AGE-RELATED MACULAR DEGENERATION (AMD): The disease and consequences

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In Britain, AMD is responsible for half of all cases of registered blindness. AMD occurs in two main forms, non-neovascular ('dry') and neovascular ('wet'), with the non-neovascular form accounting for the majority of cases. However, the neovascular form is responsible for most of the cases of severe central vision loss and blindness associated with AMD. In this article, clinicians involved in a new service explain more about the disease, the treatments and effects for patients. Thanks to Dr Likthai Lim, STR in Ophthalmology, and Dr Mike Gavin, Consultant Ophthalmologist, for this contribution.

Wet AMD is characterised by sudden, rapid loss of central vision which, if untreated, can rapidly and severely disrupt a patient's ability to carry out activities of daily living that are essential for independence, such as reading, driving, recognising faces and mobility.

Wet AMD is caused by proliferation of abnormal choroidal blood vessels behind the retina. The aetiology is complex and not fully understood, and the growth of new choroidal vessels involves many factors. However, there is now considerable evidence that choroidal neovascularisation (CNV) may involve a change in the balance between locally produced growth factors, in particular vascular endothelial growth factor (VEGF) and pigment-epithelium-derived factor, which inhibits vascular growth. Endothelial cells in vessels of the normal retina undergo negligible proliferation. However, certain stimuli, such as ischaemia or hypoxia, can initiate neovascularisation which can result in haemorrhage or fluid collection into the subretinal pigment epithelial space, leading to disruption of the photoreceptor layer and thus central visual disturbances.

Treatment options for wet AMD
Until fairly recently, ocular photodynamic therapy was one method of antiangiogenic treatment. Verteporfin (Visudyne®), an intravenously administered, light-sensitive dye, preferentially targets new blood vessels, causing localised choroidal neovascular thrombosis through a non-thermal chemotoxic reaction. Although it generally does not improve vision, it does limit visual loss in neovascular AMD.

A new era of wet AMD treatment: anti-VEGF drugs
Intravitreal antiangiogenic therapy (injection directly into the vitreous) is currently the primary therapy for wet AMD. This localises therapy to the eye, avoids systemic administration and possibly reduces the incidence of systemic adverse effects. These procedures are generally performed in a clean room setting using an aseptic technique and a topical or subconjunctival anaesthetic. Although generally well tolerated, intravitreal injections can, on rare occasions, cause serious adverse events such as endophthalmitis, retinal detachment, intraocular haemorrhage, increased intraocular pressure, ocular inflammation and anaphylaxis. Rarely, there are systemic adverse effects including thromboembolic events and death (small risk).

Pegaptanib (Macugen®) was the first intravitreal agent approved by the EMEA for neovascular age-related macular degeneration. It is a messenger RNA aptamer and a very specific VEGF-A (isoform 165 only) antagonist. The number of patients whose visual acuity improved with pegaptanib was limited.

Ranibizumab (Lucentis®) is a humanised monoclonal antibody fragment that binds to, and inactivates, all forms of VEGF, unlike pegaptanib. Data from major studies (MARINA and ANCHOR trials) have shown that ranibizumab not only stabilised the progression of wet AMD in the majority of patients, but a significant proportion of patients (25-40%) experienced significant vision improvement.

Bevacizumab (Avastin®), a monoclonal antibody to VEGF used intravenously as an anticancer agent, has also been used off-label as intravitreal therapy for wet AMD. Although data from long-term studies are not yet available, several short-term studies and case-series have shown improvement in visual acuity that is similar to the improvement with ranibizumab (with similar systemic adverse events).

NICE guidance (**guidance.nice.org.uk/TA155**), endorsed by NHSQIS, issued August 2008, supercedes previous SMC advice, and recommends ranibizumab and not pegaptanib for the treatment of wet AMD. Ranibizumab is currently the only anti-VEGF in the GGC drug *Formulary* for use in wet AMD.

Service model/referral pathway
Referral to the macula service generally falls under three categories; optician referrals, GP referrals and self-referral to eye casualty. Patients diagnosed clinically with wet AMD will undergo fluorescein angiogram and optical coherence tomography (OCT). Those deemed to have met the criteria in the guidelines issued by NICE, ie best-corrected visual acuity of between 6/12 and 6/96, with no permanent structural damage to the central fovea, progressive worsening of symptoms and a lesion size no larger than 12 disc area, will be given ranibizumab.

contd on page 3

Alphabetical list of most recent ADTC decisions

For full details of SMC advice, visit **www.scottishmedicines.org** For NICE advice, visit **www.nice.org.uk** For previous ADTC decisions, visit **www.ggcformulary.scot.nhs.uk**

Drug	Indication under consideration (There may be other licensed indications)	NHSGGC decision	
Darunavir (Prezista®)	Co-administered with low dose ritonavir and in combination with other antiretroviral medicinal products for the treatment of human immunodeficiency virus (HIV-1) infection in antiretroviral therapy naïve adults.	(S) Total *Formulary*. Acknowledge new indication. Restricted to use by HIV specialists.	✓R
Etanercept (Enbrel®)	Treatment of chronic severe plaque psoriasis in children and adolescents from the age of eight years who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies.	(S) Total *Formulary*. Acknowledge new indication. Restricted to initiation and supervision only by specialist physicians in accordance with the criteria below: a) The disease is severe as defined by a total Psoriasis Area Severity Index of 10 or more and a Dermatology Life Quality Index of more than 10. b) The psoriasis has failed to respond to standard systemic therapies including ciclosporin, methotrexate and psoralen and long-wave ultraviolet radiation; or the person is intolerant to, or has a contraindication to, these treatments. c) Etanercept treatment should be discontinued in patients whose psoriasis has not responded adequately at 12 weeks.	✓R
Estradiol/dienogest (Qlaira®)	Contraception.	Non-*Formulary*.	x
Etonogestrel/ ethinylestradiol vaginal ring (Nuvaring®)	Contraception.	(S) Total *Formulary*. Restricted to patients unable to use other methods of contraception and for prescribing by specialists in family planning.	✓R
Etoricoxib (Arcoxia®)	Treatment of ankylosing spondylitis.	Non-*Formulary* for this indication.	x
Fosamprenavir (Telzir®)	In combination with low dose ritonavir for the treatment of human immunodeficiency virus (HIV-1) infected adolescents and children of six years and above in combination with other antiretroviral medicinal products.	(S) Total *Formulary*. Acknowledge new indication. Restricted to use by HIV specialists.	✓R
Hydroxycarbamide (Siklos®)	Prevention of recurrent painful vaso-occlusive crises including acute chest syndrome in paediatric and adult patients suffering from symptomatic Sickle Cell Syndrome.	Non-*Formulary* for this indication.	x
Lamivudine/zidovudine fixed-dose combination (Combivir®)	In antiretroviral combination therapy for the treatment of human immunodeficiency virus (HIV-1) infection in paediatric patients weighing 14kg to 30kg.	(S) Total *Formulary*. Acknowledge new indication. Restricted to use by HIV specialists.	✓R
Mecasermin (Increlex®)	For the long-term treatment of growth failure in children and adolescents with severe insulin-like growth factor-1 deficiency (primary IGFD).	(S) Add to Orphan Drugs section of Formulary restricted to use in accordance with paediatric protocol.	✓R
Methotrexate pre-filled syringes (Metoject®)	Treatment of severe recalcitrant disabling psoriasis which is not adequately responsive to other forms of therapy such as phototherapy, PUVA, and retinoids, and severe psoriatic arthritis in adult patients.	(S) Total *Formulary*. Acknowledge new indication. Restricted to use under specialist dermatological supervision.	✓R
Olmesartan medoximil/ amlodipine besilate (Sevikar®)	Treatment of essential hypertension in patients whose blood pressure is not adequately controlled on olmesartan medoxomil or amlodipine monotherapy.	Non-*Formulary*.	x
Pegaptanib (Macugen®)	Neovascular (wet) age-related macular degeneration.	Non-*Formulary*. To be removed from *Formulary* following QIS and NICE recommendations.	x
Quetiapine (Seroquel®)	Treatment of major depressive episodes in the framework of bipolar disorder.	Non-*Formulary* for this indication.	x
Ranolazine (Ranexa®)	Add-on therapy for the symptomatic treatment of patients with stable angina pectoris who are inadequately controlled or intolerant to first-line antianginal therapies (such as beta blockers and/or calcium antagonists).	Non-*Formulary*.	x
Romiplostim (Nplate®)	For adult chronic immune (idiopathic) thrombocytopenic purpura splenectomised patients who are refractory to other treatments, eg corticosteroids, immunoglobulins. Also as second line treatment for adult non-splenectomised patients where surgery is contra-indicated.	(S) Total *Formulary*. Restricted to use in patients with severe symptomatic ITP or patients with a high risk of bleeding.	✓R
Rotigotine patch (Neupro®)	Symptomatic treatment of moderate to severe idiopathic restless legs syndrome in adults.	(S) Total *Formulary*. Acknowledge new indication. Restricted to specialist initiation. Also restricted to those patients with a baseline score of 15 points on the International Restless Legs Scale and who do not respond to, or tolerate, oral preparations.	✓R
Sunitinib (Sutent®)	First line treatment of advanced and/or metastatic renal cell carcinoma.	(S) Total *Formulary*. Restricted to specialist initiation and use in accordance with regional protocol.	✓R
Temsirolimus (Torisel®)	Treatment of advanced and/or metastatic renal cell carcinoma.	Non-*Formulary*.	x
Topotecan (Hycamtin®)	Monotherapy for the treatment of adult patients with relapsed small call lung cancer for whom re-treatment with first-line regimen is not considered appropriate.	(S) Total *Formulary*. Acknowledge new indication. Restricted to use in accordance with regional protocol.	✓R
Vildagliptin (Galvus®)	Treatment of type 2 diabetes mellitus as dual oral therapy in combination with a sulphonylurea, in patients with insufficient glycaemic control despite maximal tolerated dose of a sulphonylurea or for whom metformin is inappropriate due to contraindications or intolerance.	(S) Total *Formulary*. Acknowledge new indication. In primary care it is expected that initiation would follow interaction between the GP/Diabetic Specialist Nurse and the consultant contact within the acute sector.	✓

✓ =*Formulary* ✓R =*Formulary* (restricted) **x** =non-*Formulary* **?** = awaiting final decision (S) =specialist initiation only (S) =specialist use only

Age-related macular degeneration *contd from page 1*

This guidance does not override the individual responsibility of ophthalmologists to make appropriate clinical judgement on a case by case basis. All eligible patients will receive ranibizumab monthly for three consecutive months, with subsequent regular and frequent follow-up to see if further treatment is required. Visual acuity and OCT are also used as parameters to monitor progress of patients under treatment. Initially it had been anticipated that patients would require 8 injections in year one and a further 6 injections in year 2, however clinical experience has indicated that patients generally do well on a reduced frequency of injections.

There has been a substantial investment in this development over the last few years. Each injection of ranibizumab costs £875 and the total medicines expenditure was around £2m in 2008/09 for GGC. The majority of patients report minimal discomfort with the procedure and very positive outcomes in terms of their sight. In one case, the subjective response was “amazing - you have given me my life back”.

Summary

1 Current primary treatment for wet AMD is with intravitreal ranibizumab (Lucentis®). The main aim of this treatment is to stabilise the disease and not primarily to cure. A significant proportion of patients (25-40%) will experience visual improvement and that is an added bonus.

2 The use of ranibizumab is based on the NICE/QIS guidelines

3 Visual acuity, fundus fluorescein angiography and OCT are documented as a baseline in wet AMD patients. Subsequently, visual acuity and OCT are used as parameters to monitor progress of such patients under treatment.

4 All eligible patients receive ranibizumab monthly for three consecutive months, with regular follow-up to see if/when further treatment is required.

Vaccine storage and the H1N1 vaccination programme

It is vital that the cold chain is properly maintained and managed to ensure the safety and efficacy of vaccines. A breach of the storage guidelines may invalidate the product licence and therefore a patient specific direction should be used in preference to PGD.

Recently work has been undertaken to improve the quality assurance of the cold chain in primary care settings (with an initial focus on GP practices) in NHS Greater Glasgow & Clyde. All GP practices have been audited and more than half have also undertaken self audit. Frequent concerns include temperatures outside recommended range, lack of regular review of temperature records and not resetting the thermometer. The latest results demonstrate improvement in systems and processes for vaccine management, and a decline in the incidence of breaks in the cold chain.

Information regarding storage was made available as part of the immunisation resource pack circulated to all practices in January 2008. This can be downloaded from **www.nhsggc.org.uk/phpu** This guidance is currently being revised to provide more information including detailed specifications for fridges. It will be distributed to all practices in the near future.

When a practice reports an incident to one of the vaccine holding centres, immediate advice is provided on the suitability for future use. In addition, since March 2009, an individualised report for the affected GP practice is prepared, providing recommendations to minimise the risk of recurrence and an invitation to undertake a self audit of vaccine storage arrangements. Copies of this report are also sent to the CHCP Clinical Director and CHCP lead clinical pharmacist

Supplies of H1N1 vaccine are being distributed to GP practices commencing Monday 2 November. Initially, while supplies are limited, these are being allocated according to practice population and will be presented in boxes of 5 vials (antigen and adjuvant) sufficient for 50 patients.

It is therefore timely for surgeries to review their vaccine storage arrangements to minimise any risk in the storage of limited supplies of H1N1 vaccine. Practices should:

• ensure a pharmaceutical fridge with adequate storage capacity is available,
• investigate fluctuations in temperature (eg door opened on delivery etc),
• record maximum, minimum and actual temperatures twice daily and ensure thermometer is reset after each reading,
• investigate any variations in temperature and report any incident to vaccine holding centre,
• quarantine stocks, where storage guidelines have been breached, in an alternative refrigerator until advised otherwise,
• ensure that alternative refrigeration facilities are in place in the event of breakdown, defrosting etc,
• ensure fridge is no more than 66% full, eg do not store more than two weeks' anticipated requirement of childhood immunisation vaccines.

For enquiries about vaccine handling and storage, contact your local vaccine holding centre or pharmaceutical public health for advice.

RAH	0141 314 6148
Leverndale	0141 211 6675
Pharmaceutical Public Health	0141 201 4502/4777

Generic prescribing

Following some recent concerns over new generics with limited licensed indications, the NHS Greater Glasgow & Clyde Area Drug and Therapeutics Committee has issued a statement which supports a policy of generic prescribing for the majority of medicines.

In some cases, the generic versions of a medicine may not have the exact same indications listed on the market authorisation as the original branded medicine, but as bioequivalence to the original branded medicine must have been demonstrated as part of the generic market authorisation process, ADTC considers that any additional risks of prescribing and dispensing the medicine generically are negligible.

Exceptions to the generic prescribing policy are:
• when the pharmacokinetic profiles of different brands of the same medicine differ widely,
• medicines with a narrow therapeutic index where any variation in the drug concentration in the blood increases the risk of toxicity or treatment failure for the patient.

Where formulary medicines should be prescribed by brand name, this will be indicated in the prescribing notes of the GGC *Formulary*. This advice does not override an individual clinician's decision to prescribe what he/she believes to be the most appropriate treatment for an individual patient.

One of the examples where switching between brands is undesirable is the case of ciclosporin. The BNF notes that, because of differences in bioavailability, the brand oral ciclosporin to be dispensed should be specified by the prescriber.

The clinicians with the renal service have concerns that the recent introduction of the branded generic Deximune® could lead to patients being inadvertently switched from one version to another if prescriptions are issued generically. The consequences could be very serious, ie rejection if levels drop or potential nephrotoxicity if the levels are too high. Neoral® is currently the ciclosporin of choice in renal transplant patients. There are likely to be similar issues if generic tacrolimus becomes available.

NHS Greater Glasgow and Clyde

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