Northern Treatment Advisory Group

Minutes of meeting held on the 8th September 2015, 9-12am,

Meeting Room 4, The Durham Centre

Present:

- Tim Donaldson (TD) Chief Pharmacist, Northumberland, Tyne & Wear NHS Foundation Trust
- Chris Gray (CG) Medical Director, County Durham and Darlington NHS Foundation Trust.
- Matthew Grove (MG) Consultant Rheumatologist and Head of Service, Northumbria Healthcare NHS Foundation Trust.
- Paul Madill Consultant in Public Health, South Tyneside Council.
- Jill McGrath (JM) Head of Finance, Newcastle Gateshead CCG.
- Nick Quinn (NQ) Consultant Physician, South Tees Hospitals NHS Trust.
- Bhavana Reddy (BR) Head of Prescribing Support, RDTC (professional secretary)
- Janette Stephenson (JS) Head of Medicines Optimisation, North East Commissioning Support Unit
- Neil Watson (NW) Director of Pharmacy, Newcastle upon Tyne NHS Foundation Trust
- Roger Wheeler (RW) General Medical Practitioner, Middlesbrough (Chair)
- Ali Wilson (AW) Chief Officer, Hartlepool & Stockton-on-Tees CCG.

Apologies were received in advance from: Ian Davidson, Mike Lavender, Joe Corrigan, Andrea Loudon and Simon Thomas.

RW had agreed to chair the meeting as Vice Chair to NTAG and in the absence of ID.

The Chair invited declarations of interest relating to the agenda. None were made.

1) Draft Minutes June Meeting

The group approved the June minutes with no changes. Actions within the minutes were verified.

ACTION: Secretary to publish June minutes on the NTAG website.

2) Matters Arising

a. Membership Update

It was noted that the group had a new member; Dr Matthew Grove, Consultant Rheumatologist from Northumbria NHS Trust. The Trust had contacted the secretary shortly after the last meeting to put him forward as their representative rather than resigning their membership.

The secretary informed the group of the resignation from Sunderland Hospitals. It was noted that whilst the Trust valued the work of NTAG they were not in a position to send a regular representative so it was with regret that they had resigned their membership.

The issue of patient representation was raised again. The secretary fed back that conversations had taken place with representatives from the North Tyneside patient forum however no representation had resulted from the contact. It was noted that often patient representatives felt that the work of NTAG was too specialist for them to be able to input into

the agenda. It was agreed that this would not be the case and that training and support would be provided as necessary. The group felt that more than one patient representative should be sought if possible. A suggestion was put forward that perhaps Health Watch Durham should be approached since the meetings took place in Durham so this may be prove to be more convenient.

ACTIONS:
Secretary to contact Health Watch Durham.
Secretary to contact other Trusts to fill vacancy.
Secretary to update membership list with changes outlined above.

3) Infliximab Biosimilars (Remsima® & Inflectra®): Review of data around switching

It was noted that the infliximab biosimilar recommendation had been brought back to the group because there was now some more information around switching patients in the form of case studies within the NICE Health Technologies Adoption Programme Document. The group noted that the switching case study included within the document was based on a switch programme carried out in University Hospital Southampton NHS foundation Trust (UHSFT) within the gastroenterology department. The group agreed that the process carried out by UHSFT was comprehensive and good practice. The group also noted that NHS Scotland also allows switching stating that: *individual patients may be switched to another biological medicine as part of a clinician led management programme which has appropriate monitoring in place.* It was noted that in Europe several countries had issued statements outlining the interchangeability of infliximab biosimilars with the branded product, therefore switching patients is more wide-spread in Europe and the emerging data shows that there have been no problems with regards adverse effects.

The group therefore agreed that the infliximab biosimilars recommendation should be updated to allow switching in light of this new information. It was agreed that a link to the NICE document should be provided and that any switching must take place in a managed way in conjunction with the clinician and the patient. It was also suggested that infliximab biosimilars should be the first line choice for new patients as they were more cost effective than the branded product. The group felt that a managed approach across the North East and Cumbria would be useful to prevent variation in implementation, however this was outside the remit of NTAG so would need to be taken up by the regional contracting group.

ACTION:
Secretary to draft decision summary as above.

4) Appraisal: Certolizumab pegol for the treatment of psoriatic arthritis.

The appraisal report concerning certolizumab pegol for the treatment of Psoriatic Arthritis (PsA) was introduced by the secretary. It was noted that this request had been on the previous NETAG work plan as NICE were no longer going to produce a TA specifically for certolizumab.

The secretary summarised the current management of PsA. It was noted that PsA is a chronic inflammatory spondylarthropathy which affects up to 40% of patients with psoriasis.

It can occur at any age but the majority of cases occur in the fourth decade of life and it affects both genders equally. Prevalence of PsA is estimated at around 0.3-1 % of the population. Patients with PsA are managed in consultation with specialists in dermatology and rheumatology. The main goals of treatment are to relieve pain, reduce inflammation, prevent joint damage, and to improve the signs and symptoms of skin manifestations. Mild PsA can generally be managed with non-steroidal anti-inflammatory drugs (NSAIDs) and physiotherapy, with added intra-articular corticosteroid injections when necessary. Topical therapies are used for the skin. Disease modifying anti-rheumatic drugs (DMARDs), including methotrexate, sulfasalazine, leflunomide, azathioprine and ciclosporin are used to reduce joint damage and limit disability. After initial treatment with NSAIDs and DMARDs, most people with non-responsive PsA will be treated with a tumour necrosis factor-alpha inhibitor (TNF inhibitor).

The following TNF inhibitors are licensed for PsA: adalimumab, certolizumab pegol, etanercept, golimumab and infliximab. The two biosimilar infliximab products (Inflectra®▼ and Remsima®▼) were also approved for use in the UK across all current licensed indications, including PsA.

Certolizumab pegol is a TNF inhibitor which consists of the humanised antigen-binding fragment (Fab) of a mouse antibody, conjugated to polyethylene glycol (PEG). PEGylation improves drug bioavailability and pharmacokinetic profile, and has been shown to increase the circulating half-life of Fab molecules. Certolizumab pegol was licensed for the treatment of PsA in March 2014. It is indicated, in combination with methotrexate (MTX), for the treatment of PsA in adults whose disease has not responded adequately to previous DMARD therapy. It may also be given as monotherapy when MTX is not tolerated, or if continued MTX treatment is inappropriate. It is also licensed for treatment rheumatoid arthritis and axial spondyloarthritis.

Efficacy was assessed in a randomised double-blind phase III RAPID-PsA trial, which lasted 216 weeks, however only data up to 24 weeks is currently fully published. Certolizumab was more effective than placebo for the outcome of American College of Rheumatology 20% improvement in psoriatic arthritis at both 12 weeks (primary clinical outcome) and 24 weeks. Certolizumab was also more likely to produce 50% and 70% improvements in psoriatic arthritis. There are no available data comparing certolizumab pegol with other systemic biologic therapies for the treatment of PsA, and there are limited safety and efficacy data beyond that presented in the 24 week published report. The full 216 week pivotal RAPID-PsA trial was due to be completed in August 2015, with additional data presented to the regulator in the second quarter of 2016.

Certolizumab was previously licensed for the treatment of rheumatoid arthritis, and no new safety concerns were highlighted in the psoriatic arthritis population. The most commonly-reported adverse effects were minor infections. Serious adverse events were not common, and no serious event occurred in more than one person. However indirect comparison in a meta-analysis found that certolizumab was associated with a higher risk of serious adverse events and serious infections than other biologic therapies. This finding should be viewed with caution due to the lack of direct comparisons

The cost of certolizumab is similar in cost to the other subcutaneously-administered systemic biologic treatments for psoriatic arthritis: adalimumab, etanercept, golimumab and ustekinumab. Infliximab is also licensed for psoriatic arthritis and may have a lower acquisition cost in some cases, but the cost for intravenous infusion must be considered

The secretary also fed back some views from local specialists regarding place in therapy of certolizumab for patients with PsA. The group noted that most specialists would reserve certolizumab for use third or fourth line use as the safety data isn't as extensive for this agent currently. One specialist suggested that it may be useful in young women of child bearing age or in pregnancy as due to larger molecules it is thought not to cross the placenta; however there isn't any specific data available that has evaluated use in this way and designing clinical trials specifically for this indication would be ethically challenging.

The group agreed that certolizumab should be approved as an option. However other more established therapies would remain first line.

ACTION Secretary to draft decision summary as above

5) Appraisal: The use of sequential TNF Inhibitors in the management of psoriatic arthritis

The appraisal report concerning the use of sequential TNF inhibitors in the management of PsA was introduced by the secretary. This appraisal was referred to NTAG by CCGs.

Up to a third of PSA patients may fail on first-line TNF inhibitor therapy due to inefficacy or adverse events, and ustekinumab is currently the only recommended treatment options for these patients. However, an increasing number of specialists may consider switching to an alternative TNF inhibitor before ustekinumab.

No randomised controlled trials have specifically investigated the sequential use of biological drugs in the treatment of PsA. The evidence to support the sequential use is limited to registry data, observational studies and regional audits.

The response rates to sequential treatment varied significantly between these studies, but overall responses were lower during second and third treatment courses. Patients achieving an ACR20 response to a second TNF inhibitor ranged from 22% in the DANBIO study to 53.9% in the RAPID-PsA trial.

Safety data relating to specifically to the sequential use of biological drugs in the treatment of PsA are very limited, however it would seem reasonable to assume that their safety profile would be comparable to that observed when a TNF inhibitor is used as a first-line.

NICE guidance on biologics recommends that treatment should normally be started with the least expensive drug (taking into account administration costs, required dose and product price per dose).

Several TNF inhibitors are licensed for the treatment of PsA. Adalimumab, etanercept, golimumab and certolizumab are administered by SC injection, while infliximab requires IV infusion. The price of some biologics differs substantially from list prices due to locally negotiated procurement discounts and National Patient Access Schemes. The introduction of biosimilars is also leading to a shift in the market and manufacturers are bringing in more

'value' added services such as variations of homecare and additional nursing support etc. However the cost of treatment of using a subcutaneously-administered sequential TNF inhibitor after the first line option has failed is likely to be minimal or cost neutral as one agent would be stopped prior to starting another.

The estimated average annual first year cost per PsA patient ranges from around £7,000 to £17,000 including administration costs, but excluding VAT *(costs for branded infliximab + administration = £17,286 which is currently the most expensive treatment option)*

NICE TA199 (2010) concluded that there were insufficient data to make a recommendation on the sequential use of TNF inhibitors in PsA. However, TA340 (2015) noted that the sequential use of TNF inhibitors is established practice in the NHS, and that the NICE commissioning guide on biologic drugs for the treatment of inflammatory disease in rheumatology, dermatology and gastroenterology and the published TAs did not preclude sequential use.

Both the BSR and EULAR recommend switching to an alternative TNF inhibitor in the case of failure due to inefficacy or AEs, but acknowledge there was insufficient evidence to establish a preference for a particular TNF inhibitor in this situation.

The group noted that in patients who fail a first line TNF inhibitor due to side effects or lack of effect, who still have active disease, most specialists would try a second TNF inhibitor. Treatment in these patients is about choosing the right agent for the right patient. In choosing the next treatment option the patient should be assessed and reviewed by a multidisciplinary team and the patient must continue to fulfil the NICE criteria for initiation of a TNF inhibitor.

The group approved the sequential use of TNF inhibitors in patients with active PsA. It was agreed that the choice of subsequent TNF inhibitor should be led locally by the specialist teams and this may need to be varied for individual patients based on the reason for primary failure. The group noted good practice around sequential use at both Northumberland and Newcastle NHS Foundation Trusts and recommended a similar approach across the region.

ACTION Secretary to draft decision summary as above

6) Re-Review: Functional Electrical Stimulation (FES) for orthotic correction of drop foot of neurological origin.

The group noted that this had previously been reviewed by NETAG in 2012. The group had reviewed this as an option alongside ankle orthotics and had not recommended use, however they did note that individual patients in exceptional circumstances may be suitable for treatment and such cases were to be referred via IFR mechanisms. It was noted that the application from the specialist stated that due to the number of requests this was no longer being approved via the IFR process.
The secretary introduced the updated appraisal. It was noted that the re-review and proposed place in therapy is slightly different to the original application and subsequent recommendation from 2012, in that the specialists are proposing a different place in the pathway i.e. for trial in those patients not suitable for or able to tolerate ankle or soft orthotics. All other options must be tried prior to referral for FES.

Drop foot refers to a particular waling gait often present in individuals with a neurological deficit of the central nervous system i.e. common causes include stroke, MS, cerebral palsy and spinal or brain injuries. Drop foot occurs as a result of poor control of muscles in the ankle and toe which causes the foot to hang downwards (drop) and drag along the ground during normal walking. As a consequence patients develop a new less stable gait which can result in falls.

Functional Electrical Stimulation (FES) has been developed to help those with drop foot to move more easily. It works by producing muscle contractions that mimic normal voluntary gait movement by applying electrical pulses to nerves, either directly or indirectly. FES devices are considered Class II Medical Devices by the MHRA. Unless custom made, they must have a CE marking

The main benefits of FES are thought to be twofold. Orthotic effects are immediate, and are experienced whilst the device is in place. Therapeutic effects develop over time with continued use of the device, and would be expected to occur even in the absence of the device being used (e.g. increased muscle mass due to repeated use of the device). Whether FES is used as an orthotic or therapeutic device is at the moment largely a local clinical decision and may be dependent on the original neurological condition.

There is a large volume of evidence for FES in drop foot of various neurological origins, though much of it is of low quality. (e.g. non-randomised studies, no control groups, short follow up, small patient numbers) However the difficulty in designing and undertaking a randomised controlled trial due to the nature of the intervention was acknowledged. New data since the last review include the Functional Ambulation: Standard Treatment Versus Electrical Stimulation Therapy (FASTEST) trial, which was a randomized, controlled, single blinded study of 197 patients in the chronic phase of stroke recovery. It is the only trial to date which has directly compared FES with AFO. The results showed no significant difference between the two patient groups.

The group noted the updated specialist treatment pathway which had been sent to the group for review. The group agreed that this was a robust approach. All other options should be trialled before the patient is considered for FES. It was suggested that it would be better if commissioners could fund a whole package of support from the specialist service i.e. so the specialist service could provide the consumables as well; currently this is prescribed by GP's.

Whilst there have been several cost effectiveness analyses presented at conferences, there are no fully published, independent economic assessments in the medical literature. No cost effectiveness studies assess the costs of FES as a subsequent treatment to AFO, in line with their place in therapy according to UK guidance. A rough estimate of the total cost of skin-surface FES over five years is estimated at about £3680. A significant proportion of the cost of FES would be incurred in the first year of treatment and therefore cost-effectiveness would improve over time with longer duration of use.

The aim of the supply and support of the use of FES is to reduce the incident of falls within a vulnerable patient group, therefore reducing the potential hospital admissions associated with this.

The group approved the use of skin surface functional electrical stimulation for orthotic correction of 'drop foot' as an option for patients who fulfil all of the following criteria: Drop foot is impeding gait and in whom the use of all orthotics (AFO) has proven to be unsuccessful following specialist assessment, the patient has demonstrable functional improvement from an individual trial of FES and the intervention is recommended by a multidisciplinary team specialised in rehabilitation.

The group agreed that any use of FES should be assessed and reviewed regularly as part of an approved specialist service under a defined protocol for use such as that proposed by Northumberland, Tyne and Wear Trust.

ACTION Secretary to draft decision summary as above

7) Work plan

The group discussed the work plan. It was agreed that both PCSK9 inhibitors would be discussed in November as it would be useful to look at both these drugs together despite the fact that one of them would be reviewed by NICE in April 2016. The group also agreed that it would be useful to review insulin glargine high dose and insulin glargine biosimilar as although these were not high cost drugs they could potentially be high volume. This had been referred to the group from an APC.

The group noted that they were nearing the end of items that had been put forward for review. It was agreed that items would need to be added from horizon scanning and that APC's could be contacted for other suggestions.

ACTION: Secretary to add the above items to the agenda for the November meeting.

8) AOB

No other business was raised and the meeting concluded.

The date of the next meeting was noted to be 24th November 2015, Meeting Room 4, The Durham Centre.

Minutes produced by B Reddy, Professional Secretary to NTAG, 24th September 2015