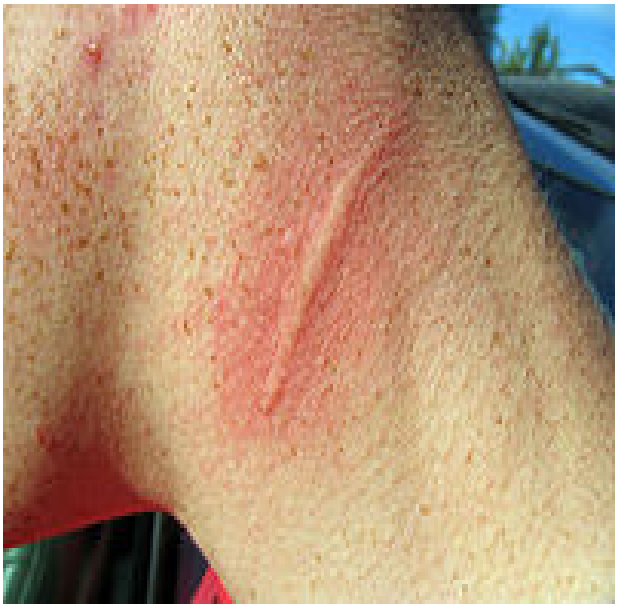

Emerging Biomarkers and Therapeutic Pipelines for Chronic Spontaneous Urticaria

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慢性蕁麻疹は少なくとも 6 週間以上すぐに消える膨疹、血管浮腫、もし

くは両方出現するものとして定義されている。

慢性蕁麻疹は強い痒み、QOL の低下とともに高頻度で鬱、不安、睡眠障害を伴う。

これまでの所、慢性蕁麻疹でのいくつかの治療に対する反応に伴った疾患の程度と経過の評価は純粋に患者の既往歴と報告された治療の結果に基づいている。

近年いくつかの報告ではあるパラメータは潜在的に疾患と関連した生物学的マーカと考えられることを示唆している。

さらにそのような生物学的マーカの到来とともに新しい生物学的製剤が慢性蕁麻疹のような潜在的難治疾患治療の革新をきたしている。

この論文の目的は疾患活動性、治療に対する反応、疾患の自然経過のような慢性蕁麻疹の重要な側面と関連した最も有望な生物学的マーカについてレヴューし、抗ヒスタミン薬抵抗性の慢性蕁麻疹に対する最近使用されるようになった薬剤もしくは現在開発中の薬剤の作用メカニズムと治療効果について述べた。

これらの知識は慢性蕁麻疹患者を治療し経過観察するために重要なインパクトをもたらすであろう。

慢性蕁麻疹において最も期待できるバイオマーカ

Biomarker	CSU feature	No. of studies showing significant association*	Comment	References
D-dimer	Disease activity	13	Higher levels are associated with more active disease	12-24
C-reactive protein	Disease activity	11	Higher levels are associated with more active disease	12,13,25-33
Prothrombin fragment 1+2	Disease activity	8	Higher levels are associated with more active disease	14,16,17,22-24,34,35
IL-6	Disease activity	4	Higher levels are associated with more active disease	28,29,33,36
Mean platelet volume	Disease activity	3	Higher levels are associated with more active disease	37-39
D-dimer	Response to antihistamines	2	Higher levels are associated with insufficient clinical response	13,40
Basophil histamine release assay	Response to cyclosporine	2	Positive result is associated with satisfactory clinical response	41,42
D-dimer	Response to cyclosporine	1	Lower levels are associated with satisfactory clinical response	43
IL-31	Response to omalizumab	1	Lower levels are associated with satisfactory clinical response	44
Basophil FcεRI receptor	Response to omalizumab	1	Lower expression is associated with insufficient clinical response	45
Total IgE levels	Response to omalizumab	1	Lower baseline levels and a lesser increase after start of treatment are associated with insufficient clinical response	46
Antithyroid antibodies	Disease course	2	Its presence is associated with longer disease duration	7,47
CD63 expression	Disease course	1	Higher levels are associated with earlier spontaneous resolution in pediatric CSU	48

CSU, Chronic spontaneous urticaria; *FcεRI*, high-affinity IgE receptor.
*Information adapted from Ref. 5.

この表では多くの生物学的マーカが記載されていますが、保険の関係から実際に日本で一般に使用できるのは CRP、総 IgE、抗甲状腺抗体ぐらいです。この表にはありませんが、

論文中にビタミン D が記載されています。ある論文（Rasool R Chronic urticaria merits serum vitamin D evaluation and supplementation a randomized case control study WAO Jounal 2015 8 15）では慢性蕁麻疹患者では血中ビタミン D が低く、ビタミン D を加えると改善したので、ビタミン D 併用を勧めているものもあります。

慢性蕁麻疹治療における臨床上の生物学的治療の現時点での概観

Biologic agent	Drug category	CSU dosing/frequency	Mechanism of action in CSU	Clinical trials identifier	References
Omalizumab*	Anti-IgE	FDA approved: 150 or 300 mg every 4 wk Off-label: doses up to 600 mg every 4 wk or 300 mg every 2 wk have been used successfully in refractory cases	Binding of IgE at the Fc region reduces free IgE levels leading to downregulation of FcεRI expression on mast cells, basophils, and dendritic cells, resulting in decreased mediator release	N/A	86-89
IVIg	IVIg	0.15 g/kg every 4 wk for 6-51 mo or 2 g/kg over 2 d every 4-6 wk	Blocks FcεRI activity on mast cells, which prevents IgE binding and degranulation. Also may decrease B-cell autoantibody production	N/A	90
TNF-α inhibitors (etanercept, adalimumab, infliximab)	TNF-α inhibitor	Etanercept: 50 mg SC weekly Adalimumab: 40 mg SC every 2 wk Infliximab: 5 mg/kg IV every 8 wk	Used in the treatment of CSU or urticarial vasculitis because TNF-α may be upregulated in the lesional and nonlesional skin of patients with CSU	N/A	91-93
Rituximab	Chimeric murine/human anti-CD20 mAb	375 mg/m^2 weekly injections for 4 wk	B-cell depletion via complement and antibody-dependent cytotoxicity results in decreased circulating autoantibody levels	N/A	94
IL-1 inhibitors (anakinra, canakinumab)	IL-1 inhibitor	Anakinra: 100 mg SC Canakinumab: 150 mg SC every 8 wk	Inhibition of IL-1β may modify the clinical course of urticarial lesions in CSU	NCT01635127	9,11,95
Ligelizumab (QGE031)	Anti-IgE	QGE031 every 4 wk × 13 wk	Similar to omalizumab excepts binds to free IgE with greater affinity	NCT02477332 NCT02649218	96
GSK2646264	Syk inhibitor	Topical application for 28 d	Upregulates transcription factors responsible for the synthesis and degranulation of proinflammatory mediators	NCT02424799	95,97
AZD1981	PGDR2 antagonist	40 mg orally 3 times daily for a total of 7 d	CRT_H2 inhibition could reduce frequency and severity of urticarial lesions because of overexpression of CRT_H2 on eosinophils in patients with CSU	NCT02031679	98
GDC-0853	Btk inhibitor	Oral administration twice daily for a total of 56 d	Unknown	NCT03137069	99

Btk, Bruton tyrosine kinase; *CRT_H2*, chemoattractant receptor homologous molecule expressed on T_H2 cell; *CSU*, chronic spontaneous urticaria; *FDA*, Food and Drug Administration; *IVIg*, intravenous immunoglobulin; *PGD2R*, prostaglandin D2 receptor; *SC*, subcutaneous; *Syk*, spleen tyrosine kinase.
Table adapted from Refs. 9 and 95.
*FDA approved in the United States for the treatment of CSU in 2014.

最近使用されるようになったのは Omalizmab（商品名：ゾレア）です。抗 IgE 抗体です。難治性蕁麻疹に効果があります。しかしそれ以外では未だほとんど使用されていません。