

## Pharmacology and therapeutics

**Azathioprine as a therapeutic alternative for refractory chronic urticaria**Yuval Tal<sup>1,†</sup>, MD, PhD, Ori Toker<sup>1,†</sup>, MD, Nancy Agmon-Levin<sup>2,3</sup>, MD, and Meir Shalit<sup>1</sup>, MD

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**Abstract**

**Background** Chronic urticaria (CU) affects up to 1% of the general population. Its impact on quality of life is immense, and patients might require multiple drugs to control symptoms. The main therapeutic challenge in the treatment of CU is to maintain symptomatic control while minimizing the use of glucocorticosteroids and their plethora of side effects.

**Methods** Two patients with severe, refractory CU after treatment failure with various drugs, including high-dose cyclosporine, were administered azathioprine.

**Results** In both patients, the treatment with azathioprine resulted in a significant clinical improvement, enabling steroid withdrawal.

**Conclusion** Azathioprine should be considered as a therapeutic option for chronic, steroid-dependent urticaria, refractory to other treatments.

**Introduction**

Chronic urticaria (CU) affects up to 1% of the general population.<sup>1</sup> While the natural course of CU is limited, with an average of 2–5 years duration, many patients have long periods of impaired quality of life and require multiple drug treatments to control their symptoms.<sup>2–4</sup> The accepted management of CU utilizes a step-wise approach, trying to achieve symptomatic relief while minimizing the use of systemic glucocorticosteroids.<sup>5,6</sup> CU treatment consists of increasing doses of H<sub>1</sub> antihistamines as first-line therapy. Patients whose symptoms cannot be controlled with antihistamines require treatment with various immunosuppressive and anti-inflammatory drugs. Some patients, however, do not reach remission and receive repeated or extended courses of glucocorticosteroids to the point of becoming “steroid dependent.”<sup>7</sup> Thus, herein we present the successful use of azathioprine in the treatment of two patients with refractory CU, expanding the available therapeutic possibilities.

**Case 1**

A 51-year-old woman had urticaria for three months and was treated with standard doses of H<sub>1</sub> antihistamines and intermittent corticosteroids prior to her referral to our Allergy and Clinical Immunology Unit. While being treated with antihistamines, CU remission was achieved for short periods only after the addition of high doses of prednisone. Physical examination revealed extended, non-painful, itchy urticarial lesions with no residual pigmentation. Comprehensive laboratory results were within normal limits, while autologous serum skin test was non-reactive.

Her treatment protocol was modified to a combination of high doses of H<sub>1</sub> blockers, H<sub>2</sub> blockers, and prednisone. After two months of limited success, hydroxychloroquine was added to the treatment, leading only to a partial and transient response. The patient abruptly stopped all medication, which was followed by a severe flare-up, mandating high doses of prednisone and H<sub>1</sub> blockers, without

achieving symptomatic relief. Thereafter, cyclosporine A at a dose of 3 mg/kg was added, with a temporary successful response but a new onset of hypertension and elevated liver enzymes. Cyclosporine A was withdrawn, and azathioprine was added to the prednisone and H<sub>1</sub> antihistamine treatment. Azathioprine dosage was gradually increased (while blood counts and liver function tests remained within normal limits) up to 150 mg/d over the next several weeks, allowing patients to taper off the prednisone while maintaining CU remission. After 16 months on azathioprine as a single therapy, with no significant symptoms, azathioprine was gradually decreased, while the patient occasionally experienced only short episodes of mild pressure urticaria. Unfortunately, after several weeks after cessation of treatment, the urticaria reappeared, requiring prednisone for immediate control of her symptoms. Azathioprine treatment was reinitiated, and the steroid treatment was tapered off again. After three months of treatment with 150 mg/d azathioprine and low doses of antihistamines, no residual disease activity was observed.

## Case 2

A 39-year-old woman with severe urticarial rash for 13 years was referred to our Allergy and Clinical Immunology Unit by her general practitioner. The patient was treated with high doses of antihistamines and glucocorticoid on a regular basis. Her physical examination revealed extended, non-painful, itchy urticarial lesions covering more than 60% of her body. Comprehensive laboratory results were within normal limits except for osteoporosis that was attributed to prolonged exposure to corticosteroids. An autologous serum skin test performed following cessation of therapy for 72 hours was reactive. Treatment with a combination of high doses of H<sub>1</sub> blockers, H<sub>2</sub> blockers, and high-dose mast cell stabilizers (ketotifen) was initiated. After two months of limited success, as prednisone was repeatedly required, cyclosporine A was added. During the first two months of cyclosporine A therapy, striking improvement was noted, and both prednisone and ketotifen could be stopped. Alas, during the third month of therapy symptoms reoccurred. Cyclosporine A therapy was withdrawn, and methotrexate was initiated at a dose of 15 mg/week, in addition to H<sub>1</sub> blockers, prednisone, and ketotifen. Gastrointestinal adverse events as well as failure to control the urticaria led to change of therapy from methotrexate to azathioprine, while other medications were maintained. Azathioprine dosage was gradually increased up to 150 mg/d over several weeks (while blood counts and liver functions remained within normal limits), allowing tapering of the prednisone while maintaining the rash under control. Once remission was approached, prednisone and ke-

totifen were stopped. Azathioprine dose was decreased to 100 mg/d, and antihistamine dose was reduced to a minimal dose, taken "as-needed" usually once or twice a month. The patient has been on remission for the last three years.

## Discussion

To the best of our knowledge, these are the first published reports of successful treatment of refractory CU with azathioprine. The main therapeutic challenge in treating CU is maintaining symptomatic control while minimizing the use of glucocorticosteroids and their multiple side effects. Based on various levels of evidence, when high-dose H<sub>1</sub> antihistamines fail to induce remission, immunomodulating drugs are used as an alternative treatment.<sup>7</sup> Cyclosporine A was shown in several studies to be effective.<sup>8,9</sup> Additional drugs, e.g., hydroxychloroquine, dapsone, methotrexate, and mycophenolate mofetil, have also been reported as effective agents,<sup>10</sup> and recently the use of anti-IgE (Xolair) was found to be a promising treatment for CU.<sup>11</sup> However, these treatments have inherent limitations, including side effects, high cost, the need for intensive monitoring, and limited evidence of efficacy as even in the best scenarios up to one-third of patients do not reach remission. In the two patients reported here, a trial administration of hydroxychloroquine, ketotifen, and methotrexate was initiated before treatment with azathioprine. Studies of these drugs are limited, and there is little convincing evidence regarding their effect in patients with CU. Furthermore, none of these drugs has been studied in a double-blind placebo-controlled fashion.<sup>12</sup> Nevertheless, these drugs were introduced to our patients as steroid-sparing agents, mainly for their low side effects (hydroxychloroquine, ketotifen), or after cyclosporine A has failed to induce remission (methotrexate).<sup>13</sup> Our limited present experience is in support of using azathioprine following failure with the standard of care drugs.

Over the past 50 years, azathioprine was found to be an effective corticosteroid-sparing agent in a variety of autoimmune and inflammatory diseases. The prodrug azathioprine and its metabolites inhibit lymphocytes by suppressing purine nucleotide biosynthesis. Azathioprine was shown to induce apoptosis of T cells in chronic inflammatory states and in a healthy control group. The suggested mechanism of action consists of a mitochondrial pathway of T-cell apoptosis induced by azathioprine and its metabolites. Apoptosis required CD28 costimulation, leading to specific blockage of Rac1 activation and inhibition of Rac1-dependent mitogen-induced activation.<sup>14</sup> This mechanism could explain the role of azathioprine not only in autoimmune and inflammatory diseases but also in CU,

where T cells are known to be involved in the pathogenesis of the disease. As in autoimmune diseases, the complete response to azathioprine in CU was achieved within 2–3 months in both of our patients. However, initial response was evident as early as one month after treatment started. An inherent limitation of the presented study is the lack of structured measurement of responses to azathioprine by daily quality of life index (DQLI) and urticaria activity score over seven days (UAS7).<sup>15,16</sup>

Notably, one of the major side effects of azathioprine, namely myelosuppression, is related to intrinsic low thiopurine methyltransferase activity. Thus, one might consider measuring the enzyme activity level before initiating therapy, or gradually increase the azathioprine dose while monitoring complete blood count.

In light of the vast experience with cyclosporine A and of the promising data regarding anti-IgE antibodies in the treatment of CU, it is advisable to use them following failure of first-line agents. While there is a need for further comparative studies, in case the latter treatments fail or cause significant adverse events (mainly in the case of cyclosporine A), or when the drug is not easily available or too costly (mainly in the case of anti-IgE), and particularly in patients with probable autoimmune CU, which is steroid dependent, azathioprine could be considered as an effective, relatively safe, therapeutic option.

## References

- 1 Greaves M. chronic urticaria. *J Allergy Clin Immunol* 2000; **105**: 664–672.
- 2 Kozel MM, Mekkes JR, Bossuyt PM, *et al.* Natural course of physical and chronic urticaria and angioedema in 220 patients. *J Am Acad Dermatol* 2001; **45**: 387–391.
- 3 Zuberbier T, Bindslev-Jensen C, Canonica W, *et al.* EAACI/GA2LEN/EDF guideline: management of urticaria. *Allergy* 2006; **61**: 321–331.
- 4 Zuberbier T, Asero R, Bindslev-Jensen C, *et al.* Dermatology Section of the European Academy of Allergy and Clinical Immunology; Global Allergy and Asthma European Network; European Dermatology Forum; World Allergy Organization. ACI/GA(2)LEN/EDF/WAO guideline: definition, classification and diagnosis of urticaria. *Allergy* 2009; **64**: 1417–1426.
- 5 Powell RJ, Du Toit GL, Siddique N, *et al.* British Society for Allergy and Clinical Immunology (BSACI). BSACI guidelines for the management of chronic urticaria and angioedema. *Clin Exp Allergy* 2007; **37**: 631–650.
- 6 Zuberbier T, Asero R, Bindslev-Jensen C, *et al.* Dermatology Section of the European Academy of Allergy and Clinical Immunology; Global Allergy and Asthma European Network; European Dermatology Forum; World Allergy Organization. EAACI/GA(2)LEN/EDF/WAO guideline: management of urticaria. *Allergy* 2009; **64**: 1427–1443.
- 7 Maurer M, Weller K, Bindslev-Jensen C, *et al.* Unmet clinical needs in chronic spontaneous urticaria. A GA2LEN task force report. *Allergy* 2011; **66**: 317–330.
- 8 Vena GA, Cassano N, Colombo D, *et al.* Neo-I-30 Study Group. Cyclosporine in chronic idiopathic urticaria: a double-blind, randomized, placebo-controlled trial. *J Am Acad Dermatol* 2006; **55**: 705–709.
- 9 Loria MP, Dambara PP, D'Oronzio L, *et al.* Cyclosporin A in patients affected by chronic idiopathic urticaria: a therapeutic alternative. *Immunopharmacol Immunotoxicol* 2001; **23**: 205–213.
- 10 Shahar E, Bergman R, Guttman-Yassky E, *et al.* Treatment of severe chronic idiopathic urticaria with oral mycophenolate mofetil in patients not responding to antihistamines and/or corticosteroids. *Int J Dermatol* 2006; **45**: 1224–1227.
- 11 Maurer M, Rosén K, Hsieh HJ, *et al.* Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria. *N Engl J Med* 2013; **368**: 924–935.
- 12 Kaplan AP. Treatment of chronic spontaneous urticaria. *Allergy Asthma Immunol Res* 2012; **4**: 326–331.
- 13 Perez A, Woods A, Grattan CE. Methotrexate: a useful steroid-sparing agent in recalcitrant chronic urticaria. *Br J Dermatol* 2010; **162**: 191–194.
- 14 Tiede I, Fritz G, Strand S, *et al.* CD28-dependent Rac1 activation is the molecular target of azathioprine in primary human CD4<sup>+</sup> T lymphocytes. *J Clin Invest* 2003; **111**: 133–145.
- 15 Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI) – a simple practical measure for routine clinical use. *Clin Exp Dermatol* 1994; **19**: 210–216.
- 16 Mlynek A, Zalewska-Janowska A, Martus P, *et al.* How to assess disease activity in patients with chronic urticaria? *Allergy* 2008; **63**: 777–780.