b 2-agonist use. CsA treatment allowed a reduction in oral steroid dosage which was not significantly greater than placebo. High number of aspirin sensitive asthmatics recruited due to center interest in aspirin sensitive asthma. All adverse effects resolved following CsA withdrawal.

1. Alexander AG, Barnes NC, Kay AB. Trial of cyclosporin in corticosteroid-dependent chronic severe asthma. Lancet 1992;339(8789):324-8.
2. Bernstein IL, Bernstein DI, Dubb JW, Faiferman I, Wallin B. A placebo-controlled multicenter study of auranofin in the treatment of patients with corticosteroid-dependent asthma. Auranofin Multicenter Drug Trial. J Allergy Clin Immunol 1996;98(2):317-24.
3. Kishiyama JL, Valacer D, Cunningham-Rundles C, Sperber K, Richmond GW, Abramson S, et al. A multicenter, randomized, double-blind, placebo-controlled trial of high-dose intravenous immunoglobulin for oral corticosteroid-dependent asthma. Clin Immunol 1999;91(2):126-33.
4. Lock SH, Kay AB, Barnes NC. Double-blind, placebo-controlled study of cyclosporin A as a corticosteroid-sparing

agent in corticosteroid-dependent asthma. Am J Respir Crit Care Med 1996;153(2):509-14.
5. Nierop G, Gijzel WP, Bel EH, Zwinderman AH, Dijkman JH. Auranofin in the treatment of steroid dependent asthma: a double blind study. Thorax 1992;47(5):349-54.
6. Nizankowska E, Soja J, Pinis G, Bochenek G, Sladek K, Domagala B, et al. Treatment of steroid-dependent bronchial asthma with cyclosporin. Eur Respir J 1995;8(7):1091-9.