ABOUT THE AUTHOR

Matthew Karpman MD, FRCPC

Dr. Matthew Karpman is a board-certified dermatologist in his hometown of Edmonton. He completed his medical degree at the University of Calgary before pursuing his residency at the University of British Columbia. He is currently affiliated with the Division of Dermatology at the University of Alberta and is an advocate for the medical profession on many fronts.

TREATMENT OPTIONS FOR GRANULOMA ANNULARE

The few paragraphs devoted to granuloma annulare (GA) in classic dermatology textbooks do not provide justice to the volume of patients seen with this condition in clinical practice. The epidemiology of GA is such that it affects patients of all ages. Most cases of localized granuloma annulare are diagnosed in patients before 30 years of age. Incidence is highest in women, with a ratio of 2.3 to 1.0 over men[1]. Approximately 15 percent of all patients with granuloma annulare will have more than 10 lesions (i.e. disseminated granuloma annulare). These patients are usually children younger than 10 years or adults older than 40 years. Although uncommon, cases of granuloma annulare occurring in siblings, twins, and successive generations have been reported[2]. Seasonal peaks of granuloma annulare in the spring and fall also have been described[3]. The duration of the skin eruption varies. In more than one half of patients, it resolves spontaneously within two months to two years. However, cases of disseminated granuloma annulare may last three to four years or as long as 10 years. The eruption may recur as well, with 40% of children having recurrent lesions[4].

This leaves dermatologists with the task of sifting through the abundance of poor evidence in the literature for treatment options, or basing treatment on what has clinically worked in their own patients in the past. The paucity of good clinical data might also be attributed to the self-resolving nature of this condition, which can inflate successful outcomes in coincidental treatments. So, what are my options?

This non-infectious granulomatous skin disease has a wide array of clinical presentations. The most commonly encountered variant is the localized form, characterized by its annular pink-brown plaques, often on the dorsal hands or feet (Figure 1).

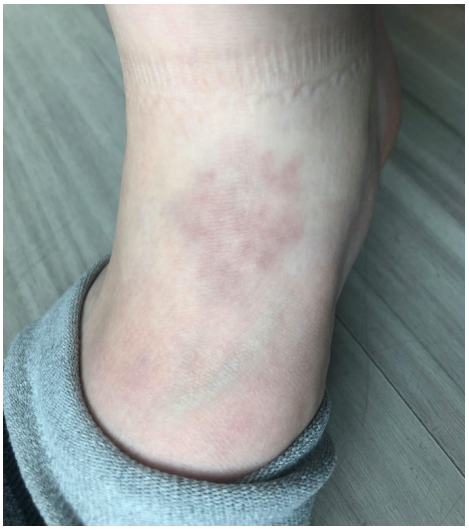

Figure 1. A case of granuloma annulare in a female

Although, localized GA starts off with a small cluster of coalesced papules, treatment is often sought by a patient after its centrifugal spread. The terms 'generalized' and 'disseminated' GA are used interchangeably in the literature and is usually defined by more than 10 papules or plaques on the body. Other rare morphologies include subcutaneous, perforating, and patch variants. GA can often be recognized clinically, but if in doubt, pathologic confirmation remains a valuable tool.

For a practical approach, treatments can be subdivided into those optimized for localized versus generalized disease. There are numerous treatment options described, but only one randomized controlled study to date involving eight patients which showed that super saturated potassium idode solution failed to demonstrate efficacy versus placebo[5]. This result may not be clinically informative given the limited access and limited use of this treatment by most dermatologists. For locally directed skin treatments, the most commonly used agents are topical corticosteroids. Despite the lack of formal evidence, the ease of application and high safety profile of these agents along with proper counselling make this first-line treatment well tolerated by patients. Potent Class I topical corticosteroids are favored for efficacy. Depending on the affected body site, topical pimecrolimus or tacrolimus can be considered and there are reports of topical dapsone having efficacy as well[6].

Intralesional triamcinolone dosed at 5mg/ml is another commonly used and efficacious modality. Nearly 70% of patients had resolution with this treatment compared to just 44% with normal saline injections[7]. Another option is cryosurgery with the application of liquid nitrogen to any erythematous papules or the annular rim of active plaques. Most anecdotal reports suggest 10-60 second freeze-thaw times, but this is somewhat dependent on the risk of blistering and scarring. When discussing treatment options with patients, I have found the progression from a topical to intralesional corticosteroid a logical idea to convey. Because of this, I have had more patients treated and more success with intralesional triamcinolone than cryotherapy thus far.

Resistant or more disseminated disease warrants consideration of systemic treatment options. Phototherapy is the most described therapy. Complete or partial clearance has been noted in up to 70% of patients using nbUVB[8]. Despite many of my patients having successes with nbUVB, recurrence can still be an issue and there may be a need for longer-term maintenance therapy. There are no phototherapy cessation guidelines for GA, so phototherapy holidays should be trialed to test whether or not sustained improvement has been achieved. The inconvenience of attending phototherapy or lack of accessibility to this treatment option itself has also been a noted barrier for some patients and should be considered when choosing this modality. Oral, topical, and bath PUVA, as well as UVA1 are also described for those who have access to one of these devices. For further elucidation of potential therapies for the treatment of generalized GA, Table 1 summarizes the key studies in this area.

For patients who require additional therapy, there are several oral options. Hydroxychloroquine at doses ranging from 200 mg to 400 mg daily have shown efficacy, although cutaneous response is often delayed by 3-6 months or more[9]. I have found it important to convey to patients the probable delayed cutaneous response to hydroxychloroquine and that no adequate clinical endpoints exist with regard to discontinuation. Despite having two cases of marked resolution on hydroxychloroquine, other patients have stopped treatment after several months because they had yet to notice a response. It is hard to counsel patients and set expectations around a formal treatment duration since response times are variable. To date, I have been individualizing the duration a patient's treatment course based on his or her motivation to achieve clear skin. If a patient has not noticed a cutaneous response after 6 months of therapy and has lost motivation to continue with an oral medication, I generally discontinue treatment.

Isotretinoin is another option with reports suggesting a starting does of 40 mg daily.

TABLE 1
Summary of Publications on Treatment of Generalized Granuloma Annulare

TREATMENT TYPE	NUMBER OF PATIENTS	DOSAGE AND DURATION	OUTCOME	SIDE EFFECTS
DAPSONE				
Steiner, 1985	10	100 mg daily for 2 to 18 weeks	Four had complete resolution, three had partial response	Headache or weakness
Czarnecki, 1986	6	100 mg daily for 4 to 12 weeks	All resolved	Fatigue
Saied, 1980	2	100 to 200 mg daily for 4 to 44 weeks	One had complete resolution, one was resolving	None
ISOTRETINOIN (ACCUTANE)				
Schleicher, 1985	1	40 mg once to twice daily for 12 weeks	90 percent resolution	Dry lips, elevated triglyceride levels
Tang, 1996	1	30 to 50 mg daily for 16 weeks	Complete response	None
Buendia-Eisman 2003	1	50 mg daily for eight weeks	90 percent resolution	None
Schleicher, 1992	7	40 mg daily for 10 weeks	100 percent response; three recurred after initial clearing, and drug discontinued	Elevated liver function test results
HYDROXYCHLOROQUINE (PLAQUENIL)/CHLOROQUINE (ARALEN)				
Carlin, 1987	1	Hydroxychloroquine 200 mg twice daily for 12 weeks	Near complete clearing	None
Simon, 1994	1	Two hydroxychloroquine, 6 mg per kg daily for six weeks	Complete clearing	None
		Four chloroquine, 3 mg per kg daily for six weeks		
CYCLOSPORINE (SANDIMMUNE)				
Fiallo, 1998	2	3 mg per kg daily for 12 weeks	Complete clearing	None
NIACINAMIDE				
Ma, 1983	1	1,500 mg daily for 24 weeks	Complete clearing	None
NARROWBAND UVB (NB-UVB)				
Cunningham et al	10	12 courses of treatment	clearance or minimal residual disease (MRD) in seven patients	None
Pavlovsky et al	13	20 treatments	54% of patients had complete response(defined as complete clearance of the lesions) or partial response (defined as >50% clearance of lesions)	None
VITAMIN E/ZILEUTON (ZYFLO)				
Smith, 2002	3	Vitamin E, 400 IU daily	Complete clearing	None
		Zileuton, 600 mg daily for eight to 12 weeks		
TOPICAL TACROLIMUS 0.1% OINTMENT (PROTOPIC)				
Harth, 2004	4	Apply twice daily for eight weeks	Two patients had healing of inflammation.	Burning, itching
TOPICAL PIMECROLIMUS 1% CREAM (ELIDEL)				
Rigopoulous, 2005	1	Apply twice daily for 12 weeks	Partial clearing	None
POTASSIUM IODIDE				
Smith, 1994	8	3 to 10 drops three times dailyfor 24 weeks	No benefit over placebo	Rhinorrhea, metallic taste, acneform eruption
INFLIXIMAB (REMICADE), ADALIMUMAB (HUMIRA), TUMOR NECROSIS FACTOR α INHIBITOR,				
Hertl, 2005	1	5 mg per kg intravenously at 0, 2, and 6 weeks and monthly for four months	Near complete clearing	None
Min and Lebwohl, 2016	7	Initial 80 mg dose, followed by 40 mg every other week	An average of 87% BSA improvement	None

IU = international units

The advantage with this treatment is that results can be seen as soon as one month[10]. I have had several patients trial this medication, with many showing marked early success. Unfortunately, several patients who showed improvement have relapsed after cessation of isotretinoin. The prospect of re-experiencing mucocutaneous side effects has been a barrier to restarting this otherwise good option.

Given its use in other inflammatory cutaneous diseases, many dermatologists would be comfortable prescribing doxycycline at 100 mg daily to try and clear GA. The mechanism of action is likely associated with its anti-inflammatory effect, but given the pathologic similarities of GA and infectious granulomas, researchers have speculated that there may be an unknown infectious etiology implicated in GA. The limiting factor with using an antibiotic would be duration of treatment in an effort to control antimicrobial resistance, but its safety profile warrants consideration. Studies of average treatment duration are sparse, as is my personal long-term use with this medication in GA.

Lastly, a new and interesting frontier in the treatment of GA includes biologic therapies with anti-TNFα agents being the most widely used. However, it should be noted that the cost of off-label biologic medication utilization would be a major barrier for most patients in Canada. Keeping access and cost in mind, there are reports of improvement in as little as 2-6 weeks and follow up showing that efficacy is sustained.[11,12]

In summary, therapeutic choice should be guided by a combination of the available data, clinical efficacy, and patient preference. Of course, given that GA has no known systemic complications, observation is an option for those who decline treatment. Generally, high-potency topical corticosteroids are a worthwhile starting point for treatment with a subsequent transition to serial intralesional triamcinolone injections or cryotherapy for those who are more motivated to see results. If desired efficacy is not achieved or if the GA is more generalized in its manifestation, nbUVB is likely the most effective and easiest next line of treatment if available. Hydroxychloroquine and isotretinoin can also be used in the right patient after discussion of expectations for improvement and potential side effects. As more biologics enter the market and costs decrease, it will be interesting to see if anti-TNFα or other immunomodulatory agents become mainstream options for off-label disease use in the future.

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