North Central London
Joint Formulary Committee

Guideline for the treatment of Chronic Spontaneous Urticaria in adult patients

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Groups / Individuals who have overseen the development of this guidance:	M Radcliffe – Consultant Allergologist (UCLH) G Grewal – Pharmacist (NCL JFC) M Dziadzio – Consultant Immunologist (UCLH) R Dixon – General Practitioner (Islington CCG) N Patel – Pharmacist (Camden CCG)
Groups which were consulted and have given approval:	W Bakkour – Consultant Dermatologist (UCLH) S Berkovitz – Consultant, General Medicine (UCLH) M Buckland – Consultant Immunologist (RFL)
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Contents

1. Target audience

This guideline is for the treatment of chronic spontaneous urticaria in adult patients. It does not apply to pregnant or breastfeeding women or paediatric patients due to limited evidence to support the safe and effective use of medicines detailed in this guideline in these patient groups. These patients should be referred to the relevant secondary care clinic (see Appendix 1).

2. Purpose

This document is intended to advise primary and secondary care clinicians of prescribing options and referral points in the treatment of chronic spontaneous urticaria in adult patients..

3. Introduction

Urticaria is a superficial swelling of the skin (epidermis and mucous membranes) that results in red, raised, itchy wheals.[1] Theories regarding the pathogenesis of urticaria include mast-cell-derived pro-inflammatory mediators (such as histamine), which is amongst one of the best developed hypotheses.[2] Chronic Spontaneous Urticaria is defined as urticaria, histaminergic angioedema, or both – for a period of six weeks or longer. Angioedema causes painless swelling usually around the eyes, lips, face, extremities or genitals. Urticaria may occur alone (50% of cases), with angioedema (40% of cases), or histaminergic angioedema may occur alone (10% of cases). Whether urticaria occurs with or without angioedema, and also in histaminergic angioedema without urticaria, the same treatment guidelines apply.[1,2] An initial presentation of angioedema without urticaria should prompt re-consideration of other acute causes of angioedema[2] (e.g. ACE inhibitors, even after long duration of use) – for these cases, other treatment guidelines apply.

Type I allergy is an extremely rare cause of Chronic Spontaneous Urticaria, though non-allergic hypersensitivity reactions to NSAIDs or food can occur (i.e. worsening of symptoms after intake, thought to be the result of the histamine content or innate histamine-releasing properties – though the benefit of dietary measures has not been demonstrated in controlled trials).[2–4]

Chronic spontaneous urticaria may spontaneously remit and relapse and it may last for months or years. It rarely becomes life-threatening,[5,6] but it has a significant negative impact on quality of life that is frequently overlooked. Most patients will suspect allergy and their fears need to be addressed. Allergy tests are not routinely necessary but selected tests may be unavoidable to provide reassurance.

A minority of chronic urticaria cases fulfil the criteria for chronic inducible urticaria. Various physical triggers may apply (cold, heat, dermographism etc.) and some patients may suffer from several types. The same treatment guidelines apply, although it should be noted that these cases tend to last longer and are typically less responsive to standard antihistamine doses.[6]

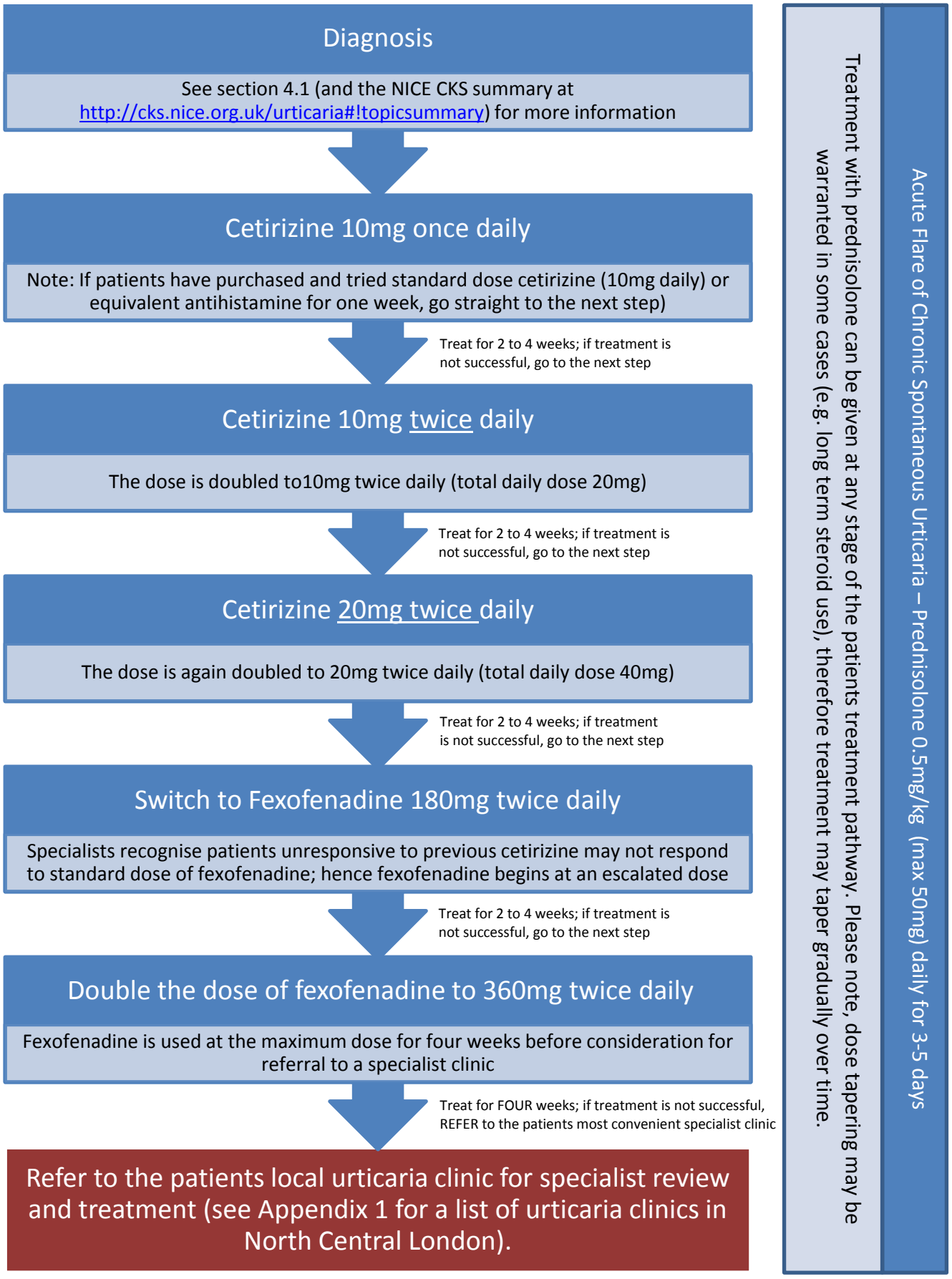
Unlike chronic spontaneous urticaria, chronic inducible urticaria are less likely to go into remission (spontaneously or after treatment).

Second generation antihistamines (such as cetirizine and fexofenadine) are selective H_1-receptor antagonists, which reduce histamine effects (decreased vascular permeability & reduction of pruritus), reduce the migration of inflammatory cells, and prevent the release of mediators associated with the late phase allergic response.[7] These antihistamines have a long duration of action and are less likely to cause anticholinergic and sedative effects associated with first generation antihistamines.[8]

The 2018 European Academy of Allergy and Clinical Immunology (EAACI) guideline is endorsed by allergology, dermatology and immunology bodies worldwide. The EAACI guideline gives an evidence and consensus based suggestion to titrate doses of second generation antihistamines up to fourfold in patients unresponsive to standard doses. The EAACI guidelines also gives evidence and consensus based support for the third-line use of omalizumab and subsequent fourth-line ciclosporin use (both under the care of a specialist). A drugs and therapeutics bulletin (DTB) article written in April 2018 reviewed the evidence for high dose antihistamine use for chronic spontaneous urticaria in adults, which demonstrates an evidence base for the use of cetirizine and fexofenadine at high doses – both of which are on formulary in North Central London, with cetirizine used first-line as the cost-effective option.[8,9]

4. Primary Care Diagnosis and Management

4.1. Quick Reference Pathway



5. Diagnosis

The initial diagnosis and management of Chronic Spontaneous Urticaria generally takes place in Primary Care. Chronic Spontaneous Urticaria by definition lasts for 6 weeks or longer and no identifiable external cause can be identified. Investigations are not normally required but may sometimes be indicated to identify associations and triggers, or to exclude differential diagnoses.[1] Avoidance of possible contributory co-factors, including alcohol and certain medications (e.g. NSAIDs) may need to be considered. Where contributory factors of urticaria have been explored and ruled out, management of chronic spontaneous urticaria begins with an explanation to the patient that allergy is not the cause. Clinicians can find further information on diagnostic criteria for Chronic Spontaneous Urticaria at http://cks.nice.org.uk/urticaria#!topicsummary.

6. Primary Care Treatment Pathway

Antihistamines form the mainstay of treatment offered in primary care. Safety information for antihistamines can be found in Section 9.1. General Practitioners should be aware that patients may have been using licensed doses of antihistamines purchased themselves prior to attending a GP appointment. In these cases, where they have trialled the treatment for a significant amount of time without adequate response, they can be classed as treatment failure and can proceed immediately to Section 6.2.

Chronic Spontaneous Urticaria is known to be a self-limiting condition, although it is unknown how long each individual case will last. If treatment is successful following the initial course at any stage of antihistamine therapy (6.1 to 6.4), the medication should be reviewed to consider whether there is a further need for therapy (based on duration of symptoms during the treatment period). If further treatment is needed, the last effective treatment should be continued and reviewed again every 3-6 months.[1]

In specialist centres, measurements obtained via questionnaire can be beneficial in patients unresponsive to standard therapy via the UAS7 scoring system for wheals, the AAS scoring system for angioedema or the urticaria QoL scoring system for quality of life measures. In all primary care cases, GPs can determine if high dose antihistamine treatment is successful if the drug derives symptomatic benefit after two to four weeks at each step in the pathway.

6.1. Step One – Cetirizine at licensed dose

Treatment begins with licensed doses of a cost-effective second generation antihistamine for two to four weeks. Cetirizine 10mg once daily is on formulary in North Central London as an clinically- and cost-effective option. Patients who do not derive symptomatic benefit should go to Step Two (6.2).

6.2. Step Two – High dose cetirizine

Treatment failure at licensed doses will necessitate the use of higher unlicensed doses. Cetirizine can be doubled to 10mg twice daily and maintained on treatment for two to four weeks to determine treatment efficacy. If this does not work, the dose may be doubled again to 20mg twice daily and again maintained for two to four weeks to determine efficacy. Treatment should always be at the lowest effective and tolerated dose.

If reaching the maximum dose of cetirizine, the patient should maintain on this dose for two to four weeks; If treatment is not successful, move on to Step Three (6.3).

6.3. Step Three – Fexofenadine at escalated dose

Following unsuccessful cetirizine treatment, an alternative antihistamine is given. Fexofenadine is a second-generation antihistamine on the NCL Joint Formulary reserved as a second-line option to treat Chronic Spontaneous Urticaria. The patient can be initiated on 180mg twice daily, as specialists in NCL have found the patient is highly unlikely to derive benefit on lower doses if unresponsive to maximum dose cetirizine in the past. The patient is reviewed after two to four weeks. If the treatment is not successful the patient moves on to Step Four (6.4).

6.4. Step Four – High dose fexofenadine

The dose of fexofenadine can be doubled to 360mg twice daily (total daily dose of 720mg). If the maximum dose is reached, it should be maintained for four weeks before deemed treatment failure.

6.5. Referral to Specialist Clinic

Specialist consultants within North Central London recommend primary care physicians to use high dose antihistamines as detailed in 4.1 in patients suffering from Chronic Spontaneous Urticaria before referral to the specialist clinic.

Referral can be made to the relevant clinic convenient to the patient (see Appendix 1 for a list of specialist clinics in North Central London).

6.6. Treatment of acute flare of Chronic Spontaneous Urticaria with prednisolone

Whilst stable on antihistamine therapy, patients may develop an acute flare of Chronic Spontaneous Urticaria (in the form of histaminergic angioedema).

This is treatable in either primary or secondary care with a short course of prednisolone.

This dose for prednisolone varies greatly between sources. A standard dose of 0.5mg/kg (up to a maximum of 50mg) daily for 3-5 days can be used.

Some patients may require a longer period of treatment, and some may warrant a period of dose tapering. This should be tailored to the individual patients requirements, and consideration should be given to dose and duration of treatment, repeated courses of corticosteroids, history of long-term corticosteroid therapy, and other causes of adrenal suppression.[10]

6.7. Intermittent Urticaria

When short duration urticarial attacks are occurring infrequently, for example one episode per month or less, treatment may be considered. However, regular daily antihistamine treatment has been shown to be significantly more effective than treatment taken when required and is more appropriate for those patients who suffer from frequent attacks.[4]

7. Secondary/Tertiary Care Treatment Pathway

7.1. Omalizumab

Omalizumab is the standard option in secondary care following treatment failure with licensed-dose and high-dose antihistamines. Omalizumab (Xolair®) is an anti-IgE monoclonal antibody approved by NICE for the treatment of Chronic Spontaneous Urticaria. Omalizumab is preferred to other unlicensed treatments because of its effectiveness, licensing and body of evidence; in the case of ciclosporin, omalizumab has a preferable adverse effect and interaction profile.[4,11]

7.1.1. Dose of Omalizumab

Omalizumab is given as a 300mg dose administered subcutaneously once every four weeks for between four to six months. Spontaneous remission can sometimes be observed following completion of a treatment course. If no clinical benefit is observed after four months, treatment should be discontinued. Omalizumab treatment can be restarted if the patient relapses following a successful treatment course.

7.1.2. NICE Technology Appraisal (NICE TA) 339

Omalizumab can be used after failure of high dose antihistamines for severe Chronic Spontaneous Urticaria after the severity of the condition has been objectively assessed (e.g. using a weekly urticaria activity score, UAS7, of 28 or more).[11] Although the NICE TA for omalizumab states to use it after failure of antihistamines and leukotriene antagonists, montelukast is non-formulary for treating Chronic Spontaneous Urticaria in North Central London[12] and does not need to be trialled prior to omalizumab use (see 8.1).

7.2. Ciclosporin

The last line treatment option is ciclosporin, which has some supporting evidence for its use, though the presence of systemic adverse effects limits its use in practice.[4,13] Despite this, ciclosporin has been found to have a better risk/benefit ratio compared with long term corticosteroid use. Ciclosporin has a moderate direct effect on mast cell mediator release. Effectiveness in studies was demonstrated in combination with a second generation antihistamine.

7.2.1. Dose of Ciclosporin

The starting dose of ciclosporin is 1.25mg – 2.5mg per kg twice daily (i.e. a maximum of 5mg/kg/day). If the initial dose is low and no improvement is demonstrated within one month, the dose may be titrated upward gradually to the maximum dose (or the highest tolerated dose). If there is no improvement at the maximum dose for one month, the medication should be discontinued. In all instances, ciclosporin should be prescribed by brand name.

The duration of ciclosporin therapy has been limited due to low long-term responder rates, and so patients are initially given 3 months of treatment at the maximum tolerated dose. In non-responders, the treatment is discontinued. However, in those that do respond, treatment may continue for up to a year, with the dose tapered over several months to the lowest effective dose during this period.[3]

Ciclosporin has many listed drug interactions – care must be taken to ensure the patient can safely be initiated on treatment (see 9.3.1 for a list of possible interactions).

7.2.2. Transfer of Care

Prescription of ciclosporin can be transferred to primary care once the dose has been stable for six weeks. Details of the baseline and continuous monitoring can be found in the North Central London DMARDs Quick Reference Guide (found at https://www.ncl-mon.nhs.uk/wp-content/uploads/Interface_prescribing/Quick_Reference_DMARDs.pdf). Further information of baseline tests and period of prescribing before transfer of care can be found in 9.3.2.

8. Treatment options not used in North Central London

8.1. Treatment Options Not on Formulary in North Central London

Loratadine in high doses was previously used in North Central London for Chronic Spontaneous Urticaria. A review of the evidence by the Joint Formulary Committee found evidence marginally favouring high dose fexofenadine use over high dose loratadine; fexofenadine also has advantages such as being non-sedating at high doses, has a metabolism by a non-CYP450 pathway and does not have significant cardiac side effects.[8,9,14] Therefore, loratadine has now been removed as an option for high dose antihistamine use and replaced by fexofenadine as a second line option following cetirizine.

Montelukast has been removed from recently published algorithms[4]. An evidence review at the Joint Formulary Committee found that antihistamine therapy to be more effective than montelukast alone, and the combination use of montelukast and antihistamine therapy failed to show a significant advantage over antihistamine monotherapy, and therefore not included in the North Central London Joint Formulary.[12] Montelukast is therefore non-formulary and is subject to a non-formulary request.

H_2-antagonists is perceived to have little evidence to support its routine use.[4] It is not on the North Central London Joint Formulary and therefore any prescription is subject to a non-formulary request.

8.2. Options with Recommendations Against Their Use

Sedating antihistamines are discouraged for routine initiation in Primary Care to treat Chronic Spontaneous Urticaria (even at night) due to their shorter duration of action.[4]

The EAACI guideline recommends against (i.e. not to use) a **combination of antihistamines** and recommends against the use of **antihistamines higher than four times** the licensed dosage.[4]

9. Safety and Monitoring

Additional support relating to adverse effects, interactions, precautions and contraindications may be found in the summary of product characteristics for each drug (obtainable via www.medicines.org.uk/emc).

9.1. Antihistamines

Patients should be counselled prior to antihistamine therapy to monitor for possibility of sedation.

Antihistamines[15] are known to cause sedation and psychomotor impairment.[15] The most common adverse effects with the antihistamines in this guidance, as reported by their manufacturers, include headache, somnolence, insomnia, dizziness, increased appetite, fatigue, dry mouth, nausea and pharyngitis.[16,17]

9.1.1. Cetirizine

Cetirizine given at the high daily dose of 60 mg for seven days did not cause statistically significant prolongation of the QT interval. Cetirizine is excreted via the renal route and therefore requires dose reductions in renal impairment.[15] The lowest effective and tolerated dose should be used (not exceeding 10mg daily in patients with eGFR <10ml/min).[18] Specialist in NCL have found cetirizine to be sedating at high doses in some patients; those severely affected should be switched to fexofenadine, which has shown to be non-sedating at high doses.[15]

9.1.2. Fexofenadine

A review on the safety of second generation antihistamines reports no ECG changes or cardiac effects were demonstrated with fexofenadine in comparison with placebo when used at 20mg to 690mg for 28.5 days. The review also states clinical data indicates fexofenadine to be non-sedating for the majority of patients, even at very high doses.[15]

9.1.3. Loratadine

Loratadine may have been trialled by the patient at standard doses (i.e. 10mg daily) prior to seeking medical opinion.

9.2. Omalizumab

Omalizumab use is associated with immune system disorders (allergic reactions type I and serum sickness). This can occur as early as two hours following a dose, but delayed reactions can occur up to give days following administration. Patients should be informed of these and other possible side effects – arthritis/arthralgia, fever, lymphadenopathy, pyrexia, fatigue, injection site reactions (such as pain, pruritus, swelling and erythema), upper abdominal pain and headache.[19]

Most reactions in trials were mild to moderate in severity. Data stated in the summary of product characteristics for omalizumab states that anaphylactic reactions account for a reporting rate of 0.2% of all estimated exposure of the drug. The manufacturer recommends that medicinal products for the treatment of anaphylactic reactions should always be available for immediate use following administration of omalizumab.[19]

EPGA (formerly known as Churg-Strauss syndrome) and hypereosinophilic syndrome can occur in patients with severe asthma; physicians should be alert to the development of marked eosinophilia, vasculitic rash, worsening pulmonary symptoms, paranasal sinus abnormalities, cardiac complications and/or neuropathy. Discontinuation of omalizumab should be considered in all of these cases.[19]

9.3. Ciclosporin

Ciclosporin was the subject of a double-blind, randomised, placebo-controlled trial. Four patients on ciclosporin withdrew due to adverse events. In the two active treatment groups, 64.5% and 72.7% respectively suffered from adverse events. The most common adverse events were gastrointestinal disturbance, paraesthesia, infection and elevated serum creatinine.[13] Common adverse reactions reported include leucopoenia, hyperlipidaemia, tremor, headache, convulsions, hypertension, flushing, hepatic function abnormalities, hirsutism, acne, hypertrichosis, myalgia, muscle cramps, renal dysfunction pyrexia and fatigue.[20] Because of the adverse event profile, ciclosporin is used as a last line treatment and is initiated by a secondary care specialist.

9.3.1. Interactions Affecting Ciclosporin Blood Levels

Medications that can induced CYP3A4 enzymes or P-glycoprotein can decrease ciclosporin levels (such as barbiturates, oxcarbazepine, phenytoin, orlistat, St. John's Wort, terbinafine and bosentan).

Medications that inhibit CYP3A4 enzymes of P-glycoprotein can increase ciclosporin levels (such as nicardipine, metoclopramide, oral contraceptives, methylprednisolone (high dose), allopurinol, protease inhibitors, imatinib and colchicine).

Grapefruit juice, macrolide antibiotics, azole antifungals, verapamil, telepravir, danazol and diltiazem can increase ciclosporin exposure significantly.

Amiodarone can also increase exposure of ciclosporin but has a very long half-life – this interaction can occur for up to 50 days post cessation of amiodarone.

Rifampicin can induce intestinal and liver metabolism of ciclosporin – ciclosporin doses may need to be increased during co-administration.

Octreotide decreases absorption of ciclosporin and an increase in ciclosporin dose could be necessary.

This list is not exhaustive, and other examples of interactions (including those which increase the risk of nephrotoxicity and those where ciclosporin affects other drug levels) can be found in the Summary of Product Characteristics (found via www.medicines.org.uk/emc).

9.3.2. Blood Monitoring

Blood monitoring is required prior to treatment (including full blood count, urea and electrolytes, renal function testing, lipid profile and virology). This should be conducted at baseline, every two weeks until dose stable for six weeks; then this must be monitored monthly for at least 12 months (usually the maximum duration of prescribing). Blood pressure monitoring must be performed at every visit. Additional blood monitoring is required when altering the dose. Further information on monitoring requirements can be found in the DMARDs Quick Reference Guide (found at https://www.ncl-mon.nhs.uk/wp-content/uploads/Interface_prescribing/Quick_Reference_DMARDs.pdf).

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Appendix 1 – List of Urticaria clinics in North Central London

Hospital Name	Department	Contact Number	E-mail address
Royal National Throat, Nose and Ear Hospital (RNTNE)	Immunology clinic	07890 536085	uclh.rntne.immunologyenquiries@nhs.net
University College London Hospitals (UCLH)	Specialist Allergy and Clinical Immunology	020 3456 5242	uclh.referrals.adult.allergy@nhs.net
Royal London Hospital for Integrated Medicine (RLHIM)	Adult Allergy Service	020 3448 2000	uclh.enquiry.rlhim.patients@nhs.net
Whittington Hospital	Dermatology Department	020 7288 5266	No generic email available
Royal Free London (RFL) Hospitals	Dermatology services	Contact number as per clinic found on the RFL website	Rf-tr.Royalfreedermatologypatientqueries@nhs.net