TOPICAL IMMUNO-SUPPRESSANT THERAPY FOR ECZEMA

PostScRxipt
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PostScript Primary Care, *December 2003, contained an article on standard treatments for atopic eczema by Dr C S Jury (Department of Dermatology, Southern General Hospital). Here she considers two newer treatment options.*

Two topical immunosuppressants have been licensed for atopic eczema (AE). Tacrolimus ointment (Protopic®) and pimecrolimus cream (Elidel®) both act by blocking the calcineurin pathway, inhibiting T-cell activation and the production of pro-inflammatory cytokines. They have been added to the *Glasgow Formulary* restricted to use as per the NICE guidance and recent EMEA safety advice detailed below.[1,2]

Tacrolimus ointment is licensed for use for the treatment of moderate to severe AE not adequately responsive to conventional therapy in patients over the age of 2 years. 0.1% ointment is applied twice daily for up to three weeks reducing to daily, then to 0.03% ointment until clearance. NICE recommended topical tacrolimus as an option for the second-line treatment of moderate to severe AE in adults and children aged 2 years and older.

Pimecrolimus cream is less potent and licensed for treatment of mild to moderate eczema in patients over the age of 2. The cream should be applied twice daily and discontinued after six weeks if there is no improvement. NICE recommended topical pimecrolimus as an option for the second-line treatment of moderate AE on the face and neck in children aged 2 to 16 years.

The main adverse effect is a local burning sensation on application. This is usually self-limiting. Cutaneous infection, commonly with herpes simplex, has been reported; this complication should always be kept in mind with AE. Tacrolimus or pimecrolimus should be initiated only after careful discussion with the patient about the potential risks and benefits of all appropriate second-line options. They are not recommended for the treatment of mild AE or as first-line treatments for AE of any severity.

Recently, safety concerns regarding skin cancers and lymphomas have been considered by the EMEA who issued the advice opposite.

For further information, please check the Summary of Product Characteristics

New agents are a welcome addition to the armamentarium; optimal conventional treatment undoubtedly fails some patients. They are not a substitute for established treatment and they are 'black triangle' drugs so adverse effects should be reported via Yellow Cards. Costs are in the region of £20 for 30g compared to £1-£5 for topical steroids.

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Website
http://www.glasgowformulary.scot.nhs.uk

SAFETY ADVICE REGARDING SKIN CANCERS AND LYMPHOMAS ISSUED BY THE EMEA

• These medicines should only be used in patients over the age of 2 years with mild or moderate disease (pimecrolimus) and moderate to severe disease (tacrolimus), when treatment with topical corticosteroids should not or cannot be used. This can be because the areas to be treated are not suitable for corticosteroid treatment (such as the face and neck), because corticosteroids don't work, or because the patient cannot tolerate them.
• Only doctors with experience in the diagnosis and treatment of AE should start the treatment.
• The products should be applied to affected skin surfaces only using a thin layer.
• Continuous long-term use should be avoided. Treatment should be carried out until the eczema clears, then stopped.
• If the disease does not get better, or worsens, the diagnosis of AE should be re-evaluated and further therapeutic options considered.
• These medicines should not be used in immunocompromised adults or children.
• These medicines should not be applied to cancerous or pre-cancerous lesions.
• Cases of cancers, including cutaneous and other types of lymphoma, and skin cancers, have been reported in patients using these medicines.
• If a patient has lymphadenopathy at the start of treatment, the doctor should investigate it and keep it under review.
• The lowest strength of the medicine should be used whenever possible.
• Once daily application should be used whenever possible.

Alphabetical list of most recent ADTC decisions
For full details of SMC advice, visit **www.scottishmedicines.org**
For previous ADTC decisions, visit **www.glasgowformulary.scot.nhs.uk**

Drug	Indication under consideration (There may be other licensed indications.)	Glasgow decision
Aprepitant (Emend®)	Prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy.	Non-*Formulary*
Bivalirudin (Angiox®)	Anticoagulant in patients undergoing percutaneous coronary intervention.	Non-*Formulary*
Budesonide (Easyhaler®)	Treatment of mild, moderate or severe persistent asthma in adults and children over 6 years of age.	*Formulary* Acknowledge new formulation
Cinacalcet (Mimpara®)	Treatment of secondary hyperparathyroidism in patients with end-stage renal disease on maintenance dialysis therapy.	Non-*Formulary*
Daptomycin (Cubicin®)	For the treatment of complicated skin and soft-tissue infections in adults.	*Formulary* Restricted to use in patients with known or suspected MRSA infection and on the advice of a microbiologist or specialist in infectious disease.
Glyceryl Trinitrate (Rectogesic®)	Relief of pain associated with chronic anal fissure.	Non-*Formulary*
Lumiracoxib (Prexige®)	Symptomatic relief in the treatment of osteoarthritis only for patients in whom a COX-2 inhibitor is deemed appropriate.	*Formulary*
Modafinil (Provigil®)	Treatment of excessive sleepiness associated with obstructive sleep apnoea/hypopnoea syndrome.	Non-*Formulary*
Rasagiline (Azilect®)	Treatment of idiopathic Parkinson's disease as monotherapy (without levodopa).	Non-*Formulary*
Rasagiline (Azilect®)	Treatment of idiopathic Parkinson's disease as adjunct therapy (with levodopa) in patients with end of dose fluctuations.	Non-*Formulary*
Sildenafil (Revatio®)	Treatment of patients with pulmonary arterial hypertension classified as WHO functional class III, to improve exercise capacity.	*Formulary* Restricted to initiation by specialists working in the Scottish Peripheral Vascular Unit and by physicians experienced in the management of pulmonary vascular disease.
Sodium oxybate (Xyrem®)	Treatment of cataplexy in adult patients with narcolepsy.	Non-*Formulary*
Somatropin (Genotropin®)	Treatment of growth disturbance in short children born small for gestational age who fail to show catch-up growth by 4 years of age or later.	*Formulary* Restricted to initiation and monitoring by a paediatrician with expertise in managing childhood growth disorders and growth hormone therapy.
Temozolomide (Temodal®)	For the treatment of newly diagnosed glioblastoma multiforme in combination with radiotherapy and subsequently as monotherapy.	Non-*Formulary*
Lansoprazole (excluding FasTabs®)		*Formulary* ADTC review; additional Drug of Choice

For all article references, check our website
http://www.glasgowformulary.scot.nhs.uk

Medication incident review: Drug interactions with statins

Incident summary
A patient who was intolerant of beta blockers was prescribed verapamil following an MI and a coronary angiogram. Existing medication included simvastatin. Blood tests showed signs of rhabdomyolysis during a subsequent admission.

Learning points
The most common adverse reactions of statins are relatively non-serious and transient. A rare but clinically important adverse effect is myopathy including rhabdomyolysis which is potentially life threatening. The exact mechanism by which statins cause rhabdomyolysis remains unclear, but it appears to be dose-related. Risk factors include:

- **Underlying muscle disorders, renal impairment, untreated hypothyroidism, alcohol abuse and age >70 years.**
- **Concomitant use of other lipid lowering agents, ie gemfibrozil, fibrates or nicotinic acid.**
- **A history of myopathy with any lipid-lowering treatment.**
- **Interactions. Some statins, including simvastatin and atorvastatin, are metabolised by cytochrome P450 isoenzymes (CYP3A4). Co-administration of medicines that inhibit this enzyme may increase the plasma levels of the statin and so increase the risk of dose-related side-effects.**

Statins are increasingly prescribed in both acute and primary care in accordance with evidence-based guidelines and are being used at higher doses, so interactions may become more significant. Simvastatin is the drug of choice in NHS Greater Glasgow.

Advice on interactions is available from the SPC for each drug and from pharmacists. The CSM issued guidance on managing interactions with statins in 2004. The advice for simvastatin is summarised below.

Interacting drug	Simvastatin prescribing advice
Potent CYP3A4 inhibitors, eg HIV protease inhibitors, azole antifungals, erythromycin, clarithromycin	Avoid simvastatin
Ciclosporin, gemfibrozil, niacin (>1g/day)	Do not exceed 10mg simvastatin
Verapamil, amiodarone	Do not exceed 20mg simvastatin
Diltiazem	Do not exceed 40mg simvastatin
Grapefruit juice	Avoid grapefruit juice

Patients receiving any statin should be asked to report muscle pain, weakness or cramps immediately, and stop treatment until this has been investigated. If symptoms are severe or if creatine kinase >5 times the upper limit of normal, treatment should be withheld.

Cilostazol
Cilostazol (Pletal®) **has not been added** to the *Glasgow Formulary*. The SMC did not recommend cilostazol for improvement of the maximal and pain-free walking distances in patients with intermittent claudication (IC), who do not have rest pain and who do not have evidence of peripheral tissue necrosis.

Two 24-week double-blind trials recruited patients aged at least 40 years with moderate to severe IC secondary to peripheral vascular disease (PVD). Patients had a pain-free walking distance (PFWD) of <30 or 54m and a maximal walking distance (MWD) of >450 or 540m. Patients were randomised to placebo, cilostazol 100mg twice daily or pentoxifylline (oxpentifylline) 400mg three times a day. The primary outcome was change in MWD. In one study, cilostazol 100mg significantly increased MWD (by 63m) compared to placebo (39m) and pentoxifylline (31m). In the other study, there were no significant differences in MWD between cilostazol (31m) and placebo (23m) or pentoxifylline (29m). Pentoxifylline is classed as less suitable for prescribing by the BNF.

A further six double-blind trials in similar patients randomised subjects to cilostazol 100mg twice daily or placebo for 12, 16 or 24 weeks. In all but one trial, improvement in MWD was significantly greater with cilostazol than placebo. In these trials, cilostazol increased MWD by up to 70m (28-51%) whereas placebo altered distances by -2-28m.

Use is contraindicated in patients with a predisposition to bleeding. Caution should be exercised when co-administering drugs which inhibit platelet aggregation, such as aspirin and clopidogrel. If co-administration is undertaken, the SPC recommends that the dose of aspirin should not exceed 80mg daily.

The most common adverse effects were headache (>30%) and GI upset (>15%), which were usually of mild to moderate severity and sometimes alleviated by dose reductions. Adverse cardiovascular effects were also common and included dizziness, oedema and palpitations.

The exact mechanism by which cilostazol improves blood flow to the extremities is not fully understood, but is thought to be multifactorial. Cilostazol has antiplatelet and vasodilatory effects. All except one of the phase 3 trials excluded patients taking antiplatelet doses of aspirin. There are limited trial and long-term safety data relating to the concomitant administration of these two drugs. Thus, in practice, both the efficacy and safety of this combination is unknown.

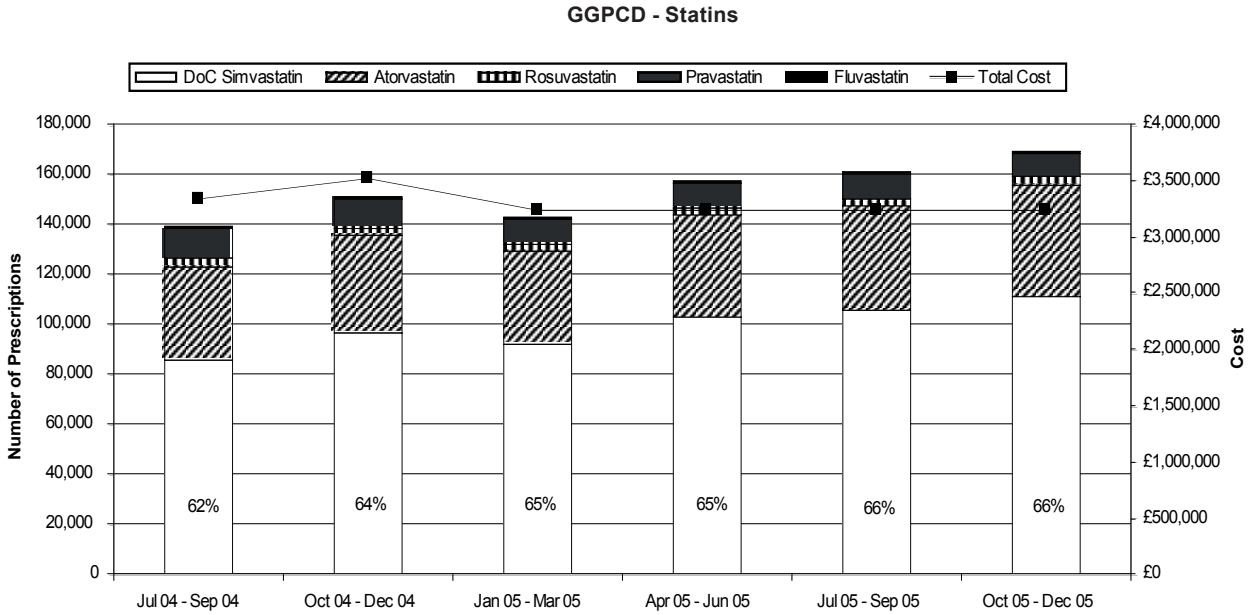
The SIGN guidelines for PVD (currently under review) recommend that patients with IC should receive low dose aspirin as prophylaxis against cardiovascular events. Antiplatelets may improve walking distance by a degree similar to cilostazol. The full benefits of cilostazol, therefore, may not be seen in patients already taking aspirin.

Bottom line
- Cilostazol (Pletal®) has not been added to the *Glasgow Formulary*.
- Cilostazol produces small increases in pain free and maximal walking distances compared to placebo.
- Patients with PVD should receive low dose aspirin as prophylaxis against cardiovascular events. Cilostazol is a peripheral vasodilator and has antiplatelet effects, therefore it may interact with aspirin. Antiplatelets can improve walking distances to a similar degree to cilostazol. The safety and efficacy of the combination is not known at present.

Drugs of choice update: Simvastatin

The *Glasgow Formulary* and local guidelines for prevention of cardiovascular events recommend simvastatin 40mg as the lipid lowering drug of choice. This is due to the significant evidence for the benefits of simvastatin therapy, lack of evidence of superiority of other statins and the well established safety profile.

The availability of generics has meant that the ongoing rise in prescribing of statins has not been matched by increasing costs. In primary care in Greater Glasgow for 2005, there were more than 600,000 prescriptions for these drugs at a total cost of over £12million.



The differing potencies of statins means that different doses need to be prescribed to give the same level of cholesterol reduction. However there is no evidence that any one product is more effective than another at equipotent doses. As can be seen from the table below, simvastatin 40mg (drug of choice) gives a similar effect to atorvastatin 10mg at less than a quarter of the cost.[1]

Reduction in LDL cholesterol[2]

Drug	10mg	20mg	40mg	80mg
Atorvastatin	37%	43%	49%	55%
Pravastatin	20%	24%	29%	33%
Rosuvastatin (non-*Formulary*)	43%	48%	53%	Unlicensed
Simvastatin	27%	32%	37%	42%

Simvastatin accounts for around 65% of statins prescribed in both primary and secondary care and this has remained relatively stable over the past year. Although atorvastatin prescribing has remained at around 25% of issues, the spread of doses has changed. In April-June 2003, more than 50% of atorvastatin was prescribed at the 10mg dose; by October-December 2005 this had reduced to less than 40%. Use of the two highest strengths approximately doubled to around 40% of atorvastatin prescribed.

Bottom line

• Simvastatin prescribing (as a proportion of all statins) may have reached its threshold. There have only been modest increases in simvastatin prescribing within primary care in recent quarters and prescribing within secondary care remains stagnant.

• The increased growth in atorvastatin prescribing (particularly high doses) within primary and secondary care may be linked to the need to meet cholesterol lowering targets and the results of the PROVE-IT trial[3]. This showed that atorvastatin 80mg improved cardiovascular outcomes (above that of pravastatin 40mg) in a select patient population with acute coronary syndrome. It is likely that atorvastatin prescribing will continue to increase with a resultant rise in costs.

• SIGN guidelines on primary and secondary prevention of CHD are currently under review. These may prompt review of local guidelines. At present, the Glasgow guidelines and GMS targets for GP prescribing remain to lower cholesterol to below 5mmol/l. Primary prevention should be aimed at patients with a 10-year coronary event risk > 30%.

PostScRipt

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Atopic Eczema References

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