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THERAPEUTIC UPDATE


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Treatment of Chronic Spontaneous Urticaria

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Episodes of urticaria that recur more than six weeks are considered chronic. Chronic urticaria may be divided into chronic spontaneous urticaria with chronic idiopathic and autoimmune subtypes and chronic inducible or physical urticaria. More than one type of chronic urticaria may occur in the same individual. Consensus conferences and various organizations have recommended guidelines for the management of chronic spontaneous urticaria based on high levels of evidence and suggest the initial use of H1 antihistamines followed by montelukast, cyclosporine, and omalizumab.[1,2] However, there are other therapeutic agents with low levels of evidence that may be of value, and their use is off-label. Therapeutic agents approved for chronic spontaneous urticaria by the Food and Drug Administration include certain H1 antihistamines and omalizumab.

H1 Antihistamines

H1 antihistamines are the first-line therapeutic agents in the treatment of chronic spontaneous urticaria. The older agents are known as first-generation H1 antihistamines. Newer agents are known as low/non-sedating or second- generation H1 antihistamines and have reduced sedative and anticholinergic side effects. As first-line therapy, second- generation H1 antihistamines are preferred over first-generation H1 antihistamines. At times, first-generation H1 antihistamines may be used if high doses of second-generation antihistamines are not effective. H1 antihistamines initially should be administered in standard doses and may be increased to four times the initial dose.[3] Combinations of H1 antihistamines from different classes may be used. H1 antihistamines should be used continuously rather than on an as needed basis.

Cyclosporine

Cyclosporine, which has immunosuppressive and immunomodulatory activities, has been examined in several randomized, controlled trials. In a prospective and randomized trial in 40 subjects with autoimmune urticaria, 5mg/kg/day of cyclosporine was administered for eight weeks and then 4 mg/kg/day for eight weeks; 82.5% of subjects achieved remission in one week and the remaining 17.5% in three weeks. At a nine-month follow-up evaluation, 16 subjects were still in remission.[4] In an open trial in 35 subjects with chronic idiopathic and autoimmune urticaria, 3mg/kg/day of cyclosporine was administered for six weeks and then 2mg/kg/day for three weeks and then 1mg/kg/day for three weeks; 13 of 19 subjects achieved remission at week 12. At a three-month follow-up evaluation, 11 of 13 subjects were still in remission.[5] In an open trial in 120 subjects with chronic idiopathic urticaria, the use of 3mg/kg/day of cyclosporine for three months was associated with remission in 30. In the same study, the long-term administration of 1 to 1.5mg/kg/day for 60 to 120 months was not associated with an increase in malignant conditions, an increase in infections, or abnormal glomerular filtration rates.[6] The appropriate dosing of cyclosporine is as yet unknown.

Dapsone

Dapsone, which is an anti-inflammatory agent, has been used in case series and a double-blind study. In a prospective and randomized trial in 65 subjects with chronic idiopathic and autoimmune urticaria, the reduction in the number of wheals and pruritus was greater with the use of 50 mg of dapsone and 10 mg of desloratadine daily that it was with the use of 10 mg of desloratadine.[7] In a double-blind, placebo-controlled, parallel study in 22 subjects with chronic idiopathic urticaria, improvement of greater than 50% in weekly pruritus scores was observed in 9 subjects and in weekly wheal scores in 7 with the use of 100 mg of dapsone daily but not with placebo. Three patients achieved remission.[8]

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Intravenous Immunoglobulin

Intravenous immunoglobulin may provide a therapeutic approach in patients with severe chronic spontaneous urticaria, who have not responded to other therapy.[9] In a retrospective analysis in 6 patients with chronic idiopathic and autoimmune urticaria, 2 gm/kg (high-dose) of intravenous immunoglobulin was administered every four to six weeks for three to 11 cycles; remission was achieved in 5 patients that was maintained in four patients with a median follow-up evaluation at 16 months.[10]

Leukotriene Receptor Antagonists

Leukotriene receptor antagonists have been shown in some but not in all studies to be effective therapeutic agents. In a double blind, placebo-controlled trial in 81 subjects with chronic idiopathic urticaria, the use of 10 mg of montelukast and 10 mg of desloratadine daily decreased pruritus, wheals, and episodes of urticaria more effectively than did the use of 10 mg of desloratadine or placebo daily.[11] If a leukotriene receptor antagonist is used, it should be combined with an H1 antihistamine.

Methotrexate

Methotrexate is an antimetabolite that interferes with DNA synthesis through inhibition of dihydrofolate reductase. In a retrospective chart review of 8 patients with chronic idiopathic urticaria, the administration of 25 mg of methotrexate once a week orally or intramuscularly for 4.5 ± 3 months resulted in remission in 7 patients in 4.6 ± 1.6 weeks. At follow-up evaluation at 8.75 ± 4.6 months, 5 patients were in remission. [12] In a double-blind, placebo-controlled, randomized trial, the use of methotrexate 15 mg weekly or placebo did not show differences in wheals or pruritus between 10 subjects on methotrexate and 7 on placebo.[13]

Mycophenolate Mofetil

Mycophenolate mofetil inhibits inosine-5- monophosphate dehydrogenase and alters the proliferation of T- and B-lymphocytes. In a retrospective chart review of 19 patients with chronic idiopathic and autoimmune urticaria, remission was achieved in 10 patients and improvement in 7. The median time to remission was 12 weeks, and the median dose at remission was 2000 mg twice daily.[14]

Omalizumab

Omalizumab, which is an anti-IgE monoclonal antibody that binds to free IgE, has been studied in several, large, double-blind trials. In an international, multicenter, randomized, double-blind, placebo-controlled trial in 323 subjects with chronic idiopathic and autoimmune urticaria, the use of 300 mg of omalizumab subcutaneously monthly for 12 weeks resulted in the remission of wheals in 52% and the remission of pruritus and wheals in 44%.[15] After discontinuation of omalizumab, symptoms gradually recur over about ten weeks.[16] In an international, randomized, multicenter, double-blind, placebo-controlled trial in 319 subjects with chronic idiopathic and autoimmune urticaria, the use of 300 mg of omalizumab subcutaneously monthly for 24 weeks resulted in remission in 35.8%.[17]

Narrow-Band Ultraviolet B Phototherapy

Narrow-band ultraviolet B phototherapy (NB-UVB) was used to treat chronic idiopathic urticaria in 94 subjects in an open trial with three treatments weekly for a median of 22 treatments over a mean duration of nine weeks. Remission was achieved in 30%, marked improvement in 29%, and moderate improvement in 20%.[18] Narrow-band ultraviolet B phototherapy was used to treat chronic idiopathic urticaria in 22 subjects in a prospective trial with three treatments weekly for a median of 31.4 treatments. Remission was achieved in 45%, marked improvement in 22%, and moderate improvement in 31%. At a six-to-12-month follow-up evaluation, 40% of the patients were in remission.[19]

Tumor Necrosis Factor- α Inhibitors

There is a retrospective chart review of the use of inhibitors of tumor necrosis factor-α in a few patients with chronic spontaneous urticaria. In 4 patients with chronic idiopathic urticaria, the use of etanercept 50mg subcutaneously weekly for three to ten months resulted in remission or almost complete remission in 3.[20] In 14 patients with chronic idiopathic urticaria, the use of adalimumab 40mg twice monthly for 2 to 39 weeks resulted in remission or almost complete remission in 9.[20] These therapeutic agents should be examined in double-blind, placebo-controlled studies.

Conclusions

There are a variety of therapeutic agents that may be used to treat chronic spontaneous urticaria. Second-generation H1 antihistamines are the initial agents of choice and may be used in various combinations in up to four times the normal doses. There are recommendations to next use cyclosporine and omalizumab, owing to their high level of evidence. However, there are other agents with low levels of evidence, such as leukotriene receptor antagonists, dapsone, methotrexate, mycophenolate mofetil, intravenous immunoglobulin, and NB-UVB, which also may be of benefit and are worthy of use.

Disclosure

The author has no conflicts of interest to declare.

References

1. Zuberbier T, Aberer W, Asero R, et al. The EAACI/GA² LEN/EDF/WAO Guideline for the definition, classisfication, diagnosis, and management of urticaria: the 2013 revision and update. *Allergy* 2014; 69: 868-87.
2. Bernstein JA, Lang DM, Khan DA, et al. The diagnosis and management of acute and chronic urticaria: 2014 update. *J Allergy Clin Immunol* 2014; 133:1270-7.
3. Staevska M, Popov TA, Kralimarkova T, et al. The effectiveness of levocetirizine and desloratadine in up to 4 times conventional doses in difficult-to-treat urticaria. *J Allergy Clin Immunol*. 2010;125:676-82.

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4. Di Gioacchino M, Di Stefano F, Cavallucci E, et al. Treatment of chronic idiopathic urticaria and positive autologous serum skin test with cyclosporine: clinical and immunological evaluation. *Allergy Asthma Proc* 2003; 24:285-90.
5. Toubi E, Blant A, Kessel A, et al. Low-dose cyclosporin A in the treatment of severe chronic idiopathic urticaria. *Allergy* 1997; 52:312-6.
6. Kessel A, Toubi E. Cyclosporine-A in severe chronic urticaria: the option for long-term therapy. *Allergy* 2010; 65:1478-82.
7. Engin B, Őzdemir O. Prospective randomized non-blinded clinical trial on the use of dapsone plus antihistamine vs. antihistamine in patients with chronic urticaria. *J Eur Acad Dermatol* Venereol 2008; 22:481-6.
8. Morgan M, Cooke A, Rogers L, et al. Double-blind placebo-controlled trial of dapsone in antihistamine refractory chronic idiopathic urticaria. *J Allergy Clin Immunol Pract* 2014; 5:601-6.
9. Watkins C, Peiris E, Saleh H, et al. Intravenous immunoglobulin as a potential therapy for refractory urticaria - a review. *Inflamm Allergy Drug Targets* 2012; 11:375-81.
10. Mitzel-Kaoukhov H, Staubach P, Műller-Brenne T. Effect of high-dose intravenous immunoglobulin therapy in therapy-resistant chronic spontaneous urticaria. *Ann Allergy Asthma Immunol* 2010; 104:253-8.
11. Nettis E, Colanardi MC, Paradiso MT, et al. Desloratadine in combination with montelukast in the treatment of chronic urticaria: a randomized double-blind, placebo-controlled study. *Clin Exp Allergy* 2004; 34:1401-7.
12. Sagi L, Solomon M, Baum S, et al. Evidence for methotrexate as a useful treatment for steroid-dependent chronic urticaria. *Acta Derm Venereol* 2011;91:303-6.
13. Sharma VK, Singh S, Ramam M, et al. A randomized placebo-controlled double-blind pilot study of methotrexate in the treatment of H1 antihistamine-resistant chronic spontaneous urticaria. *Indian J Dermatol Venereol Leprol* 2014:80:122-8.
14. Zimmerman AB, Berger EM, Elmariah SB, et al. The use of mycophenolate mofetil for the treatment of autoimmune and chronic idiopathic urticaria: experience in 19 patients. *J Am Acad Dermatol* 2012; 66:767-70.
15. Maurer M, Rosen K, Hsieh HJ, *et al.* Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria. *N Engl J Med* 2013; 368:924-35.
16. Kaplan A, Ledford D, Ashby M, et al. Omalizumab in chronic idiopathic/spontaneous urticaria patients symptomatic despite standard combination therapy. *J Allergy Clin Immunol* 2013; 132:101-9.
17. Saini SS, Bindslev-Jensen C, Maurer M, et al. Efficacy and safety of omalizumab in patients with chronic idiopathic/spontaneous urticaria who remain symptomatic on H_1 antihistamines: a randomized, placebo-controlled study. *J Invest Dermatol* 2015; 135:67-75.
18. Berroeta L, Clark C, Ibbotson SH, et al. Narrow-band (TL-01) ultraviolet B phototherapy for chronic urticaria. *Clin Exp Dermatol* 2004; 29: 97-8.
19. Aydogan K, Karadogan SK, Tunali S, et al. Narrowband ultraviolet B (311 nm, TL01) pototherapy in chronic ordinary urticaria. *Int J Dermatol* 2012; 51:98-103.
20. Sand FL, Thomsen SF. TNF-alpha inhibitors for chronic urticaria: experience in 20 patients. *J Allergy (Cairo).* 2013; E pub 2013Sep 18.

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