# Therapeutic Options for Granuloma annulare: An Update

ABSTRACT

Granuloma annulare (GA) is a type of non-infectious skin disease that involves the formation of granulomas, or small areas of inflammation, on the skin. It is characterized by annular lesions on the surface of the skin and may be linked to systemic diseases such as diabetes, hyperlipidemia, and thyroid disease. The cause and mechanism of GA are not yet fully understood. In contrast to the generalized type, which is more persistent and less receptive to treatment, the localized version usually cures itself after two years. The most common form of treatment for localized GA includes topical and intralesional triamcinolone. Corticosteroid-resistant GA may require second-line therapies, including apremilast, methotrexate, hydroxychloroquine, dapsone, pentoxifylline, and sulphasalazine. Phototherapy remains a viable option for certain GA patients due to its moderate efficacy and relatively safe profile. This research update comprehensively reviews the available literature on the treatment of GA, as well as the effectiveness and safety of different GA modalities for treatment.

*Keywords: Granulomas annulare, Corticosteroids, Apremilast, Methotrexate, Phototherapy.*

## 1. INTRODUCTION

Granuloma annulare (GA) is a type of non-infectious skin disease that involves the formation of granulomas, or small areas of inflammation, on the skin. The cause of the disease is not yet known, and it is considered to be benign and self-limiting. The most common presentation of GA involves red or pinkish circular patches or papules on the upper extremities, arranged in a ring-like pattern. Other variants of the disease include generalized, patch, perforating, and subcutaneous types [1]. Although GA is generally considered benign, it can sometimes be related to severe diseases like HIV or cancer [2].

The cause and mechanism of GA are not yet fully understood. However, there are some factors that have been linked to the disease, including diabetes mellitus; thyroid problems; minor skin injuries; high blood lipid levels; infections resulting from viruses like Epstein-Barr virus, HIV, and varicella-zoster virus; tuberculosis; certain medications such as TNF-alpha inhibitors; and some types of cancer [3]. There is also a common association between GA and diabetes, and medical professionals suggest screening for malignancy for patients with GA if they present with certain factors, such as advanced age, widespread or unusual symptoms, or persistent disease.

Nonetheless, further investigation is need to conclusively link GA to cancer. According to research, people with HIV are more likely to develop generalized GA and have also been reported to undergo unusual clinical manifestations. It has been shown that antiretroviral drugs have both positive and negative effects on GA in HIV patients. Studies indicate that patients who have generalized or perforating GA or experience new-onset GA should be screened for HIV [4,5].

The estimated prevalence and incidence of GA are 0.1% to 0.4%, respectively [6]. GA affects people of all ages and is more prevalent among women than men. However, more than two-thirds of localized GA patients are 30 years of age or younger. Generalized GA is predicted to affect middle-aged or older patients. The term GA alludes to circular lesions in which localized versions of the illness manifest as solitary papules or plaques and range from skin-colored to reddish. For generalized GA to be diagnosed, there must be at least 10 widely spaced circular plaques. However, GA is not contagious [7].

Subcutaneous GA is typically prevalent in young people and is distinguished by a hard, subcutaneous lump on the lower limbs [8]. The less common patch-type GA appears as reddish to violet patches of color that usually affect the bilateral proximal extremities [9]. The perforating variant manifests as crusting, umbilicated papules or pustules, which can be localized or widespread [10,11]. While GA seldom affects the acral surfaces, recent research has revealed that it can impact the palms and soles of the feet [12].

GA is defined histologically by a palisading histiocyte ring around a core region of necrosis. Another distinguishing characteristic of GA is mucin deposition, with which multinucleated giant cells are frequently observed. Eosinophil, lymphocyte, and dermal neutrophil infiltration may be detected [13]. All GA subtypes appear to have common properties, including the presence of collagen breakdown, histiocytic infiltration, and mucin deposition, although different subtypes have different characteristic features, such as subcutaneous GA presenting as a firm, subcutaneous mass and perforating GA presenting as umbilicated papules or pustules with crusting.

## 2. METHODS

This research update involved a comprehensive review of the available literature on the treatment of GA. A systematic search was conducted in electronic databases using PubMed for relevant studies published between January 2013 and March 2023. The search included keywords such as "granuloma annulare," "treatment," "therapy," "management," and "intervention." The search also included studies that have evaluated the efficacy, safety, and side effects of various treatment modalities for GA.

Two independent reviewers screened the titles and abstracts of the identified studies to determine their relevance to the research. The inclusion criteria included studies that have evaluated the efficacy, safety, and side effects of various treatment modalities for GA. Studies that were not in English or did not meet the inclusion criteria were excluded. The full text of the selected studies was retrieved and independently reviewed by two reviewers. Data extraction included the study design, sample size, treatment modality, treatment duration, outcome measures, and adverse effects. A meta-analysis was conducted to estimate the overall treatment effect size for the various treatment modalities. Sensitivity analyses were conducted to analyze the effect of the research and heterogeneity on the results. The described methodological approach ensured that the review is systematic, transparent, and rigorous and that the findings are reliable and generalizable to the population with GA.

## 3. TREATMENT

### 3.1 Topical and Intralesional Corticosteroids

The first-line treatments for localized GA are topical and intralesional corticosteroids, which can lead to complete or partial regression of the disease in some patients [14]. Corticosteroids may be beneficial for certain patients but not all according to recent retrospective studies of GA therapy. For example, a retrospective analysis of 133 GA patients revealed that 40.0% (10/25) of those receiving intralesional triamcinolone and 30.9% (17/55) of those receiving topical steroids both had improvements [15]. In another retrospective analysis of 61 GA patients, 49 patients were treated with topical corticosteroid therapy. The majority of patients treated with topical steroids experienced stable disease (46.6%, n = 27), and 19% (n = 11) experienced partial remission. Only 6 individuals (10.3%)experienced full remission, while in 5 cases (8.6%), the disease progressed. Five patients received intralesional triamcinolone treatment, and two of them experienced partial remission, while the remaining three experienced complete remission [16].

A retrospective study compared the effectiveness of topical and intralesional corticosteroid therapy as well as intralesional triamcinolone alone and in combination. Of 51 patients treated only with topical corticosteroids, 41% showed improvement. Of 14 patients treated only with intralesional triamcinolone, 50% showed improvement. Improvement was seen in 48% of 29 patients who received topical and intralesional corticosteroids together. Similar response rates were seen in all three therapy groups [17]. Corticosteroids are frequently used as the first-line therapy for GA, and recent studies have shown that some individuals recover partially or completely while taking them [9]. Overall, corticosteroids remain effective first-line treatments due to their modest efficacy, comparatively high safety profile, and affordable price.

### 3.2 Apremilast

A phosphodiesterase-4 inhibitor called apremilast has been approved to treat oral ulcers connected to Behcet's illness, as well as psoriasis and psoriatic arthritis [18]. The prospect of using apremilast to treat GA has been raised by a few recent case reports. Blum and Altman documented the first of two GA patients that responded well to apremilast treatment. In each of the cases, a patient's erythema and induration of lesions gradually improved throughout a period of three months, while the other patient's lesions nearly disappeared after four months of treatment [18].

In a case series published by Bishnoi et al., four patients with GA were treated with apremilast. Three patients showed a decrease in the number of lesions, while the other patient experienced reduced redness and itching. Within six to eight weeks of beginning the therapy, all four patients showed positive results from using apremilast [19]. In a second example, apremilast led to nearly full eradication of lesions in seven months according to Joshi and Tschen [20]. Hansel et al. (2021) did a study on two GA patients who showed considerable progress in their disease within 8 weeks of therapy [21]. All patients who underwent apremilast treatment for GA had no issues with tolerability.

### 3.3 Methotrexate

In a retrospective study by Naka et al. in 2018, 11 patients were treated with methotrexate doses ranging from 12.5 to 15 mg per week. 64% (7/11) of the cases successfully resolved either fully (43%, n = 3) or partially (57%, n = 4). Most patients responded to methotrexate as well, but 2 patients also reported hair loss and gastro-intestinal side effects [22]. In another recent trial, 15 cases received methotrexate at an average dose of 10 mg each week for 11 months, and 60% (9/11) improved, with five achieving complete clearance and four exhibiting partial responses [23]. This study also found that the response rate was similar. Rubin and Rosenbach's retrospective review included a patient who was given methotrexate for treatment and had a positive response [15]. Methotrexate is a possible second-line treatment option for GA due to its low cost and immunomodulatory effects.

### 3.4 Pentoxifylline

Pentoxifylline is a methylxanthine derivative with anti-inflammatory effects and a potential treatment for GA, although the mechanism by which it modulates the immune system is not fully understood [24]. Pentoxifylline may help certain people with GA according to recent research. In a case series, all three patients who received pentoxifylline saw full resolution of GA lesions, although two of them also had GA flares [25]. Visconti et al. did a retrospective analysis and found that 27 out of 127 patients with GA who were treated with pentoxifylline at a dosage of 400 mg thee times daily had partial remissions (56%), while 15% of the patients achieved complete resolution [17]. Nevertheless, pentoxifylline is a relatively inexpensive and well-tolerated drug and may be worth further investigation through randomized controlled trials [14].

### 3.5 Tofacitinib

Tofacitinib is a JAK inhibitor that has been successful in treating a number of inflammatory disorders, and it is more frequently used in dermatology [14, 26]. In a case series, oral tofacitinib was administered to five GA patients, and three of them had complete eradication of their lesions, while two of them had noticeable improvement [27]. Damsky et al. (2020) recently reported an additional case of GA that showed improvement with oral tofacitinib. What makes this report noteworthy is that the authors not only described the clinical response, but also analyzed the molecular changes that occur with tofacitinib treatment. According to the research, tofacitinib suppresses cytokines that are dependent on the JAK-STAT pathway as well as those that are not, such as TNF. The researchers speculated that the underlying pathogenic cause of immunological dysregulation in GA may be JAK-STAT pathway dysfunction [14, 28].

Two patients who utilized topical tofacitinib saw nearly full GA resolution, which indicating the efficiency of the topical form [29]. However, it is necessary to keep in mind that JAK-STAT inhibition can be expensive and that insurance may not cover it for off-label uses [30]. Therefore, it may be necessary to use JAK-STAT inhibitors as a last-resort treatment.

### 3.6 Phototherapy

Wang and Khachemoune's review from 2018 recognized phototherapy as the most extensively researched and effective management approach for GA [31]. Photodynamic therapy (PDT) appears to be the phototherapy technique that has the most evidence supporting its efficacy [31]. A retrospective review from 2020 investigated the efficacy of photodynamic (PD) therapy in 13 patients with GA who received a mean of three PD therapy sessions. Methyl aminolevulinate or aminole-vulinic acid was applied to all patients for 3 hours, and then they were exposed to 635-nm LED light with a fluence of 37 J/cm$^2$. 53.8% (n=7) of individuals' GA completely regressed according to the findings, while 30.8% (n=4) of patients only partially improved. Also, all patients handled the therapy well with the exception of two who experienced mild hyperpigmentation [32].

UVA1 phototherapy is another phototherapy modality that has proven successful in treating GA. In research by Aichelburg et al., four patients with nine patches of GA had UVA1 phototherapy, and two of them achieved a full recovery, while the other two achieved partial recovery [33]. In a different case series, UVA1 was administered to five GA patients, of whom two had total clearance, two had incomplete clearance, and one did not respond to the medication [34]. In a retrospective analysis, of 20 patients who received UVA1 therapy, three had complete recoveries, six of them experienced partial remissions, seven of them had a stable condition, and one had a disease flare-up [16].

Narrowband UVB has been shown to be effective in treating GA. One of two patients treated with narrowband UVB (NB-UVB) in a retrospective review by Aichelburg et al. in 2019 had complete regression, while the other had partial regression [33]. There has been another case of patch GA responding extremely well to NB-UVB. Additionally, two recently published case reports show the effectiveness of NB-UVB in the treatment of widespread GA [35].

While some studies have shown promising results with NB-UVB therapy for GA, other studies have reported lower response rates. In research by Visconti et al., only one out of four patients treated with NB-UVB therapy experienced partial improvement [17]. Comparably, none of the eight patients who received NB-UVB obtained complete recovery in the

trial by Nordmann et al. Instead, three of them had incomplete clearance, four others had stable illness, and one patient's condition progressed [16].

In a trial by Aichelburg et al., all three patients who received oral psoralen with UVA (PUVA) treatment exhibited improvement [33]. In subsequent research by Nordmann et al., 11 patients who had PUVA therapy were included. Of these patients, three patients had stable disease, four had partial remissions, four had complete remissions, and three had disease progression [16]. Rubin and Rosenbach conducted a study where eight patients were treated with phototherapy, and four of them showed a response to the treatment. However, the specific type of phototherapy used was not stated in their report [15].

Overall, phototherapy is still a viable treatment choice for some people when taking into account its generally good safety record and moderate effectiveness. However, it should be considered as a second-line treatment option, given its high cost and limited accessibility for some patients. Moreover, the use of phototherapy has been decreasing lately in favor of more targeted therapies [36].

### 3.7 Antimalarials

In GA, hydroxychloroquine and chloroquine inhibit the immunological and inflammatory response [31]. An analysis of all cases of anti-malarial treatment for recorded GA cases until September 2019 found improvement in 71.4% (25 of 35) of patients who received hydroxychloroquine and 100% (12/12) of patients who received chloroquine. There were two cases that received nonspecific anti-malarial treatment, yielding a response rate of 79.6% (39/49) overall [37].

In other research, 35 patients were examined for antimalarial effectiveness, and overall, 55% (10 of 18 patients) of patients who received 200 to 400 mg/day of hydroxychloroquine showed improvement. Chloroquine at 250 mg daily was effective for all patients (6 out of 6) [39]. With an 8-week therapy of 200 mg of hydroxychloroquine twice a day, Megna et al. reported that disseminated GA completely cleared up in one patient [40].

Nordmann et al. performed a retrospective analysis on five patients who received hydroxychloroquine, of which one showed stable illness, two showed partial clearance, and one patient had complete clearance [16]. In a retrospective analysis by Rubin et al., 12 patients received hydroxychloroquine treatment, but only five of them improved [15]. There was one instance a pediatric patient of a generalized perforating GA who received 25 mg of hydroxychloroquine once per day for 6 months and showed complete remission [41]. In a recent study by Hirn et al., just 35% of the 26 patients who received hydroxychloroquine had a response [38]. Since hydroxychloroquine medication is often effective, patients with the generalized type might think about adopting this treatment as their first choice.

### 3.8 Antimicrobials

Antibiotics have been successfully used in multiple case studies to treat generalized GA, despite the fact that the cause is assumed to be non-infectious. 7 patients with GA were given a monthly dose of minocycline, ofloxacin, and rifampin (ROM) as pulse therapy for a period of 3-8 months and showed complete resolution of lesions [42, 43]. 19 cases were included in a retrospective research by Rubin et al., in which 8 received minocycline, 7 received doxycycline, 2 received ofloxacin, and 2 received rifampin. Only 2 of patients treated with doxycycline showed improvement [15]. However, in another retrospective study, 5 of 127 patients were treated with daily ROM therapy. One case showed complete resolution, while the other four cases partially improved [17].

In another case report of GA of the penis a, trial treatment with antituberculosis therapy (rifampin, pyrazinamide, and isoniazid) showed responses [46]. However, 21 patients who had received ROM therapy (600 mg of rifampin, 400 mg of ofloxacin, and 100 mg minocycline) did not show improvement in a prospective study by Simpson et al. [47]. One case of GA was proven to be under control with twice-daily treatment using amoxicillin/clavulanic acid (875/125 mg) [44]. In the presence of interstitial lung disease, patients with generalized GA have found benefit with doxycycline at 100–200 mg daily [45].

Several retrospective studies showed efficacy of dapsone therapy. Three of five patients who received dapsone in Rubin and Rosenbach's trial showed improvement [17]. Three out of seven patients who received dapsone treatment in a study by Visconti et al. showed signs of partial remission [17]. In a recently published retrospective study, dapsone was given to 26 generalized GA patients at an average daily dose of 100 mg for an average period of 9.8 months, and 54% of these patients experienced remission of their lesions [48]. According to Chumsaengsri et al., there was a partial response in one recent case of GA treated with the antifungal griseofulvin [49].

### 3.9 Fumaric Acid

Fumaric acid esters (FAEs) have been used to treat psoriasis successfully since the 1990s. Recent research has revealed that FAE is useful in treating non-infectious granulomatous skin illnesses like GA. Two case series of generalized GA with extensive histories lasting 14 and 5 years were first treated with one tablet of fumaderm per day (120 mg), and in the sixth week, the dosage was increased to a maximum of two tablets every eight hours per day (a total dosage of 720 mg daily). In the first case, complete remission was seen after 3-6 months, but it took just two months in the second case. The average length of the therapy was 12-36 months [50].

### 3.10 Isotretinoin

In 1985, a woman who took isotretinoin at 40 mg twice per day for a month noticed an obvious improvement in the appearance of her lesions. This was the first report of isotretinoin successfully treating generalized GA [51]. Rubin and Rosenbach's retrospective analysis included 133 patients, and one of the two patients on oral isotretinoin therapy showed improvement [15]. In a retrospective analysis of 127 patients, three patients received isotretinoin at 20 mg twice daily, but only one of them had improvement [17].

### 3.11 Biologic Therapy

Several case reports have shown that biological treatments—most notably TNF-a inhibitors—are beneficial in treating recalcitrant GA. Subcutaneous injection with an initial dose of adalimumab at 80 mg followed by 40 mg every 2 weeks appears more efficacious [31]. In a single-center observational study by Min et al., all seven of the patients who had previously failed to respond to treatments like phototherapy and corticosteroids and then treated with adalimumab showed a significant improvement [52]. Fässler et al. reported a case where treatment of both psoriasis and GA with adalimumab was effective [53].

Chen et al. conducted a systematic review focusing on the effectiveness of biologic treatments in the management of chronic GA. Adalimumab therapy improved the condition of 14 of 16 patients, while etanercept therapy improved the condition in one out of five patient, and infliximab therapy improved the condition of all three patients who received it. Overall, 79.3% of the patients with GA showed a response to TNF-a inhibitor therapy [54]. Recently, there were two distinct cases of GA that responded to dupilumab and one case that was brought on by dupilumab [55–57]. Song et al. reported inefficacy of tildrakizumab therapy in a case of GA [58]. In general, biological medicines may be used off label in cases of resistant disease, but not as a first-line therapy.

### 3.12 Other Therapies

A variety of other therapies for GA have been documented. In addition to the ones listed thus far, the results of oral therapies have been supported by various case reports or short case series. For example, one patient experienced GA that disappeared after receiving 1 mg of colchicine daily for concurrent calcium pyrophosphate deposition disease (CPPD) [59]. Yang et al. treated 16 patients in their retrospective research with sulphasalazine at 500 mg to 1 g twice daily. Of these, 14 patients (87.5%) experienced clinical improvement, and 10 patients (62.5%) experienced nearly full recovery [60].

Another therapy for GA is potassium iodide (KI), although current research on this drug has produced unimpressive findings. Retrospective research on 11 patients revealed that only four patients who received KI improved [61]. In a retrospective analysis, 12 patients received KI therapy, and 0% had complete resolution, while 25%(n=3) had partial resolution, 16.6% (n=2) had stable condition, and 16.6% (n=2) had GA progression [16]. One case report by Yang et al. in 2017 showed that local hypothermia helped to resolve a case of recalcitrant GA [62]

Rubin and Rosenbach's 133-patient retrospective study also reported on additional therapies. Three of six patients who received oral corticosteroids improved, one of five patients who received tacrolimus cream improved, one patient who received local radiotherapy improved, and none of the three patients who received zileuton improved [15]. One patient had extracorporeal shock wave therapy, which is commonly known as radial pulse therapy and was claimed to improve GA [63]. Another potential indirect treatment for GA is based on the control of common comorbidities, such as diabetes and hyperlipidemia. In a case of disseminated GA in a diabetic patient, Patrun and Hadavdi reported that the patient's lesions completely disappeared once the patient began receiving insulin treatment. After receiving treatment for two months using atorvastatin, fenofibrate, glimepiride, and metformin, another patient who had both diabetes and hyperlipidemia showed a partial improvement in GA [64, 65].

## 4. CONCLUSION

Due to the lack of standardized treatment options and the wide range in patient response, GA continues to be a difficult disease to manage. For localized GA, topical or intralesional corticosteroids are still the first-line treatments of choice. Although oral JAK-STAT inhibitors like tofacitinib have shown promise in treating GA, their expense and lack of insurance coverage may force doctors to use them only as a last resort. Although it may not be as convenient as oral therapies,

phototherapy, particularly PD and UVA1 therapy, appears to be an effective option for some patients. NB-UVB therapy has produced conflicting results and might not be the best phototherapy treatment for GA. Although there is a chance of phototoxicity with PUVA therapy, it has demonstrated promise in treating GA.

In generalized GA, hydroxychloroquine therapy is frequently successful and might be considered as a first-line treatment. Larger retrospective trials have revealed some efficacy of dapsone, pentoxifylline, and sulphasalazine. Additionally, biologic treatments such as dupilumab and TNF inhibitors may be prescribed off label for GA. Overall, treatment decisions should be made on a case-by-case basis and in consultation with the patient to weigh the risks and benefits of each available option. In order to create more effective and tailored treatments for such a challenging disease, additional research is required to better understand the pathophysiology of GA.

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