

ARE ANTIBIOTICS OF ANY USE IN THE MANAGEMENT OF GRANULOMA ANNULARE IN CHILDREN?

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Abstract

Background: Granuloma annulare (GA) is a benign inflammatory dermatosis of unknown cause, of which generalised granuloma annulare (GGA) is a subtype that tends to be resistant to treatment. Various antibiotics have been used to treat GGA, the most recent being combination therapy with rifampicin, ofloxacin and minocycline (ROM). This study aims to explore the efficacy of antibiotics in treating GGA, and whether antibiotics may be useful in children with GGA.

Materials and Methods: A systematic review of literature published from 1947 to 2017 was undertaken in order to evaluate the use of antibiotics in treating GGA. Data on characteristics of children with GGA were extracted and eligible studies were then qualitatively analysed.

Results: Seven hundred and ninety (790) potential studies were identified, of which 16 were eligible for inclusion in the final analysis. Of these 16 studies, majority were case studies (n=9, 56.3%), with 2 case series (12.5%), 2 retrospective studies (12.5%) and 3 open-label prospective studies (18.8%). Main antibiotic treatments reported were either monthly combination therapy of rifampicin, ofloxacin and minocycline (ROM), or monotherapy with dapsone or doxycycline. Out of a total of 158 patients with GA, 72 patients (45.6%) were treated with antibiotics. Of the 72, 48.6% (n=35) of these patients had GGA while 4 were children; two with GA (2 with GGA), all of whom were treated with dapsone.

Conclusion: There is paucity of evidence to support the use of antibiotics in the treatment of GGA in children. Although ROM has shown promising results in adults, more studies are needed to validate these findings in children.

Key words: granuloma annulare; generalised granuloma annulare; antibiotics; children; outcome.

List of abbreviations: Granuloma Annulare (GA); Generalised granuloma annulare (GGA); Rifampicin, ofloxacin and minocycline (ROM); Localised granuloma annulare (LGA); Perforating granuloma annulare (PGA); Subcutaneous granuloma annulare (SGA); Patch granuloma annulare (PaGA); Medical subject headings (MeSH); Complete resolution (CR); Partial Resolution (PR).

Introduction

Granuloma annulare (GA) is a benign, granulomatous dermatosis (Lukács et al., 2015) of unclear aetiology with polymorphic skin presentations (Thornsberry & English, 2013). It is usually asymptomatic, although skin lesions may sometimes be pruritic or tender (Steiner et al., 1985). The 3 most common variants of GA include localised granuloma annulare (LGA), generalised granuloma annulare (GGA) and subcutaneous granuloma annulare (SGA), while rare variants include perforating granuloma annulare (PGA) (Cyr, 2006; Piette and Rosenbach, 2016).

The histological appearance of LGA is made up of foci of granulomatous inflammation and collagen alteration in the upper to middle dermis (Brey et al., 2006). There is peripheral pallisading of infiltrates consisting of histiocytes, lymphocytes and occasional giant cells around the degenerative collagen bundles (Brey et al., 2006). LGA tends to occur in patients under the age of 30, affecting female and male patients in a 2:1 ratio; and accounts for majority of cases of GA, comprising 75% of GA presentations (Cyr, 2006). It predominantly affects the dorsum of the hands or feet (Thornsberry and English, 2013) and generally resolves spontaneously within 2 years (Cyr, 2006). It can be managed conservatively, although several therapeutic options including high-potency topical corticosteroids, intralesional injections of glucocorticoids or cryotherapy, have also been shown to be effective in its treatment (Lukács et al., 2015).

On the other hand, although interstitial histiocytic infiltrate is also seen on histological examination in GGA, there is less apparent collagen alteration (Brey et al., 2006). GGA is clinically characterised by the presence of 10 or more skin lesions or widespread annular plaques, accounts for up to 15% of GA cases, and has a bimodal age distribution involving patients over 40 or

under 10 years of age (Cyr, 2006; Thornsberry and English, 2013). It has a longer disease course than LGA (Cyr, 2006) and is more resistant to treatment (Lukács et al., 2015) in spite of its histological similarity with LGA.

In PGA, the most common of the rare GA variants, skin papules, have a central crust or scale which may sometimes be umbilicated, whereas in SGA, deep dermal or subcutaneous nodules are observed (Cyr, 2006; Muhlbauer, 1980). Other rarer forms of GA will not be discussed within the remit of this review.

While there remains interest in identifying effective therapeutic options for GGA for both symptomatic and cosmetic reasons, there is a lack of good quality evidence to support one form of treatment over another in GGA, with most of the current literature surrounding treatment of GGA consisting of case reports or case series or small retrospective studies (Thornsberry and English, 2013). Examples of therapeutic options which have been reported include high-potency topical or systemic corticosteroids, immunosuppressants, and antibiotics. Various antibiotics have been proposed as potential therapy for GGA, the most recent being combination therapy with rifampicin, ofloxacin and minocycline (ROM)(Garg and Baveja, 2015). This article aims to explore the use of antibiotics in treating GGA with focus on the paediatric GA sub-group.

Material and Methods

Search strategy

A search strategy was designed to identify original articles (including case reports and observational studies) reporting the use of antibiotics in the management of granuloma annulare. MEDLINE, EMBASE and Cochrane library were searched from August 1947 to July 2017. Papers using the ISI web of knowledge were also searched, to identify relevant articles and conference proceedings. The medical subject headings (MeSH) terms used included “granuloma annulare”, “generalised granuloma annulare”, “antibiotics”, “children” and “child”. Additional searches were also carried out with the individual antibiotic names generated from the initial search (dapson, doxycycline, rifampicin, minocycline, ofloxacin, ROM). The full search strategies are shown in Appendix 1. Only studies published in English language and with full text availability were included in the review. In addition, reference lists of selected papers were screened to retrieve relevant studies.

Study selection

Studies were eligible for inclusion if they reported use of antibiotics in the management of granuloma annulare, with the intent of treating GGA in adults or children. The included studies were then further assessed for the efficacy of antibiotics in treating GGA and relevant data extracted on their use in the paediatric sub-group. Granuloma annulare was defined as groups of flesh-coloured or erythematous papules arranged in an annular shape. Localised GA was defined as GA lesions, which were limited to a specific body area, most commonly the extremities. Generalised granuloma annulare was defined as the presence of 10 or more GA lesions (Cyr, 2006). A clinical diagnosis was accepted for the different types of GA based on their clinical appearance. Histological confirmation of diagnosis was desirable but not obligatory if the authors had reported a clinical diagnosis of GA.

Exclusion criteria were articles where full text was not available in English or where duplicate data was reported. This was done by assessing whether the articles were using the same or too similar data to come to their conclusions. In such cases, only the original article was used so as not to bias the results. Articles were also excluded if they did not address the use of antibiotics to treat GGA. Two of the authors of this study (G.C. and G.O.), working independently, screened the title and abstract of papers identified by the electronic searches, evaluating inclusion and exclusion criteria for all papers. Full articles of included publications were retrieved, where available, and each article was then independently reviewed for eligibility. Discrepancies were resolved by discussion with a third author (L.A).

Quality assessment and data extraction

Two reviewers (G.C. and G.O.) independently reviewed the methodological quality of included studies, comparability of case and cohorts, and outcomes. The explanatory variables extracted included: study design, country, description of study subjects, clinical presentation, antibiotics used, side effects and outcome of treatment. The study quality assessment was undertaken according to the Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement for the conduct and reporting of systematic reviews (Moher et al., and PRISMA Group, 2009).

Data analysis

Data from eligible studies were pooled for descriptive and qualitative analysis to provide an overview of the demographic distribution of adults and children with GA, the use and efficacy of antibiotics in treating GA, risk of disease recurrence after antibiotic use, and associated side effects. The response to antibiotics (whether partial or complete resolution was achieved) was assessed qualitatively from the data provided and accepted if described as such by the authors. We also descriptively compared these outcomes of interest in children versus adults where data was available. Results were then summarised in Table format.

Results

Study characteristics

Seven hundred and ninety potential studies were identified during the initial search, of which 229 were duplicates. Of the remaining 561 studies, 545 studies were excluded on the basis of title, abstracts and duplicate data (Figure 1). The 16 eligible studies (Boyd, 2012; Cheng et al., 2016; Duarte et al., 2009; Garg and Baveja, 2013; Garg and Baveja, 2015; Gualco et al., 2007; Kiremitci et al., 2006; Kovich and Burgin, 2005; Kozic and Webster, 2011; Mahmood et al., 2015; Marcus et al., 2009; Martín-Sáez et al., 2008; Saied et al., 1980; Simpson et al., 2014; Steiner et al., 1985; Yun et al., 2009) included in the final analysis were from USA (n=7, 43.8%), Europe (n=5, 31.3% – Turkey considered to be in Europe for purposes of this review), Asia (n=4, 25%), and none from South America or Africa. Majority were case studies (n=9, 56.3%), with 2 case series (12.5%), 2 retrospective studies (12.5%) and 3 open-label prospective studies (18.8%). Main antibiotic treatments reported were monthly combination therapy with rifampicin 600mg, ofloxacin 400mg and minocycline 100mg (ROM), or monotherapy with dapsone or doxycycline. Of the open-label studies, 2 looked at ROM combination therapy (Garg and Baveja, 2015; Simpson et al., 2014) and one studied the use of dapsone in GGA (Steiner et al., 1985). Of these, one study (Simpson et al., 2014) did not state that patients had GGA and their selection criteria for treatment was patients with more than 5 GA lesions. It was, therefore, unclear how many patients in this study met the criteria for GGA according to the American definition of at least 10 lesions. Nevertheless, this article seemed to be targeting patients with disseminated GA and was, therefore, included under ‘Other/unknown GA subtypes’ of the summary table of study characteristics. Only 4 of the 16 studies reported GA in children (Cheng et al., 2016; Saied et al., 1980; Steiner et al., 1985; Yun et al., 2009).

In addition, only 3 out of the 16 eligible studies reported recurrence/relapse of disease. This occurred between 1-3 months post-treatment in 2 articles and between 3 months and 10 years in 1 article. Two of the 16 articles reported treatment failure. The remaining 13 articles did not report recurrence or state that no recurrence had occurred either during their period of follow up – it was, therefore, not possible to draw any conclusions about disease recurrence or follow up period in those studies as this may not be long enough to allow for this outcome. Where reported, length of follow up varied from 4 weeks in one of the studies to 10 years in another of the studies. Two of the 16 studies (Mahmood et al., 2015 and Simpson et al., 2014) reported progression of lesions after treatment. Most of the studies (87.5%, n=14/16) had a histopathological diagnosis of GA. A summary of the study design, study subjects, antibiotics used and outcome is presented in Tables 1 to 3.

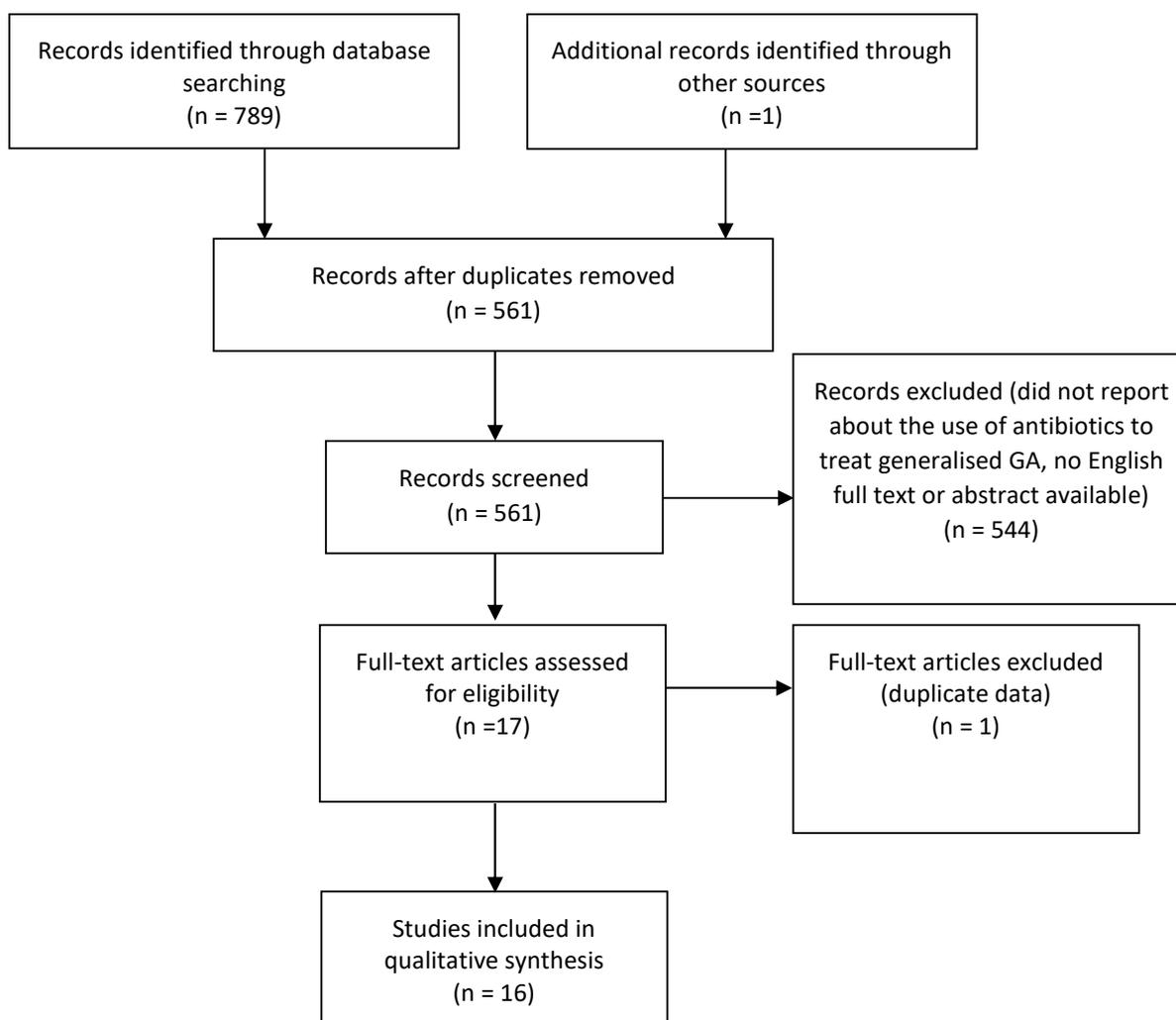


Figure 1: PRISMA flow diagram demonstrating identification and selection of eligible studies

Table 1: Description and Characteristics of GGA treated with antibiotics in the published studies that were included in the systematic review

First author	Year	Country	Study design	No. of subjects receiving antibiotics	Age	Sex	Histological confirmation of diagnosis	Antibiotic	Treatment duration	Side effects	Treatment outcome	Prior treatment	Post-antibiotic treatment
Garg (Garg & Baveja, 2015)*	2015	India	Open label prospective trial	5/6	48y-53y	F	Yes	ROM	4-8months	-	Complete resolution with post-inflammatory hyper-pigmentation/ epidermal atrophy; no recurrence	Anti-tuberculosis therapy, deflazacort pulse therapy, Clobetasol propionate 0.05% cream	-
Simpson (Simpson et al., 2014)	2014	USA	Open-label prospective study	<i>See Table 3</i>				ROM	<i>See Table 3</i>				
Mahmood (Mahmood et al., 2015)	2015	USA	Case report	1	64y	F	Yes	ROM	6 months	-	50% improvement at 3 months then progression of lesions	Topical/ intralesional corticosteroids	Adalimumab
Garg (Garg & Baveja, 2013)	2013	India	Case report	1	52y	F	Yes	ROM	5 months	-	Complete clearance after 5 months with mild epidermal atrophy, no recurrence at 3 months of follow-up	-	-
Marcus (Marcus et al., 2009)	2009	USA	Case series	4/6	49y-81y	1M 3F	No	ROM	3 months		Improvement at 3 months, complete clearance +/- residual hyper-pigmentation at 3-4 months	Liquid nitrogen, pimecrolimus hydrocortisone 1%, clarithromycin, tacrolimus, fluticasone propionate, intralesional/ topical triamcinolone acetonide, excimer laser	-
Steiner (Steiner et	1985	Austria	Open-label prospective	10/16	33y-72y	4M 6F	Yes	Dapsone 100mg	2-18 weeks	Headache and	4 Complete remission (CR)	Cryotherapy, PUVA, topical	-

al., 1985)*			study							weakness (5/16 patients) resulting in discontinuation of therapy in 2 patients.	3 partial response (PR) 1 no response 2 not evaluable All adults relapsed between 1-3 months.	steroids, retinoids	
Boyd (Boyd, 2012)	2012	USA	Case report	1	40y	F	Yes	Dapsone	-	-	Failed treatment	Topical steroids, hydroxychloroquine, pioglitazone, acitretin	Calcitriol
Martín-Sáez (Martín-Sáez et al., 2008)	2008	Spain	Case report	1	72y	F	Yes	Dapsone 100mg OD	15 months	-	Complete clearance	Topical/oral steroids, PUVA, oral potassium iodide	-
Gualco (Gualco et al., 2007)	2007	Italy	Case report	1	73y	F	Yes	Dapsone 100mg (with prednisone 25mg OD)	Ongoing at time of report	-	Clearance of lesions	Ceftriaxone	-
Kiremitci (Kiremitci et al., 2006)	2006	Turkey	Case report	1	54y	M	Yes	Dapsone 200mg OD (with concurrent topical steroid)	-	-	Clearance of majority of lesions with residual hyper/hypo-pigmented areas/anetoderma	PUVA	
Saied (Saied et al., 1980)	1980	USA	Case series	2	16y	F	Yes	Dapsone 100mg OD <i>then</i> Dapsone 100mg alternate days	2 weeks 2 weeks	-	Complete clearance at 4 weeks with slight residual hyper-pigmentation, no relapse	-	-
					50y	M	Yes	Dapsone 200mg OD <i>then</i> Dapsone 100mg OD	4 weeks -	-	Clearance of GA lesions at 4 weeks with residual post-inflammatory	0.1% halcinonide cream, fluocinonide cream, flurandrenolide tape	-

											ry hyper-pigmentation at 10month follow up			
Cheng (Cheng et al., 2016)	2016	Taiwan	Retrospective study	<i>See Table 3</i>				Dapsone	<i>See Table 3</i>					
Yun (Yun et al., 2009)	2009	Korea	Retrospective study	<i>See Table 3</i>				Dapsone	<i>See Table 3</i>					
Kozic (Kozic & Webster, 2011)	2011	USA	Case report	1	50y	F	Yes	Doxycycline 100mg BD	-	-	Ineffective	Topical steroids, oral prednisone	Pentoxifylline (ineffective), methotrexate (lost effectiveness), adalimumab	
Duarte (Duarte et al., 2009)	2009	Portugal	Case report	1	52y	F	Yes	Doxycycline 100mg OD	10 weeks	-	Almost complete resolution, sustained at 1 year	Dapsone, pulsed light	-	
Kovich (Kovich & Burgin, 2005)	2005	USA	Case report	1	94y	M	Yes	Doxycycline 100mg BD	3 months	GI disturbance leading to dis-continuation of therapy	Partial improvement	Fluocinonide ointment	Fluocinonide ointment	

*See Table 2

USA=United States of America; y=years; m=months; F=female; M=male; ROM=rifampicin, ofloxacin and minocycline; CR=complete response, PR=partial response, PUVA=photochemotherapy with psoralen/UVA; mg=milligrams; OD= once daily; BD=twice daily; GI=gastrointestinal

Table 2: Description and Characteristics of Localised GA treated with antibiotics reported in articles listed in Table 1

First author	Year	Country	Study design	No. of subjects receiving antibiotics	Age	Sex	Histological confirmation of diagnosis	Antibiotic	Treatment duration	Side effects	Treatment outcome	Prior treatment	Post-antibiotic treatment
Garg (Garg & Baveja, 2015)**	2015	India	Open label prospective trial	1/6	55y	F	Yes	ROM	8 months	-	Complete clearance with post-inflammatory hyper-pigmentation, no recurrence at 12 month follow up	Clobetasol propionate 0.05% cream	-
Marcus (Marcus et al., 2009)**	2009	USA	Case series	2/6	44y	1M 1F	No	ROM	3 months	Insomnia, body fluid discolouration	Improvement at 3 months, complete clearance with residual hyper-pigmentation at 5 months/post-inflammatory pigmentation	Pimecrolimus hydrocortisone 1%, desoximetasone, mometasone furoate, topical triamcinolone	-
Steiner (Steiner et al., 1985)**	1985	Austria	Open-label prospective study	6/16 (1 10 year old girl, 5 adults)	10y, 22y-69y	4M 2F	Yes	Dapsone 100mg (adults)/ Dapsone 50mg (child)	6-18 weeks	-	2CR, 4PR All adults relapsed between 1-3 months. Remission sustained in 10 year old girl.	-	-
Cheng (Cheng et al., 2016)	2016	Taiwan	Retrospective study	<i>See Table 3</i>				Dapsone	<i>See Table 3</i>				

**See Table 1

USA=United States of America; y=years; m=months; F=female; M=male; ROM=rifampicin, ofloxacin and minocycline; CR=complete response, PR=partial response, PUVA=photochemotherapy with psoralen/UVA; mg=milligrams; OD= once daily; BD=twice daily; GI=gastrointestinal

Table 3: Description and Characteristics of other GA subtypes/treatment modalities reported in articles listed in Tables 1 and 2

Author	Year	Country	Study design	No. of subjects	Age	Sex	GA subtype	Treatments	Treatment duration	Side effects	Treatment outcome
Simpson (Simpson et al., 2014)	2014	USA	Open-label prospective study	21	18y-75y	1M 20F	Not reported – all subjects had more than 5 lesions; biopsy proven in 15 of 21 subjects	ROM	6 months	-	10 subjects had at least 50% improvement in lesions, of which 3 had 75% improvement and 1 had complete resolution. No response or worsening of existing lesions in 6 subjects. <50% improvement in the remainder (n=5)
Cheng (Cheng et al., 2016)	2016	Taiwan	Retrospective study	44	2y-75y (16 children, 28 adults)	23M 21F	16 generalised (13 adults, 3 children) 22 localised (14 adults, 8 children) 2 perforating (both children) 4 subcutaneous (1 adult, 3 children) All biopsy proven	Reported in 35/44 patients Dapsone: 5 adults (unclear how many generalised, how many localised GA) and both children with perforating GA, unclear if other children received dapsone Intralesional/topical steroids: 12 adults (unclear how many generalised, how many localised GA), unclear how many children 17 adults (13 generalised, 4 localised) and 8 children (3 generalised, 3 localised, 2 perforating) received treatment in total No treatment: 5 adults (4 localised, 1 s/c) and 5 children (2 localised, 3 s/c) Not reported: 6 adults and 3 children, all with localised GA	-	-	Reported in 35/44 patients Adults receiving dapsone: 2/5 PR and 3/5 CR Adults receiving intralesional/ topical steroids: 3/12 CR, 5/12 PR, 4/12 not in remission (CR or PR) PR/CR achieved in all 8 children who received treatment (of which at least 2 with perforating GA received dapsone) No treatment: 4/5 good response (adults), 4/5 remission (children) Recurrence noted in 3 adults and 2 children (GA subtype/treatment modality not stated); disease free interval 3m to 10y
Yun (Yun et al., 2009)	2009	Korea	Retrospective study	54	3m-84y (24 children out of 54)	29M 25F	Generalised; all biopsy proven	5 dapsone 13 topical steroids 8 systemic steroids 3 hydroxychloroquine 2 PUVA 2 cyclosporine 2 isotretinoin 19 not reported Unclear how many adults/children received each type of treatment	-	-	Efficacy: Dapsone 2/5 Topical steroids 10/13 Systemic steroids 6/8 Hydroxychloroquine 1/3 PUVA 1/2 Cyclosporine 1/2 Isotretinoin 1/2

USA=United States of America; y=years; m=months; F=female; M=male; ROM=rifampicin, ofloxacin and minocycline; CR=complete response, PR=partial response, PUVA=photochemotherapy with psoralen/UVA; mg=milligrams; OD= once daily; BD=twice daily; GI=gastrointestinal

Antibiotic treatment in Granuloma Annulare

A total of 158 patients of all ages in 16 studies were included in the final analysis (Table 1), of which 72 patients (45.6%) were treated with antibiotics. Of these 72 patients, there were 63 adults, 4 children, and 5 patients whose age could not be determined from the original articles.

Patients with GGA constituted 48.6% of patients who received antibiotic therapy (n=35/72). Of the remaining patients, 9 had LGA (12.5%), 2 had PGA (2.8%) and the GA subtype was unknown in 26 patients (36.1%). Patient demographics and treatment modalities, including types of antibiotics used, are summarised in Tables 4 and 5.

Table 4: Summary of the characteristics of included studies

Characteristic	Number (% of total)
Total number of patients	158
Gender	
Male	66 (41.8)
Female	92 (58.2)
Age	3months – 94 years
Adults (>=18y)	116 (73.4)
Children (0 to <18y)	42 (26.6)
GA subtype	
Generalised	100 (63.3%)
Localised	31 (19.6%)
Perforating	2 (1.3%)
Subcutaneous	4 (2.5%)
Unknown	21 (13.3%)
Treatment	
Antibiotics	72 (45.6%)
Other treatments	42 (26.6%)
No treatment	10 (6.3%)
Unknown/not reported	34 (21.5%)

Table 5: Types of antibiotic treatment given by subtype of GA.

Antibiotic treatment (n=72)	Generalised GA	Localised GA	Perforating GA	Unknown
Dapsone only	19 (26.4%)	6 (8.3%)	2 (2.8%)	5 (6.9%)
Dapsone with steroid	2 (2.8%)	0 (0%)	0 (0%)	0 (0%)
Doxycycline	3 (4.2%)	0 (0%)	0 (0%)	0 (0%)
ROM combination therapy	11(15.3%)	3 (4.2%)	0 (0%)	21 (29.2%)

Type of antibiotic treatment given by subtype of GA. R, Rifampin; O, ofloxacin; M, minocycline; ACA, amoxicillin/clavulanic acid.

Granuloma annulare in children (less than 18 years old)

Children made up 26.6% (n=42/158) of the subjects. Of these, only 9.5% (4/42) of children received antibiotic therapy. This constituted 5.6% (4/72) of the total number of patients who were treated with antibiotics (Figure 2). These consisted of 1 child with GGA, 1 child with LGA, and 2 children with PGA. All 4 children were treated with dapsone. A further 5 out of 42 children (11.9%) did not receive any treatment (2 had LGA and 3 had SGA). Treatment modalities in the remaining 33 children (78.6%) were not reported.

Treatment outcomes

Outcomes of antibiotic treatment in adult patients (18 years old and above)

From the data, 82.5% (52/63) of the adult patients had partial or complete response to antibiotic therapy, with the remaining 17.5% (11/63) of adults having no response, disease progression or unevaluable treatment outcome in spite of antibiotics. Also, 4 of the 5 adults (80%) receiving no treatment achieved spontaneous remission. Of the initial responses to treatment, disease relapse/recurrence was reported in 12 adults with GGA who received dapsone. A further 3 adults also had recurrence of disease; however, it was unclear from the original articles what treatment modality or GA subtype they had.

Outcomes of antibiotic treatment in children (less than 18 years old)

All 4 children treated with antibiotics achieved partial to complete remission. This was sustained in the 2 children with GGA and LGA respectively. Four of the five children who received no treatment (80%) also achieved remission spontaneously. Disease recurrence was reported in 2 children, although it was not clear from the original article (Cheng et al., 2016) what treatment modality or disease subtype these children had, including whether or not these were the 2 children with PGA who were treated with dapsone.

Side effects reported following treatment with antibiotics

Side effects reported included headache and weakness in patients treated with dapsone, gastrointestinal disturbance in a patient treated with doxycycline, and insomnia and body fluid discoloration in patients treated with ROM. These adverse effects led to discontinuation of dapsone and doxycycline but not ROM treatment in the respective patient groups, although no inferences can be made regarding the statistical significance of this (Tables 1 and 2). Of note, all side effects were reported in adults with no side effects to antibiotic treatment reported in children.

Discussion

GGA does not have a universally recognised gold standard treatment. Indeed, many of the subjects in the articles reviewed had failed one or more treatment modalities before being commenced on a trial of antibiotic therapy. This is consistent with the findings of Lukacs et al. (2015) looking at various treatment modalities for GGA, with no conclusive evidence that one treatment is more effective than the other. Similarly, there is no single recommended treatment modality for GGA in children, albeit GGA is uncommon in this patient population. Given the antecedent side effects of other treatments, it is not surprising that antibiotics are gaining acceptance in the treatment of GGA.

Among the articles reporting antibiotic use in GA, we observed that dapsone was the most efficacious treatment modality, followed by ROM combination therapy. Only a small number of articles reported on monotherapy with doxycycline/minocycline. Dapsone has the ability to suppress non-specific inflammatory changes, hence its wide use in a number of dermatological conditions, and particularly its success in the management of GGA (Hoxtermann et al., 1998; Wollina, 2008). Each of the 3 main types of antibiotic therapies (ROM vs doxycycline vs dapsone) appears to be largely effective at inducing at least partial remission in GGA lesions, with few reports of initial (primary) treatment failure, although, this could be secondary to publication bias rather than a true reflection of the efficacy of antibiotic treatment. Disease relapse was noted in a small number of patients treated with dapsone and ROM. In these patients, where reported, next-line treatment options included adalimumab, calcitriol, pentoxifylline, methotrexate and fluocinonide ointment. While it is not possible to recommend one antibiotic choice over another on the basis of our current findings, combination therapy with ROM appears to be the best tolerated by subjects with none of the reported side effects leading to discontinuation of treatment. From observational studies to date, ROM therapy appears to have shown promise in small open-label prospective trials and may, therefore, warrant further studies with larger, randomised, controlled trials to determine if this may, in future, be a potential treatment modality recommended for the management of GGA.

Our results showed the potential strengths of combining outcomes of rare events through a systematic review of the literature. However, these findings should be interpreted with caution, as it is most likely that we might have under-estimated the number of cases of GGA due to slight differences in author definitions and regional differences in what constitutes GGA. For example, Simpson et al. (2014) appeared to target patients with disseminated GA but their selection criteria for treatment was patients with more than 5 GA lesions, which does not qualify as GGA as per the American definition of at least 10 lesions. Subjects in this article have, therefore, not contributed towards our overall count and analysis of patients with GGA, but rather have been classified as 'Other/unknown GA subtype'. Furthermore, not all of the studies included stated if histopathological confirmation of the diagnosis of GA had been sought, and, therefore, classification relied on authors' descriptions of the lesions.

In addition, the lack of robust studies such as randomised controlled trials was a significant limitation, and none of the literature looking at ROM combination therapy was in children. The paucity of evidence to support the use of antibiotics in the treatment of GGA in children is further hampered by tetracycline and, in some regions, the quinolones not being licensed for use in children. Given that GA often resolves spontaneously without treatment, albeit this may take many years and it is not possible to predict a time frame by which the disease could resolve, conservative management may be an appropriate course of action. Ultimately, until there is good quality evidence to recommend any specific treatment modality, it is necessary to exercise clinical judgment

and weigh up the risks and benefits of different treatment options versus conservative management on a case-by-case basis while taking into consideration the individual needs of the patient when determining the best management plan for the patient.

Conclusion

This review demonstrates that dapsone is currently the most frequently used single antibiotic in the treatment of GGA in children. Although ROM has shown some promising results in adults, there is paucity of evidence to support its use in the treatment of GGA in children, and more studies are therefore needed to validate these findings.

Conflicts of interest: The authors declare that they have no competing interest

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Authors' contributions

GC reviewed the literature, analysed the data, was involved in the interpretation of the data and writing the report (including the first draft), co-ordinated the production of the manuscript, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis, and approved the final manuscript as submitted. LA carried out the initial analyses, was involved in the interpretation of the data and writing the report, and approved the final manuscript as submitted. GO conceptualised and designed the study, was involved in the interpretation of the data and writing the report, co-ordinated the production of the manuscript, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis and approved the final manuscript as submitted. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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