Optimal treatment regimens according to the INSAID variant classification and the Eurofever criteria in patients with variants of the *TNFRSF1A* gene: data from the Eurofever registry

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ABSTRACT

Background

TNF receptor-associated periodic syndrome (TRAPS) is a rare autoinflammatory disease caused by dominant mutation of the *TNFRSF1A* gene, often complicated by AA amyloidosis and infertility. Data regarding long-term treatment outcomes is lacking.

Objective

To assess the correlation of genotype-phenotypes in TRAPS patients, as defined by INSAID classification and Eurofever criteria, with treatment responses.

Methods

Data from 226 patients with variants of the *TNFRSF1A* gene and enrolled in the Eurofever registry were classified according to INSAID classification in group A (pathogenic or likely pathogenic variants), B (VUS or not classified variants), and C (benign or likely benign variants) and screened if fulfilling Eurofever criteria.

Results

In group A (127/226 patients, 56%) fulfilled Eurofever criteria and 20/127 patients (16%) developed AA amyloidosis. In group B (78/226 patients, 35%), 40/78 patients (51%) did not fulfill Eurofever criteria, displaying a lower incidence of abdominal pain ($p<0.02$) and higher efficacy rate of on-demand NSAIDs ($p<0.02$) and colchicine ($p<0.001$). Group C (21/226 patients, 9%) presented a milder disease ($p<0.02$) and none fulfilled Eurofever criteria. Anti-interleukin (IL)-1 drugs were the most frequently used in patients fulfilling Eurofever criteria, with the highest efficacy rate (>85% complete response). No patients on anti-IL-1 treatments developed AA amyloidosis and seven women with history of failure to conceive had successful pregnancies.

Conclusion

Anti-IL-1 drugs are the best maintenance treatment in patients with TRAPS. The diagnosis of TRAPS should be considered very carefully in patients of group B not fulfilling Eurofever criteria and C, and colchicine may be preferable as first maintenance treatment.

HIGHLIGHTS BOX

1. What is already known about this topic?

Patients carrying pathogenic variants of the *TNFRSF1A* gene may present with recurrent fevers, abdominal pain, and rash, and risk developing AA amyloidosis and infertility. Maintenance treatment may be required in order to avoid these long-term complications.

2. What does this article add to our knowledge?

Anti-IL-1 drugs are the most effective drugs in TRAPS patients with pathogenic variants. Colchicine may be attempted as the first maintenance treatment in patients carrying variants of the *TNFRSF1A* gene but not fulfilling Eurofever criteria for TRAPS.

3. How does this study impact current management guideline

Stratifying patients in accordance with the new INSAID variant classification and the Eurofever criteria may help guide optimal maintenance treatment to prevent long-term complications in patients carrying variants of the *TNFRSF1A* gene.

KEW WORDS

- Autoinflammatory diseases
- TRAPS
- AA amyloidosis
- Colchicine
- Anakinra

ABBREVIATIONS

Tumour necrosis factor (TNF)
TNF receptor-associated periodic syndrome (TRAPS)
TNF super family receptor 1A (*TNFRSF1A*)
Disease modifying anti-rheumatic drugs (DMARDs)
International Study Group for Systemic Autoinflammatory Diseases (INSAID)
Pathogenic (P)
Likely pathogenic (LP)
Likely benign (LB)
Benign (B)
Variants of uncertain significance (VUS)
Not classified (NC)
Autoinflammatory Disease Activity Index (AIDAI)
Periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA)
Systemic undefined recurrent fevers (SURF)

INTRODUCTION

Tumour necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS) is a well-known monogenic autoinflammatory disorder resulting from an autosomal dominant mutation in the TNF super family receptor 1A (*TNFRSF1A*) gene (1-5). TRAPS patients usually present with recurrent episodes of fever, abdominal pain, rash, with up to 10% developing systemic AA amyloidosis if untreated. NSAIDs or steroids are effective in the short-term, but colchicine, disease modifying anti-rheumatic drugs (DMARDs) and biologicals may be needed as maintenance therapy (6). Little is known about treatment responses and long-term outcomes, especially in relation to the genotype.

The Eurofever and EUROTRAPS projects are two parallel European EU funded initiatives aimed at increasing the knowledge on autoinflammatory diseases in general (Eurofever) and for TRAPS (EUROTRAPS) in particular. To this purpose the two projects built a common international registry (7). In the present study, we reviewed all data of patients with *TNFRSF1A* variants enrolled in the Eurofever registry, providing correlations of genotype-phenotypes in accordance with the new variant classification proposed by the International Study Group for Systemic Autoinflammatory Diseases (INSAID) (8-11) and the new Eurofever classification criteria (12) (Table E1), with a particular focus on response to treatment and long-term outcomes.

METHODS

This retrospective study was performed at the Gaslini Institute in Genoa, Italy, and the National Amyloidosis Centre in London, United Kingdom. Data from the Eurofever registry from November 2009 to January 2018 date were reviewed on 226 patients, and included demographics, family history, clinical features, laboratory results and imaging findings. Patients were enrolled by 18 centers in 11 countries. All patients but two were enrolled by European centers: United Kingdom (100 patients), Italy (47), France (19), Germany (18), Spain (13), Netherlands (6), Poland (6), Russian Federation (5), Ireland (4), Greece (2), Czech Republic (2), Turkey (1), Slovenia (1). Two patients were enrolled in Argentina. Informed consent and ethical committee approval for entering patients in the registry were obtained according to the local regulatory requirements.

Inclusion criteria were symptomatic inflammatory disease associated with at least one sequence variation in the *TNFRSF1A* gene. All completed cases were anonymously and independently evaluated by at least one expert in the disease (HJL, PW, MG) in order to confirm the quality of entered data.

All *TNFRSF1A* variants were classified according to the INSAID classification as pathogenic (P), likely pathogenic (LP), likely benign (LB), benign (B), of uncertain significance (VUS) or not classified (NC) variants. We defined highly penetrant variants as those associated with symptoms in more than two members in one family (13). We considered only P/LP variants as confirmatory genotypes for the Eurofever classification criteria.

The Eurofever registry defines “recurrent disease pattern” as disease alternating with symptom-free intervals associated with negative acute phase reactants; otherwise, the pattern is considered chronic or subchronic. All clinical variables included in the Eurofever registry were considered.

In order to give an estimate of the global burden of the disease for each patient we performed the so-called “global Autoinflammatory Disease Activity Index (AIDAI) score”. AIDAI is a well-established outcome measure for disease activity specifically developed for autoinflammatory diseases (14). This

tool is based on the occurrence of 12 clinical items observed in a given period, of which 10 were considered for TRAPS (abdominal pain, nausea/vomiting, diarrhoea, headaches, chest pain, painful lymph nodes, arthralgia or myalgia, swelling of the joints, eye manifestations, skin rash). For the calculation of the "global AIDAI", the presence of each AIDAI item in the clinical history of the patients was scored as 1, with a final score ranging from 0 (no AIDAI items) to 10 (all AIDAI items).

Treatment response was defined according to the Eurofever registry criteria as either complete (absence of clinical manifestations and negative acute phase reactants), partial (general amelioration of the clinical picture according to the judgement of the physician without a complete normalization of the clinical manifestations and/or systemic inflammation), or failure (lack of response according the judgment of the physician) (6).

Statistical analysis was performed using frequencies and percentages for categorical variables; median and range for numerical variables. Differences among groups were assessed by Kruskal-Wallis H test and X^2 test for discrete variables and by Mann-Whitney U test for continuous variables.

RESULTS

Demographic and genetic data

The vast majority of patients (204/226, 90%) were western Caucasians. Five patients were of African descent, four of Jewish descent, four of Arabic descent from the Middle East, three of Asian descent and two of Caribbean descent. Four patients reported mixed ethnic backgrounds.

Demographic characteristics are reported in Table 1. The mean age at the time of enrolment was 32 years. The mean age of symptoms onset was 5.3 years and 43/226 patients (19%) presented during adulthood.

A total of 66 sequence variants of the *TNFRSF1A* gene were reported (Figure 1, Table E2). The majority of patients were heterozygous for missense variants involving exon 2 (43/226 patients, 19%), exon 3 (76/226 patients, 34%), and exon 4 (67/226 patients, 30%). Two patients presented a mutation in exon 1 and 6 respectively, and 29/226 patients (13%) carried an intron missense mutation, of which only the c.194-14G>A and c.472+1G>A have been previously associated to TRAPS (15, 16). Nine patients (4%) carried deletions of exon 3 (6 patients), exon 4 (2 patients), and intron 2 (1 patient). The low penetrance R92Q and P46L variants were detected in 47 and 6 patients, respectively. One patient presenting with an atypical gonosomal mosaicism has already been reported in detail (17). Twenty-five variants (38%) were identified in more than one family and ten (H22Q, H22R, I28S, C29S, C33Y, D42del, T50M, C52Y, C73G, and C96Y) showed high penetrance (15%). The heterozygous p.I591T variant of the *MEFV* gene presented segregation with the *TNFRSF1A* variant in one family (18-20).

Six VUS in other genes related to recurrent fevers are reported in Table E3. All patients were classified according to the INSAID variant classification in three groups: i) patients carrying P/LP variants (group A), ii) patients carrying VUS/NC variants (group B), and iii) patients with B/LB variants (group C).

Clinical manifestations and genotype-phenotype correlation

Symptoms are reported in Table 1. Twenty-six patients (12%) presented with a chronic disease course, while the vast majority (83%) reported recurrent fevers. The mean duration of fever attacks was 10 days (range 1-42), with a mean of 6 episodes/year (range 1-48). Triggers were reported in 31/226 patients (14%): the most frequent was stress (12 patients), followed by physical exercise (10), periods (9), infections (8), vaccination (4), cold (4), travel (3), trauma (3), and alcohol (2). The most common manifestations accompanying fevers were arthromyalgia, abdominal pain, and skin rash, respectively reported by 67%, 61% and 46% of patients. Notably, abdominal pain is rarely associated with other gastrointestinal symptoms, such as nausea/vomiting (13%) or diarrhoea (16%). Eye manifestations were reported in 27% of patients, while other manifestations (headache, chest pain, painful lymphadenopathy, arthritis and stomatitis) were less frequently noted. Only two patients had testicular swelling. The mean global AIDAI was 4.4.

Genotype-phenotype correlations. All patients in group A and 38/78 (49%) of patients in group B fulfilled the Eurofever criteria. Group A usually presented during childhood (2.6 years; $p<0.0001$) and displayed more abdominal pain and skin rashes and less nausea/vomiting and stomatitis than other groups ($p<0.02$). Fewer adults had enrolled in group B then in other groups ($p<0.0001$). Patients belonging to group B were divided according their meeting of the Eurofever criteria. Patients fulfilling the criteria had more abdominal pain and less nausea/vomiting and swelling of the joints ($p<0.02$). The mean global AIDAI was lower in the group C ($p<0.02$; Figure 2).

Response to treatment and adverse events

Treatment data are reported in Table 2. Patients belonging to group A displayed a lower response to NSAIDs on demand in comparison to group B (Figure 3). Oral corticosteroids on demand were generally effective in controlling disease flares in all groups. However, most of the patients needed steroid-sparing drugs as maintenance treatment. Colchicine was attempted in 19/88 (22%) patients of group A, with

complete response in two patients only. Conversely, when colchicine was given to patients of group B not fulfilling the Eurofever criteria, all patients displayed a complete response. Anti-IL-1 treatments (anakinra and canakinumab) were the biologic drugs most frequently used (52/88, 59%) with the highest efficacy rate (>85% complete response). Anakinra was significantly more efficacious in patients of group A. A similar pattern was observed for canakinumab though without statistical significance due to the lower number of treated patients. Etanercept was administered to 26/88 (30%) patients, being less effective (<16% complete response) and discontinued in 17/26 patients (65%). Other biologics (rituximab, tocilizumab and adalimumab) were rarely used, and overall were not beneficial.

Relevant drug adverse events were identified in less than 10% of patients treated with biologics: the majority were treatable infections (Table E4). Anakinra caused severe injection site reactions in four patients (10%), requiring early discontinuation. One patient with complete response to canakinumab developed pericarditis after the second drug administration, requiring resumption of anakinra.

Complications and long-term outcomes

Secondary AA amyloidosis was the most frequent and severe complication identified in our cohort (20 patients, 7%). This complication was observed in 19 patients of group A (95%) and in one patient carrying the c.473-72G>A LB variant (Table E2). This patient displayed a long history of untreated rheumatoid arthritis, suggesting an alternative cause for the AA amyloid deposition. No patients of group B developed AA amyloidosis.

In the 19 patients of group A, systemic AA amyloidosis caused a CRD at the mean age of 43 years (range 19-75). In the majority of these patients (75%), TRAPS was diagnosed after the onset of AA amyloidosis. All these patients had a history of fever episodes during childhood except the one patient who presented a chronic inflammatory disease course. None had been treated with biologicals before the diagnosis of

AA amyloidosis. The majority (55%) required dialysis and seven were transplanted. Two relapsed, despite one achieving a partial response to etanercept, and one patient died from carcinoma after 21 years of immunosuppressive therapy with azathioprine. One patient achieved a complete response with anakinra after kidney transplantation and displayed the longest transplanted kidney survival (23 years) without any immunosuppression complications. No one developed AA amyloidosis after the availability of the anti-IL-1 treatment and some patients had a partial resolution of pre-existing amyloid deposits after initiation of IL-1 blockade.

Nine patients (3%) had fertility problems, six having had miscarriages for a total of 8 episodes. One patient had failed three cycles of IVF before referral. She had a complete response to anakinra and conceived spontaneously within 6 weeks of starting treatment. Seven experienced a normal pregnancy after complete disease control and six required anakinra. One patient presented a spontaneous reduction of attacks frequency during the adulthood.

Explorative laparotomy was performed in eight patients and 50% developed adhesions, requiring intestinal resection in two cases. Tonsillectomy had been ineffective in two patients and surgical scrotal exploration for suspected testicular torsion had been performed in one patient without benefit.

The mean adult height was normal compared to general population, while a mean increase of 1.2 kg/m^2 in the body mass index was noted in case of complete disease control. In a subgroup of patients in whom quality of life had been monitored, the score increased after starting anakinra indicating improved quality-of-life (Figure 4).

Among 100 patients on whom information about education and employment was available, only three declared difficulty attending school during childhood and 23% were going to finish their educational program at the time of this study. Four completed higher education at University and 54% obtained a degree and now work in a related position. Only six were either unemployed or on state benefit.

DISCUSSION

In the present study, we reviewed all data from patients with *TNFRSF1A* variants enrolled in the Eurofever registry, describing for the first time the long-term treatment efficacy and outcomes. Genotype-phenotype correlations were analysed according to the novel variant classification proposed by the INSAID project (8) and we analysed the performance of the Eurofever classification criteria. In a subgroup of patients we also evaluated the disease impact on quality of life, educational achievements and work goals. Data were retrospectively analysed but prospectively collected during the last 20 years by each enrolling centre. Finally, we propose for the first time, an easy-to-calculate global AIDAI that may help physicians in testing the global burden of TRAPS and other recurrent fevers. The actual usefulness of this possible new tool will need a proper validation in future studies.

Overall the demographic and clinical data confirm our previous study (2), showing how patients with P/LP variants have a predominantly childhood onset, with longer attack duration at lower frequency (almost two weeks every two months) compared to other recurrent fevers. Limb pain is a common manifestation, especially in adults. This finding highlights the need for adult rheumatology centres to maintain higher suspicion for TRAPS. Routine screening for serum amyloid A and C reactive protein, in conjunction with a symptom diary, may help physicians in these cases.

Half of patients in our cohort carried VUS or B/LB variants of the *TNFRSF1A* gene according the new INSAID classification (8). There is increasing evidence suggesting that patients with these variants may be asymptomatic or just present a pro-inflammatory phenotype without typical TRAPS symptoms (21-23). The implications of p.R92Q in the molecular structure of the TNF receptor type 1, such as the minor angle changes in the extracellular domain, seem to confer a minor functional effect of this variant (19). Although the clinical impact of a *TNFRSF1A* variant cannot be determined only by the molecular changes, as demonstrated by the absence of difference between patients with or without variants in the cysteine residues of the protein (2), the high frequency in the European population of p.R92Q and p.P46L

variants led us to define these two variants as functional polymorphisms with a low penetrance, and thus are classified as VUS by the INSAID group.

In line with previous smaller studies (22), the analysis of clinical manifestations presented by patients with VUS/NC and B/LB variants not fulfilling the Eurofever classification criteria showed that the symptoms usually associated with their fever attacks resemble those in the non-monogenic periodic fever, stomatitis, pharyngitis, and adenitis (PFAPA) syndrome rather than TRAPS, as the classical abdominal pain and rash are less frequently reported. Moreover, maintenance treatment with colchicine was frequently effective to control disease flares, while the rate of complete response to anti-IL1β drugs was much less, suggesting an alternative driver of inflammation in these patients. No patients carrying VUS/NC or B/LB variants developed typical adverse long-term outcomes such as AA amyloidosis or infertility. The mean global AIDAI score was lower for patients with B/LB variants. On the other hand, the high prevalence of inflammatory symptoms in these patients may be related to the fact that only patients with inflammatory symptoms were referred to the enrolling centres. Collectively, our data confirm the clinical usefulness of the INSAID classification criteria for *TNFRSF1A* variants.

Due to its observational and inclusive nature, the Eurofever registry was aimed to include all patients labelled as TRAPS by the enrolling centres, mainly based on the presence of *TNFRSF1A* variants. The Eurofever classification criteria were able to identify all patients carrying P and LP variants as TRAPS. Notably, in 6/14 (43%) patients with NC variants, the clinical manifestations allowed their classification as TRAPS, indicating the practical usefulness of the Eurofever classification criteria. As expected, only a fraction of patients with VUS/NC (49%) could be classified as TRAPS according to the new criteria. Interestingly, among patients carrying VUS/NC, those fulfilling the new classification criteria displayed a better response to biologics in respect to those that did not fulfill the new criteria.

It is important to underline that classification criteria are meant to identify with high specificity those patients that should be included in clinical trials or translational studies and should not be used in the

daily practice as a diagnostic tool. However, the present paper shows that the combination of the Eurofever classification criteria and INSAID criteria for the classification of variants allows one to identify a definite subgroup of patients carrying VUS, NC or LB *TNFRSF1A* variants. Those patients present a clinical phenotype, disease severity, long term-complication and response to treatment dramatically divergent from those carrying P and LP variants. In our view, these results should help the clinicians to interpret data coming from genetic analysis in the clinic.

The use of steroids on demand confirmed their efficacy in the management of single fever episodes. However, in most patients the repetitive use of steroids leads to a progressive reduction of the interval between disease flares, indicating the need of a continuous treatment with steroid-sparing agents. Anti-IL-1 drugs had proven to be the best maintenance treatment in TRAPS. Newly diagnosed patients who had a positive response to anti-IL1β drugs given since disease onset, do not develop typical long-term complications, such as AA amyloidosis and infertility. Adult patients with a positive response to anti-IL1β may obtain a partial or complete regression of clinical disease. In particular, the risk of transplanted kidney failure is decreased and pregnancy becomes an opportunity for TRAPS women with history of infertility or multiple miscarriages. Moreover, the expected anti-IL1β effect in TRAPS patients suggests that drug resistance may support an alternative diagnosis, especially in patients with VUS/NC and B/LB variants. On the other hand, the new criteria were able to differentiate patients with VUS/NC variants better responding to colchicine as maintenance therapy, as already described in patients with systemic undefined recurrent fevers (SURF) (24, 25).

A safety profile has been reported for anti-IL-1 treatments in our cohort. These drugs have been demonstrated to be generally safe in pregnant women and our cohort seems to confirm these findings (26-27).

An increase of the body mass index has been noted when inflammation was well controlled in TRAPS, becoming an indirect parameter of treatment efficacy, especially during the first three months after

treatment initiation. More efficient calorie utilization has been suggested as the leading cause of the weight gain in these patients (28). Mediterranean diet and regular aerobic physical exercise may reduce the clinical impact of these common adverse events and should be proposed by physicians at the treatment start. On the contrary, long-term educational achievements and employment goals seems to not be affected by TRAPS in our cohort.

In summary, TRAPS has a severe impact on general health if not recognized and treated in a timely manner**.** Anti-IL-1 drugs are the best maintenance treatment in TRAPS with potential to reverse the most serious disease complications of AA amyloidosis and infertility. Effective treatment is associated with an increase in quality of life and body mass index. The diagnosis of TRAPS should be considered with caution in patients carrying VUS, NC and LB variants according the INSAID variant classification. In these patients, a course of colchicine may have a beneficial impact on the disease course. Notably, the exponential use of next generation sequencing in the diagnostic work-up of patients with an inflammatory phenotype will lead to the identification of a growing number of patients carrying VUS, NC and LB *TNRFS1A* variants, with a possible risk of mis-interpretation. The Eurofever classification criteria help to distinguish two subpopulations among patients carrying *TNFRSF1A* variants and should be aplied in clinical trials and translational studies focused on TRAPS.

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FIGURE LEGENDS

Figure 1. Variants of the *TNFRSF1A* gene in our cohort.
CRD=cysteine-rich domain.

Figure 2. The mean global Autoinflammatory Disease Activity Index (AIDAI) according to the INSAID variants classification and the Eurofever criteria.
Group A=patient with pathogenic or likely pathogenic variants; Group B=patients with variant of uncertain significance or not classified variants; Group C=patients with benign or likely benign variants; *p<0.02.

Figure 3. Treatment efficacy according to the INSAID variants classification and the Eurofever criteria.
Group A=patient with pathogenic or likely pathogenic variants; Group B=patients with variant of uncertain significance or not classified variants; Group C=patients with benign or likely benign variants; *p<0.04.

Figure 4. Quality of life in patients with TRAPS after anakinra.
Data in red shows the median score in 8 patients with TRAPS immediately before starting anakinra. Data in green shows quality of life on anakinra in the same group of patients plus another 9 patients on long-term anakinra treatment. For the assessment of the health-related quality of life we used the Medical Outcome Short Form (36) Health Survey (SF-36®).

TABLES

Table 1. Demographic data and clinical characteristics according to the INSAID variants classification and the Eurofever criteria.

Characteristics	Whole population	Patients with P/LP variants (group A)	Patients with VUS/NC variants (group B)		Patients with B/LB variants (group C)	p value
TRAPS according to the Eurofever criteria	-	**Yes**	**Yes**	**No**	**No**	-
Number of patients	226 (100)	127 (56)	38 (17)	40 (18)	21 (9)	-
Male	107 (47)	61 (48)	20 (57)	14 (35)	12 (57)	0.295
Median age at onset (years; range)	5.3 (0-63)	2.6 (0-50)	5.6 (0-53)	6.2 (0-63)	19.2 (1-45)	<.0001
Median age at diagnosis (years; range)	23.7 (0-76)	29.2 (0-76)	14.6 (1-63)	15.1 (0-65)	31.9 (13-74)	0.003
Median age at the time of enrolment (years; range)	32 (0-84)	41.1 (4-84)	15.2 (1-63)	15.3 (0-65)	33 (13-74)	<.0001
Patients with age at the time of disease onset ≥18 years	43 (19)	13 (10)	11 (29)	9 (26)	10 (48)	<.0001
Patients with age at the time of enrolment ≥18 years	127 (56)	73 (58)	16 (42)	18 (45)	20 (95)	<.0001
Median diagnostic delay (years; range)	10 (0-63)	13.9 (0-63)	6.4 (0-51)	2.8 (0-32)	9.3 (1-43)	0.003
Median disease duration (years; range)	12.3 (0-60)	17.1 (0-60)	7.3 (1-26)	13.1 (3-26)	10.5 (1-44)	0.575

Patients with intronic variant(s)	29 (13)	2 (2)	5 (16)	14 (35)	21 (100)	-
Continuous disease pattern	26 (12)	16 (7)	6 (16)	3 (8)	1 (5)	0.464
Recurrent disease pattern	188 (83)	100 (87)	32 (84)	36 (93)	20 (95)	
Median episodes/year (range)	6 (1-48)	5 (1-25)	8 (1-25)	8 (1-24)	12 (1-48)	0.09
Median duration of episodes (range)	10 (1-42)	10 (2-25)	6.5 (1-21)	7 (2-21)	3.5 (1-42)	0.049
Fever ≥38^{0}C	156 (69)	78 (61)	27 (71)	35 (88)	16 (76)	0.018
Malaise	120 (53)	68 (54)	24 (63)	23 (58)	5 (24)	0.008
Abdominal pain	137 (61)	87 (69)	24 (63)	21 (53)	5 (24)	0.01
Nausea/vomiting	30 (13)	10 (8)	6 (16)	12 (30)	2 (10)	0.004
Diarrhea	35 (16)	17 (13)	6 (16)	8 (20)	4 (19)	0.066
Headaches	37 (16)	12 (9)	7 (18)	14 (35)	4 (19)	0.564
Chest pain	38 (17)	24 (19)	7 (18)	4 (10)	3 (14)	0.543
Painful nodes	28 (12)	16 (13)	3 (8)	7 (18)	2 (10)	0.297
Arthralgia or myalgia	151 (67)	90 (71)	19 (50)	30 (75)	12 (57)	0.879
Swelling of the joints	39 (17)	25 (20)	0 (0)	10 (25)	4 (19)	0.001
Eye manifestations	62 (27)	44 (35)	6 (16)	9 (23)	3 (14)	0.329
Skin rash	103 (46)	70 (55)	13 (34)	14 (35)	6 (29)	0.001
Stomatitis	20 (19)	3 (2)	8 (21)	7 (18)	2 (10)	0.002
Triggers of episodes	31 (14)	19 (15)	4 (11)	7 (18)	1 (5)	0.240
Mean global AIDAI (standard deviation)	4.4 (±1.1)	4.5 (±1.7)	4.3 (±1.9)	4.9 (±2.6)	3.2 (±1.1)	0.011

Results are shown as number (%) unless stated otherwise; P=pathogenic; L=likely; B=benign; VUS= variant of uncertain significance; NC=not classified; AIDAI=Autoinflammatory Disease Activity Index.

Table 2. Treatment efficacy according to the INSAID variants classification and the Eurofever criteria.

	Complete response	**Whole population**	**Patients with P/LP variants (group A)**	**Patients with VUS/NC variants (group B)**		**Patients with B/LB variants (group C)**	**p value**
TRAPS according to the Eurofever **criteria**	**-**	**-**	**Yes**	**Yes**	**No**	**No**	**-**
NSAIDs	No	22 (44)	17 (70.8)	3 (21.4)	0 (0)	2 (66.7)	0.001
	Yes	28 (56)	7 (29.2)	11 (78.6)	9 (100)	1 (33.3)	
Steroids	No	16 (21.3)	12 (22.6)	1 (16.7)	2 (20)	1 (16.7)	0.974
	Yes	59 (78.7)	41 (77.4)	5 (83.3)	8 (80)	5 (83.3)	
Colchicine	No	23 (60.5)	17 (89.5)	3 (50)	0 (0)	3 (60)	<.0001
	Yes	15 (39.5)	2 (10.5)	3 (50)	8 (100)	2 (40)	
Anakinra	No	7 (12.5)	2 (4.8)	1 (12.5)	2 (100)	2 (50)	<.0001
	Yes	49 (87.5)	40 (95.2)	7 (87.5)	0 (0)	2 (50)	
Canakinumab	No	3 (13.6)	3 (13.6)	0	0	0	-
	Yes	19 (86.4)	19 (86.4)	0	0	0	
Etanercept	No	27 (81.8)	22 (84.6)	1 (33.3)	3 (100)	1 (100)	0.124
	Yes	6 (18.1)	4 (15.4)	2 (66.7)	0 (0)	0 (0)	

Results are shown as number (%) unless stated otherwise; P=pathogenic; L=likely; B=benign; VUS= variant of uncertain significance; NC=not classified.