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## Efficacy and safety of treatments in cutaneous polyarteritis nodosa: A French observational retrospective study

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35 **Disclosures:** none to declare

36 **Key words:** vasculitis, cutaneous polyarteritis nodosa, treatment, colchicine, glucocorticoids,  
37 azathioprine, methotrexate

38

39

40

41 **Abstract**

42 **Background:** Cutaneous polyarteritis nodosa (cPAN) is a form of medium-sized vessel  
43 vasculitis. Despite a disabling and prolonged course, data on treatment efficacy and safety  
44 remain scarce.

45 **Objectives:** We aimed to describe treatment efficacy and safety in patients with cPAN.

46 **Methods:** This was a multicentre retrospective observational study, recording clinical and  
47 biological data together with treatments received. The primary outcome was the rate of  
48 complete response (CR) at month 3. Secondary outcomes included drug survival, and safety  
49 was assessed.

50 **Results:** We included 68 patients who received a median of 2 therapeutic lines (interquartile  
51 range 1-3). Overall, 13/42 (31%) patients achieved CR with colchicine, 4/17 (23%) with  
52 dapson, 11/25 (44%) with glucocorticoids (GCs) alone, 1/9 (11%) with NSAIDs, 11/13  
53 (84%) with GCs+azathioprine (AZA) and 7/15 (47%) with GCs+methotrexate. GCs+AZA  
54 had the best drug survival (median duration 29.5 months [IQR 19.5-36.0]). Response at  
55 month 3 was decreased with peripheral neurological involvement (odds ratio 0.19 [95%  
56 confidence interval 0.03-0.81], p=0.04). Overall, the rate of treatment-related adverse events  
57 was 18%, which led to treatment discontinuation in 7% of patients.

58 **Limitation:** Retrospective study

59 **Conclusion:** Colchicine seems to confer good benefit–risk balance in cPAN without  
60 peripheral sensory neuropathy. GCs+AZA seems the best treatment for disease relapse.

61

## 62 **Introduction**

63 Polyarteritis nodosa is a rare necrotizing vasculitis affecting medium-sized vessels.<sup>1</sup>  
64 Among adults, two clinical entities are distinguished: systemic polyarteritis nodosa<sup>2</sup> (sPAN),  
65 an acute systemic life-threatening disease<sup>2</sup>, and cutaneous polyarteritis nodosa (cPAN), a  
66 skin-limited vasculitis, although joint or peripheral sensory neurological involvement is often  
67 associated.<sup>3</sup> The treatment of sPAN relies on high-dose glucocorticoids (GCs) associated or  
68 not with conventional immunosuppressants (ISs) according to the disease severity and on  
69 plasma exchange and anti-viral therapy in patients with hepatitis B virus (HBV)-related  
70 sPAN.<sup>4</sup> cPAN is a particular form of single-organ vasculitis,<sup>5</sup> with a chronic non-fatal  
71 disabling course and frequent relapse.<sup>6</sup> cPAN features earlier disease onset and a female  
72 predominance as compared with sPAN.<sup>6</sup> Moreover, cPAN seems unrelated to HBV,<sup>3,7</sup> and  
73 evolution from cPAN to sPAN is unlikely.<sup>3,8,2</sup>

74 Several studies focused on the clinical and biological evolution of cPAN.<sup>3,6,9</sup> However,  
75 to our knowledge, data on treatment efficacy remain scarce, without any consensus. First-line  
76 treatments usually consist of colchicine, dapsone or non-steroidal anti-inflammatory drugs  
77 (NSAIDs).<sup>5,10</sup> Second-line treatment is represented by GCs, associated or not with an IS,  
78 mostly azathioprine (AZA), methotrexate (MTX)<sup>5,6</sup> and more rarely cyclophosphamide  
79 (CYC).<sup>5</sup> Likewise, intravenous immunoglobulins (IVIgs) are commonly used for childhood-  
80 onset PAN, with good response, but among adults, data are limited to case series.<sup>5,11,12</sup>

81 No study has focused on response rates with each therapeutic line.<sup>5,13</sup> Patients with  
82 cPAN do not have poor prognostic features according to the Five Factor Score<sup>14</sup>, and the  
83 place of ISs in the therapeutic armamentarium is questionable regarding the benefit–risk ratio.  
84 However, a relapsing course has been shown in up to 45% of patients receiving GCs,<sup>3</sup> so the  
85 prescription of an IS is unavoidable in patients with refractory disease and disability.<sup>3,6,13</sup>  
86 Therefore, the optimal benefit–risk balance between efficacy and adverse reactions of  
87 treatment is unknown.<sup>5</sup>

88 We performed an observational retrospective study to evaluate the efficacy and safety  
89 of treatments used in cPAN.

## 90 **Methods**

### 92 *Setting*

93 We performed a multicentre observational retrospective study in three tertiary French  
94 centers and included patients with a diagnosis of cPAN between January 1, 1998 and  
95 December 31, 2018. The study was approved by the review committee for publications of the

96 Cochin University hospital (decision AAA-2021-08006) and conformed to scientific  
97 principles and research ethical standards.

### 98 *Population*

99 Patients >18 years old were selected from the PMSI chart of the medical information  
100 department database (International Classification of Diseases, 10<sup>th</sup> revision, code M300). We  
101 included patients who had cutaneous involvement associated with a cutaneous biopsy  
102 revealing medium-sized vessel arteritis confirmed by a pathologist. We excluded patients with  
103 small-sized vessel leukocytoclastic vasculitis. Joint involvement and sensory neuropathy in the  
104 same territory as the cutaneous lesions were allowed. We excluded patients with sPAN  
105 according the 2012 Chapel Hill definition<sup>1</sup>, proven adenosine deaminase 2 (ADA-2)  
106 deficiency<sup>15</sup> and macular lymphocytic arteritis. Specifically, we excluded patients with  
107 biopsy-proven nerve vasculitis. Patients with a clinical sensory-only neuropathy in the region  
108 of cutaneous involvement could be included if electromyography excluded a mononeuritis  
109 multiplex. We excluded patients with cPAN onset related to medication side effects.

110

111

### 112 *Covariates of interest*

113 For each patient, we collected demographic variables, including age at beginning of  
114 symptoms, age at diagnosis and sex. We also recorded clinical data, including constitutional  
115 symptoms, cutaneous lesions and topography, joint and neurologic involvement, and  
116 biological data at baseline, including viral serologies, leukocyte count, gammaglobulin levels,  
117 anti-nuclear antibody (ANA) and antineutrophil cytoplasm antibody (ANCA) positivity,  
118 cryoglobulin and C-reactive protein (CRP) levels. For each treatment, we collected the  
119 regimen, treatment line (e.g., first and second line), treatment duration, and efficacy and  
120 safety, including all adverse events. A serious adverse drug reaction was defined as an  
121 adverse event leading to hospitalization or death.

122

### 123 *Outcomes*

124 The primary outcome was the rate of complete response (CR) at month 3 (M3) after  
125 treatment initiation, defined as a complete disappearance of cutaneous lesions. When the  
126 treatment was changed before M3, it was considered a failure of the therapeutic line.  
127 Secondary outcomes were partial response (PR), defined by improvement of cutaneous  
128 lesions without CR and drug survival of each treatment, defined by the time from treatment  
129 initiation to treatment stop (i.e., the time that a patient remained on a particular treatment

130 course). Each therapeutic regimen was evaluated separately. We also assessed variables  
131 associated with CR in first-line therapy; prescription of an IS, biologics or systemic GCs; and  
132 prescription of a second-line therapy. For the IS agent evaluation, we defined the “GC  
133 weaning time” as the time before reaching a daily dosage < 10 mg/day.

#### 134 135 *Statistics*

136 We assessed variables associated with CR to a first-line therapy and to prescription of  
137 an IS, biologics and systemic GCs. We used univariate logistic regression analysis to assess  
138 variables potentially associated with CR, including age, sex, fever, nodules, livedo, ulcers,  
139 joint involvement, neurologic involvement and baseline CRP level, estimating odd ratios  
140 (ORs) and 95% confidence intervals (CIs). In a second step, given the presence of potential  
141 confounders, we performed multivariate logistic regression analysis. Variables finally  
142 included in the multivariable model were treatment, age, sex and those with  $p < 0.20$  on  
143 univariate analysis. Regarding secondary outcomes, the survival of each treatment was  
144 assessed by the Kaplan-Meier method. Because CYC was prescribed for six IV infusions  
145 according to protocols established in ANCA-associated vasculitis<sup>16</sup> and GC monotherapy  
146 should be tapered swiftly, we did not include them in the persistence model. AZA+GC was  
147 the reference for computations. We used the Wald test to assess variables associated with CR  
148 and the log-rank test to compare drug survival for the secondary outcome. All tests were two-  
149 tailed, and  $p < 0.05$  were considered statistically significant. Data are expressed as median  
150 (interquartile range [IQR]) for quantitative variables and number (percentage) for categorical  
151 variables and were analyzed by using R CRAN 3.6.2.

#### 152 153 **Results**

##### 154 *Population*

155 We included 68 patients (53 females, 78%); the median age at diagnosis was 39 years  
156 (IQR 26-51). The clinical and biological characteristics at baseline are presented in  
157 **Supplemental Table 1**. Median time from the beginning of cutaneous signs to diagnosis was  
158 12 months (IQR 5-26). At diagnosis, 53 (78%) patients presented livedo, 47 (69%) nodules,  
159 12 (18%) purpura and 11 (16%) ulcers; 22 (32%) patients had asymmetric clinical sensory  
160 neuropathy of the legs confirmed by electromyography. No patients were positive for HBV,  
161 HIV or hepatitis C virus. Twenty (29%) patients were positive for ANAs without specificity.  
162 All patients were negative for ANCA, cryoglobulinemia and phospholipid antibodies.

163 A total of 144 therapeutic lines were initiated, with a median number of 2 therapeutic  
164 lines (IQR 1-3, range 0-8) for each patient. Altogether, 42 patients received colchicine  
165 (median dosage 1 mg [IQR 1-1], 17 dapsone (median dosage 100 mg [IQR 100-100]), 8  
166 hydroxychloroquine (HCQ), 9 NSAIDs, 13 GCs+AZA, and 15 GCs+MTX. Six patients also  
167 received pulses of CYC, 6 patients IVIg, 2 patients rituximab (RTX) infusions and one patient  
168 tocilizumab (TCZ). Median prednisone dosage at treatment initiation was 60 mg/day (60-60)  
169 for CYC, 60 mg/day (50-60) for GCs alone, 30 mg/day (30-60) for both GC+AZA and  
170 GCs+MTX, and 30 mg/day (20-30) for IVIg.

171 Therapeutic management by line of treatment is summarized in **Figure 1**. For first-line  
172 therapy, the most common treatments were colchicine for 34 (50%) patients, GC  
173 monotherapy for 15 (22%) and NSAIDs for 5 (7%). Five patients received a GCs+IS regimen  
174 and only 2 patients (3%) received dapsone for first line therapy. Four patients never received  
175 any pharmacological treatment and only received venous compression stockings, without  
176 achieving CR.

177 Overall, 42 (63%) patients had relapsing/refractory cPAN and received a second-line  
178 treatment, mainly dapsone (n=11), GCs (n=8), and GCs+AZA (n=7). Second-line versus no  
179 or single treatment was more frequent with sensory neuropathy (45% vs 11%, p=0.007), fever  
180 (19% vs 0%, p=0.02) and nodules (78% vs 54%, p=0.04) at the time of diagnosis (**Table 1**).

181 Factors associated with the prescription of systemic GCs, biologics or IS at any  
182 therapeutic line (first, second, etc.) are presented in **Supplementary Table 2**.

183

#### 184 *Outcomes*

185 Results of the primary outcome are presented in **Figure 2**. Response rates were  
186 moderate with colchicine, dapsone and GC monotherapy: CR was 13/42 (31%), 4/17 (23%)  
187 and 11/25 (44%), respectively. For conventional IS agents, 11/13 (84%) patients achieved CR  
188 with GC+AZA but only 7/15 (46%) with GC+MTX. All patients receiving CYC pulses (6/6,  
189 100%) achieved CR. Regarding other treatments, 5/6 (83%) patients achieved CR with IVIg,  
190 0/2 patients with rituximab and 1/1 patient with TCZ.

191 In total, 21 (31%) patients achieved CR after first-line therapy. Clinical and biological  
192 factors associated with CR to first-line therapy are in **Table 2**. CR was less frequent with than  
193 without neurological involvement (2/17, 12% vs 19/51, 38%) and less likely on univariable  
194 and multivariable analysis (OR 0.22 [95% CI 0.04-1.09], p=0.06; and 0.19 [0.03-0.81],  
195 p=0.04 respectively, adjusted on treatment, age and sex). Likewise, CR was achieved with

196 colchicine, NSAIDs or HCQ for only 2/15 (13%) patients with peripheral neuropathy versus  
197 13/31 (42%) without (p=0.07).

198 Drug survival is depicted in **Figure 3**. Drug survival was greater in patients with  
199 GCs+AZA (median duration 29.5 months [IQR 19.5-36.0]) than colchicine (6 months [3-13],  
200 p=0.007), dapsons (6 months [5-11], p=0.04), HCQ (1 month [1-4], p=0.05; HCQ was  
201 stopped early for 2 patients because of intolerance and for 2 others because of lack of  
202 efficacy); and GCs+MTX (12 months [3-23], p=0.001). Drug survival did not significantly  
203 differ between GCs+AZA and NSAIDs (median duration 3 months [1-11], p=0.10) or  
204 GCs+IVIg (16 months [7-36], p=0.70).

205 GC dosage was decreased to < 10 mg/day for 11/13 (84%) patients receiving AZA,  
206 5/6 with CYC (83%), 5/6 (83%) with IVIg and 5/13 (38%) with MTX, after a median of 3.5  
207 (3-7), 7 (4-12), and 3 (2-3) months and not reached, respectively. At M3, the median GC  
208 dosage was 10 mg/day (10-14) for AZA, 12 mg/day (10-21) for MTX, 20 mg/day (20-30) for  
209 CYC, and 10 mg/day (6-10) for IVIg.

210 The rate of adverse reactions was 26/144 (18%), and treatment was stopped because of  
211 adverse reactions in 10/144 (7%) of cases. Four episodes of diarrhea and 1 episode of  
212 neutropenia were observed under colchicine. Patients receiving dapsons had symptomatic  
213 anemia, dizziness and symptomatic methemoglobinemia in 5, 2 and 1 cases, respectively.  
214 Rates of discontinuation because of adverse reactions were similar with dapsons, CYC, IVIg  
215 and HCQ (from 12% to 25% of cases) (**Supplementary Table 3**). The only serious adverse  
216 reaction was peritonitis observed under CYC therapy, leading to hospitalization in the  
217 intensive care unit.

218 Median follow-up was 60 months (IQR 16-137). Two patients died during follow-up,  
219 one death linked to colon cancer and another to ischemic cardiopathy. No death was related to  
220 the vasculitis course or treatment adverse events.

221

## 222 **Discussion**

223 We report a large case series retrospectively evaluating treatment efficacy and safety  
224 in patients with cPAN. CR was variable for patients receiving colchicine and dapsons (31%  
225 and 24%, respectively), who showed rare and benign adverse events. Second-line therapy  
226 versus no or single therapy was more frequent with peripheral sensory neurological  
227 involvement (45% of cases), fever (19%) and nodules (78%). For patients who required  
228 second-line therapy, CR rate was good with GCs+AZA (84%), with good drug survival  
229 (median duration 29.5 months).



230 Our finding of female predominance and a median age of 40 years with cPAN is  
231 consistent with the literature.<sup>5,9</sup> Similar to results of a retrospective Japanese study, sensory  
232 neurological involvement in the same territory as cutaneous lesions seemed associated with  
233 poor outcomes.<sup>6</sup> Although we carefully excluded patients with sPAN, patients with sensory  
234 neuropathy and fever had increased treatment requirements, which questions the existence of  
235 a continuum between cPAN and sPAN. These systemic symptoms could characterize “cPAN  
236 with systemic features”, a clinical form more often requiring GC or IS treatment. In contrast,  
237 we did not find any association with other clinical variables, particularly ulcers, found  
238 associated with poor outcomes in other studies.<sup>6,17</sup> In addition, we observed a large  
239 heterogeneity among treating physicians, ranging from therapeutic abstention to CYC pulse  
240 therapy, also reported previously.<sup>5,18,19</sup>

241 Colchicine and dapsone have been proposed as first-line therapy for cPAN<sup>5</sup>, and their  
242 efficacy, although inconsistent, has been reported in several case series.<sup>18</sup> With the favorable  
243 benefit–risk balance, our data support the use of colchicine and dapsone in patients with a  
244 mild disease course. In our study, the benefit of HCQ or NSAIDs seemed more limited.  
245 Nonetheless, median treatment length for HCQ was only 1 month (IQR 1-3), but HCQ takes  
246 longer to work in most cases, so interpreting the primary outcome is difficult. GC  
247 monotherapy was often prescribed for cPAN in this study and in the literature.<sup>3,19,20</sup>  
248 Nevertheless, Alibaz-Oner et al. reported that more than 45% of cPAN patients experienced  
249 relapse after CR and that CR was never reached for 17% of patients, which emphasizes the  
250 need to add IS to achieve sustained CR.<sup>3</sup>

251 AZA and MTX have been proposed for treating cPAN<sup>18,21</sup>, but a head-to-head  
252 comparison has never been performed. In our study, CR was achieved more often with  
253 GCs+AZA than GCs+MTX or GCs alone, and the former exhibited longer drug survival and  
254 more frequently GC dosage decreased to < 10 mg/day. Therefore, the GCs+AZA combination  
255 might be the preferred second-line treatment. Likewise, with severe disease characterized by  
256 neurological involvement, it might be the preferred first-line option because of the decreased  
257 likelihood of CR with colchicine, NSAIDs or HCQ.

258 Considering the small size of treatment groups, we cannot draw definitive conclusions  
259 regarding CYC or IVIg that might be used for refractory patients. Their exact place in the  
260 treatment strategy remains unclear.

261 The strength of the study is the large scale considering the rare prevalence of cPAN. In  
262 addition, our sample characteristics are consistent with those in previous reports<sup>6,11</sup>, and we  
263 confirm the female predominance (3:1 sex ratio at disease onset) of cPAN versus sPAN,

264 which mainly occurs in men. The median age of 39 years at the time of diagnosis supports a  
265 clinical pattern distinct from pediatric PAN and ADA-2 deficiency.<sup>8</sup> Moreover, the ANA  
266 positivity in 29% of patients agrees with previous reports.<sup>9</sup>

267 A first limitation is that our patients were all recruited from tertiary care centers, so  
268 they might have had more severe disease. This might explain the primary resistance to  
269 NSAIDs we observed as compared with other studies.<sup>10</sup> Moreover, treatment allocation was  
270 not randomized, and indication biases remain. Thus, the analyses of treatment effect are less  
271 precise, especially taking into account the heterogeneity of the disease. For instance,  
272 colchicine and dapsone were mainly given as first and second line therapy respectively. It  
273 might explain the apparent more frequent success of colchicine. However, we assessed the  
274 efficacy of treatment with several outcomes, including drug survival, which might reflect a  
275 balance between efficacy and safety. Specifically, sensory neuropathy could be interpreted as  
276 a manifestation of sPAN, so classifying these patients is difficult. Nonetheless, sensory  
277 neuropathy was previously reported as a manifestation of cPAN,<sup>5,6,9</sup> and we excluded patients  
278 with motor neuropathy and biopsy-proven nerve vasculitis, performed with clinical suspicion,  
279 and patients were followed for a long time without changes to sPAN. Another limitation is the  
280 retrospective design associated with inherent confounding bias and the risk of missing data  
281 (specifically for adverse reactions). The recruitment period was long, and we cannot exclude a  
282 shift in patient recruitment and therapeutic management strategy. In addition, only a few  
283 patients with a recent diagnosis were included in the study, and we cannot draw definitive  
284 conclusions on the treatment efficacy and safety of TCZ and RTX, which might be considered  
285 a future option.

286 This study helps to better define the efficacy and safety of treatment in cPAN. It  
287 supports a favorable benefit–risk balance of colchicine for mild to moderate disease (i.e.,  
288 without neurological involvement) and the use of GCs+AZA for severe cPAN (i.e., with  
289 neurological involvement). Prospective studies remain warranted to assess the best treatment  
290 for cPAN and to evaluate other treatments.

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354  
355

356 **Table 1** Clinical characteristics of patients with cutaneous polyarteritis nodosa (cPAN) who  
 357 received a second-line treatment versus no or a single therapeutic line (n=68).  
 358

|                                       | <b>Second-line<br/>treatment (n=42)</b> | <b>No or single<br/>treatment (n=26)</b> | <b>P-value</b> |
|---------------------------------------|---|--|----------------|
| <b>Age, years, median (IQR)</b>       | 39 (25-49)                              | 39 (28-56)                               | 0.28           |
| <b>Sex</b>                            | 32 (76)                                 | 21 (81)                                  | 0.76           |
| <b>Fever</b>                          | 8 (19)                                  | 0 (0)                                    | <b>0.02</b>    |
| <b>Livedo</b>                         | 30 (71)                                 | 23 (88)                                  | 0.13           |
| <b>Nodules</b>                        | 33 (78)                                 | 14 (54)                                  | <b>0.04</b>    |
| <b>Purpura</b>                        | 10 (24)                                 | 2 (8)                                    | 0.11           |
| <b>Ulcers</b>                         | 7 (17)                                  | 4 (15)                                   | 0.89           |
| <b>Arthralgia</b>                     | 16 (38)                                 | 9 (35)                                   | 0.80           |
| <b>Sensory neuropathy</b>             | 19 (45)                                 | 3 (11)                                   | <b>0.007</b>   |
| <b>Baseline CRP level &gt; 5 mg/L</b> | 24 (57)                                 | 9 (34)                                   | 0.08           |

359 Data are n (%) unless otherwise indicated.  
 360 IQR: interquartile range; CRP: C-reactive protein  
 361

362 **Table 2** Univariate and multivariate analysis of factors associated with complete remission  
 363 with first-line treatment.  
 364

|                              | Univariate analysis     |             | Multivariate analysis   |             |
|------------------------------|-------------------------|-------------|-------------------------|-------------|
|                              | cOR (95% CI)            | P-value     | aOR (95% CI)            | P-value     |
| <b>Age &gt; 40 years</b>     | 1.80 (0.63-5.09)        | 0.27        | 2.43 (0.79-7.83)        | 0.13        |
| <b>Sex</b>                   | 1.30 (0.36-4.68)        | 0.69        | 1.41 (0.39-5.88)        | 0.61        |
| <b>Livedo</b>                | 0.86 (0.25-2.94)        | 0.81        |                         |             |
| <b>Nodules</b>               | 0.85 (0.28-2.55)        | 0.77        |                         |             |
| <b>Purpura</b>               | 0.39 (0.08-1.96)        | 0.26        |                         |             |
| <b>Ulcers</b>                | 1.34 (0.35-5.20)        | 0.67        |                         |             |
| <b>Fever</b>                 | 0.72 (0.13-3.90)        | 0.70        |                         |             |
| <b>Arthralgia</b>            | 1.09 (0.37-3.14)        | 0.88        |                         |             |
| <b>Neuropathy</b>            | <b>0.22 (0.04-1.09)</b> | <b>0.06</b> | <b>0.19 (0.03-0.81)</b> | <b>0.04</b> |
| <b>CRP level &gt; 5 mg/L</b> | 1.30 (0.29-5.86)        | 0.72        |                         |             |

365 cOR: crude odds ratio; aOR: adjusted odds ratio, adjusted on treatment, age and sex; 95% CI: 95% confidence  
 366 interval; CRP: C-reactive protein; P-value obtained by Wald test.  
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## Legends

**Figure 1** Treatment received by patients with cutaneous polyarteritis nodosa (cPAN) by line of therapy (n=68). Inner circle is first-line treatment, second circle is second-line treatment, etc.

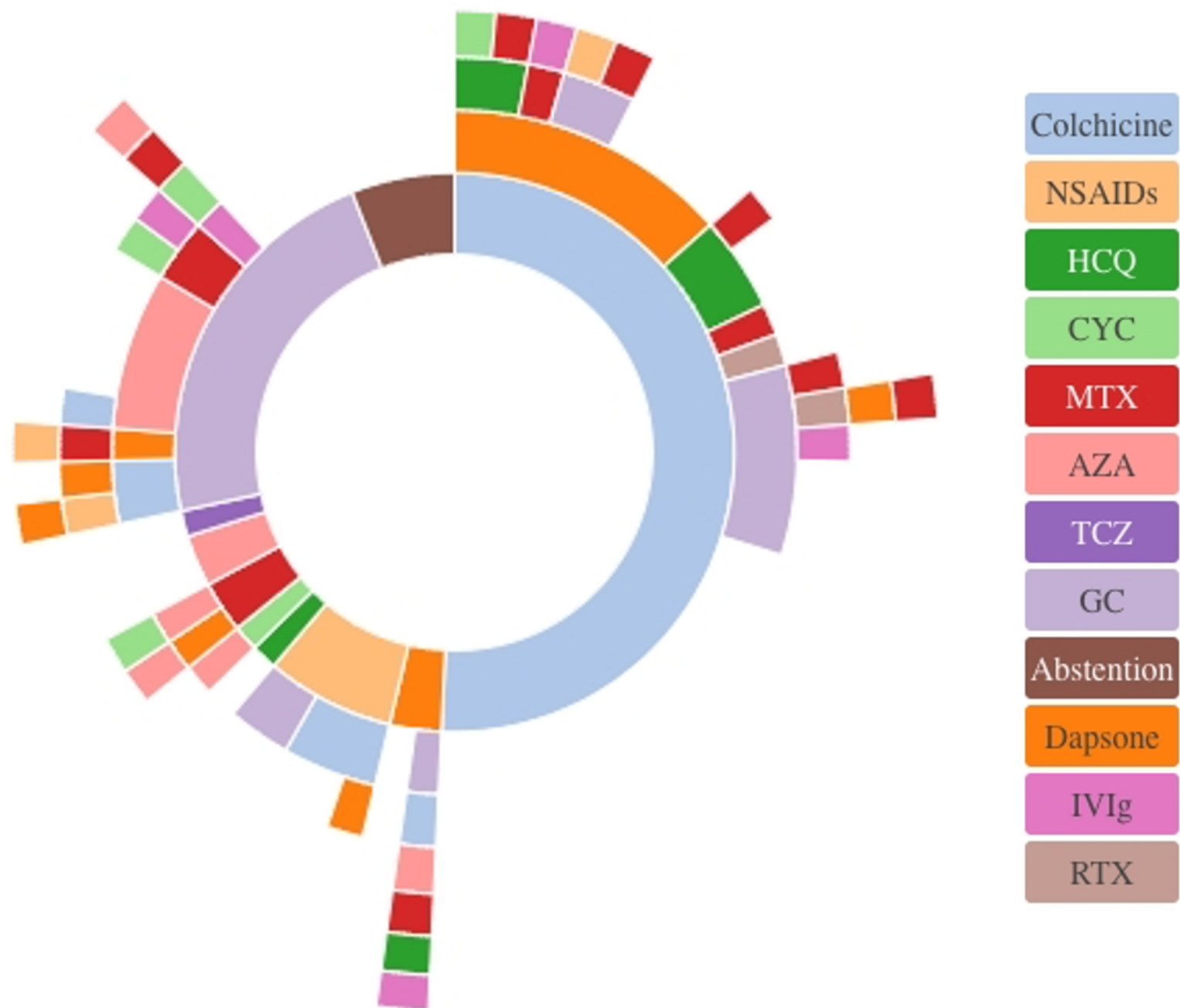
AZA: azathioprine; CYC: cyclophosphamide; GC: glucocorticoids; HCQ: hydroxychloroquine; IVIg: intravenous immunoglobulins; MTX: methotrexate; NSAIDs: non-steroidal anti-inflammatory drugs. RTX: rituximab; TCZ: tocilizumab

**Figure 2** Clinical response by treatment regimen.

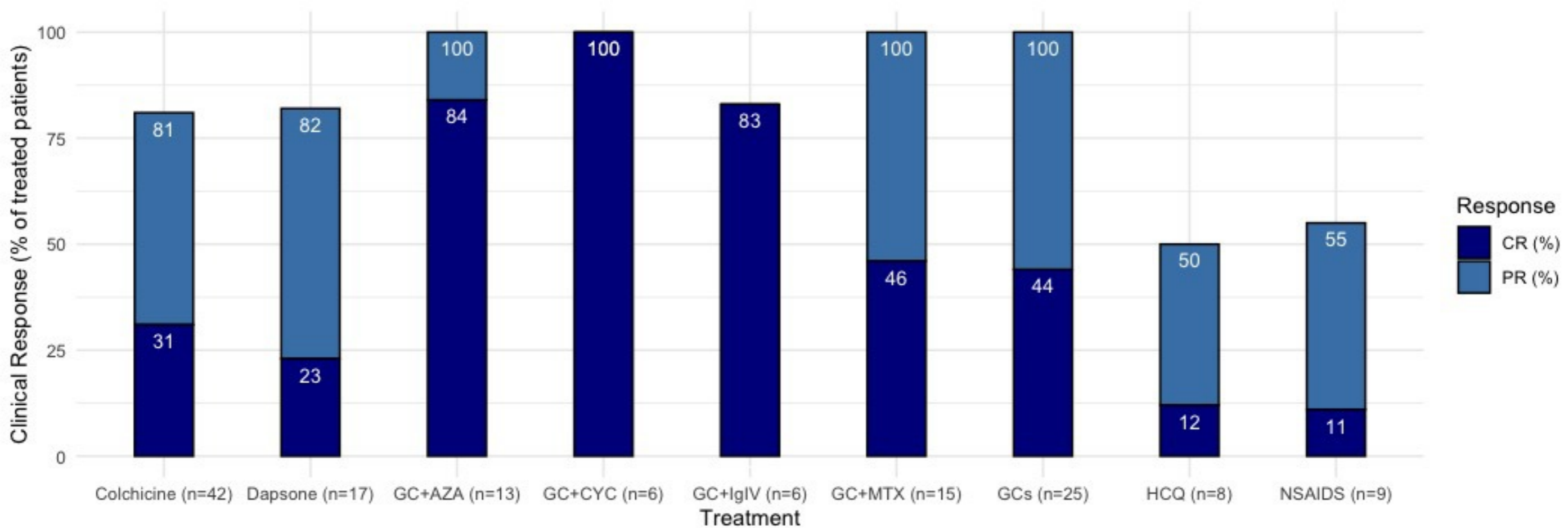
AZA: azathioprine; CR: complete response; CYC: cyclophosphamide; GC: glucocorticoids; HCQ: hydroxychloroquine; IVIg: intravenous immunoglobulins; MTX: methotrexate; NSAIDs: non-steroidal anti-inflammatory drugs; PR: partial response

**Figure 3** Kaplan-Meier analysis of drug survival by treatment regimen.

AZA: glucocorticoids (GCs)+azathioprine; CYC: GCs+cyclophosphamide; HCQ: hydroxychloroquine, IVIg: GCs+intravenous immunoglobulins; MTX: GCs+methotrexate; NSAIDs: non-steroidal anti-inflammatory drugs







Treatment

|        |            |      |     |
|--------|------------|------|-----|
| NSAIDs | Colchicine | IVIg | HCQ |
| AZA    | Dapsone    | MTX  |     |

