Consequences of disease and treatment in ANCA-associated vasculitis

Tuin, Janneke

Chapter seven

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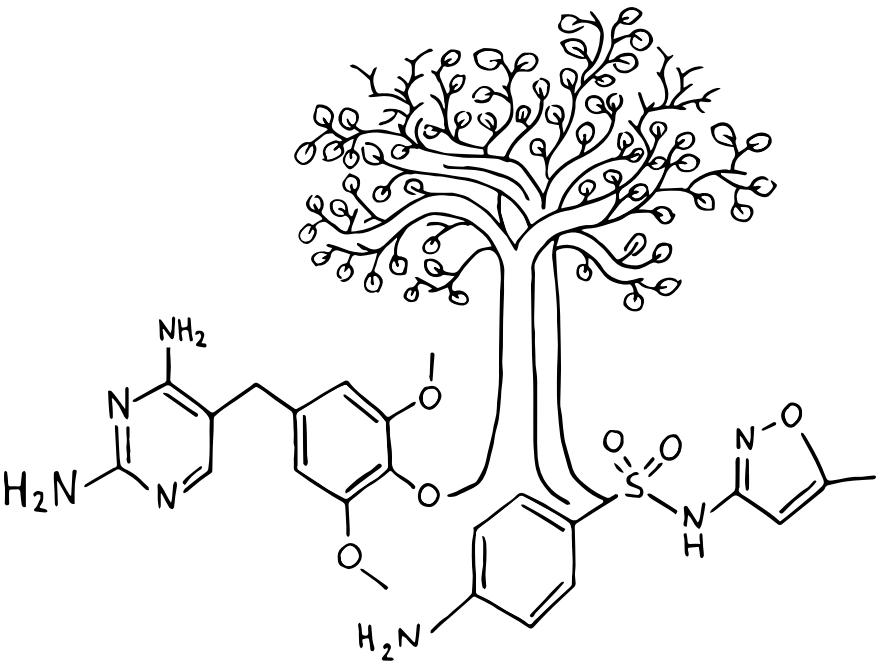

Trimethoprim/sulfamethoxazole for the induction of remission in localised and early systemic granulomatosis with polyangiitis: a cohort study

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Abstract

Background. In a selected group of granulomatosis with polyangiitis (GPA) patients, disease is limited to the upper and/ or lower airways without organ- or life-threatening symptoms. The literature suggests that these patients can be treated successfully with trimethoprim/ sulfamethoxazole (T/S). However, data remain conflicting about its effectiveness.
Aim. The aim of this study was to evaluate effectiveness and safety of T/S therapy.
Design. Retrospective cohort study.

Methods. We evaluated effectiveness and safety of T/S therapy in 55 patients with localised (n= 31) and early systemic (n= 24) GPA treated at our center between 1989 and 2013.

Results. Fifty patients were treated with T/S monotherapy 800/160 mg twice daily and five received T/S as add-on to other immunosuppressive medication. With T/S therapy 36 patients (66%) attained remission. A relapse developed in 18 patients (50%) after a median disease free survival of 21 [IQR 10-26] months. In 19 patients (34%) therapy failed, 14 patients had refractory disease and started additional immunosuppressive therapy, 5 patients stopped T/S due to adverse drug reactions, primarily rash and nausea. A CRP threshold of 12.5 mg/L, calculated from the ROC curve, yielded a sensitivity of 76.9% and specificity of 68.6% for therapy response. Below this threshold, 89% of patients (n=24) attained remission, whereas 11% had refractory disease (n=3).

Conclusions. T/S therapy can induce remission in a substantial number of GPA patients with localised and early systemic disease. T/S can be considered as first-line therapy in these patients if at presentation CRP is low.

Background

Granulomatosis with polyangiitis (GPA) is an autoimmune disease causing granulomatous inflammation in the respiratory tract and systemic necrotizing vasculitis of the small to medium sized blood vessels. In the majority of patients antineutrophil cytoplasmic antibodies (ANCA) are present, mostly directed against proteinase 3 (PR3) and in the minority against myeloperoxidase (MPO) (1,2).

Generalized disease with widespread inflammation is often preceded by an initial phase of localised or early systemic disease. However, in approximately 5% of patients, GPA will remain confined to the respiratory tract without the development generalized disease during long-term follow-up (3,4).

Several case-reports and small series have demonstrated that trimethoprim/sulfamethoxazole (T/S) monotherapy can successfully induce remission in this selected group of patients, including one prospective study (5-8). However, others report poor effectiveness with T/S monotherapy (3). Patients treated with T/S will not be exposed to the side-effects of standard immunosuppressive induction therapy, comprising cyclophosphamide, rituximab or methotrexate in combination with glucocorticoids (9). T/S could be an attractive alternative for these patients.

Data are scarce on the effectiveness of T/S monotherapy. Therefore, the objective of this study was to analyse the effectiveness and safety of T/S as induction therapy for patients with localised and early systemic GPA.

Patients and methods

Patients

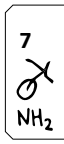
All consecutive patients treated with T/S monotherapy or as add-on for the induction of remission of newly diagnosed and relapsing GPA in the University Medical Center Groningen between 1989 and 2013 were included in this retrospective cohort study. Patients were classified as having GPA according to definitions adopted from the Chapel Hill Consensus Conference Nomenclature and the algorithm developed by Watts et al (1,10). Patient and clinical characteristics were collected from medical records. For this study no formal IRB approval was required. Patients who attained remission were followed until a relapse developed, death or lost to follow-up, whichever came first.

Treatment

Induction therapy was T/S 800/160 mg twice daily for at least 2 years. One minor (11 years) received 600/120 mg daily. Most patients with episcleritis received additional local therapy. Patients on low dose maintenance immunosuppressive therapy after generalized diseased, who developed a localised or early systemic relapse were also included, provided that the immunosuppressive therapy was not changed, making it plausible that the observed outcome was attributable to T/S. T/S was stopped in consultation with the patient after two years.

Measures

Disease activity at diagnosis was scored using the Birmingham Vasculitis Activity Score (BVASv.3) (11). ANCA were detected by indirect immunofluorescence and through antigen specific enzyme-linked immunosorbent assay (ELISA).



Definitions

Localised disease was defined as GPA confined to the ENT tract or lungs without vasculitis outside these regions, without threatening vital organ functions and serum creatinine <120 µmol/L. Patients who only experienced malaise as a constitutive symptom in addition to ENT or pulmonary symptoms were classified as localised disease. Early systemic disease was defined as GPA involving the ENT tract or lungs and systemic vasculitis outside these regions without threatening vital organ functions and serum creatinine <120 µmol/L. In addition, to be considered for therapy with T/S only, signs of active renal (erythrocyturia > 25/ul, proteinuria, change in renal function) or peripheral neurologic involvement (sensible/motoric neuropathy) had to be absent. Generalized disease was defined as systemic vasculitis outside the ENT tract and lungs, and with threatening vital organ functions, but serum creatinine <500 µmol/L, whereas severe disease was accompanied by organ failure or serum creatinine >500 µmol/L. These definitions were adopted from the EUVAS study group (12).
Effectiveness of T/S therapy was defined by induction of remission (BVAS=0). Refractory disease was defined as persistent or increased disease activity necessitating immunosuppressive medication. A relapse was defined as the worsening, or new onset of disease activity attributable to active inflammation. Adverse drug reactions were defined as symptoms or signs possible attributable to, and occurring after the start of T/S, and improving after discontinuation of T/S. Nasal swabs were performed in patients during follow-up. Patients with at least two cultures testing for Staphylococcus aureus (S. aureus) were considered persistent carrier when all tested positive for S. aureus, patients were considered non- carrier when none tested positive, and the remaining patients were considered intermittent carriers.

Statistics

Statistical analysis were performed using SPSS 22.0 and GrapPad Prism (version 5.00). Parametric data are reported as mean and standard deviation (SD) and nonparametric data as median and interquartile range [IQR]. Differences between groups were tested using the Student's T-test, Mann-Whitney U or the Fisher's exact test as appropriate. Disease free survival was calculated using Kaplan-Meier curves with log-rank testing. Receiver operating characteristics (ROC) showing sensitivity and 1- specificity were used to determine cut-off levels of CRP with significant difference between therapy outcome. Sensitivity reflects the proportion of patients with refractory disease and high CRP, whereas specificity reflects the proportion of patients with remission and low CRP. The optimal cut-off value was determined by the Youden index (13). A two-sided p value of < 0.05 was considered statistically significant.

Results

Patient characteristics

Fifty-five GPA patients were included in this study. Twenty-seven presented with localised disease and 20 with early systemic disease at diagnosis. Four presented with a localised relapse and four with an early systemic relapse. Five out of eight relapsing patients received immunosuppressive therapy at the time of presentation. Two received low dose (≤10mg) prednisolone, one received cyclophosphamide 25 mg and two received azathioprine 50 and 25 mg daily, respectively. A

flowchart of all assessed (n= 644) and eligible patients is shown in supplementary figure 1.
The median follow-up was 10 [IQR 4-14] years, with a total follow up of 564 patient years. Baseline characteristics of all participants are shown in table 1. Symptoms of disease activity at start of T/S therapy are shown in supplementary table 1.

Table 1. Baseline characteristic of all included patients.

Characteristics	**n= 55**
Age (years)	49 (18)
Sex (female), n (%)	33 (60%)
T/S therapy for diagnosis/ relapse, n	47/8
Diagnostic histology, n	35 (64%)
BVAS	7 [6-8]
Localised disease	6 [6-7] (n=31)
Early systemic disease	8 [6-10] (n= 24)
ANCA staining IF, titre at diagnosis	1:80 [1:40; 1:160]
cANCA, n	1:80 [1:80-1:160], n=38
pANCA, n	1:160 [1:80-1:320], n= 10
Atypical/ negative ANCA, n	n= 5/ n=2
ANCA specificity	
Anti-PR3, n	39
Anti-MPO, n	8
Negative, n	8
S. aureus, n	
Positive	24
Negative	21
Not tested	10
CRP (mg/L)11 [3-17]	
Hemoglobin (mmol/L)	8.2 (0.8)
Serum creatinine (µmol/L)	85 (20)
MCV (fL)	87.2 (5.0)

Abbreviations: SD: standard deviation; T/S: trimethoprim/sulfamethoxazole; BVAS: Birmingham Vasculitis Activity Score; ANCA: antineutrophil cytosplasmic antibodies; IF: immunofluorescence;Anti-PR3: anti-proteinase 3; Anti-MPO: anti-myeloperoxidase; IQR: interquartile range; S. aureus: Staphylococcus aureus; CRP: C-reactive protein; MCV: mean corpuscular volume

Effectiveness

Remission was induced in 36 patients (65.5%). Fourteen patients (25,5%) had refractory disease and five patients (9%) discontinued therapy due to T/S -related adverse drug reactions. T/S as add-on induced remission in four patients (80%), and one patient (20%) had refractory disease. Median time to remission was 14 weeks [IQR 11-20] (figure 1).
Treatment was switched in patients with refractory disease after a median time of 14 weeks [IQR 3-36]. In eight patients with refractory disease there was no or insufficient reduction of symptoms and in six there was progression of disease. The majority of patients were subsequently treated with cyclophosphamide and glucocorticoids (Table 2).

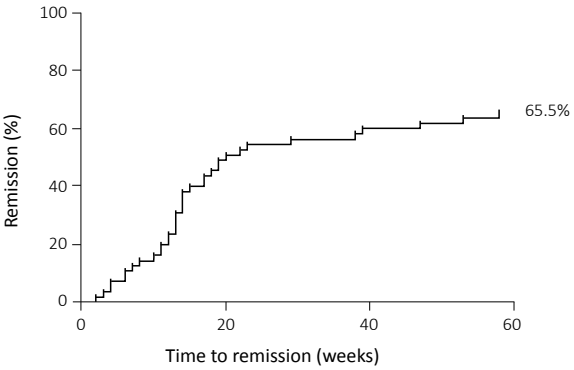


Figure 1. Time to remission after start of trimethoprim/sulfamethoxazole.

Table 2. Therapy and outcome after refractory disease with trimethoprim/sulfamethoxazole monotherapy.

Number of patients	Treatment	Outcome
9	Cyclophosphamide (n= 4) and CY and maintenance AZA (n= 4) or MTX (n=1)	7 remission; 1 persistent episcleritis; 1 died
2	Methotrexate and glucocorticoids	2 remission
1	Prednisolone added to T/S monotherapy	1 remission
2	T/S monotherapy continued	1 remission after long course of treatment; 1 persistent ENT complaints, but further treatment refused

Abbreviations: CY: cyclophosphamide; AZA: azathioprine; MTX: methotrexate; ENT: ear- nose and throat

Of note, one 86 year old patient improved clinically with T/S therapy until three months later rapidly progressive glomerulonephritis developed. Prompt immunosuppressive therapy could not induce remission. The patient died of combined renal failure, malnutrition, a gastro-intestinal bleeding, and infections of the respiratory and urinary tract.

Predictors of therapy outcome

We investigated predictors associated with therapy outcome (table 3). Patients who attained remission had a significantly lower CRP at start of treatment compared to patients with refractory disease (8 mg/L [IQR <3-17] vs. 15 mg/L [IQR 13-79]; p= 0.007). The area under the ROC curve for CRP and therapy response (remission or refractory disease) was 0.754 ([95% CI 0.600- 0.908], p= 0.007, figure 2). The optimal cut-off value was 12.5 mg/L with a sensitivity of 76.9%, a specificity of 68.6%, and a Youden Index of 0.455. Remission was attained in 89% of patients with CRP ≤12.5 mg/L (n= 24), whereas 11% had refractory disease (n=3). In contrast, 52% of patients with CRP >12.5 mg/L attained remission (n= 11), and 48% of patients had refractory disease (n= 10).

Table 3. Patients with refractory disease and remission.

Characteristics	Refractory disease (n= 14)	Remission (n= 36)	*p*
Newly diagnosis, n (%)	13 (93%)	29 (81%)	0.414
Histological confirmation of diagnosis, n (%)	9 (64%)	23 (64%)	1.000
Localised disease, n (%)	7 (50%)	16 (44%)	0.761
CRP (mg/L)	15 [13-79]	8 [<3-17]	0.007
ANCA positive(IF) at diagnosis, n (%)	11 (85%) n=13, 1 missing	29 (81%)	1.000
Anti-PR3 positive at diagnosis, n (%)	11 (79%)	24 (67%)	0.507
S. aureus positive before start	4 (36%)	16 (57%)	0.301
T/S, n (%)	n= 11, 3 missing	n= 28, 8 missing	

Abbreviations T/S: trimethoprim/sulfamethoxazole; vs: versus; CRP: C-reactive protein; IQR: interquartile range; ANCA: antineutrophil cytosplasmic antibodies; IF: immunofluorescence; anti-PR3: proteinase 3; S. aureus: Staphylococcus aureus; UMCG: University Medical Center Groningen

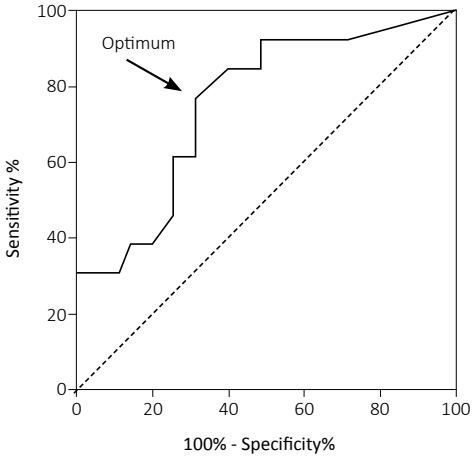


Figure 2. ROC curve for CRP and therapy outcome: remission or refractory disease. The Youden Index optimum indicates a sensitivity of 76.9% and specificity of 68.6%.

Staphylococcus aureus

Forty patients had at least two nasal cultures for S. aureus during remission induction. Fifteen patients (37,5%) were non-carriers, 21 (52,5%) intermittent carriers and 4 (10%) persistent carriers. These differences did not affect remission rate (Figure 3). Resistance to T/S therapy developed in at least four patients during the remission induction phase, of whom three attained remission.

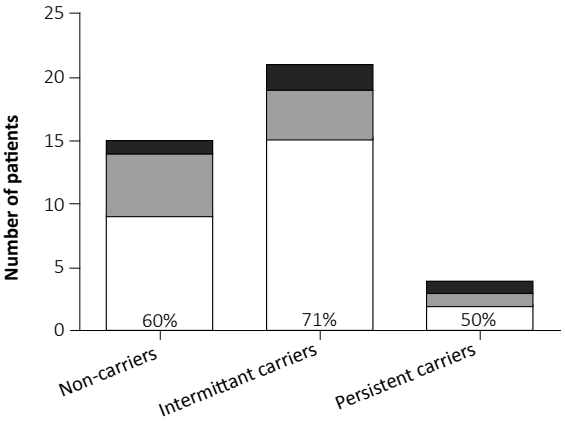


Figure 3. *S. aureus* carriage and therapy outcome.

Relapse

Eighteen of the 36 patients in remission did not develop a relapse until the end of follow-up, with a median follow-up of 151 [IQR 54-165] months. Fifty per cent of patients relapsed after a median disease free survival of 21 [IQR 10-26] months. Eleven relapses occurred during T/S use. Five relapses were localised, nine early systemic, two generalized and two severe. Disease free survival was similar for patients with localised disease and early systemic disease (p= 0.717).

Adverse drug reactions

T/S-related adverse drug reactions occurred in 12 patients and consisted primarily of nausea and rash, which were transient in most (supplementary table 2). However, therapy had to be stopped in five patients before remission could be attained. All adverse reactions were reversible within 1 day to 2 weeks after discontinuation of therapy.

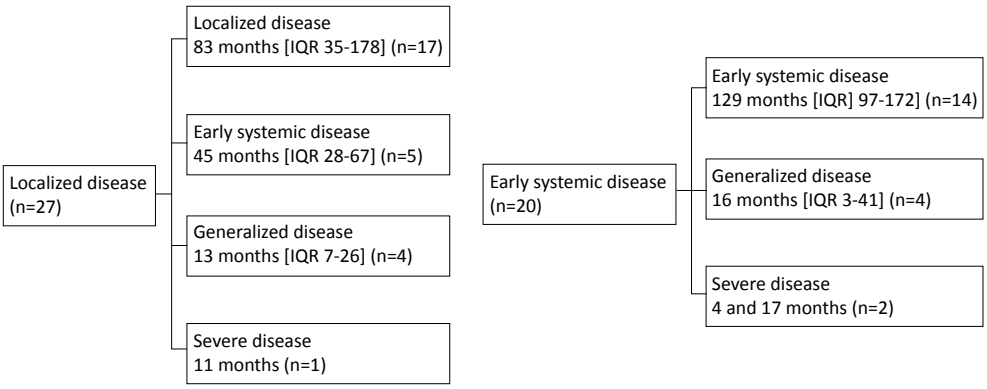


Figure 4. Disease stage at the end of follow-up, including median and interquartile range of follow-up in months.

As expected, serum creatinine and mean corpuscular volume significantly increased and hemoglobin significantly decreased after the start of T/S. These effects were small, did not necessitate therapy adjustment and were reversible after discontinuation of therapy (data not shown).

Disease progression and mortality

Disease stage at the end of follow-up for newly diagnosed patients is shown in figure 4. This includes patients with refractory disease and progression, who developed early systemic (n=1); generalized (n=3) and severe disease (n=2) shortly after diagnosis.

Twelve patients died during follow up. One patient died of exacerbated GPA 4 months after start of therapy, as described above. One patient died of a relapse 19 months after T/S therapy. Four patients died of treatment-related comorbidity, especially cyclophosphamide-related; 2 urothelial cell carcinoma (230, 245 months after start T/S), 1 myelodysplastic syndrome (223 months after start T/S), 1 systemic varicella-zoster virus infection (61 months after start T/S). All 4 patients had received one or more courses of cyclophosphamide and other immunosuppressive therapies in addition to the disease episode treated with T/S. One patient died 174 months after start of T/S of a squamous cellular carcinoma. Five patients died of unrelated causes after a median period of 94 months [IQR 86- 97] after therapy.

Discussion

This study showed that trimethoprim/sulfamethoxazole therapy can successfully induce long-term remission in approximately two-third of patients with localised and early systemic GPA in a cohort of consecutive patients. The remission rate was substantially higher, up to 89%, in patients with CRP less than 12.5 mg/L at start of therapy. CRP as a reflection of systemic inflammation appears to be a good predictor of therapy success and a better predictor than disease stage. A similar percentage of patients with localised and early systemic disease attained remission.

In the literature the reported effectiveness of T/S monotherapy varies widely with some reports showing an insufficient response in 73%, whereas others show improvement in 58% up to 93% of patients (3,5,8,14). These contradicting results might be explained by various factors; most reported studies are small, different definitions of remission or improvement are used and cohorts are heterogeneous. In addition, one of the biggest challenges is to await the therapeutic effect of T/S. In half of the patients remission can be expected after three to four months, but can take up to 5 or 6 months in some. This requires considerable patience of both patient and treating physician and necessitates close clinical monitoring for signs of disease progression during this period.

Fifty per cent of patients in remission relapsed, most within two years after induction of remission. This is in accordance with the relapse rate found by Holle et al. and similar as the relapse rate described in patients with generalized disease (3,15).

T/S monotherapy could be regarded a safe therapy. All adverse drug reactions were quickly reversible and almost all patients with refractory disease reached remission after switching to immunosuppressive therapy. Still, close monitoring remains necessary.

Finally, we showed that of all assessed GPA patients an estimated percentage of 4% (27/ 644) presents with localised disease, which is consisted with literature (3,4,16). In our study more patients showed disease progression to a generalized state. We did not exclude patients who progressed to

generalized disease within one year, in contrast to the studies of Pagnoux et al and Holle et al (3,4). In addition, we had an extensive follow-up of ten years, compared to 58 months and 4 years in both before mentioned studies, respectively.

Researchers have already speculated about an etiological role of infections in the development of GPA for many years. This is indirectly supported by studies showing reduced incidence of relapses with T/S therapy (17,18). With ensuing research, several microbes and viruses have been suggested to cause or worsen the course of disease (19-22). Up to now, the role of S. aureus has been the most convincing and various mechanisms by which S. aureus induces or exacerbates GPA have been proposed (23). For example, through super antigens of S. aureus which promote extensive T-cell proliferation, priming of neutrophils or by S. aureus derived cationic enzymes such as acid phosphatase, which bind to endothelial cells and might induce glomerulonephritis (24). However, the exact mechanism has yet to be elucidated.

Considering the evidence linking bacteria to the course of GPA, the use of an antimicrobial agent, such as T/S seems rational. However, it has been hypothesized that this folate antagonist similar to other sulfonamides and sulfones not only possess antimicrobial properties, but also exerts an anti-inflammatory effect (25). This has been supported by in vitro studies showing inhibition of the myeloperioxidase (MPO)-hydrogen peroxide-halogen (MHPH) system of neutrophils. Inhibition of the MHPH system diminishes the generation of reactive oxygen species and lysosomal enzymes (26). These are necessary for effective phagocytosis in situations of infections, but cause tissue destruction and macromoleculair alterations such as antiproteinase inactivation in normal tissue (27). This is an interesting mechanism of action, especially in a disease such as GPA in which neutrophils are thought to play a central role. We did not find evidence that T/S acts merely trough eradication of S. aureus since, persistent non-carriers, persistent carriers and patients with a S. aureus strain resistant to T/S attained remission. The potential anti-inflammatory properties of T/S are interesting for further research.

Obviously, our study has a number of limitations. This is a retrospective cohort study. It might be questioned whether all patients without diagnostic histology had GPA. Patients were diagnosed using the Chapel Hill Consensus nomenclature and the algorithm of Watts, which means that patients with histology compatible with GPA needed additional signs or symptoms, like a positive ANCA in ELISA (1,10). The assessment of treatment effectiveness is challenging, especially due to the considerable period of time before a treatment effect can be observed. The EULAR recommends to assess treatment effectiveness after a predetermined period of time (28). For T/S this has yet to be determined, but should until than be patient-tailored during close monitoring. Selection bias might have occurred, since the UMCG is a tertiary referral center. We therefore do not think our results to be overestimated. Unfortunately, our cohort is underpowered for extensive analyses; however it is a fairly large cohort with extensive follow-up in comparison with other studies in literature.

Conclusion

In conclusion, trimethoprim/sulfamethoxazole monotherapy might be considered a first-line therapy in patients with localised or early systemic GPA if at presentation CRP is low. Ideally a multicenter prospective study would confirm our results and determine the optimal treatment of this small subset of patients and the place of trimethoprim/sulfamethoxazole therein.

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AUTHORS' CONTRIBUTIONS

JT, JS and CA were all involved in the design of the study, data retrieval, analyses and interpretation of the data. All authors were involved in drafting and revising the manuscript. All approved the final manuscript.

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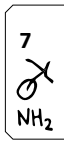

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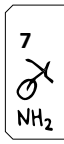
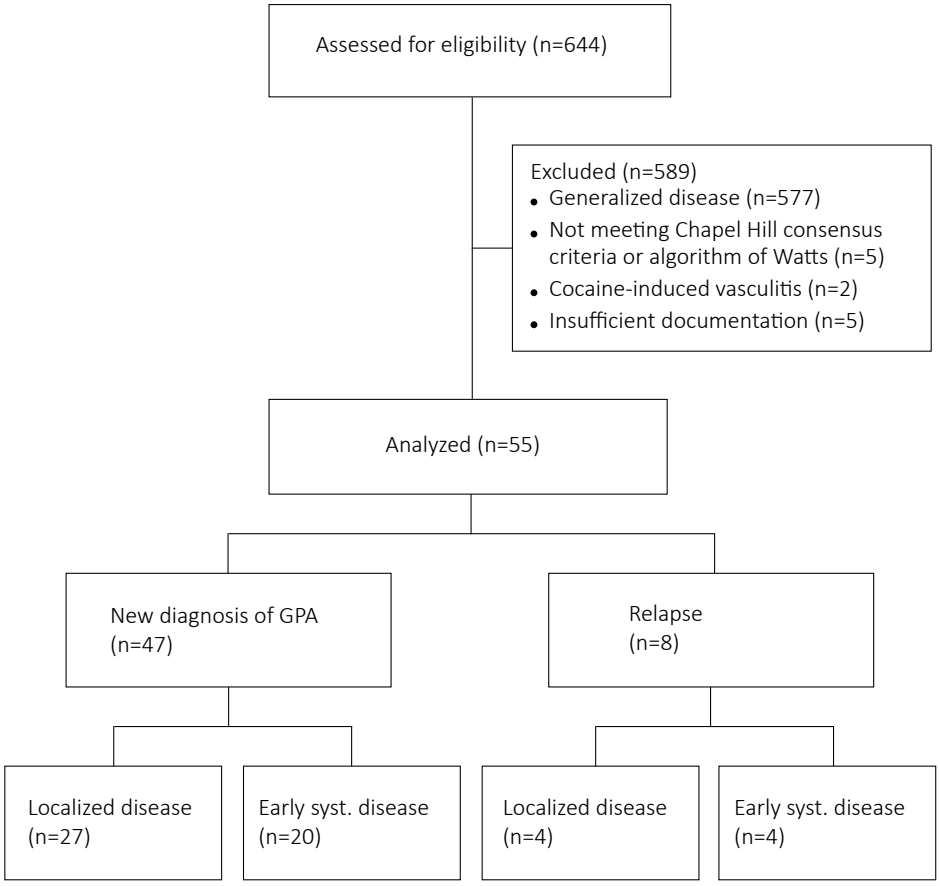


Supplementary material

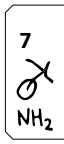


Supplementary figure 1. Flowchart of all assessed and analysed patients.

Supplementary table 1. Disease activity at start of trimethoprim/sulfamethoxazole therapy and therapy outcome.

	Therapy outcome			
	Cohort	Rem.	Ref. dis.	SE
Total number	55	36	14	5
Localised disease				
Nasal symptoms* (+ malaise)	13 (+11)	10 (+6)	1 (+3)	2 (+2)
Hearing loss, malaise, nasal symptoms,	1	1	0	0
Hearing loss, conductive hearing loss malaise	1	0	1	0
Hearing loss, malaise, nasal symptoms, significant subglottic inflammation	1	0	1	0
Significant subglottic inflammation, hoarseness stridor, nasal symptoms	2	2	0	0
Malaise, nasal symptoms, hoarseness stridor, cough, dyspneu or wheeze	1	0	1	0
Nodules fibrosis, haemoptysis	1	1	0	0
Early systemic disease				
Nasal symptoms +				
Malaise, arthralgia/arthritis (MA)	3	3	0	0
Hearing loss, MA/ fever (≥ 38.5˚C)	2	0	0/1	1/0
Headache, weight loss (≥2 kg)	1	0	1	0
Malaise, fever (<38.5 ˚C)	1	1	0	0
Lung infiltrate, nasal symptoms +				
MA, weight loss ≥2 kg	1	1	0	0
Malaise, weight loss ≥2 kg, cough	1	0	1	0
Arthralgia/arthritis, dyspneu/ weeze,	1	1	0	0
Other skin vasculitis, nasal symptoms +	1	1	0	0
MA	1	0	1	0
Malaise, episcleritis	1	0	1	0
Episcleritis +	2	2	0	0
Nasal symptoms, MA	1	1	0	0
Nasal symptoms, mouth ulcer	1	1	0	0
Conjunctivitis, arthralgia/arthritis, nasal symptoms	1	1	0	0
Conjunctivitis, blurred vision, infiltrate malaise	1	0	1	0
Dacryocystitis	1	1	0	0
Cutaneous ulcer	1	1	0	0
Significant proptosis (+ blurred vision)	2	1	0 (+1)	0
Haematuria, arthralgia/arthritis, nasal symptoms	1	1	0	0

Abbreviations: Rem.: remission; Ref. dis.: refractory disease; SE: side-effects; MA: malaise and arthralgia/ arthritis. *Nasal crusting, bloody nasal discharge, crusting and sinus involvement are grouped together as 'nasal symptoms' in order to improve readability and interpretation of the data.



Supplementary table 2. Side-effects of trimethoprim/sulfamethoxazole therapy.

Patient	Symptoms	Therapy stopped or continued
Male	Nausea	Stopped after 3 weeks
Male	Nausea, rash	Stopped after 2 weeks
Female	Fever, rash, itch	Stopped after 1 week
Male	Rash, itch	Stopped after 2 weeks
Female	Erythematous papular lesions, perivascular inflammatory infiltrate, leucopenia, myalgia	Stopped after 4 days
Female	Transient nausea	Continued
Female	Transient rash and itch	Continued
Male	Transient diarrhoea	Continued
Female	Transient nausea	Continued
Male	Rash	Stopped after 2 years
Male	Rash	Stopped after 2 years 9 months
Female	Dubious abdominal pain*	Stopped after 7 years

*Dubious side-effect since the relation with trimethoprim/ sulfamethoxazole could not univocally be proven.