Orticaria cronica spontanea: esperienze real-life con omalizumab

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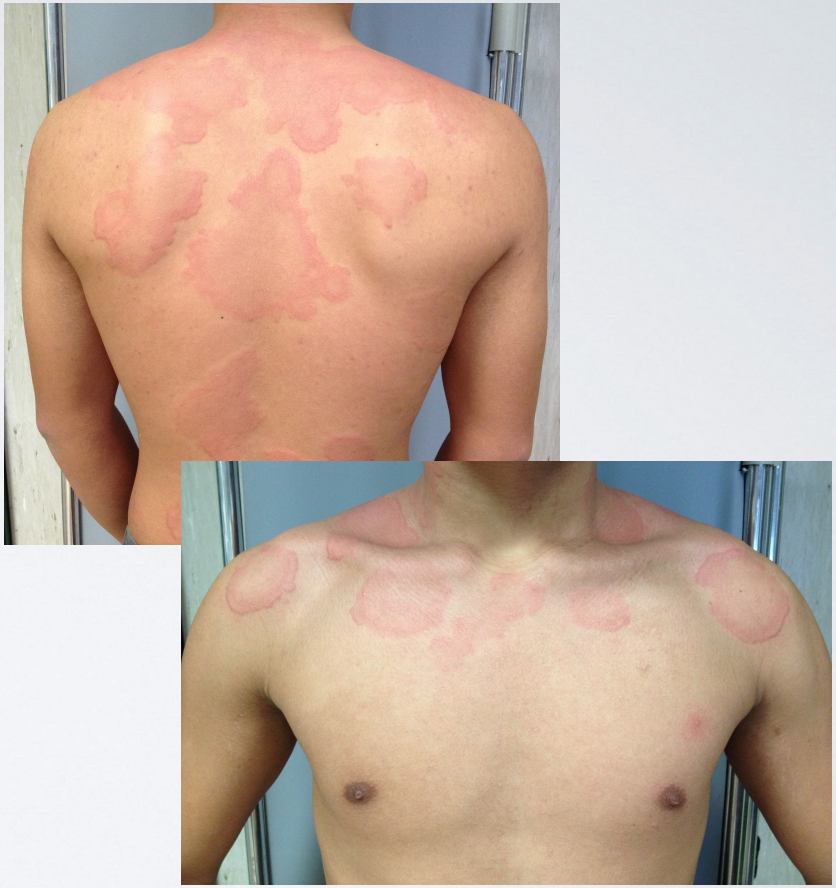
- L'orticaria è una patologia caratterizzata dall'insorgenza di pomfi associati a prurito e angioedema
- Insorge nel 20–25% della popolazione in età variabile
- Prevalenza variabile 0.05-3%
- Forma cronica (CU), spontanea (CSU) o inducibile (CIndU), viene definita dalla persistenza dei sintomi per oltre 6 settimane



Strumenti misurazione gravità CSU

- Urtcaria Actvity Score (UAS): è un punteggio composito di misurazione della gravità
- Il paziente valuta da 0 a 3 giornalmente la gravità del prurito ed il numero dei pomfi
- Il punteggio ottenuto dalla somma varia da 0 a 6
- UAS7 è la somma dei punteggi UAS giornalieri di una settmana, varia da 0 a 42.

ISTRUZIONI PER LA COMPILAZIONE DELL'UAS7[#]

Compilare il diario ogni giorno facendo riferimento all'intera giornata precedente e non solo alla situazione attuale al momento della compilazione. Dare una valutazione dei sintomi di orticaria attribuendo ai pomfi e al prurito un valore da 0 a 3 secondo quanto illustrato nella tabella seguente.

PUNTEGGIO POMFI	PUNTEGGIO PRURITO
0 = nessun pomfo	0 = nessun prurito
1 = meno di 20 pomfi	1 = lieve (presente, ma non fastidioso)
2 = tra 20 e 50 pomfi	2 = moderato (fastidioso, ma non influenza le normali attività quotidiane o il sonno)
3 = più di 50 pomfi	3 = intenso (severo, in grado di interferire con le normali attività quotidiane o il sonno)

Tabella tratta da 1-3

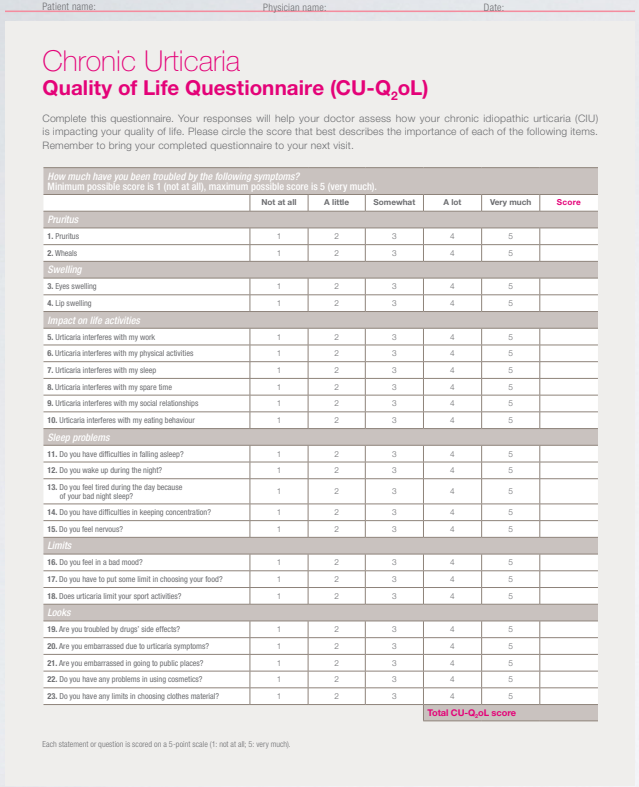
Ogni riga rappresenta un giorno: nelle caselle corrispondenti a un dato giorno, indicare per ogni domanda il valore corrispondente alla risposta corretta. Alla fine della settimana determinare il punteggio settimanale per ogni domanda.

	GIORNO	PUNTEGGIO POMFI/24 ORE				PUNTEGGIO PRURITO/24 ORE				SOMMA DEI PUNTEGGI RELATIVI A POMFI E PRURITO
		NESSUNO	<20	20-50	>50	NESSUNO	LIEVE	MODERATO	INTENSO	
SETTIMANA 1	1	0	1	2	3	0	1	2	3	
	2	0	1	2	3	0	1	2	3	
	3	0	1	2	3	0	1	2	3	
	4	0	1	2	3	0	1	2	3	
	5	0	1	2	3	0	1	2	3	
	6	0	1	2	3	0	1	2	3	
	7	0	1	2	3	0	1	2	3	

40 POMFI comparsi nelle ultime 24 h, perciò il punteggio è 2

Nelle ultime 24 ore il prurito è stato **LIEVE**, perciò il punteggio è 1

UAS7 .....



Patient name: Physician name: Date:

Chronic Urticaria

Quality of Life Questionnaire (CU-Q_2oL)

Complete this questionnaire. Your responses will help your doctor assess how your chronic idiopathic urticaria (CIU) is impacting your quality of life. Please circle the score that best describes the importance of each of the following items. Remember to bring your completed questionnaire to your next visit.

How much have you been troubled by the following symptoms?
Minimum possible score is 1 (not at all), maximum possible score is 5 (very much).

	Not at all	A little	Somewhat	A lot	Very much	Score
Pruritus						
1. Pruritus	1	2	3	4	5	
2. Wheals	1	2	3	4	5	
Swelling						
3. Eyes swelling	1	2	3	4	5	
4. Lip swelling	1	2	3	4	5	
Impact on life activities						
5. Urticaria interferes with my work	1	2	3	4	5	
6. Urticaria interferes with my physical activities	1	2	3	4	5	
7. Urticaria interferes with my sleep	1	2	3	4	5	
8. Urticaria interferes with my spare time	1	2	3	4	5	
9. Urticaria interferes with my social relationships	1	2	3	4	5	
10. Urticaria interferes with my eating behaviour	1	2	3	4	5	
Sleep problems						
11. Do you have difficulties in falling asleep?	1	2	3	4	5	
12. Do you wake up during the night?	1	2	3	4	5	
13. Do you feel tired during the day because of your bad night sleep?	1	2	3	4	5	
14. Do you have difficulties in keeping concentration?	1	2	3	4	5	
15. Do you feel nervous?	1	2	3	4	5	
Limits						
16. Do you feel in a bad mood?	1	2	3	4	5	
17. Do you have to put some limit in choosing your food?	1	2	3	4	5	
18. Does urticaria limit your sport activities?	1	2	3	4	5	
Looks						
19. Are you troubled by drugs' side effects?	1	2	3	4	5	
20. Are you embarrassed due to urticaria symptoms?	1	2	3	4	5	
21. Are you embarrassed in going to public places?	1	2	3	4	5	
22. Do you have any problems in using cosmetics?	1	2	3	4	5	
23. Do you have any limits in choosing clothes material?	1	2	3	4	5	
					Total CU-Q_2oL score	

Each statement or question is scored on a 5-point scale (1: not at all; 5: very much).

The Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL)

is an instrument that was specifically developed to assess quality of life in patients with CU.1,2
It is a self-administered 23-item questionnaire, where patients have to indicate, on a Likert scale, how much they have been troubled by each problem, with higher scores indicating worse quality of life. Value range: 23-115.

1. Zuberbier T, Asero R, Bindslev-Jensen C et al. Allergy 2009 Oct;64(10):1417-26.
2. Khan DA. Chronic urticaria: Standard management and patient education. In: UpToDate, Waltham, MA.

EPIDEMIOLOGY

BJD
British Journal of Dermatology

Epidemiology of chronic spontaneous urticaria: results from a nationwide, population-based study in Italy

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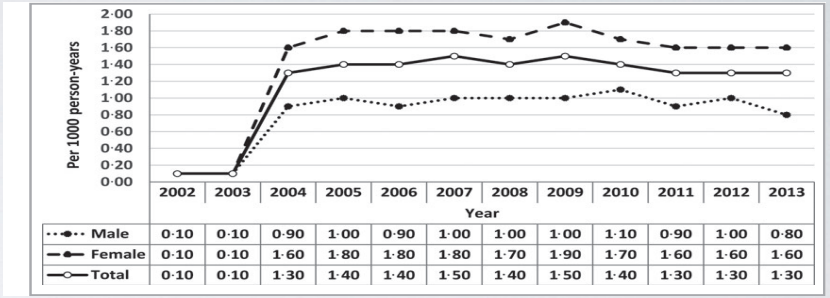
Conflicts of interest
F.L. and I.C. have provided consultancies in protocol preparation for epidemiological studies and data analyses for Novartis, Bayer and AbbVie. G.A.V. has been a speaker and/or scientific consultant and/or advisory board member for Novartis, AbbVie, MSD, Pfizer and LEO Pharma. N. Cassano has been a scientific consultant and/or speaker for Novartis, AbbVie, LEO Pharma, MSD and Pfizer. V.P., N. Cataldo and F.H. have all received grants from Astellas, Astra Zeneca, Bayer, DOC Generici, Helsinn, Hisamitsu, Kyowa, Lundbeck, Merck Serono, Novartis, Otsuka, Pfizer, Pierre Fabre and Recordati. C.C. has provided clinical consultancies for Novartis and Bayer. D.C. and E.Z. are employees of Novartis Farma Italy. M.L. declares no conflicts of interest.

DOI 10.1111/bjd.14470

Summary

Background Chronic spontaneous urticaria (CSU) is a common skin disease, but there is a paucity of precise epidemiological data on this disease.
Objectives To obtain information on the epidemiology of CSU in Italy.
Methods The data source was the Health Search IMS Health Longitudinal Patient Database. The study population was formed by patients aged ≥ 15 years, registered with a total of 700 general practitioners, homogeneously distributed across Italy. An algorithm based on the International Classification of Diseases, ninth revision, Clinical Modification was used for the identification of patients with CSU. The annual prevalence and incidence rates of CSU over a 12-year period (2002–2013) were estimated, along with demographic and clinical determinants.
Results The annual prevalence of CSU ranged from 0·02% in 2002 to 0·38% in 2013. The incidence was 0·10–1·50 per 1000 person-years. For both prevalence and incidence rates, female patients outnumbered male. The risk of CSU was statistically significantly higher in the presence of the following variables: obesity; anxiety, dissociative and somatoform disorders; malignancies; use of immunosuppressive drugs; and chronic use of systemic corticosteroids. History of autoimmune thyroiditis showed a trend towards an increased risk of CSU, though it was not statistically significant. Smoking was associated with a significantly reduced risk of CSU.
Conclusions Our findings on CSU prevalence are consistent with those obtained in previous studies. Furthermore, this large population-based study provides important information regarding the association of CSU with demographic and clinical determinants, which have been examined in the primary-care setting.

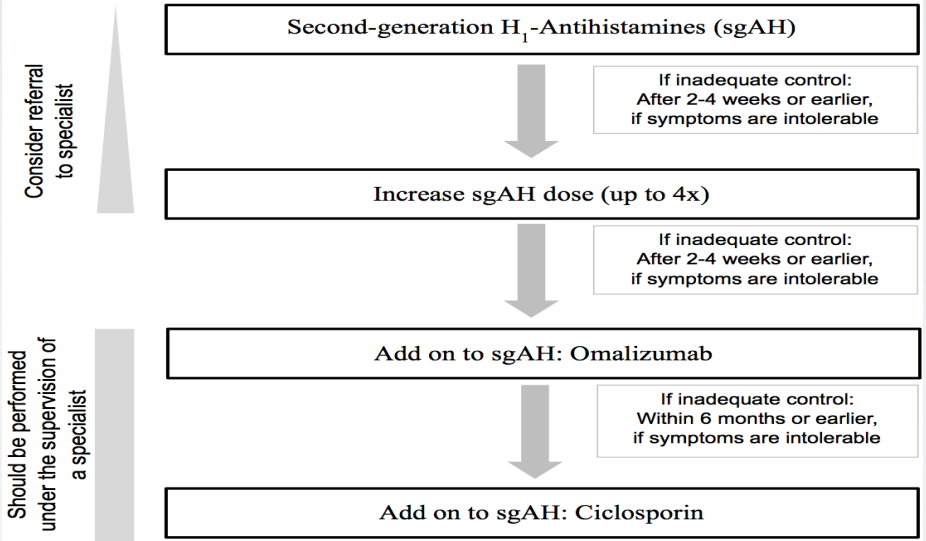


	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
Male	0·10	0·10	0·90	1·00	0·90	1·00	1·00	1·00	1·10	0·90	1·00	0·80
Female	0·10	0·10	1·60	1·80	1·80	1·80	1·70	1·90	1·70	1·60	1·60	1·60
Total	0·10	0·10	1·30	1·40	1·40	1·50	1·40	1·50	1·40	1·30	1·30	1·30

Incidenza CSU significativamente maggiore:
Sesso femminile
Obesità
Disturbo ansia, dissociativo e somatoforme
Neoplasie
Impiego farmaci mmunosoppressori
Impiego CCS sistemici
Tiroidite Autoimmune (NS)
Fumo di sigaretta (< rischio)

The EAACI/GA²LEN/EDF/WAO Guideline for the Definition, Classification, Diagnosis and Management of Urticaria. The 2017 Revision and Update

Recommended treatment algorithm for urticaria



Allergy. 2018 Jan 15. doi: 10.1111/all.13397.

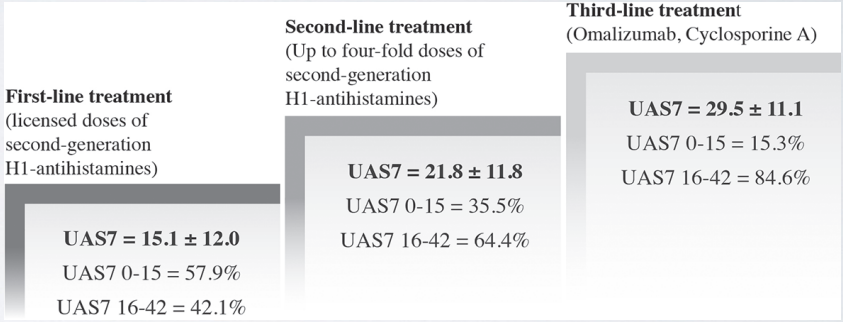
ActaDV

CLINICAL REPORT

Clinical Features of Chronic Spontaneous Urticaria that Predict Disease Prognosis and Refractoriness to Standard Treatment

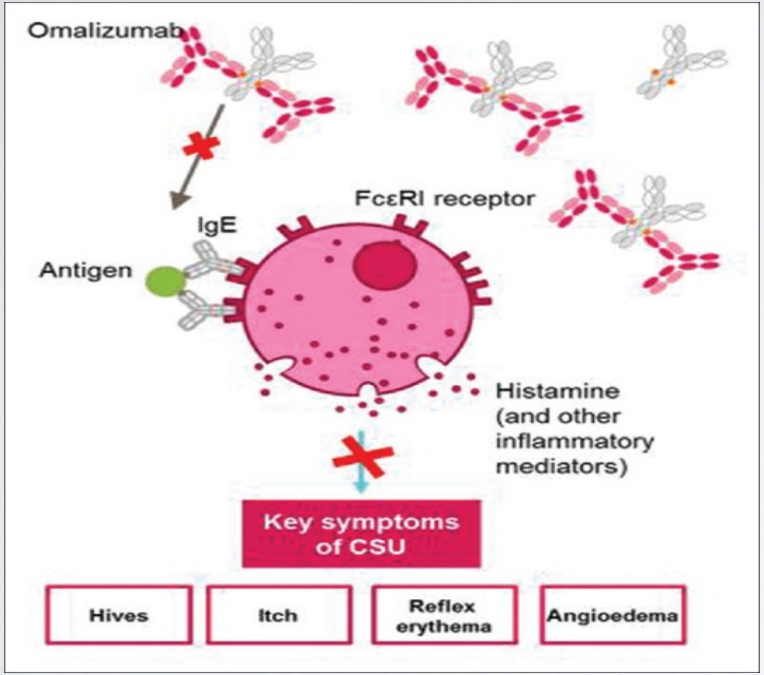
Laia CURTO-BARREDO[1], Laura RIBA ARCHILLA[2], Guillem ROURA VIVES[2], Ramon M. PUJOL[1] and Ana M. GIMÉNEZ-ARNAU[1]
[1]Department of Dermatology, Hospital del Mar – Institut Mar d'Investigacions, Mèdiques (IMIM), Universitat Autònoma de Barcelona (UAB), and [2]Adknoma Health Research, Barcelona, Spain

- Activity and the clinical course of CSU differ widely between patients
- Clinical predictors of longer course of CSU include late-onset, a concomitant chronic inducible urticaria (CIndU) and a relapsing course. Higher CSU activity is shown with serum auto-reactivity and concomitant CIndU
- More than 75% of patients were refractory to first-line treatment with licenced doses of H1-antihistamin
- Baseline UAS7 has been demonstrated to be a parameter able to predict refractoriness to H1-antihistamines
- Almost 90% of patients with baseline UAS7>16 needed cyclosporin A or omalizumab combined with antihistamines in order to control CSU symptoms.



Retrospective study on medical records of 1,056 patients registered with the Urticaria Unit of the Hospital del Mar, Barcelona, Spain, from 2001 to 2014

Omalizumab



Anticorpo monoclonale anti-IgE circolanti a bassa immunogenicità (95% umano-5% murino)

Legame Dominio Ce3 IgE con formazione di trimeri ed esameri che impediscono il legame con FceRI sulla superficie di mastociti e basofili

- diminuzione IgE libere circolanti

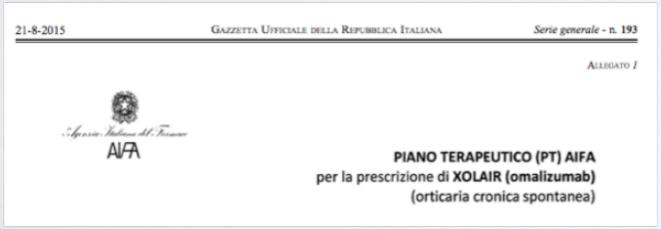
- down regulation FceRI

Modalità Somministrazione s.c.

Posologia: 300mg /4 settimane durata 6 mesi

Indicazione AIFA

Agenzia Italiana del Farmaco
AIFA


21-8-2015 GAZZETTA UFFICIALE DELLA REPUBBLICA ITALIANA Serie generale - n. 193

ALLEGATO 1

AIFA

PIANO TERAPEUTICO (PT) AIFA
per la prescrizione di **XOLAIR (omalizumab)**
(orticaria cronica spontanea)

Indicazioni registrate oggetto di valutazione	Trattamento dell'orticaria cronica spontanea in pz adulti e adolescenti (età ≥ 12 anni) con risposta inadeguata al trattamento con antistaminici H1.
Posologia	La dose raccomandata è 300 mg s.c. ogni quattro settimane, nella regione deltoidea del braccio. In alternativa, le iniezioni possono essere praticate nella coscia se vi sono motivi che precludono la somministrazione nella regione del deltoide. Vi sono esperienze limitate riguardo l'autosomministrazione, pertanto il trattamento deve essere effettuato esclusivamente da un operatore sanitario.
ATC	R03DX05
Classe di rimborsabilità e regime di fornitura	A RRL (prescrizione di centri ospedalieri o di specialista - allergologo, pediatra, dermatologo), Piano terapeutico cartaceo (template AIFA), PHT
Procedura registrazione	Centralizzata
Confezioni disponibili e prezzo	1 siringa prer. di soluz. iniett. 150mg/1ml 351,12 € (prezzo ex factory, IVA esclusa)

REVIEW

Critical appraisal of the unmet needs in the treatment of chronic spontaneous urticaria with omalizumab: an Italian perspective

Riccardo Asero[a], Giorgio W. Canonica[b], Antonio Cristaudo[c], Maria T. Fierro[d], Giampiero Girolomoni[e], Angelo V. Marzano[f], Eustachio Nettis[g], Patrizia Pepe[h], Paolo Pigatto[i], and Oliviero Rossi[j]

Purpose of review
The humanized anti-IgE antibody omalizumab has been available for patients with chronic spontaneous urticaria (CSU) in Italy since 2015. This review summarizes the unresolved issues and unmet therapeutic needs associated with omalizumab and discusses practical recommendations for its use in the management of CSU.

Recent findings
Although modern second-generation H_1-antihistamines are the standard of care for patients with CSU, adjunctive treatments (including omalizumab) may be required for effective control of symptoms in many patients. Evidence from clinical trials and experience from daily clinical practice suggest that the use of omalizumab in patients with CSU who have inadequate response to H_1-antihistamines remains challenging.

Summary
Based on current international guidelines, omalizumab labelling information and our experience in clinical practice, we provide treatment recommendations regarding the use of omalizumab in patients with CSU. These include: optimal treatment duration, the use of concomitant antihistamine therapy, the definition and management of disease relapse after treatment, and the management of patients with late or no response to treatment.

Keywords
chronic spontaneous urticaria, omalizumab, second-generation H_1-antihistamines, treatment recommendations

INTRODUCTION

Urticaria is a skin disorder that is characterized by the appearance of wheals (hives), angioedema, or both [1,2]. Chronic urticaria is defined as wheals (with or without angioedema) that persists for at least 6 weeks, and is further classified into two subtypes: chronic spontaneous urticaria (CSU) and chronic inducible urticaria [2]. CSU is the most common type of chronic urticaria [3,4], although few epidemiologic data are available. The prevalence of CSU has been reported to range from 0.1 to 0.8% [5–7], and in Italy, the annual prevalence increased from 0.02 to 0.38% between 2002 and 2013 [8**]. Adults aged 20–40 years are most frequently affected, and CSU is twice as common in women as in men [4,9].

The pathogenesis of CSU is not fully elucidated; however, a combination of mechanisms is thought to be involved [9,10]. The release of histamine from mast cells in the skin is thought to be a key factor in

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Table 1. Summary of practical recommendations concerning unresolved issues related to omalizumab treatment in patients with chronic spontaneous urticaria

Treatment duration
Recommendation
At least six doses of 300 mg of monthly omalizumab should be administered to establish whether or not there is treatment response
Treatment with antihistamines in patients receiving omalizumab
Recommendation
Maintain antihistamine therapy for the first 4 weeks of add-on omalizumab treatment, after which antihistamines may be: Discontinued or used as needed in patients with complete response Tapered to the lowest effective dosage in patients with partial response Maintained without change in patients with limited/no response
Definition of disease relapse following omalizumab discontinuation
Recommendation
Disease relapse is defined as the gradual recurrence of CSU symptoms, as measured by UAS >3 or UAS7 >16 after 30 days of H_1-antihistamines at maximum approved dosages
Management of disease relapse
Recommendation
Administer a second cycle of omalizumab (five doses of 300 mg every 4 weeks) in patients with disease relapse, repeating the cycle of six and five doses in patients with a further relapse
Management of patients with a late response to omalizumab
Recommendation
Extend omalizumab treatment for up to 6 months in patients with partial response to omalizumab (i.e., >50% to <90% improvement in UAS7) before discontinuation
Management of patients with no response to omalizumab
Recommendation
Discontinue omalizumab in patients who do not respond after 6 months of treatment, and consider ciclosporin treatment

CSU, chronic spontaneous urticaria; UAS, urticaria activity score; UAS7, urticaria activity score over 7 days

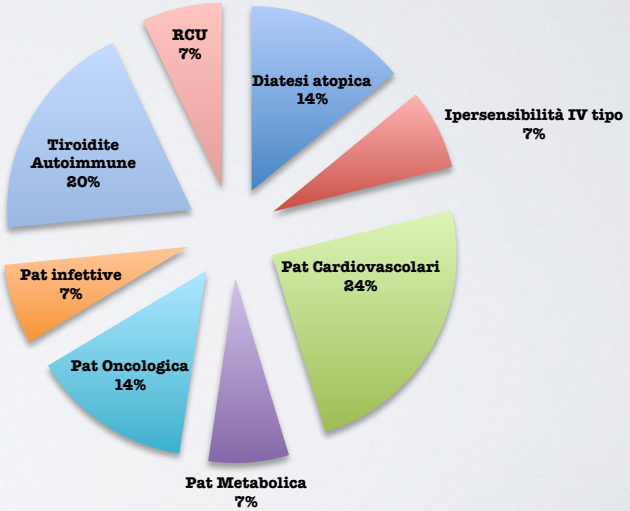
Esperienza personale

Casistica clinica

Pazienti	22
Maschi, n (%)	9 (41%)
Femmine, n (%)	13(59%)
Età media, anni (range)	42.5 (29-73)
Durata della malattia, anni (range)	4.09 (1-18)
Pazienti over 65	7/22 (31%)
% pazienti II Ciclo	4/22 (18%)
UAS basale	4.83
UAS7 basale	34,8
IgE positività	12/22 (54,5%)

Tabella I. Pazienti in terapia dal 2016 al 2018

Comorbidità

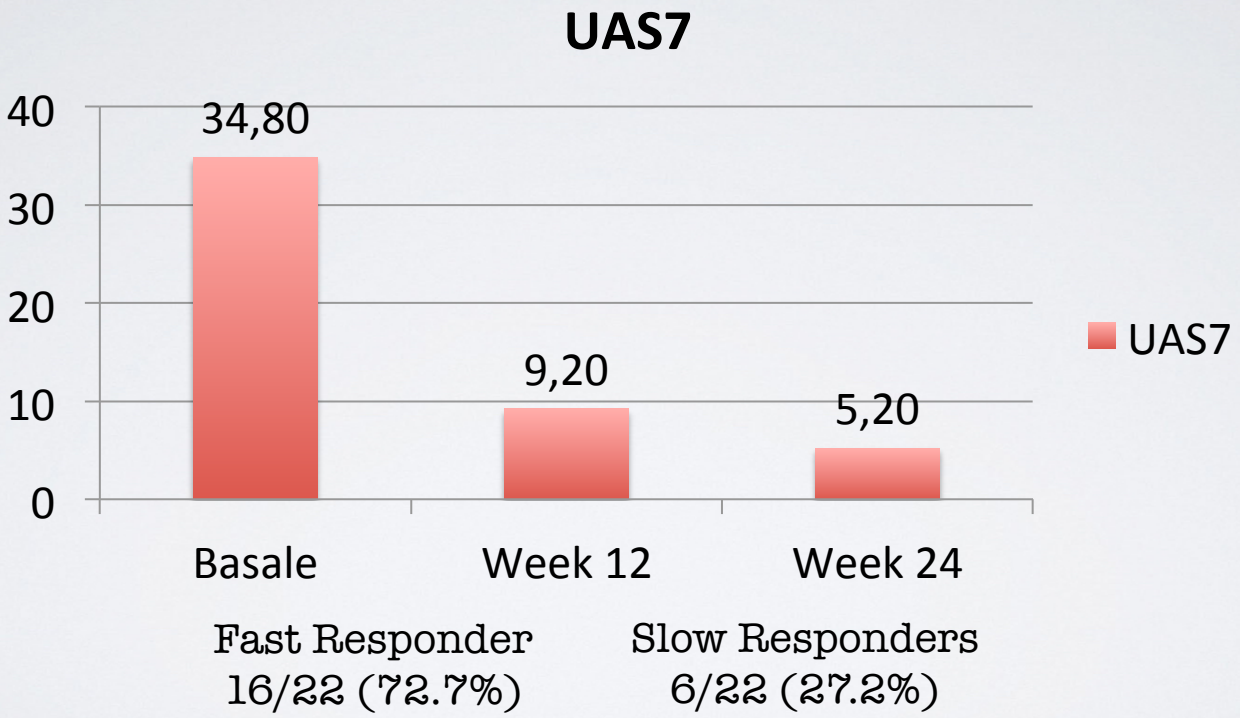


Terapie precedenti

Antistaminico H1 */**	22/22	100%
Antistaminico H2	4/22	18%
Montelukast	3/22	13.6%
Ciclosporina	3/22	13.6%
Metotressato	1/22	4.5%
Plasmaferesi	1/22	4.5%
Corticosteroide	18/22	81.8%

*Cetirizina, levocetirizina, desloratadina, fexofenadina, ebastina, bilastina, rupatadina fumarato

**Add-on Anti-H1+Omalizumab 12/22 (54.5%)


UAS7
40
30
20
10
0
34,80
9,20
5,20
Basale
Week 12
Week 24
UAS7
Fast Responder
16/22 (72.7%)
Slow Responders
6/22 (27.2%)

Esperienza personale

Sicurezza

Non sono stati osservati eventi avversi

Nessun peggioramento parametri comorbidità

Miglioramento dermatite atopica in tutti i pazienti con un caso di risoluzione completa (FU >9 mesi)

Esperienza personale

Conclusioni

Omalizumab ha dimostrato:

- Efficacia
- Velocità d'azione
- Ottimo profilo di sicurezza
- Capacità di influenzare UAS/UAS7
- Miglioramento comorbidità atopica
- Nessuna problematica sicurezza nei pazienti con altre comorbidità rilevanti

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Alessandro Giunta
Luca Bianchi