ANTI-TNFα THERAPY IN ADULT CROHN'S DISEASE: New guidelines

PostScRxipt
from the
NHSGGC Area Drug & Therapeutics Committee
Issue 61 January 2011

Crohn's disease is a chronic inflammatory bowel disorder of unknown aetiology which can affect any part of the gastrointestinal tract and is characterised by relapses and remissions. There is an increasing incidence of early onset Crohn's disease, which has major implications for long-term care. It is incurable and a combination of medical and surgical therapies is often required. Dr Daniel Gaya, Consultant Gastroenterologist at Glasgow Royal Infirmary and lead author on the recently approved GGCHB guideline, highlights some of the key issues and controversial areas to be considered by those looking after patients on these potent and expensive medications. A more detailed article including references is available on our website.

There are two biological drugs licensed for the treatment of Crohn's disease, infliximab and adalimumab, which both block the proinflammatory cytokine, tumour necrosis factor alpha (TNFα). Infliximab is a part human, part murine monoclonal antibody. Adalimumab is a recombinant fully human monoclonal antibody which antagonises TNFα. NICE has published its multi-technology appraisal (187) on the maintenance use of both these drugs in Crohn's disease. These recommendations were adopted by NHS QIS and supersede previous SMC advice.

Indications and follow up

Biologic therapy is generally not considered until an adequate trial of conventional immunosuppression has been ineffective, not tolerated or contra-indicated (the conventional 'step up' approach). Prescribing should ideally follow discussion in a multi-disciplinary team environment which includes gastroenterology, colorectal surgical, pathology, radiology, nursing and pharmacy input. Prescribers must ensure appropriate time and information is given to counsel patients of the risk benefit ratio of these medications.

Patients should have their disease reassessed at least annually by way of clinical examination, faecal markers, imaging and endoscopy/colonoscopy as appropriate to ensure that there is a continued indication for anti-TNF prescription.

Adverse effects, consent and counselling

GPs do not have any specific monitoring responsibilities for anti-TNF therapy for Crohn's Disease patients. They should be familiar with the potential adverse effects and the information provided to patients by their gastroenterology physician. If the patient develops an infection while on anti-TNFs, the secondary care team should be informed and the patient should be asked to stop taking any treatment (which, if adalimumab, could be self administered). Other potential complications of therapy should be discussed with the secondary care team.

In this issue . . .

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

Contra-indications

- active sepsis
- active cancer
- pregnancy/breastfeeding (including six months after stopping therapy)
- demyelinating disorder
- moderate to severe congestive cardiac failure
- active or latent tuberculosis (see below)
- clinically significant hepatic or renal impairment
- hypersensitivity to infliximab/adalimumab, to other murine proteins or to any of the excipients
- stricturing with evidence of mechanical hold-up (relative)
- hepatitis B, hepatitis C (relative)

Before commencing anti-TNF therapy, patients should be given a verbal and written explanation by the hospital team of the following potential issues and side-effects.

Infection and screening

Anti-TNF treatment can reactivate latent tuberculosis (TB) infection. The combination of corticosteroids and immunomodulators or anti-TNF increases the risk of opportunistic infection fifteenfold compared to threefold with these drugs in isolation.

Before commencing therapy, current or previous TB should be actively excluded by a detailed patient and family history, clinical examination and chest X-ray. Those with latent TB or at high risk of recurrence should receive isoniazid chemoprophylaxis under the supervision of a respiratory physician. Active TB should be adequately treated under the supervision of a respiratory physician before starting anti-TNF therapy.

Malignancy

This is rarely associated with anti-TNF therapy. Leukaemias, lymphomas and solid organ tumours have all been described.

Demyelination

Both anti-TNF therapies have rarely been associated with the new onset of central demyelination.

contd on page 3

Latest ADTC decisions

For full details of all ADTC decisions and links to SMC recommendations go to:
www.ggcformulary.scot.nhs.uk/Latest%20news/formulary%20update%20bulletin.pdf

MAJOR changes to the *Formulary*

Ⓢ **Certolizumab Pegol (Cimzia®)** Moderate to severe active rheumatoid arthritis in adults. Total *Formulary*.

Ⓢ **Eslicarbazepine acetate (Zebinix®)** Adjunctive therapy in adults with partial-onset seizures with or without secondary generalisation. Total *Formulary*. **Restricted** to specialists in epilepsy.

Ⓢ **Plerixafor injection (Mozobil®)** In combination with G-CSF, to enhance mobilisation of haematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in patients with lymphoma and multiple myeloma whose cells mobilise poorly. Total *Formulary*. **Restricted** to use in accordance with regional protocol.

NON-*Formulary*

• **Amifampridine (Firdapse®)** Treatment of Lambert-Easton Myasthenic Syndrome in adults.

• **Canakinumab (Ilaris®)** Cryopyrin-Associated Periodic Syndromes.

• **Denosumab (Prolia®)** Bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures.

• **Dexamethasone Intravitreal implant (Ozurdex®)** Treatment of macular oedema following either branch retinal vein occlusion or central retinal vein occlusion.

• **Diclofenac (Mobigel Spray®)** For the local symptomatic relief of mild to moderate pain and inflammation following acute blunt trauma of small and medium-sized joints and periarticular structures.

• **Docetaxel (Taxotere®)** Adjuvant treatment of patients with operable node-negative breast cancer.

• **Eculizumab (Soliris®)** Treatment of patients with paroxysmal nocturnal haemoglobinuria (PNH).

• **Fondaparinux (Arixtra®)** Treatment of acute symptomatic spontaneous superficial-vein thrombosis of the lower limbs without concomitant deep-vein thrombosis.

• **Gefitinib (Iressa®)** Treatment of adult patients with locally advanced or metastatic non small cell lung cancer with activating mutations of epidermal growth factor receptor tyrosine kinase.

• **Glucosamine (Glusartel®)** Relief of symptoms in mild to moderate osteoarthritis of the knee.

• **Prucalopride (Resolor®)** Symptomatic treatment of chronic constipation in women in whom laxatives fail to provide adequate relief.

• **Ranolazine (Ranexa®)** Add-on therapy for the symptomatic treatment of stable angina pectoris.

• **Sevelamer carbonate (Renvela®)** Control of hyperphosphataemia in adult patients receiving haemodialysis or peritoneal dialysis.

• **Trabectedin (Yondelis®)** Treatment of patients with advanced soft tissue sarcoma, after failure of anthracyclines and ifosfamide, or who are unsuited to receive these agents.

Added with MINOR changes to the *Formulary*

Ⓢ **Adalimumab (Humira®)** Severe active Crohn's disease. Total *Formulary*. **Restricted** to use in accordance with local protocol.

Ⓢ **Bortezomib (Velcade®)** Progressive multiple myeloma in patients who have received at least one prior therapy and who have already undergone, or are unsuitable for, bone marrow transplantation. Total *Formulary*. **Restricted** to use in accordance with regional protocol.

• **Calcichew D3 500mg/400iu Caplet®** Calcium and vitamin D3 supplementation. Total *Formulary*. **Restricted** to patients who cannot tolerate chewable tablet formulations.

• **Etonogestrel implant (Nexplanon®)** Contraception. *Formulary* Preferred List.

Ⓢ **Infliximab (Remicade®)** Severe active or active fistulising Crohn's disease. Total *Formulary*. **Restricted** to use in accordance with local protocol.

• **Lidocaine 4% cream (LMX4®)** Local topical anaesthesia prior to venepuncture. Total *Formulary*. **Restricted** to hospital use.

Ⓢ **Moxifloxacin IV (Avelox®)** Community acquired pneumonia. Total *Formulary*. **Restricted** to use only on the advice of microbiologists or specialists in infectious diseases.

Ⓢ **Oxycodone 50mg/ml injection (OxyNorm®)** Moderate to severe pain in patients with cancer. Total *Formulary*. **Restricted** to use in the community and hospice setting, where oxycodone is appropriate choice.

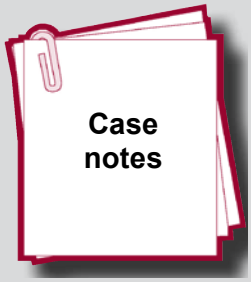
Ⓢ **Pemetrexed (Alimta®)** First line treatment, in combination with cisplatin, of patients with locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology. Total *Formulary*. **Restricted** to use in accordance with regional protocol.

Ⓢ **Sunitinib (Sutent®)** Treatment of unresectable and/or metastatic malignant gastrointestinal stromal tumour after failure of imatinib mesilate treatment due to resistance or intolerance. Total *Formulary*. **Restricted** to use in accordance with regional protocol.

Ⓢ **Tacrolimus granules for oral suspension (Modigraf®)**
- Prophylaxis of transplant rejection in adult and paediatric, kidney, liver or heart allograft recipients.
- Treatment of allograft rejection resistant to treatment with other immunosuppressive medicinal products in adult and paediatric patients.
Total *Formulary*. **Restricted** to patients who are unable to swallow capsules or who require small changes in dosing increments.

Ⓢ specialist use only Ⓢ specialist initiation only

A ten-fold error in opioid dose



An 80-year-old man with lung cancer, living at home, was receiving input for symptom control from a hospice Clinical Nurse Specialist (CNS). He had a troublesome cough, not controlled by codeine linctus; the CNS advised his GP to prescribe Oramorph® oral solution 10mg/5ml. As he was strong opioid naïve, she advised the patient's wife to give him "a quarter to half a teaspoonful" for the first dose, to see how he responded and tolerated it. The prescription was issued on a Friday.

The patient's daughter took the prescription to her father's usual community pharmacy, which did not have the medicine in stock and referred her to another pharmacy which holds an agreed list of palliative care medicines. They did not have it in stock either and ordered it for the next day. The prescription was dispensed on Saturday morning and given to the patient's daughter. The patient took a quarter of a teaspoonful as recommended for the first dose and was very sick; the sickness lasted all weekend. No further doses were taken.

On Monday morning, the patient's wife contacted the CNS. On questioning, the CNS established that the Oramorph was pink and immediately knew it was Oramorph concentrate 100mg/5ml. She advised his wife to give no further doses and contacted the GP. The GP found that the computer-generated prescription had been incorrectly issued for the concentrate.

Why did it happen?
A number of failings can be attributed to systems failures, lack of knowledge and inadequate communication between professionals, for example:

• The GP was unaware that two strengths of Oramorph existed.
• The concentrate is the top item in the drop-down list of morphine preparations on GPASS and was chosen in error.
• The recommendation from the CNS to prescribe was verbal, with no written back-up and no caution about the two strengths.
• The patient's usual community pharmacy did not recognise or question the inappropriate dose when only codeine linctus had previously been prescribed.
• The dispensing pharmacy did not recognise the unusual nature of the prescription.
• Nobody from the pharmacy spoke to the patient's daughter about the prescription or asked if the gentleman had had this before.

What can we learn?
The ability to highlight high strength products on GP prescribing systems may help reduce the potential for errors. This was not possible on the system used in this case, but is available for the EMIS roll out across the majority of NHSGGC GP practices.

A lack of knowledge about the two strengths was a key factor. The NPSA issued advice in 2008 on reducing errors in opioid dosing. Following their recommendations could have prevented this incident. The recommendations are pertinent for all healthcare professionals dealing with unusual or potentially dangerous medicines:

When prescribing, dispensing or administering these medicines:
• confirm any recent opioid dose, formulation, frequency of administration and any other analgesic medicines prescribed for the patient,
• check the usual starting dose, frequency of administration, standard dosing increments, symptoms of overdose, and common side effects of that medicine and formulation.

Anti-TNFα therapy *contd from page 1*

Pregnancy/breastfeeding
Both drugs are contra-indicated in pregnancy and during breastfeeding. Adequate contraception is mandatory before, during and for six months after therapy. If a patient becomes pregnant, decisions about ongoing treatment rest with the patient and the managing consultant. It is not a straightforward decision due to the risks of relapsing Crohn's disease on maternal and foetal outcomes.

Vaccination
Live vaccines are not recommended during anti-TNF therapy. Inactivated vaccines are safe and patients are encouraged to receive pneumococcal and annual influenza vaccination.

Choice of therapy
There are no head-to-head trials of infliximab and adalimumab, and they appear to have broadly equivalent efficacy. Infliximab is administered as an intravenous infusion on an eight-weekly basis while adalimumab is a fortnightly subcutaneous injection.

Both infliximab and adalimumab are included in the guideline. Infliximab is the biological of choice for fistulising disease on the basis of current evidence. Otherwise, the choice of medication depends on the clinician's view, patient preference, service capacity and cost.

Initially infliximab was administered as episodic treatment. However, in view of the higher relapse rates, lower efficacy and increased immunogenicity associated with episodic infliximab treatment, maintenance therapy is now the standard of care for infliximab. Adalimumab therapy has only been studied as maintenance therapy.

Treatment cessation
Crohn's disease has a high risk of relapse on cessation of immunosuppressive therapy or biological medications. The risk benefit ratio should be discussed with patients and duration of treatment should be individualised. At least one third of patients will suffer a clinical relapse on withdrawal of infliximab within one year. There appears to be no deleterious effect on response rates on restarting this medication.

If cessation of biological therapy is being considered, a thorough assessment should be undertaken to exclude any ongoing disease activity by way of clinical examination, faecal markers, colonoscopy and MRI scanning as appropriate.

"If I could change one thing . . ."

Dr Neil Smart, Consultant Anaesthetist, tells us that he would change people's view that higher cost is linked to higher quality and how small changes in practice are already leading to significant reductions in waste.

My granny lived her life by maxim; "You get what you pay for", "Cheap and nasty" and "Quality is remembered long after the price is forgotten" were among her favourites. It undoubtedly served her well - she lived to a magnificent 96 - although I always thought "One tequila, two tequila, three tequila, floor" was of more practical use. But if I could change one thing, it would be her view on the relationship between cost and quality.

For high cost does not automatically equate to high quality. Equally, quality can be maintained as costs are reduced, within reason. This is particularly important in healthcare in the current financial climate where NHS Boards can expect to receive diminishing uplifts from Government. Reducing costs without compromising quality, or more importantly safety, may appear counter-intuitive but several recent initiatives in stock, equipment and materials management suggest otherwise.

Standardisation is a familiar theme in the Scottish Patient Safety Programme. Early work looking at laparoscopic equipment identified considerable variation across NHSGGC. For example, in Nissen fundoplication, one surgeon used £250 of equipment per case while at the other end of the cost spectrum another used alternative products costing almost four times as much. There were no demonstrable differences in clinical outcome between surgeons attributable to the kit used. This observation stimulated a review of equipment preferences by the general surgical users themselves and resulted in standardisation of much of the kit. Choice was preserved for products where strong clinical preferences were identified. Significant cost savings result. Similarly in orthopaedics, clinician choice in hip and knee prostheses has also been maintained, in this instance by local contract initiatives pursued through procurement.

Bulk buying saves money. Many stock contracts are now made nationally, bringing savings from economies of scale. All such products must pass through a process where they are scored by clinicians and procurement personnel using a balanced scorecard. Attributes are weighted and then scored. Weighting changes from product to product but typically around one third is assigned to cost, the remainder being accounted for by perceived quality and the performance record of the supplier in service. For safety critical products, quality is heavily emphasised.

Reducing waste and variation in stock ordering, storage and replenishment can also cut costs without compromising quality or safety. Recent pilot projects in theatres using Lean methodology have improved process reliability, reduced the risk of 'stockouts' and made more effective use of storage space. At the same time, considerable financial benefits have been achieved by revising stockholdings to reduce and eliminate the cost of overstocking and the risk of creating 'out of date' stock.

Given cash releasing efficiency savings targets and funding issues, messages about savings often tend to become confused. Patient safety continues to be of paramount importance and efficiencies can be made without compromising quality.

Perhaps Granny had the answer after all: "waste not, want not".

Correction: *PostScript* 60

In the 'Diabetes Update' article there was a typographical error. Metformin can be prescribed in patients with a reduced kidney function, if stable, down to an eGFR of 30ml/min/1.73m^2.

New lipid lowering guidelines: Additional guidance for GPs on existing patients prescribed atorvastatin 80mg daily for Acute Coronary Syndrome (ACS)

The new NHSGG guideline (**www.staffnet.ggc.scot.nhs.uk/Clinical%20info/Documents/002_2010_Cholesterol%20guidelines.pdf**) for the management of cholesterol no longer includes first line treatment with atorvastatin 80mg daily for patients diagnosed with acute coronary syndrome (ACS). Patients with newly-diagnosed ACS should receive simvastatin 40mg daily and be treated in line with the guideline for the secondary prevention of coronary heart disease (CHD) and stroke. High dose atorvastatin may be used where lower doses of statin have failed to control cholesterol levels.

In primary care, patients prescribed atorvastatin 80mg daily for ACS may be switched to simvastatin 40mg daily.

Before switching:

- ensure the indication for prescribing atorvastatin 80mg daily is ACS and not to achieve target cholesterol levels,
- check cholesterol levels. It may not be appropriate to switch patients who have a high cholesterol level on atorvastatin 80mg. Other aspects of care, such as treatment concordance, may need to be considered.

NHS Greater Glasgow and Clyde

Area Drug & Therapeutics Committee
Chair: Dr J Fox

Communications Sub-group
Chair: Mrs A Thompson

Published by the Communications Sub-group to reflect the views of the Area Drug & Therapeutics Committee but not necessarily those of NHS Greater Glasgow and Clyde.

PostScript

PostScript Editor: Mrs A Thompson
Prescribing Team, NHS Greater Glasgow & Clyde
Pharmacy & Prescribing Support Unit
Queen's Park House, Victoria Infirmary, Langside Road
Glasgow G42 9TY Tel: 0141 201 5214 Fax: 0141 201 5338
E-mail: audrey.thompson@nhs.net

PostScript Web editor: Dr A Power

Design, layout and production control:
Strathcashel Publications Project Management (01505 850 344)