

# Treatment of the “difficult case” of chronic urticaria

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# Treatment of the difficult case of chronic urticaria :

## *issues that need to be addressed*

- What is “adequate treatment” of CU ?
- What is the recognised “benchmark” routine treatment for CU ?
- How can I get the most out of antihistamines, including H2 antihistamines and doxepin ?
- Is there a role for systemic steroids ?
- Do antileukotrienes work ?
- *If all the above fail* - what should I **not** do ?
- What **should** I do ?
- Is there anything new “round the corner” ?
- What to do if all else fails – *revisit the diagnosis !*

# CU causes severe impairment of QOL, and adequate treatment should achieve normality

- the degree of personal social and occupational disability matches that of patients with triple coronary heart disease disease awaiting bypass surgery

*(O'Donnell B et al, the impact of chronic urticaria on quality of life. Br J Dermatol. 1997; 136: 553-6)*

- There is no cure
- Adequate treatment should enable patient to lead an essentially normal life
- Patients are entitled to expect effective treatment to achieve this goal, *which in selected cases may involve potent and expensive medications*



# The recognised benchmark routine treatment of chronic urticaria : the *European guidelines*

(Zuberbier et al, EAACI/GA<sub>2</sub>LEN/EDF guideline: management of urticaria. Allergy 2006; 61: 321-331)

- The recommended first line standard treatment is non – sedating antihistamines and they recommend if necessary increasing dosage up to fourfold (off - label dosage)
- The guidelines “*strongly recommend not to use old sedating antihistamines*”
- However “first generation” H1 antihistamines do have a role particularly in patients with sleep disturbance due to urticaria

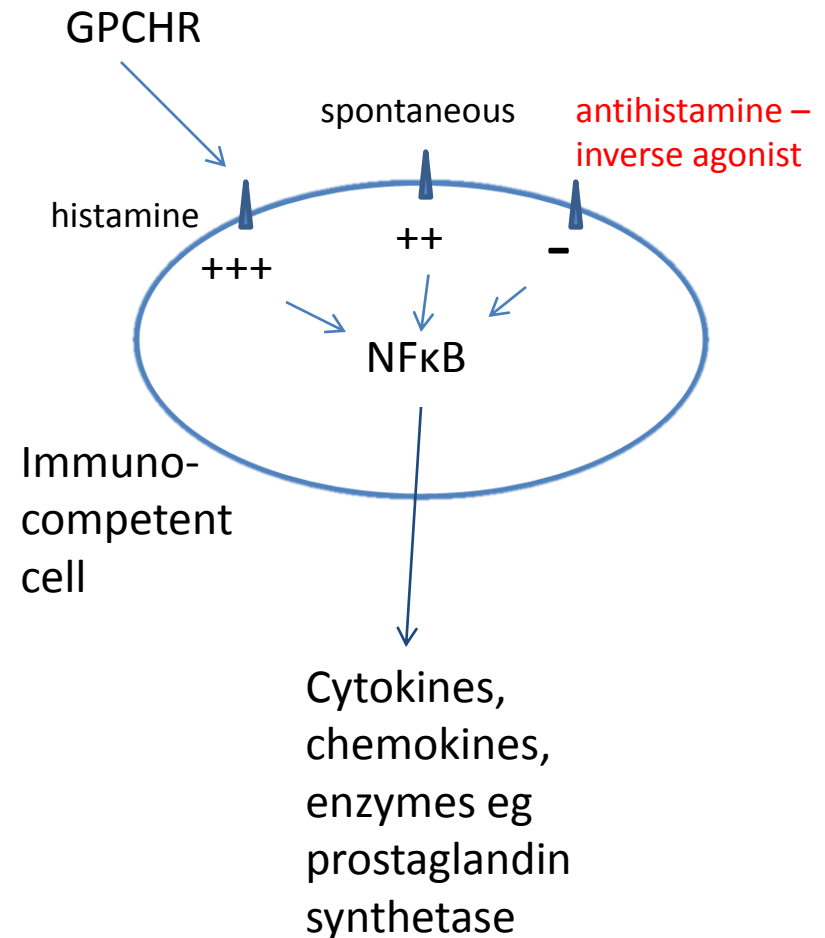
# How can my “difficult” patient get the most out of H1 antihistamine treatment ?

- Regular dosage avoids “pseudotachyphylaxis” (*syn* tolerance, sub-sensitivity)
- Off - label dosages of 2nd generation antihistamines : **efficacy** - supported by mounting experimental evidence, and they are recommended in European and UK guidelines
- Off - label dosages of 2nd generation antihistamines : **safety** - generally assumed safe even in 3-4x licensed dosages on the basis of derivative evidence.  
(also off - label dosages of 1<sup>st</sup> generation antihistamines have been used for years without safety problems)

# How to get the most out of H1 antihistamine therapy : *anti-inflammatory actions*

H1 antihistamines behave as inverse agonists, down-regulating spontaneous firing of the H1 receptor leading to reduced transcription of pro-inflammatory cytokines, chemokines, enzymes

Although the evidence is incomplete, in vitro and laboratory animal data indicate that these actions are dose-related



# Doxepin for antihistamine – resistant chronic urticaria

Doxepin is a tricyclic antidepressant which is useful in the treatment of antihistamine – resistant urticaria

- Dose range is 25-75mg daily
- High affinity for H1 receptor (8x greater than diphenhydramine)
- Significant H2 blocking activity
- Cautions :
  1. Never withdraw abruptly
  2. Do not administer concurrently with other anti-depressants
  3. Do not administer to patients with significant heart disease
  4. Possesses significant anti-muscarinic activity

# Do H2 antihistamines have a role in H1 antihistamine - resistant urticaria ?

- Rationale : skin blood vessels express both H1 and H2 receptors; cimetidine (but not ranitidine) and all first generation H1 antihistamines + mizolastine and loratidine are metabolised via Cyp450 pathway
- RDBCT have shown a significant benefit of combining H1 and H2 antihistamines (Bleehen et al. Cimetidine and chlorpheniramine in the treatment of chronic idiopathic urticaria: a multicentre randomised double blind study. *BJD* 1987; 117: 81-88)
- However this statistical difference may not be clinically significant (Sharpe and Shuster. In dermatographic urticaria H2 receptor antagonists have a small but therapeutically irrelevant effect compared with H1 antagonists alone. *BJD* 2006; 129: 575-9)
- In practice H2 antihistamines are useful in patients with chronic urticaria suffering gastro-oesophageal reflux, and those with dyspepsia complicating systemic corticosteroid treatment

# Is there a role for systemic corticosteroids in treatment – resistant chronic urticaria ?

- There are no controlled trials of systemic steroids in chronic urticaria
- In Europe including the European guidelines, systemic steroids are not recommended for maintenance, but can be used as short tapering courses to deal with relapses. (Zuberbier et al, EAACI/GA<sub>2</sub>LEN/EDF guideline: management of urticaria. Allergy 2006; 61: 321-331)
- In USA 10mg / day or 20mg alternate days systemic corticosteroid treatment is regularly used on a long term basis and minimal adverse consequences are claimed.

# Antileukotrienes for treatment - resistant chronic urticaria

Antileukotriene	Trial design	Outcome	Comment	Reference
Montelukast	DBRPCT montelukast vs cetirizine vs placebo	Montelukast better than cetirizine or placebo	All patients NSAID reactive	Pacor et al 2004
	DBRPCT desloratidine + montelukast vs desloratidine vs montelukast vs placebo	Addition of montelukast to desloratidine was not advantageous	CIU; no NSAID - or ASST – positive patients	Di Lorenzo et al 2004
	SBRPCT cross over montelukast + cetirizine vs cetirizine	Montelukast better than cetirizine	CIU	Erbagci 2002
	DBRPCT desloratidine + montelukast vs desloratidine vs placebo	Desloratidine + montelukast better than desloratidine alone	DPU	Nettis et al 2006
Zafirlukast	DBRPCT cetirizine + zafirlukast vs cetirizine vs placebo	Cetirizine + zafirlukast better than desloratidine alone	All patients were CIU and ASST +	Bagenstose et al 2004

## Antileukotrienes for treatment - resistant chronic urticaria

Overall, the evidence suggests that antileukotrienes are effective, especially in NSAID – reactive patients

The dosage is 10mg at night, and there is little risk of side effects

A Churg – Strauss like syndrome has been reported in patients on systemic steroids in whom montelukast has been abruptly withdrawn

# What not to do if all these measures fail : *treatments that don't work*

- **Trying yet another antihistamine** no evidence that “playing roulette” with antihistamines (*“you havnt tried this antihistamine have you ?”*)
- **Anti – *Helicobacter pylori* treatment** : many people with or without chronic urticaria have *H pylori* infection. There is no evidence that this infection has anything to do with the pathogenesis of urticaria and this notion will, if we wait long enough, be dropped
- **Thyroxine replacement** : it has been claimed that euthyroid chronic urticaria patients with thyroid autoantibodies respond to thyroxine supplements. Again, this claim is unsubstantiated
- **Special diets** : These are strongly advocated by some European groups, but dietary causation can only be substantiated by placebo controlled oral challenge
- **Rituximab**

What to do if all these measures fail :  
*treatments with evidence of efficacy*

- cyclosporin
- methotrexate
- intravenous immunoglobulin
- plasmapheresis

# Cyclosporin for severe refractory chronic urticaria

- 3 RCT`s have attested to the safety and efficacy of cyclosporin in selected patients with chronic ordinary urticaria (Grattan et al, BJD 2000; 143: 365-72; Vena et al, JAAD 2006; 5: 705-09; Inaloz et al, J Dermatol. 2008; 35: 276-82).
- **Indications** : daily or almost daily extensive urticaria / angioedema with severe QOL impairment, resistant to antihistamines. Patients previously on long – term systemic steroids are also candidates for cyclosporin. Works in autoimmune or non – autoimmune cases
- **Dose range** is 3-6mg/kg/day, usually given for 2-3 months
- **Outcome** : about 80% experience remission ( total or almost total cessation of urticaria)
- **Relapse rate** : about 1/3 - remain in remission; 1/3 – minor relapse; 1/3 more severe relapse
- **Cautions** : hypertension, renal impairment.

## When to use methotrexate

- There are no RCT`s of MTX in chronic urticaria
- There are several anecdotal reports (Weiner, Ann Int Med.1989;110: 848; Gach et al. BJD 2001; 145: 340-43; Perez et al. Abs WCD 2007) describing successful outcomes in selected cases
- Dosage : 10-15mg MTX per week for 3-6 months
- Despite paucity of published data MTX is used quite widely for severe treatment resistant urticaria in the Urticaria Clinic at St John`s Institute of Dermatology - mainly in patients unresponsive to / intolerant of cyclosporin

# Intravenous immunoglobulin and plasmapheresis

- There are no RCT`s
- **IVIG** was reported (O`Donnell et al BJD 1998; 138: 101-6) to be effective in 9/10 patients with severe treatment - resistant chronic urticaria all of whom had a positive ASST (dosage 0.4g/kg/day for 5 days). 3 patients remained in long- term remission. Good results with a lower dosage (0.2g/kg/day for 2 days) have also been reported (Croiss et al. Archs Derm 2000; 80: 225)
- Caution : minor side effects (esp headache) are common; IgA - free IVIG should be used inpatients with a low IgA
- **Plasmapheresis** : 8 patients with proven autoimmune severe chronic urticaria underwent plasmapheresis (Grattan et al, Lancet 1992; 339: 107-800). Total or partial remission occurred in 6 and functional anti - FcεR1 autoantibody levels showed concordance with clinical response

# Is there anything new “round the corner” ?

## *Omalizumab*

- Omalizumab is a recombinant humanised mAb that selectively binds to, and lowers serum IgE and as a consequence lowers the population density of IgE receptors expressed on mast cells and basophils.
- Patients with autoimmune urticaria due to autoantibodies directed against FcεR1 or IgE itself should benefit from treatment with Omalizumab since there would be a sufficient FcεR1 reduction to nullify antibody mediated cross linking
- In a open study in 12 patients with CAU 11 out of 12 patients showed a good or excellent response (*Kaplan et al. JACI 2008; 122: 569-73*) and in
- In an RDBPCT in 20 patients with unselected treatment resistant CU, all patients allocated to Omalizumab (given every 2-4 weeks for 16 weeks) showed substantial improvement in symptom score and QOL (*Gober et al JACI 2008; 121: S147*)
- Three patients with unselected treatment resistant CU all responded well to omalizumab (*Spector et al. Ann Allergy 2007; 99: 190-03*)
- The results are impressive but mechanism of action is unclear

## If nothing works : *reconsider the diagnosis*

Consider the following alternative diagnoses :

- Urticarial vasculitis (*do skin biopsy*)
- Schnitzler`s syndrome (*paraprotein screen*)
- Adult – onset Still`s disease (*fever, joint pain*)
- Autoinflammatory syndrome (*early onset periodic fever, cryopyrins*)
- Urticarial dermatitis (*“wheals” desquamate*)

# Conclusions

- Chronic urticaria is a disabling condition and patients deserve adequate treatment, beyond “playing roulette” with the latest antihistamines
- Don't waste time on unproven and ineffective treatments and “allergy tests”
- Don't be afraid of trying off – label dosages of low sedation antihistamines - before going on to second and third line treatments
- When all else has failed – revisit the diagnosis