North Central London
Medicines Optimisation Network

JOINT FORMULARY COMMITTEE (JFC) – MINUTES

Minutes from the meeting held on 18 November 2019
G12 Council Room, South Wing, UCL, Gower Street, WC1E 6BT

Present:	Dr R Sofat	NCL JFC Chair	(Chair)
	Dr M Kelsey	WH, DTC Chair	
	Ms R Clark	Camden CCG, Head of Medicines Management	
	Mr S Semple	MEH, Chief Pharmacist	
	Dr R Urquhart	UCLH, Chief Pharmacist	
	Mr P Gouldstone	Enfield CCG, Head of Medicines Management	
	Mr A Dutt	Islington CCG, Head of Medicines Management	
	Ms P Taylor	Haringey CCG, Head of Medicines Management	
	Ms K Delargy	BEH, Deputy Chief Pharmacist	
	Ms W Spicer	RFL, Chief Pharmacist	
	Dr K Tasopoulos	NMUH, DTC Chair	
	Ms L Reeves	C&I, Chief Pharmacist	
	Dr S Ishaq	WH, Consultant Anaesthetist	
	Dr A Sell	RNOH, DTC Chair	
	Ms P McCormick	WH, Lead Pharmacist – Medicine	
In attendance:	Dr P Bodalia	UCLH, Principal Pharmacist	
	Mr A Barron	NCL MEP, Project Lead	
	Ms M Kassam	NCL JFC, Support Pharmacist	
	Mr G Grewal	NCL JFC, Support Pharmacist	
	Ms K Davies	NEL CSU, Deputy Director Medicines Management	
	Ms K Saxby	UCLH, Formulary Pharmacist	
	Dr J Sun	UCLH, Foundation Year 2 Doctor	
	Mr I Quarm	Haringey CCG, Prescribing Advisor	
	Mr V Talaulikar	ULCH, Associate Specialist in Reproductive Medicine	
	Dr S Eriksson	NHNN, Consultant Neurologist	
	Ms L Stockford	NHNN, Pharmacist	
	Ms J Cambitzi	UCLH, Lead Nurse for Abdominopelvic Pain	
	Dr A Fayaz	UCLH, Consultant in Anaesthesia and Pain Medicine	
	Mr J Dempster	Advanced Nurse Practitioner in Immunology and Allergy	
	Mr M Radcliff	Consultant in Adult Allergy	
Apologies:	Mr C Daff	Barnet CCG, Head of Medicines Management	
	Prof D Hughes	RFL, Consultant Haematologist	
	Mr S Richardson	WH, Chief Pharmacist	
	Prof L Smeeth	NCL JFC Vice-Chair	
	Dr A Bansal	Barnet CCG, GP Clinical Lead Medicines Management	
	Prof A Tufail	MEH, DTC Chair	
	Mr A Shah	RNOH, Chief Pharmacist	
	Mr S Tomlin	GOSH, Chief Pharmacist	
	Mr A Shah	RNOH, Chief Pharmacist	
	Mr T Dean	Patient Partner	
	Dr A Stuart	Camden CCG, GP Clinical Lead Medicines Management	

2. Meeting observers

The Committee welcomed Mr Quarm (Haringey CCG, Prescribing Advisor) as an observer of the meeting.

3. Minutes of the last meeting

Ms Davies requested that the minutes referring to the NCL rheumatoid arthritis pathway reflect that Herefordshire CCG do not recommend rituximab in the 4th or 5th line setting. Ms Clarke informed the Committee that Camden CCG has requested a minor amendment to the minutes to clarify that inhaled corticosteroid and LABA combination inhalers that are not within the scope of either the RRP COPD Guideline or the NCL Asthma Inhaler Choice Guideline would have restrictions against their use applied for the relevant indication. The minutes were otherwise accepted as an accurate reflection of the meeting.

4. Matters arising

Nil

5. JFC Work Plan & outstanding actions

These items were included for information only. Any questions should be directed to Ms Kassam.

5.1 Outstanding actions: letrozole for the management of WHO group II anovulation - switch from second-line to first-line

The Committee considered Mr Talaulikar's response to the outstanding actions arising from an application heard at JFC in August 2019 to use letrozole first-line in the management of WHO group II anovulation.

The Committee heard the use of first-line letrozole is a new addition to the 2018 international polycystic ovary syndrome consensus guideline, and that British clinicians were involved in the development of these guidelines. The Committee heard from Mr Talaulikar who proposed that letrozole results in fewer multiple pregnancies, fewer side effects (endometrial effects are not seen with letrozole), less time on treatment, and lower use of resources than the current first-line treatment (clomifene). The reproductive unit have experience of using letrozole for one year (varying number of treatment cycles); no major side effects or problems in pregnancy have been reported. In terms of practice at other centres, Kings, Coventry and Berkshire are already using letrozole first-line for ovulation induction. Many women request letrozole first-line, particularly for their second pregnancy if letrozole was effective for a prior pregnancy.

The warning letter issued by Novartis in 2005 has not been redacted, and Novartis are not applying for a licence extension despite evidence to suggest that the congenital malformation rate is not statistically significantly higher than clomifene. Globally, reproductive clinicians are in consensus that letrozole is sufficiently safe to be used first-line as demonstrated by the uptake in other centres and an international consensus guideline.

The Committee were supportive of the use of the letrozole first-line for the management of WHO group II anovulation. The importance of informing patients of the risks of treatment, prior to initiating treatment with letrozole, was emphasised in order for the patient to make an informed decision. It was requested that the UCLH Reproductive Medicines Unit (RMU) develop a Patient Information Leaflet (PIL) and Patient Consent Form for review by JFC or UCLH UMC.

Decision: Deferred pending outstanding actions
Prescribing: Secondary care
Tariff status: In tariff
Funding: Trust
Fact sheet or shared care required: No
Action: UCLH RMU to develop a PIL and consent form, detailing the advantages and risks of treatment with letrozole and clomifene. PIL and consent form to be approved by JFC or UCLH UMC.

6. Declarations of relevant conflicts of interest

No additional declarations were noted for the new medicine applications.

7. Local DTC recommendations / minutes

7.1 Approved

DTC site	Month	Drug	Indication	JFC outcome
UCLH	Oct-19	Epoprostenol	Peripheral vascular ischaemia/gangrene during high dose vasopressor treatment	Decision: UCLH only; pending protocol Prescribing: Secondary care Tariff status: In tariff Funding: Trust Fact sheet or shared care required: No
UCLH	Oct-19	Milrinone	Congestive cardiac failure and term neonates with persistent pulmonary hypertension of the newborn	Decision: UCLH only Prescribing: Restricted to the UCLH neonatal intensive care unit Tariff status: In tariff Funding: Trust Fact sheet or shared care required: No
MEH	Aug-19	5-fluorouracil 1% eye drops	Conjunctival intraepithelial neoplasia/squamous cell carcinoma (second-line)	Decision: MEH only Prescribing: Secondary care Tariff status: Excluded from tariff Funding: NHSE Fact sheet or shared care required: No
RFL	Oct-19	Cefazolin	1) Gram positive infections in haemodialysis patients 2) Second or third line for gram positive infections in non-dialysis patients where other antimicrobials are not suitable are penicillin-allergic 3) Surgical prophylaxis in primary implant orthopaedic surgery	Decision: RFL only Prescribing: Secondary care Tariff status: In tariff Funding: Trust Fact sheet or shared care required: No

7.2 Approved under evaluation

DTC site	Month	Drug	Indication	JFC outcome
RFL	Oct-19	Morphine oral solution monotherapy	High-output stoma diarrhoea (excess of 8-10 bowel motions per day) whilst on maximum dose codeine phosphate and loperamide in patients who have undergone major intestinal bowel resection	Decision: RFL only; 12 month evaluation. Prescribing: Secondary care Tariff status: In tariff Funding: Trust Fact sheet or shared care required: No
RFL	Oct-19	Morphine (Dropizol®) monotherapy	High-output stoma diarrhoea (excess of 8-10 bowel motions per day) whilst on maximum dose codeine phosphate and loperamide, and oral morphine solution monotherapy has been ineffective in patients who have undergone major intestinal bowel resection.	Decision: RFL only; 12 month evaluation. Prescribing: Secondary care Tariff status: In tariff Funding: Trust Fact sheet or shared care required: No

8. New Medicine Reviews

8.1 Vaginal oestrogen for severe vulvar and vaginal atrophy (VVA) in patients with a history of breast cancer (Mr Talaulikar, UCLH)

The Committee considered a review to address whether vaginal oestrogen was safe for patients with a history of breast cancer in light of vaginal oestrogens being contraindicated in this population. The review originated from an application to use ospemifene (a selective oestrogen receptor modulator) for the treatment of VVA in patients who are unsuitable to use vaginal oestrogen. As part of the review, patients with a history of breast cancer were proposed as a specific cohort.

Patients with a history of breast cancer suffering from severe symptoms of VVA are initially offered advice on lifestyle measures and non-hormonal lubricants/moisturisers to alleviate symptoms. For patients who do not respond to non-hormonal treatment, current practice is variable as some clinicians offer vaginal oestrogen and others do not. The difference in practice is due to different perceptions about the risk of oestrogen absorption and subsequent increased risk of breast cancer recurrence.

In terms of safety, a recent MHRA drug safety update highlighted that the risk of breast cancer is increased during use of all HRT, except vaginal oestrogen. NICE also recommend that women contraindicated to systemic HRT are considered for vaginal oestrogens. The American College of Obstetricians and Gynaecologists guidance supports the use of vaginal oestrogen for a limited period of time in patients with breast cancer in coordination with the patients' oncologist (recommendation based on cohort studies). The American College of Gynaecology and the Endocrine Society recommend that the decision to initiate vaginal oestrogen in patients with a history of breast cancer should be made as part of a multidisciplinary decision.

The Committee heard from Mr Talaulikar that patients not responding to non-hormonal treatments will be discussed between Gynaecologists and Oncologists to determine suitability for vaginal oestrogen. If appropriate, patients are initiated on the lowest dose vaginal estradiol formulation with a view to keeping treatment duration as short as possible.

The Committee agreed the benefits of treatment outweighed the theoretical risk of break cancer recurrence therefore vaginal oestrogen should be available for women with severe VVA and physical symptoms who have not responded to non-hormonal treatments, after mutual agreement between the patient, gynaecologist and oncologist.

Decision: Approved
Prescribing: Secondary care initiation, primary care continuation
Tariff status: In tariff
Funding: Trust
Fact sheet or shared care required: No

8.2 Ospemifene for vulvar and vaginal atrophy (VVA) in patients who are not candidates for local vaginal oestrogen therapy

The Committee considered an application for ospemifene for treatment of moderate to severe symptomatic VVA in post-menopausal women who are not candidates for vaginal oestrogen therapy i.e.:

- Patients in whom local oestrogen use is contraindicated (e.g. history of breast cancer; history of VTE, gynaecological diagnosis e.g. history of endometriosis, endometrial cancer, ovarian cancer)
- Women who are unwilling to use hormones (family history of breast cancer or safety fears about hormones)
- Women unable or unwilling to use a local vaginal product (prolapse; pain on touch; dislike messiness; cultural sensitivities)
- Women with inadequate response to local oestrogen or intolerant to side effects

The Committee originally heard this application in June 2019 and agreed ospemifene demonstrated a small but inconsistent benefit in terms of symptomatic improvement over placebo; more importantly, there was no evidence of superiority of oral ospemifene over vaginal oestrogen. Ospemifene is considerably more expensive than vaginal oestrogen and therefore is not cost-effective compared to vaginal oestrogen. The Committee agreed there may be a place for ospemifene for very severe and symptomatic VVA where vaginal oestrogen is contraindicated.

Patients in whom local oestrogen use is contraindicated: history of breast cancer

One cohort suggested by the applicant as being unsuitable for vaginal oestrogen are those with a history of breast cancer; a cohort for which vaginal oestrogen is now recommended (see item 8.1). The Committee heard that there are no studies of ospemifene in women with a history of breast cancer. A post-hoc analysis evaluated three pivotal Phase III studies which included 11 women with a history of breast cancer (diagnosis ≥10 years prior to enrolment) who were randomised to ospemifene 60 mg for 12 – 52 weeks. The data did not show any differences in efficacy and safety between ospemifene-treated women with a history of breast cancer versus those without. Mr Talaulikar informed the Committee that as ospemifene is a selective oestrogen receptor modulator it binds to oestrogen receptors resulting in activation of some oestrogenic pathways and blockade of others, and therefore it could be argued that ospemifene is less potent than oestrogen. The data for ospemifene's neutral (or antagonist) action at the breast in limited to *in vitro* studies and studies in healthy women who did not develop breast cancer during the 12 -52 week follow-up.

Patients in whom local oestrogen use is contraindicated (e.g history of VTE, gynaecological diagnosis e.g. history of endometriosis, endometrial cancer, ovarian cancer

It was noted ospemifene is contraindicated in some of the cohorts proposed by the applicant, including patients with a history of VTE, patients undergoing adjuvant treatment of breast cancer, endometrial cancer and patients with signs or symptoms of endometrial hyperplasia. Mr Talaulikar informed the Committee that post-menopausal women with gynaecological issues would have been successfully treated previously or have undergone a hysterectomy, therefore, although they are considered contraindicated to ospemifene it was suggested that this should not be the case as their pathology is benign.

Women who are unwilling to use hormones or unable or unwilling to use a local oestrogen product

Scottish Medicine Consortium (SMC) approved the use of ospemifene. SMC elaborated that ospemifene may be advantageous over locally administered treatment options in patients with physical limitations or reservations over using local vaginal treatment options. In patients unwilling to use hormones the Committee considered that vaginal oestrogen is a viable, cost-effective treatment option and questioned whether an unmet need exists and if ospemifene is the appropriate solution.

In camera, the Committee were unable to identify the unmet need for each of the proposed cohorts and questioned if vaginal oestrogen would be a suitable alternative given that both vaginal oestrogen and ospemifene are contraindicated in some cohorts. The Committee expressed reservations in recommending ospemifene for use in patients contraindicated to its use due to the lack of safety data. The Committee were not supportive for ospemifene to be offered to patients unwilling to use topical hormones if the risk is not evidence-based, as oestrogen appears to be the most cost-effective option and there is no evidence that ospemifene has a better risk profile than vaginal oestrogen. The Committee were supportive for the use of ospemifene in patients who are physically unable to administer topical oestrogens.

The Committee requested clarification of the intended cohort(s) eligible for treatment in view of their decision regarding unmet need and subsequent detail on the proposed patient numbers across NCL.

Decision: Deferred

Action: Applicant to clarify the proposed cohorts and to clarify the unmet need. NCL patient numbers have been requested.

8.3 Sodium oxybate and pitolisant for narcolepsy

The Committee reviewed a pathway for narcolepsy, with or without cataplexy; for which pitolisant and sodium oxybate are included as third-line agents.

In November 2019, RMOC published interim commissioning intentions for sodium oxybate, to include patients transitioning to adult services and sodium oxybate naïve adults. UCLH UMC approved the use of sodium oxybate in this setting in 2007. The proposed NCL narcolepsy pathway incorporates the RMOC commissioning intentions for sodium oxybate. Treatment is proposed for patients with narcolepsy with cataplexy if >1 anticatapletic agent and >1 stimulant for narcolepsy provide an inadequate response or are not tolerated.

JFC approved an evaluation to use pitolisant for the treatment of narcolepsy in June 2017, however funding for the evaluation was not secured. Pitolisant is proposed for two cohorts; the first is as an alternative for narcolepsy with cataplexy for patients who meet commissioning criteria for sodium

oxybate. The second is for narcolepsy without cataplexy for patients who are intolerant or have had an inadequate response to >1 stimulant. The response criteria for ongoing treatment with sodium oxybate or pitolisant is in-line with RMOC. The criteria reflects that the decrease in number attacks or the reduction in severity of cataplexy are important response markers.

The Committee re-reviewed the evidence for sodium oxybate in narcolepsy. Four double blind RCTs (n=668) were identified where sodium oxybate showed improvements in frequency of cataplexy attacks, excessive daytime sleepiness and sleep latency compared with placebo. A meta-analysis in 2012 concluded that sodium oxybate conferred significant reductions in weekly cataplexy attacks (median reduction: -8.5 95% CI -15.3 to -1.6; 2 of 4 trials) and daytime sleepiness measured by the maintenance wakefulness test (median increase 5.18, 95% CI 2.59 to 7.78; two trials).

Dr Eriksson informed the Committee that patients will be reviewed 3 months following initiation and annually once stabilised. Low numbers of sodium oxybate IFRs have been approved, however clinician experiences indicates that a significant proportion (approximately 50%) stop sodium oxybate due to side effects.

In camera, the Committee were supportive that the evidence for sodium oxybate showed an improvement in narcolepsy outcomes. The Committee acknowledged that South East London have commissioned pitolisant and sodium oxybate for narcolepsy and were aware of inequity of access for NCL patients as those referred to treatment at UCLH are not offered treatment (due to funding issues) whereas those referred to a Provider Trust within SEL are. The Committee requested patient numbers and associated budget impact be sent to NEL CSU for commissioning consideration. The Committee were supportive for specialist initiation with ongoing GP prescribing to facilitate ongoing supply of medication as neither drug requires regular reviews. Monitoring and review of patients will remain the responsibility of specialist clinicians in secondary care.

Decision: Approved clinically, subject to funding approving by NCL Commissioners
Prescribing: Primary and Secondary care
Tariff status: Not in tariff
Funding: TBC
Fact sheet or shared care required: Yes

8.4 Tapentadol to aid weaning and/or rotation of high dose opioids in patients with chronic non-cancer pain (Dr A Fayaz, UCLH)

The Committee considered an application for tapentadol to aid weaning and/or rotation of high dose opioids as part of a managed opioid reduction plan in patients receiving ≥120mg oral morphine daily or equivalent for chronic non-cancer pain. The principle treatment goal is complete withdrawal of opioids in high dose opioids users, opioid reduction to <100mg oral morphine daily or equivalent is a positive outcome.

Tapentadol is a strong analgesic which is a μ-opioid receptor agonist and noradrenaline reuptake inhibitor. The role of opioids in chronic pain has become increasingly controversial owing to the lack of robust evidence on the benefit of long-term opioids in the management of chronic pain, and the potential for patient harm (risk of overdose, addiction [opioid use disorder] and death). It is generally accepted that doses >120mg oral morphine equivalent do not have favourable risk/benefit profiles and patients using doses higher than this should be supported to reduce their dose.

In terms of opioid reduction, no guidelines were identified which specifically recommend tapentadol to support opioid weaning although 2017 Canadian guideline for opioids in chronic non-cancer pain recommends opioid rotation as a possible means to facilitate dose reduction. In contrast, the Faculty of Pain Medicine recommend incremental taper of existing drug. There is a lack of evidence to support one weaning or tapering strategy over another.

A retrospective audit from a single centre in the UK recruited patients who would otherwise have required a dose increase >200mg morphine per day or equivalent, but instead were offered the opportunity to switch to tapentadol (n=104). Patients were encouraged to reduce their opioids to 120mg of morphine or equivalent before overlapping rotation to tapendatol. Only 22% of patients were discharged back to the GP on good pain relief and reduced side effects. The authors reported that as the patients are difficult to treat the response rate was higher than anticipated. No other supportive evidence was identified.

The Committee heard from Dr Fayaz and Ms Cambitzi, that whilst tapentadol does not hold any meaningful clinical advantages over other opioids available on the formulary (specifically in relation to efficacy or safety), its availability allows clinicians an opportunity to engage and incentivise patients with a new strategy that they have not previously used in order to reduce their opioid dose. The promise of providing a 'new agent' once patients have sufficiently reduced their opioid dose therefore would provide an opportunity for patients to engage with the idea to reduce their dose of opioids. Once patients have reduced their opioid dose, the hope is they would be less reliant on opioids and possibly be motivated to reduce their opioid dose further. Tapentadol would only be offered where efforts to reduce the patient's existing opioids had failed. The applicant accepted that the objective evidence supporting the application is very weak, and poorly conducted; however the results showed improved pain management in an extremely difficult to treat cohort with a success rate higher than observed in pharmaceutical trials to treat pain.

The Committee heard experience at the 'BOW' (Benzodiazepine and Opioid Withdrawal) service run by CIFT found that patients prefer to remain on their existing benzodiazepine and choose to taper rather than switch. Switching opioids is a complicated process and it was plausible that doing so may contribute to patient anxieties.

The value of adding tapentadol to the formulary to assist with opioid reduction was considered unclear, particularly in the context of the weak evidence to support the use of long-term opioids in chronic pain, the well-documented opioid-related harms and mortality, and the lack of evidence supporting the advantage of using one opioid over another in this setting.

In camera, the Committee agreed there was no advantage of tapentadol over existing opiates for the management of chronic non-cancer pain and that the proposed advantage, specifically being able to offer patients something new, was effectively using tapentadol for its placebo-effect. Owing to the high-risk nature of opioid, its use as a placebo was not considered justified. The Committee felt that it would be preferable to utilise alternative strategies to engage patients to consider an opioid dose reduction.

In conclusion, based on the evidence available and controversy behind using opioids in chronic pain, the Committee could not recommend the use of tapentadol. However the Committee agreed that it is plausible in some patients who are not able to dose-reduce their existing opioid, switching to an alternative opioid (which may include tapentadol) may increase the likelihood of successful opioid reduction. Without sufficient supportive evidence for this hypothesis, the Committee agreed it was not appropriate to recommend the use of tapentadol outside of a clinical trial setting, the results of which would allow for firmer guidance in the future.

Decision: Not approved

9. Updated national guidance for liothyronine

In November 2019, NICE published guidance recommending against the use of liothyronine for primary hypothyroidism, either alone or in combination with levothyroxine, because there is not enough evidence that it offers benefits over levothyroxine monotherapy, and its long-term adverse effects are uncertain. This guidance is consistent with JFC recommendation from August 2016.

In contrast, RMOC guidance states that "Liothyronine is perceived to be an important medicine for a small proportion of patients in order to maintain health and wellbeing" and "it is recognised that there is a cohort of patients who require liothyronine".

The Committee considered that the RMOC guidance was not based on the best available evidence but agreed to make liothyronine available for those who meet the RMOC eligibility criteria, on the grounds of equity of access. It was noted that clinician perception of liothyronine varies significantly; from highly supportive to advocating against its use. Owing to the lack of supportive evidence and the differences in opinion amongst specialists, it was agreed that all new initiations should be made within secondary care, subject to MDT assessment, undergo review by a high-cost drugs panel (or equivalent) and require approval / monitoring via the Blueteq application process. All prescribing should remain hospital only until the 6 month review after which GPs may be asked to continue prescribing in the event of a positive assessment (specifically TSH of 0.4-2.5mU/L with the T3 and T4 in the normal range, and an improvement in quality of life [although it should be noted that the majority of randomised clinical trials have indicated a pronounced placebo effect]).

Action: Mr Barron, Ms Samuel and Mr Gouldstone to update the NCL Liothyronine Position Statement. NEL CSU to develop Blueteq forms for review at JFC.

10. Guideline update: Chronic spontaneous urticaria

This item was discussed under item 10.1.

10.1 Eligibility criteria for omalizumab – role of montelukast

The NCL 'High-dose antihistamine' and 'Chronic urticaria & angioedema' guidelines are being amalgamated into a single 'Chronic spontaneous urticaria' (CsU) guideline. During consultation, it was queried whether montelukast (a leukotriene receptor antagonist) should be trialled prior to initiation of omalizumab. The draft guideline reflects the JFC position from January 2015, where montelukast was not approved for this indication due to a lack of efficacy. In contract, NICE TA 339 requires patients to have trialled montelukast prior to omalizumab use and NCL Blueteq forms reflect this requirement.

JFC Support found no new evidence to support the use of montelukast since the original JFC decision and presented a timeline of events which explained why NICE recommends montelukast and that this recommendation is now inappropriate:

- 2009: The European Academy of Allery and Clinical Immunology (EAACI), the Global Allergy and Asthma European Network (GA^2LEN), the European Dermatology Forum (EDF) and the World Allergy Organization (WAO) published guidance recommending H_1-antihistamine, leukotriene receptor antagonists (LTRAs) and H_2-antagonists.
- 2013: Omalizumab pivotal trial (GLACIAL trial) design was informed by the 2009 EAACI guidance i.e. included patient who had failed H_1-antihistamine, LTRAs and H_2-antagonists.
- 2014: EAACI updated their guidance to remove H_2-antagonists
- 2014: Novartis submitted a technology appraisal to NICE for omalizumab after failure of H_1-antihistamine, leukotriene receptor antagonists (LTRAs) and H_2-antagonists. This was consistent with GLACIAL trial inclusion criteria.
- 2015: NICE modified the omalizumab eligibility criteria proposed by Novartis to exclude H_2-antagonists as their use in clinical practice had decreased following removal from European guidance from EAACI/GA^2LEN/EDF/WAO. NICE approved omalizumab after failure of H_1-antihistamine and LTRAs.
- 2018: NICE moved omalizumab to the static list, meaning no further reviews are anticipated.
- 2018: EAACI/GA^2LEN/EDF/WAO updated their guidance to remove LTRA.

The timeline shows NICE recommended omalizumab after failure of the oral therapies as suggested by EAACI. Since NICE TA publication, EAACI removed the recommendation for LTRA however NICE has transferred omalizumab to the 'static list' which means they will not respond to this change. The Committee reviewed a pooled analysis which concluded omalizumab therapy was safe and effective at reducing symptoms of CsU regardless of background therapy.

Dr Michael Radcliffe stated that in his experience, one patient has benefitted from an H_2-antagonist and one patient benefitted from montelukast; apart from these exceptional cases, they are generally ineffective.

In camera, the Committee acknowledged clinicians from UCLH supported the removal of montelukast from the CsU treatment pathway however it was unknown whether other centres in NCL managing CsU agreed. It was also queried whether montelukast is used for paediatrics, and assurance was sought that treatment pathways were aligned. The decision will be deferred until these actions are addressed.

Decision: Deferred

Actions: JFC Support to determine:

- ***Whether there is agreement amongst NCL clinicians that montelukast should be removed from the adult CsU treatment pathway.***
- ***Whether paediatric CsU is treated in NCL (with support from NEL), and if so, do these clinicians support a similar removal of montelukast from the paediatric CsU treatment pathway***

11. Higher frequency infliximab

The Committee reviewed an application to use high-frequency infliximab for RA in patients experiencing secondary-failure; specifically in patients who meet NICE criteria for infliximab, and reported a good

response for >6 months, but who now report good response for 4-6 weeks post infusion with the effect wearing off before their next infusion at 8 weeks.

High-frequency infliximab for RA is commonly used internationally and is licensed in the UK although not specifically advocated in international guidelines. High-frequency infliximab is also commissioned in NCL for Ulcerative Colitis and Crohn's Disease and by NHSE for Juvenile Idiopathic Arthritis.

Secondary-failure is commonly thought to be associated with low serum drug-levels secondary to anti-drug antibodies however one study found only 21% of patients with secondary-failure had detectable anti-drug antibodies and of them, only 81% had undetectable drug levels. Secondary-failure is therefore caused by a combination of immune and non-immune mechanisms which suggests therapeutic drug monitoring (TDM) should be used to guide treatment for patients with active disease, as advocated by gastroenterology. The British Society of Gastroenterology only recommends increasing the dose of anti-TNF where drug levels are low and antibody levels are not high.

One randomised study (n=141) investigated the effectiveness of infliximab treatment intensification (5mg/Kg every 8 weeks + MTX) compared to no intensification (3mg/Kg every 8 weeks + MTX) for patients reporting secondary-failure. No benefit in DAS score, swollen joint, tender joints, ESR or CRP was observed by week 28. Study strengths include the correct population of interest, randomisation, partial blinding and use of a power calculation. Limitations include the approach to intensification (i.e. increasing infusion dose rather than infusion frequency) and where dose-escalation was modest; these two factors were thought to contribute to the negative result.

A second, smaller, non-randomised study (n=37) also compared the effectiveness of high-dose (~4.5mg/Kg every 8 weeks + MTX) and high-frequency infliximab (3mg/Kg every 6 weeks + MTX) to no intensification (3mg/Kg every 8 weeks + MTX). The study had numerous methodological weaknesses and reported no significant difference between treatments. High-frequency infliximab significantly improved a symptom score from baseline.

In terms of safety, treatment was not associated with an increase in serious adverse effects although may increase non-serious adverse effects. The cost of dose-escalated infliximab is less than alternative intravenous therapies (abatacept or tocilizumab). Increased infusion frequency was perceived to be less convenient for patients than standard infusion frequency or non-infliximab agents.

The Committee heard from Prof Ehrenstein that infliximab infusions are reserved for patients whose needs are best met with infusions. UCLH have approximately 40 patients on treatment with infliximab for RA, of these approximately 25% will require 6 weekly infusions and 6% will require 4 weekly infusions. The option to be able to offer high-frequency infliximab would allow patients to remain on cost-effective biosimilars for longer.

In camera, the Committee heard there were no expressions of interest from other Trusts for this application. The negative results from the presented trials were thought to be explainable by the dose-increment being too low, and the inclusion criteria including patients who were unlikely to benefit from dose-escalation (i.e. those with non-immune causes for secondary-failure and where antibody levels were high). In summary, the Committee agreed the use of high-frequency infliximab (specifically 3mg/Kg up to every 4 weeks) for secondary-failure of rheumatoid arthritis, where TDM has shown 'low' drug levels and 'low or intermediate' antibody levels.
Decision: Approved clinically, subject to funding approving by NCL Commissioners
Prescribing: Secondary care
Tariff status: Excluded from tariff
Funding: TBC; incorporate into RA Pathway budget impact assessment
Fact sheet or shared care required: No

12. Annual report 2018/19

This item was deferred to the next meeting.

13. Next meeting

Monday 20th January 2020

14. Any other business

Nil